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Point of care testing: The impact of nanotechnology

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ABSTRACT

Point-of-care (POC) diagnostic devices are integral in the health care system and particularly for the diagnosis and monitoring of diseases. POC testing has a variety of advantages including the ability to provide rapid and accurate results, ease of use, low cost, and little need for specialized equipment. One of the goals of POC testing is the development of a chip-based, miniaturized, portable, and self-containing system that allows for the assay of different analytes in complex samples. To achieve these goals, many researchers have focused on paper-based and printed electrode technologies as the material for fabricating POC diagnostic systems. These technologies are affordable, sensitive, user-friendly, rapid, and scalable for manufacturing. Moreover, the combination such devices with nanomaterials provide a path for the development of highly sensitive and selective biosensors for future generation POC tools.

This review article discusses present technologies in on-site or at home POC diagnostic assays implemented in paper-based microfluidic and screen printing devices over the past decade as well as in the near future. In addition, recent advances in the application of nanomaterials such as gold nanoparticles, carbon nanotubes (CNTs), magnetic nanoparticles, and graphene in POC devices will be reviewed. The factors that limit POC testing to become real world products and future directions are also identified.

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1. Introduction

Major advances in healthcare system and analytical process have been focused on developing portable, reusable, and effective miniaturized platform or point-of-care (POC) systems. POC devices assume that all tests can be at or near the site of patient care. (McPartlin and O'Kennedy, 2014; Omidfar et al., 2012a; Tang et al., 2016). POC testing is a paradigm shift from traditional diagnostic tests in the clinical laboratory setting to near-patient settings, providing physicians with timely diagnostic information enabling better informed decisions regarding diagnosis and treatment (Gomez, 2013).

The guidelines generally required for developing efficient POC devices are provided by the World Health Organization (WHO). These guidelines are known as ASSURED, in which the acronym ASSURED stands for affordable, sensitive, specific, user-friendly, rapid/robust, equipment-free or minimal, and delivered to the greatest need (Mabey et al., 2004).

POC devices can be divided into two classes including small hand-held and larger bench-top devices. Small hand-held devices are developed using state-of-the-art microfabrication techniques, which automate sample preparation, assay steps, analysis and detection of signals (Srinivasan and Tung, 2015; St John and Price, 2014). These devices offer qualitative or quantitative measurement of a wide range of analytes. Larger bench-top devices are essentially miniaturized versions of mainframe central lab equipments which have been reduced in both size and complexity.

Various reports are available to document the growth in vitro diagnostics (IVD) markets including various categories such as POC testing. The global POC diagnostics market is expected to reach USD 27.5 billion by 2018 at an estimated compound annual growth rate (CAGR) of 9.3% from 2013 to 2018 (marketsandmarkets.com; Report Code: MD 2702) (Sharma et al., 2015). LFAs constitute the majority of the POC diagnostics market. Globally, more than 100 companies are producing a wide range of LF tests. The integration of molecular diagnostics with POC testing is the fastest growing area in recent years. The total molecular diagnostics market is estimated to grow and reach USD 9333.8 million by 2020. The molecular diagnostics market, by application, is categorized into infectious diseases, oncology, genetics, blood screening, microbiology, and others (cardiovascular diseases, neurological diseases, DNA fingerprinting, tissue typing, and food pathogen detection testing).

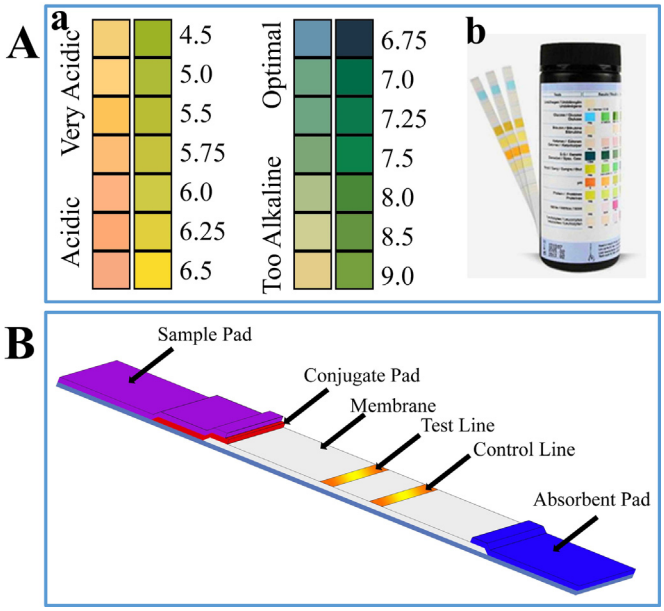

Fig. 1. Paper-based diagnostic platforms: (A) dipsticks, including (a) diagnostic pH test strips and (b) urine test strips. (B) Schematic view of a typical lateral flow test strip, including sample pad, conjugate pad, incubation and detection zone with test and control lines and final absorbent pad.

Herein, we restrict our discussion to two categories including paper-based microfluidic and printed electrodes (PE) POC diagnostic devices. Then we offer an authoritative review on the impact of nanotechnology based POC systems in the recent years to summarize and comment on their development and advances. In particular, carbon nanotubes, graphene and metal nanoparticles as well as their corresponding nanocomposites will be discussed. Finally, the future perspectives, opportunities and challenges in this field will be discussed.

2. POC testing

In the following sub-sections, POC testing based on paper-based microfluidic and printed electrodes are presented.

2.1. Strip-based POC assays: capillary flow tests

2.1.1. Dipsticks

Paper-based analytical devices (Fig. 1A), in the form of paper-based indicators and dipstick assays, have been used for rapid detection of a wide range of analytes due to simple design, easy to manufacture and convenient to use.

The first paper-based diabetes dipstick test was established in the 1950s to determine the level of glucose in urine specimens. Nowadays, standard urine test strips have been employed to detect metabolic products (e.g., protein, glucose, and salt) from patients with nephritic or diabetic diseases (Liana et al., 2012; Park et al., 2016).

2.1.2. Lateral flow tests

The capillary flow platform, also known as LFA or test strip, is a promising tool for the identification of analytes and pathogens at the POC and/or home use. This sensing platform offers an inexpensive, relatively rapid assay, and ability to operate by minimally trained personnel in regions where no sophisticated laboratory facilities are available. In LFA, the liquid sample moves along a solid paper-based membrane through capillary forces without any applied pressure which is controlled by the wettability and characteristic sizes of porous substrate.

These types of assays require small quantities of liquid sample and time of 5–15 min for detecting the presence/absence of analyte in the specimen (Li and Macdonald, 2016; Omidfar et al., 2013; Park et al., 2016; Yamada et al., 2015). LF immunoassays as are among the most commercially successful microfluidic POC devices (Omidfar et al., 2013; Posthuma-Trumpie et al., 2009; Zhou et al., 2015). When an antibody and its fragments are employed as bioreceptors, this test is called a "lateral flow immunoassay" (LFIA)

(Choi et al., 2010; Goudarzi et al., 2015a; Kashanian et al., 2002; Omidfar et al., 2010, 2011b). The combination of antigen/antibody reaction and specific tagged doubled-stranded amplicon (ds-amplicon) detection after polymerase chain reaction (PCR) is also probable and is called a "nucleic acid lateral flow immunoassay" (NALFIA).(Mens et al., 2012). Specific nucleic acid hybridization between amplicons and immobilized capture probes is another format of this assay and is called a "nucleic acid lateral flow assay" (NALF) (Qiu et al., 2015; Xu et al., 2014).

Fig. 1B shows a schematic design of a LF test. The assay consists of several component parts that are assembled together and are supported by a backing card. These components include the sample pad, conjugate pad, reaction membrane, and an absorbent pad. These pads have different functions such as loading, reagent pre-storage, reaction, detection, absorption and liquid actuation. Usually, the sample pad is made of cellulose or cross-linked silica. It is utilized to filter particles and cells as well as separate the analyte from unwanted or interfering compounds, which is absorbed in the pad. The conjugation pad consists of cross-linked silica. It is employed as dry-reagent storage for binders specific to the ligand conjugated to the signal generating particle. The length, material and pore-size (50 nm to 12 mm) of the membrane determine the incubation time. These tests come in different sizes, shapes and configurations (Liana et al., 2012; Omidfar et al., 2013; Yamada et al., 2015). A label or tracer is one of the significant components of LF tests for the signal generation and final read out, because the attachment of the ligand and binder is difficult to visualize without them. Various formats of LF tests have been developed based on the labels or tracers. An ideal label or tracer should contain some characteristics that are amenable to detection by multiple methods over a large and useful dynamic range, have low or no non-specific binding activity, as well as are stable under routine storage and different assay conditions. Furthermore, it should be easily conjugated with biological molecules or chemicals compounds without losing its integrity or activity and commercially available at a low cost (Omidfar et al., 2013; Sun et al., 2014; Zhou et al., 2015). However, one label that has all these characteristics does not exist. Therefore, label or tracer is selected based on the assay to be established. Gold nanoparticles (GNPs) were usually used as labels for the generation of a strong and stable visible signal (Omidfar et al., 2013; Singh et al., 2015; Sun et al., 2014; Zhou et al., 2015).

However, other colored materials such as carbon (Qiu et al., 2015) and selenium (Wang et al., 2014), nanoparticles, dyed polystyrene (Juntunen et al., 2012), dye-loaded liposomes as well as colored latex particles (Birnbaum et al., 1992; Ho and Wauchope, 2002) are used less often as labels in this type of assays. Fluorescence (Lee et al., 2013) and chemiluminescence emitting dyes (Mirasoli et al., 2012) along with the enzyme labels (Fung et al., 2009) are also investigated. The use of up converting phosphors (Corstjens et al., 2014), paramagnetic (Barnett et al., 2014), and quantum dot (Bruno, 2014) particles is a relatively new invention.

The strips usually contain one control and test lines. Analyte detection is performed on the test line and proof of assay validity on the control line. The readout of test is typically conducted by the naked eye. They are usually implemented as a color change in the detection area. Readout with a reader tool enables quantitative detection of analyte. More test lines can be applied permitting for multi analyte testing or for semi-quantitative evaluation of the response (Chamorro-Garcia et al., 2016). Generation of a response signal at the test line begins when a particulate tracer molecule is dispersed by the flow of the sample into a liquid containing analyte that specifically attaches to the tracer molecule through an adsorbed antibody or nucleic acid fragment as a detector reagent. A response at the control line verifies a suitable flow of the liquid through the test strip. The absorbent pad, also called wick or wicking pad, draws the liquid to the end of the test strip, therefore, maintaining the flow and determine how much sample is wicked through the strip and offers metering of the sample. Both competitive and sandwich types of assay can be designed to detect small and high molecular weight analyte with single or more than one antigenic determinant, respectively (Liana et al., 2012; Omidfar et al., 2013).

In LFAs evaluations of the color changes were normally completed by the naked eye, which may produce uncertainties due to the subjective judgment of the operators and variations in the illumination settings. In addition, when more quantitative results are needed, a suitable signal detecting instrument is required. Computer vision has been demonstrated as a useful device for solving these problems. Capturing and processing test images using computer vision and machine learning techniques can provide objective color intensity measurements of the test lines with high repeatability. Smartphone technology is the most widely used mobile device in the world, exhibiting a promising digital platform for POC diagnostics, mobile healthcare and bioanalytical needs. By using the smartphone, it is possible to measure the intensity of the colored areas on the test line by an office camera, digital camera, cell phone camera, or a more sophisticated photodetector to determine the quantity of analyte in the sample with high sensitivity. Recently, it has played an increasingly significant role in portable biosensor devices as platforms to receive, analyze and display detecting signals (Fig. 2). Detection of drug-of-abuse in saliva (Carrio et al., 2015), measurement of changes in pH of sweat and saliva (Oncescu et al., 2013), quantification of vitamin D levels (Lee et al., 2014), and detection of alkaline phosphatase activity in milk (Yu et al., 2015) are some of the recent instances of the integration of the colorimetric LFA methods and smartphones.

Given the convenient use and visual end-point, a range of on-site LF assays have been widely employed as at-home diagnostic tools to recognize various clinical and laboratory targets including drug and toxin (Ho and Wauchope, 2002; Omidfar et al., 2010), tumor markers (Barnett et al., 2014), protein (Choi et al., 2010; Goudarzi et al., 2015b; Leung et al., 2008; Omidfar et al., 2012a, 2010), DNA (Qiu et al., 2015; Xu et al., 2014), virus (Goudarzi et al., 2015a; Rohrman et al., 2012), pathogen (Corstjens et al., 2014), and hormone (Chamorro-Garcia et al., 2016).

2.1.3. *Advances in capillary flow tests*

Paper-based microfluidics or lab on paper is a class of microfluidic methods that provides a novel system for fluid handling and fluid analysis for a variety of medical applications such as healthcare and disease screening in the developing world (Gomez, 2014). It combines the simplicity, portability, disposability and low-cost of paper strip tests and the complexity of the conventional LOC devices. In fact, these analytical devices represent a new class of POC diagnostic tools that integrate some of the capabilities of microfluidic systems with the flexibility of the LF test strip technology (Yamada et al., 2015).

Paper is an attractive substrate material for fabricating microfluidic device because it is a ubiquitous and very inexpensive cellulosic material. It is compatible with many medical applications and transports liquids using capillary forces in the absence of external forces. Furthermore, the high surface area-to-volume ratio and the chemical composition of paper permit the simple physical immobilization of the reagents onto the surface. Cellulose is an essential primary component of plant cell walls. It has abundant hydroxy groups (–OH) and a few carboxylic acid groups (–COOH) that are present on the fiber surface. They can serve as scaffolds for the physical and chemical immobilization of biomolecules. Covalent bonding is often used for the strong attachment of bioactive compounds (Alila et al., 2005). Nonspecific adsorption

Fig. 2. Commercial readout devices (A) iPhone rapid diagnostic lateral flow reader. Courtesy of Detekt Biomedical L.L.C. (B) Android-based lateral flow reader. Courtesy of Holomic L.L.C. (C) Novarum reader. Courtesy of British Biocell International. (D) iBG star. Courtesy of Sanofi.

of molecules onto the cellulosic surface is a disadvantage of using paper as a substrate. It can decrease the number of target analyte molecules reaching the assay area and need to be compensated by calibration. By creating microchannels patterned on paper, liquid flow is restricted within the channels, and consequently, fluid can be directed in a controlled manner. A range of two-dimensional (2D) (Fig. 3A) and even 3D (Fig. 3B) microfluidic channels have been built on paper, which are able to transport liquids separately in the predesigned pathways on paper for performing single- or multi-step analytical assays and quantifying concentrations of different analytes in human body fluids (Liu et al., 2014; Yamada et al., 2015). In 2007, Martinez et al. (Martinez et al., 2007) reported the first μPAD for chemical analysis but its origins date back to the work of Muller and Clegg in the 1940s, except paper strips test for the determination of pH (Lisowski and Zarzycki, 2013; Müller and Clegg, 1949). In practice, several techniques can be used for fabricating μPADs such as photolithography (Martinez et al., 2007), etching (Martinez et al., 2008), writing (Dossi et al., 2013; Li et al., 2015), dipping (Songjaroen et al., 2011), printing (Martinez et al., 2008), stamping (de Tarso Garcia et al., 2014), and spraying (Nurak et al., 2013).

The basic principle underlying these fabrication techniques is to pattern hydrophilic-hydrophobic contrast on the surface of paper to make micron-scale capillary channels on paper fibers. To select the suitable technique, a range of factors including equipment availability, material costs, fabrication process simplicity, and the intended applications of paper-based microfluidic device should be considered. Printing is the one of the most commonly used techniques to achieve minimal consumption of hydrophobic material. Alkyl ketene dimer (AKD) ink jet printing and wax printing might be the most promising techniques, due to the easy, rapid fabrication process and inexpensive agents for patterning. Both techniques can produce multiple devices or multizones on a piece of A4-sized paper (Hu et al., 2014; Yamada et al., 2015). Colorimetric (Cate et al., 2015), electrochemical (EC) (Cate et al., 2015), fluorescence (Cate et al., 2015; Cho et al., 2015), chemiluminescence (CL), and electrochemiluminescence (ECL) (Cate et al., 2015; Ge et al., 2012) detection methods have been employed for the detection of analytes in a μPAD. In most assays based on colorimetric detection, the results can be visually evaluated by the naked eye, which is suitable when a yes/no answer or a semi-quantitative result is enough for analysis. Fluorescence or electrochemical methods have also been popular in μPAD designs, and are more attractive because of their high accuracy, sensitivity and much lower limit of detection (LOD) in comparison to colorimetric assays. Electrochemistry is also less prone to interference compounds present in the samples in comparison with colorimetry, because it is insensitive to local lighting conditions. Blood glucose or coagulation monitoring are one of the most common applications for such quantitative readouts. Most studies reported to date have been focusing on exploiting the colorimetric, fluorescence and the EC detection methods in μPAD. Colorimetric detection has

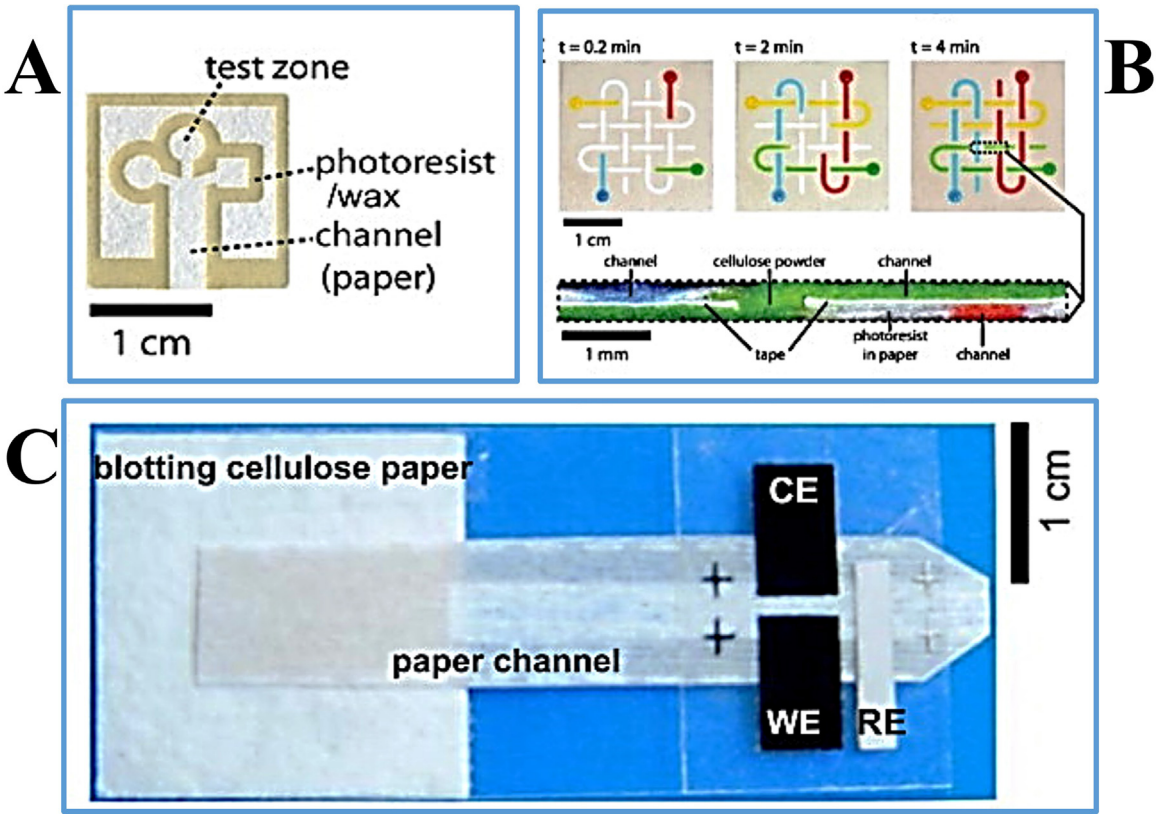

Fig. 3. (A) A typical two-dimensional (2D) μPAD. (B) A typical three-dimensional (3D) μPAD. (C) A typical microfluidic paper-based electrochemical device (μPED). Reprinted, with permission, from Ref. (Hu et al., 2014).

been extensively used due to its simplicity and compatibility with camera-phone-based telemedicine. It is based on the color caused by the chemical reaction between the analyte and colorimetric reagents spotted in detection zones on the paper (Cate et al., 2015; Mark et al., 2010). Martinez et al. (2007) developed a cost-effective μPAD for the colorimetric detection of glucose and protein. In the glucose assay, enzyme oxidizes iodide to iodine resulting in the formation of a brown coloration. In the protein assay, tetrabromophenol blue is used to afford a color change from yellow to blue. Ornatska et al. (2011) reported a colorimetric μPAD for measuring glucose concentration in blood with a LOD of 0.5 mM. The fabricated μPAD was applied for the detection of glucose using ceria nanoparticles and glucose oxidase immobilized on paper after silanization with aminopropyltrimethoxysilane (APTS).

Nei et al. (Nie et al., 2010) fabricated a microfluidic paper-based electrochemical device (*μPED)* for the analysis of glucose in aqueous solutions, including body fluids. This system consists of two printed carbon electrodes as the working and counter electrodes, and a printed Ag/AgCl electrode as the reference electrode (Fig. 3C).

Chitosan polymer has also been *used to* stabilize glucose oxidase. Yuan et al. (2012) reported a μPAD based on a fluorescence detection method using a hybrid material synthesized by encapsulating CdTe quantum dots and enzymes with a film of poly (diallyldimethylammonium chloride). The hybrid material containing glucose oxidase and tyrosinase demonstrated the appropriateness for detecting glucose and catechol using a fluorescence quenching effect, respectively. Liu and Crooks (Liu and Crooks, 2012) described a μPAD with an electrochemical sensor powered by an integrated metal/air battery. It was employed for detecting glucose in urine. The analytical signal for detecting glucose and H_2O_2 was provided using a color change of a Prussian blue as an electrochromic indicator spot on an indium tin oxide (ITO) electrode. The assembly worked as an onboard electrochromic display. The most common optical detection methods in conventional microfluidic tests are CL and ECL. They have not been widely employed in μPAD designs. There are only a few studies using these two detection methods for sensing analytes in μPADs or paper-based microarray plates (Lisowski and Zarzycki, 2013; Liu et al., 2014). In contrast to well-developed LFAs, μPADs are still at an early development stage although quite a few proof-of-concept demonstrations have been performed. Extending beyond the characteristics of commercial papers to novel hybrid composite materials with biofunctional properties can lead to more biocompatible substrates (Hu et al., 2014; Liu et al., 2014). Paper-based microfluidics are also widely used in smartphone-based POC diagnostics (Dou et al., 2015) which is based on patterning sheets of paper with hydrophilic channels bounded by hydrophobic barriers.

In recent years, μPADs have been widely extended to the health diagnostics, biochemical analysis, environmental monitoring, forensic and food quality control (Noiphung et al., 2013; Wu et al., 2013a; Zhao et al., 2015a; Zhou et al., 2015b).

2.2. Printed electrode based POC assay

The screen-printing (thick-film) technology is one of the most widely applied microfabrication techniques for large-scale production of very inexpensive and yet extremely reproducible electrochemical biosensors. This technology offers inexpensive and easy ways to make disposable devices at large scales for rapid, low-cost, on-site, and real-time analysis or monitoring of a clinical biomarker (Omidfar et al., 2011a, 2012b). Recent developments in microfabrication and nano-characterization have made it possible to prepare these inexpensive single-use devices by printing various commercial or self-made inks on different types of substrates.

Ceramics, plastic (polyvinylchloride, polycarbonate) and alumina are common matrixes in screen printed electrodes (SPEs) while gold, iron, silver, and fiber glass are also not unusual. The surface of SPEs can be easily modified with various materials to fit multiple purposes related to different analytes and to achieve a variety of improvements in their sensitivity, selectivity and stability (Ahmed et al., 2016; Daneshpour et al., 2016; Khorsand et al., 2013b; Omidfar et al., 2012b, 2015; Ping et al., 2010; Taleat et al., 2014). SPEs usually contain three electrodes: the working, counter, and reference electrodes. The working electrode is the main electrode on which electrochemical reactions are achieved. Both the reference electrode and counter electrode are also employed to complete the electronic circuit. During the printing process of SPEs, the most commonly used pastes are silver and carbon ink. Silver ink is printed as a conductive track while the working electrodes are often printed using carbon-based inks. Other materials such as gold and platinum inks can also be employed in the preparation of SPEs. It has been demonstrated that variations in the ink composition e.g. type, size or loading of particles can significantly influence the electron transfer reactivity and change the overall analytical performance of the designed screen printed biosensors. The composition of the inks used in the printing process of the electrodes determines the selectivity and sensitivity required for each analysis. Some unknown ingredients in these inks may produce unpredictable results during the detection and analysis procedure. The pastes are mostly based on a polymeric binder with metallic dispersions or graphite. They can also contain functional materials such as cofactors, stabilizers and mediators (Ahmed et al., 2016; Taleat et al., 2014). For example, a carbon-based ink typically contains particles of graphite, polymeric binder, and other additives that are applied for dispersion, printing, and adhesion tasks. Carbon-based inks are particularly attractive for sensing applications due to their relatively low-cost, low-background currents, and chemically inert and broad potential windows (Rao et al., 2006). Gold paste is also employed in SPEs but less so than carbon because of their higher cost. However, the generation of self-assembled monolayers (SAMs) through strong Au-S bonds is providing an augmented interest for gold to be used in SPEs (Bain et al., 1989; Taleat et al., 2014). The adhesion of the printing ink onto the substrate or the slow electron transfer of bare SPEs can be improved using a variety of materials and structurally related materials. Adhesive materials including resin, cellulose acetate, cyclohexanone, and ethylene glycol can be used to attach the printing inks to the substrate. Additives may be mixed with printing inks to improve the specificity, sensitivity or signal-to-noise (S/N) ratio. One of the main advantageous of SPEs is their high versatility. This feature is largely due to the wide range of ways in which the electrodes' surfaces can be modified by changing the ink composition or depositing various substances on the electrodes surface such as metal films, polymers, enzymes, and etc (Rao et al., 2006; Taleat et al., 2014). Besides, major development has been accomplished in the fabrication of SPEs by employing nanostructures materials. More recently, metallic nanoparticles, nanowires, carbon nanotubes and graphene, and their nanocomposites have also been included either in these pastes or as a later stage on the working electrode (Ahmed et al., 2016; Cui et al., 2015; Daneshpour et al., 2016; Khorsand et al., 2013a; Yao and Zhu, 2014). These materials are used to enhance the immobilization efficiency of biological molecules and accelerate the charge transfer rate on the electrode surface. Furthermore, they can increase the electrochemical mediation to amplify signals from SPEs. Attachment of the biological molecules onto the dried and cured ink can be performed through immobilization techniques such as physical adsorption, covalent interaction or chemical cross-linking, affinity interaction, and entrapment (Ahmadi et al., 2014; Amin et al., 2014; Berisha et al., 2013; Grewal et al., 2014; Khaled et al., 2010; Shirazi et al., 2016; Taleat et al., 2014). The other potential immobilization techniques are sol-gel (Kamanin et al., 2014) and electro-polymerization (Daneshpour et al., 2016; Omidfar et al., 2015) which allow better and selective analyte diffusion. SPEs are suitable to make effective, versatile, and low-cost miniature devices capable of giving reproducible results with high sensitivity in biochemical detection (Berisha et al., 2013; Daneshpour et al., 2016; Khorsand et al., 2013b). In addition, the application of SPE arrays provides the benefits of rapidity and the possibility to carry out the calibration and the analysis of several unknown samples simultaneously (Moreno et al., 2009). There are several different formats of screen printed microarrays, such as a biochip composed of eight working electrodes, one ring-shaped pseudo-reference electrode and one central auxiliary electrode (Corgier et al., 2007a, 2007b). Mann and Mikkelsen reported another type of array which was sandwiched between insulating layers to construct microwells (Mann and Mikkelsen, 2008). Disposable biosensors employing screen-printing technology have found commercial success for diabetes management and have been widely investigated in the search for early detection and quantitation of biomolecules such as protein, RNA, DNA, and enzymes (Azimzadeh et al., 2016; Bonanni et al., 2010; Daneshpour et al., 2016; Khorsand et al., 2013b; Omidfar et al., 2015). Recently, considerable advancement has been made towards integration of SPEs and fluid-handling and/or sample-processing tools to ensure portable POC devices. Consequently, screen-printing technology has emerged as the method of choice for mass production of POC disposable biosensors. Home-use blood glucose monitoring tests can be considered the most well-known electrochemical assays for POC devices currently produced on an amazing scale (Heller and Feldman, 2008, 2013; Jung et al., 2015).

3. Nanomaterial-based POC assay

The association of nanotechnology with medical diagnostics, therapeutics, treatment, and monitoring has provided a new concept in science, namely nanomedicine. Nanomedicine is an interdisciplinary field of science and many different scientists with various expertize including biochemists, chemists, physicians, mathematicians, engineers, and computer scientists should work together (Vinogradov and Wei, 2012). A wide range of nanomaterials and their nanocomposites have been widely used in medicine and have offered some of the most promising results in the fields of in vitro diagnostics, imaging, and therapeutics (Baker, 2010; Brambilla et al., 2011; Chi et al., 2012). Over the last decade, this field has been extensively investigated and a huge number of papers have been published. In particular, carbon nanotubes, graphene, and metal nanoparticles as well as their corresponding nanocomposites have been widely reported in the literature for POC biosensors development (Hibbard et al., 2013; Janegitz et al., 2014; Wang et al., 2013). Nanomaterials can be employed as carriers to load signal markers or directly as signal reporters for sensitive and specific detection of analytes (Omidfar et al., 2013). They can also accelerate electron transfer when they are applied as functional materials on the surface of electrode. The physical-chemical properties of nanomaterials such as size, shape, composition, construction, and others can be modified, in order to generate the desired materials with various specific characteristics (Singh and Nalwa, 2011; Yang et al., 2013a).

These materials are able to improve the sensitivity and specificity of detection systems, and also increase the reproducibility and reliability of assay due to their unique properties such as high surface-to-volume ratio, good electrical properties, and chemical stability (Holzinger et al., 2014; Omidfar et al., 2013). Moreover, the integration of nanomaterials in micro-biosensor devices offers

the possibility of realizing portable, easy to use, and inexpensive sensors, due to the ease of miniaturization of both the material and the transduction system (SadAbadi et al., 2013). Glucose sensing devices have almost always been the first major application, mainly due to the multi-billion dollar glucose monitoring market. Employing nanomaterials in biosensing devices enables the simultaneous multiplex detection of biomarkers and the diagnosis of diseases at a very early stage (Hibbard et al., 2013; Wang et al., 2013). They have also opened the door for detecting ultra-trace concentrations of target analytes and designing ultra-sensitive, rapid, and cost-effective assays using minimum amounts of sample volume (Janegitz et al., 2014). However, the main promising application of this technology will be in the field of POC tests, which will allow the primary-care physician and patients to achieve clinical diagnostic assays at their respective settings. These advances in nanotechnology will be extremely useful in changing the expensive late-stage diagnosis as well as socially burdensome treatment to less expensive and relatively less invasive early-stage diagnosis (Song et al., 2014). The most commonly used nanomaterials in fabrication of POC devices will be discussed in this section and the exemplified micro/nano-biosensor or POC settings are detailed in Table 1.

3.1. Nanoparticles

Over the last decade, metal nanoparticles have attracted great scientific attention because of their diversity and widespread applications. Owing to their small size (1–100 nm) and high surface area, nanoparticles offer unique chemical, physical, and electronic properties that are interestingly beneficial for the development of reliable POC assays implemented in microfluidic and screen printed devices (de la Escosura-Muniz and Merkoci, 2010; Medina-Sanchez et al., 2012).

3.1.1. Gold nanoparticles (GNPs)

Among different nanoparticles made of metals, semiconductors, or organic compounds, GNPs (including gold nanospheres, hollow spheres, nanorods, and nanorings) are by far the most preferred nanomaterial used as the label for generating the appropriate signal thereby providing the enhancement and advantage over molecular reagents (Holland et al., 2011; Omidfar et al., 2013). In addition to their excellent biocompatibility, good stability, and easy functionalization to biomolecules, GNPs have appropriate optoelectronic properties (e.g., surface plasmon resonance and surface enhanced Raman scattering) that are influenced by the size, shape, and surrounding chemical environment (Borghei et al., 2016; Omidfar et al., 2013). Generally, GNPs are synthesized by colloidal or liquid chemical synthesis, through the reduction of chloroauric acid ($HAuCl_4^{-1}$) solution in water. With the addition of reducing agent with stirring, the Au^{3+} ions are reduced to Au^0 atoms, and the solution becomes supersaturated as the number of neutral Au atoms increases. This phenomenon results in precipitation of sub-nanometer gold particles. The remaining Au^0 atoms assemble onto the existing particles under vigorous stirring conditions leading to production of uniform particles. Various reducing agents are utilized to generate Au^0 atoms, which act as nucleation centers (Omidfar et al., 2013; Zhou et al., 2015). By controlling the various synthesis conditions, such as the reducer used, thermal conditions, and reaction steps, it is possible to prepare GNPs of different sizes and shapes that will

Table 1
Summary of selected nanomaterial-based POC assays for various biomolecules and their detection performances.

Nanomaterials	Detection Method	Analyte	Linear Range	Detection Limit	Real Sample	Ref.
GNPs	Colorimetric	miRNA-224	N/A	7.5 pM	Cell lysate	(Gao et al., 2016)
GNPs	Colorimetric	Troponin I	N/A	0.01 ng mL^{-1}	serum	(Choi et al., 2010)
GNPs	Electrochemical	HSA	0.5–200 μg mL^{-1}	1 ng mL^{-1}	Urine	(Omidfar et al., 2011a)
GNPs	Electrochemical	CEA AFP	0–5.0 ng mL^{-1}	3.5 pg mL^{-1} 3.9 pg mL^{-1}	Serum	(Lai et al., 2012)
GNPs	Real-time electrochemical profiling assay	PSA	0.2–25 ng mL^{-1}	0.2 ng mL^{-1}	N/A	(Uludag and Köktürk, 2015)
MNPs	Colorimetric	PSA	N/A	0.8 ng mL^{-1}	N/A	(Barnett et al., 2014)
MNPs	Colorimetric	HBsAg	N/A	1 ng mL^{-1}	N/A	(Oh et al., 2014)
MNPs	Microfluidic system (magnetic detection)	KIM-1 Cystatin C	200–2000 pg mL^{-1} 300–10,000 ng mL^{-1}	0.1 ng mL^{-1} 20 ng mL^{-1}	Urine	(Chung et al., 2015)
GMNCs	Colorimetric	r-Tp	N/A	1 NCU mL^{-1}	Serum	(Yang et al., 2013a)
GMNCs	Electrochemical	EGFR	0–1000 pg mL^{-1}	0.05 pg mL^{-1}	Serum	(Omidfar et al., 2015)
GMNCs	Electrochemical	Methylated DNA	0.01–5000 pM	2 fM	N/A	(Daneshpour et al., 2016)
GMNCs	Electrochemical	Thrombin	0.5–100 pM	0.07 pM	N/A	(Zhao et al., 2013)
GMNCs	electrochemical	Digoxin	0.5–5 ng mL^{-1}	0.05 ng mL^{-1}	Serum	(Ahmadi et al., 2014)
CNT	Colorimetric	DNA	0.1–20 nM	40 pM	N/A	(Qiu et al., 2015)
CNT	Electrochemical	PSA	0.4–40 ng mL^{-1}	4 pg mL^{-1}	Serum	(Yu et al., 2006)
CNT	Electrochemical	CA-125 CEA	0.001–75 U mL^{-1}, 0.05–50 ng mL^{-1}	0.2 mU mL^{-1}, 0.01 ng mL^{-1}	Serum	(Wang et al., 2012)
CNT	Electrochemical	cTnT	0.0025–0.5 ng mL^{-1}	0.0035 ng mL^{-1}	Serum	(Silva et al., 2013)
CNT	Electrochemical	PSA IL-8	5–4000 pg mL^{-1} 8–1000 pg mL^{-1}	5 pg mL^{-1} 8 pg mL^{-1}	N/A	(Wan et al., 2011)
CNT	Electrochemical	hCG	$0.01-100\times10^{-9}$ g cm^{-3}	0.01×10^{-9} g cm^{-3}	N/A	(Teixeira et al., 2014b)
CNT	Electrochemical	Serotonin	0.2 nmol L^{-1}–10.0 μmol L^{-1}	0.2 nmol L^{-1}	N/A	(Moraes et al., 2012)
CNT/NiO	Electrochemical	LDL	5–120 mg dL^{-1}	0.63 mg dL^{-1}	N/A	(Ali et al., 2015)
CNT	FET	miRNA-122a	1 aM–10 fM	1 aM	N/A	(Ramnani et al., 2013)
Graphene	Electrochemical	cTnI	1–1000 pg mL^{-1}	0.1 pg mL^{-1}	N/A	(Tuteja et al., 2014)
Graphene	Electrochemical	hCG	0.001–50 ng mL^{-1}	0.286 pg mL^{-1}	Urine	(Teixeira et al., 2014a)
RGO/chitosan/NiNPs	Electrochemical	Glucose	0.2–9.0 mM	4.1 μM	N/A	(Yang et al., 2013b)
Graphene oxide	Electrochemical	hTERT	100 fg mL^{-1}–50 ng mL^{-1}	10×10^{-18} g mL^{-1}	N/A	(Choudhary et al., 2013)

HAS: Human serum albumin; CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; PSA: Prostate-specific antigen; HBsAg; Hepatitis B surface antigen; KIM-1: Kidney injury molecule-1; r-Tp: Recombinant Treponema pallidum antigen (Syphilis); EGFR: Epidermal growth factor receptor; CA-125: Cancer antigen 125; cTnT: cardiac troponin T; IL-8: Interleukin 8; hCG: Human chorionic gonadotropin; LDL: low-density lipoprotein; hTERT: Human telomerase reverse transcriptase.

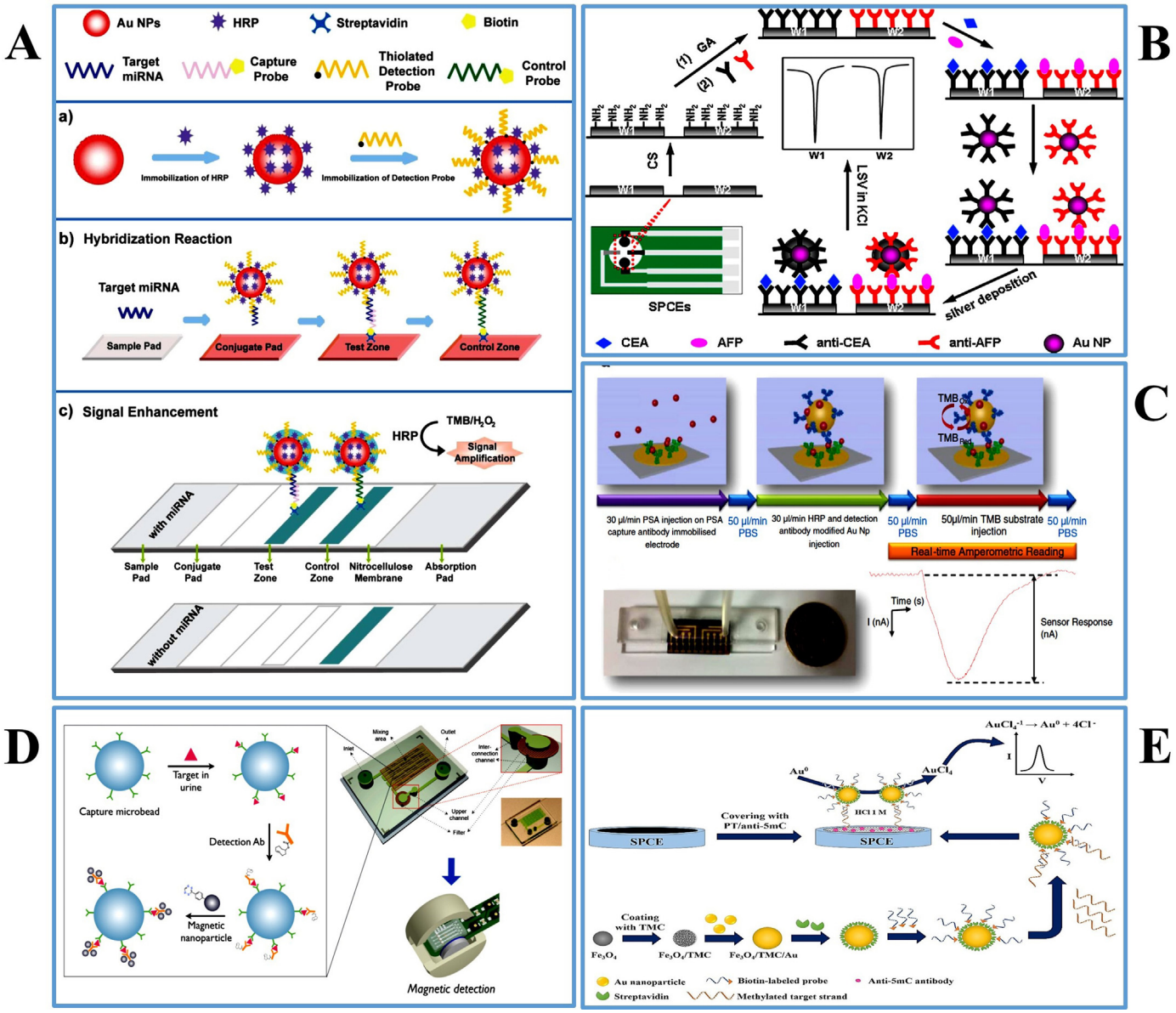

Fig. 4. Schematic diagrams illustrating the principle of operation of POC settings involving nanoparticles and nanocomposites. (A) An enzyme-amplified lateral flow strip biosensor based on dual labeled HRP-GNPs-DNA bioconjugates for visual detection of miRNA-224. (B) The preparation of a dual immunosensor and detection strategy based on gold nanolabels and silver deposition. (C) Real-time electrochemical profiling assay for PSA detection and the related electrode array integrated sensor cassette as sensing platform. (D) POC detection of kidney injury markers using a MNP-based automated on-chip assay. (E) An electrochemical nano-genosensor based on GMNCs and Polythiophene-modified SPE for DNA methylation detection. Reprinted, with permission, from Ref (Chung et al., 2015; Daneshpour et al., 2016; Gao et al., 2016; Lai et al., 2012; Uludag and Köktürk, 2015).

enhance their efficacy and usage in different applications. Special properties of GNPs manifest as an intense visible color that changes upon dispersion/aggregation and is valuable especially in colorimetric assays (Shirazi et al., 2015; Zhou et al., 2015).

GNPs are mostly used as labels for the generation of a strong and stable visible signal in LFAs (Fig. 4A). Their unique characteristics include simple and inexpensive laboratory production and modification, capability to combine with biomolecules, high stability in liquid or dried form, as well as good optical properties or signaling (Gao et al., 2014; Singh et al., 2015). The colloidal stability of nanoparticle labels in solution is very important. This significant requirement can be achieved by coating colloidal nanoparticle surfaces with macromolecules such as protein and DNA (Omidfar et al., 2011b, 2012a, 2013). Electrical charge can be generated by selecting the appropriate conditions of buffer solution such as pH, type, concentration, and ionic strength. The size of nanoparticles synthesized could be easily controlled during their production. There is a close relationship between the strength of the color, size and stability of colloidal particles (Gao et al., 2014; Zhou et al., 2015). Better sensitivity using larger particles was found; however, the stability of the colloid was reduced with particles over 40 nm. GNPs smaller than 15 nm were observed to be too small to produce a strength color. Moreover, colloidal gold particles larger than 60–70 nm showed self-aggregation after storage at 4 °C for several days (Omidfar et al., 2011a, 2013).

LFAs are characterized by their ease of use, good specificity, long shelf-life, as well as rapid and cost effective semi-quantitative results. Despite LFA strengths as a POC testing, the detection sensitivity and reproducibility of assay are still less than those of the gold standard diagnostic methods such as ELISA and PCR (Quesada-Gonzalez and Merkoci, 2015; Zhou et al., 2015). To improve sensitivity, different strategies have been integrated with

the LFAs, mostly including silver/gold NPs and enzyme based signal enhancement (Anfossi et al., 2013; Rodriguez et al., 2016; Wang et al., 2012). In silver based strategy, under the action of the reducing agent, silver ions are prone to gather around the GNPs in the form of silver, and the color of the test line is significantly increased because of the silver deposition on the GNPs surface (Anfossi et al., 2013). Several groups have also employed signal amplification methods by flowing solutions across the width of the detection zone of the test strip. These strategies can improve detection sensitivity, an approximately 1000-fold using a silver enhancement solution (He et al., 2011), and by 10-fold using an enzymatic amplification system (Mao et al., 2009). However, in these approaches, the user was still required to perform an additional liquid handling step for silver enhancement, thus limiting the suitability of the formats for employ at the POC tests. In this regard, GNP aggregates have been designed to increase the sensitivity of LFAs by subsequent introduction of two functionalized GNP-antibody conjugates. Using this methodology and under optimal conditions (10 and 40 nm for the first and second GNP, respectively), the detection sensitivity increased about a 100-fold compared to the conventional LFAs (Choi et al., 2010).

It is worth noting that in spite of interesting reports about GNPs-based lateral strip for POC nucleic acid analysis (Gao et al., 2016), this approach has not yet found a practical application and still needs some improvement. Therefore, the most successful commercial POC designed using GNPs-based LFA are focused on protein detection (Sharma et al., 2015).

Furthermore, GNPs have been involved in various electrode fabrications as a part of electrode substrate (Labib et al., 2013), signal transduction probe (Zhou et al., 2015), or nanolabel (Daneshpour et al., 2016). Using colloidal GNPs to modify solid electrodes like glassy carbon (GC) (Chang et al., 2014), screen printed (Chan et al., 2016), and crystalline gold (Tominaga et al., 2008) electrodes has been widely reported. These nanoparticles have also been used in composite electrode structures like the carbon paste electrode (CPE) (Afkhami et al., 2013) and the glassy carbon paste electrode (GCPE) (Cubukcu et al., 2007). The presence of GNPs in these electrodes has shown dual advantages: (1) the immobilization of biomolecules can be feasibly performed on gold-modified electrodes, and; (2) the GNPs can improve the electron transfer that leads to strongly amplify the electrochemical signals.

Gold-modified electrodes have been used for detection of numerous clinical factors such as Carcinoembryonic antigen (CEA) (Zhu et al., 2013), Prostate-specific antigen (PSA) (Escamilla-Gomez et al., 2009; Mani et al., 2009), α-fetoprotein (AFP) (Zhao et al., 2013a), and homocysteine (HcySH) (Madasamy et al., 2015). Although this approach has played a fundamental role in fabricating POC tests, we concentrate on studies which reported the use of GNP-labels in printed electrode-based POC tests in Table 1. According to the research, printed electrode-based devices fabricated based on these electroactive nano-labels have showed remarkable sensing performance in detecting tumor cells (de la Escosura-Muniz et al., 2009), human IgG antibodies anti-Hepatitis B surface antigen (HBsAg) (de la Escosura-Muniz et al., 2010), human serum albumin (HSA) (Omidfar et al., 2012b) CEA, (Lai et al., 2012), AFP (Lai et al., 2012), beta amyloid, and ApoE (de la Escosura-Muniz et al., 2015) due to great catalytic properties of GNPs (Fig. 4B).

Given the advantages of GNPs in the design of modern biosensing schemes or improvements of the conventional ones, it is logical to see a strong interaction between this unique nanoparticle and lab on a chip (LOC) platforms that have used GNPs as a detectable label or signal enhancer (Fig. 4C). Regarding this strategy, there are interesting studies on developing protein chip assay, chip-based biobarcode assay, and microfluidics-based integrated biochip which have been designed to detect trace amounts of clinically-valuable biomarkers such as PSA (Uludag and Köktürk, 2015), hepatitis B virus (HBV), and HCV antibodies (Duan et al., 2005). These proposed devices could simultaneously detect different analytes on one chip without non-specific reactions. Moreover, due to the requirement of small quantities of both samples and reagents, such methodology seems considerably beneficial when large quantities of samples are not available. Hence, compared to the conventional analysis such as ELISA tests, this LOC assay has been noticeably rapid and sensitive enough to show its potential as an automated POC device for clinical use (Li et al., 2010; Medina-Sanchez et al., 2012; Mohammed and Desmulliez, 2011).

3.1.2. *Magnetic nanoparticles (MNPs)*

MNPs have found extensive applications in magnetic fluids, catalysis, bioseparation, medical imaging, targeted detection, drug delivery, and hyperthermia treatment (Mahdavi et al., 2013; Thomas et al., 2013). Due to their special properties (ease of size control, low-cost production, and easy manipulation with magnetic field), MNPs have been considered an important part of biosensing approaches in novel biomedical applications (Bruls et al., 2009; Mahdavi et al., 2013). Employing appropriate surface-functionalization strategies, it has become possible to enhance uses of these particles while improving their stability (Wu et al., 2008). Although many types of MNPs have been synthesized and characterized, iron oxides (Fe_2O_3 and Fe_3O_4) are most commonly used in sensing and biosensing systems. These nanoparticles can be synthesized by different physical and chemical methods (e.g. coprecipitation, hydrothermal and high-temperature reactions, sol-gel reactions, polyol methods, flow injection syntheses, electrochemical methods, aerosol/vapor methods, and sonolysis) which have been reviewed elsewhere (Lu et al., 2007).

Naked MNPs suffer from their tendency for agglomeration because of high surface energy powerful magnetic attractions among particles, and the van der Waals force. Thus, various strategies have been employed to stabilize them including coating a shell on the surface of MNPs that make them hydrophilic, compatibility to bio-environments, and also functionalization (Lu et al., 2007; Wu et al., 2008). This shell may be composed of monomeric stabilizers (e.g. carboxylates or phosphates), inorganic materials (e.g. gold or silica), and polymers (e.g. Dextran, PEG, PVA, alginate, and chitosan) (Mahdavi et al., 2013; Wu et al., 2008). In sensing applications, these functionalized MNPs offer remarkable advantages such as improved sensitivity, low detection limit, high signal-to noise ratio, and rapid analysis process than non-MNP-based strategies (Chen et al., 2011; Choi et al., 2013; Gijs et al., 2010).

There are numerous reports on various approaches of using MNPs in electrochemical, optical, and piezoelectric biosensing systems as label or being integrated into the transducer part (Chen et al., 2011; Choi et al., 2013; Gijs et al., 2010). MNPs labels offer considerable advantages compared to fluorophores due to their stability, low production cost, and miniature size of final fabricated device valuable in POC tests (Tamanaha et al., 2008). In addition, MNPs have been extensively used in magnetic field sensing devices such as giant magnetoresistive (GMR) (Xu et al., 2008), Hall Effect (Aytur et al., 2006), magneto-optical (Hung et al., 2014), and superconducting quantum interference sensors (Granata and Vettoliere, 2015). Based on the work of Gao et al., another interesting feature of MNPs is their essential enzyme mimetic activity similar to that of peroxide. They showed that iron oxide nanoparticles and native horseradish peroxidase (HRP) have similar optimal pH and temperature for their peroxidase activity and that the catalytic activity of these MNPs increases with the decrease of particle diameter (Gao et al., 2007). Fe_3O_4 MNPs were then used as peroxidase mimetics to develop biosensors for detecting hepatitis B (Gao et al., 2007), monitoring glucose (Wei and Wang, 2008), and determining cardiac troponin-I and melamine (Ding et al.,

2010; Gao et al., 2007). In the following sections, we will detail those POC systems that have used Fe_3O_4 MNPs for generation or amplification of signal.

MNPs have been widely used as a colored label in LFA systems. Their strong brown color covers practically all the visible spectra due to the intraband transition (Gao et al., 2014). In comparison with GNPs, the main advantage of MNPs is that they are notably cheaper and their optical properties are hardly changed in an aggregated condition (Gao et al., 2014; Gubala et al., 2012; Handali et al., 2010). Due to the lack of magnetic species in biological components, these nanoparticles face low background noise and provide the possibility of detecting trace amounts of material via magnetic signal evaluation in addition to optical density analysis. Moreover, the magnetic signals generated by MNPs are quite stable over a long time period, thus the LFA strips can be rechecked whenever necessary (Quesada-Gonzalez and Merkoci, 2015; Wang et al., 2009). Use of magnetic particles as colored labels in LFA has been reported by number of researchers (Barnett et al., 2014; Chen et al., 2016; Handali et al., 2010; Liu et al., 2011; Nor et al., 2012; Oh et al., 2014; Yan et al., 2014). Furthermore, it has been evaluated how the impacts of the size and magnetite content of MNPs could affect magnetic LFIA performance (Wang et al., 2009). Additionally, there are numerous studies that reported using MNPs in fabrication of printed electrode POCs; but almost all of them employed these NPs for bioseparation (Daneshpour et al., 2016; Omidfar et al., 2015), and the only printed electrode platforms based on MNPs, have modified the surface of MNPs by various materials, especially noble metals. These nanocomposites will be discussed later.

Recent improvements in the optimized synthesis of MNPs, together with advances in instrumentation, suggest that these unique nanoparticles are promising materials for sensors in a variety of applications. NMs as labels are of particular interest offering extensive possibilities to enhance sensitivity and specificity in developing bio-detection devices (Haun et al., 2010; Jie et al., 2013). Nowadays, MNP-based labeling technologies can be employed in various sensing systems ranging from optical, electrochemical, and mass changes and play a crucial role in multiplex LOCs (Fig. 4D) (Giouroudi and Keplinger, 2013; Teste et al., 2011). There are many studies that have reported the development of MNP-based LOCs. In Table 1, we have reviewed the ones that have been more related to clinical applications.

One of the other important MNP-based technology that has been successfully used in designing diagnostic platforms is nuclear magnetic resonance (NMR) (Chung et al., 2015). Based on this technology, diagnostic magnetic resonance (DMR) mechanism has been developed which employed MNPs as proximity sensors in order to modify the spin–spin relaxation time of water molecules next to the target-conjugated MNPs (Issadore et al., 2011). Shao et al. impressively reviewed the biomedical NMR-based chips that used MNPs (Shao et al., 2010). However, the importance of magnetic nanotags (MNTs) as promising alternative to conventional labels, is more highlighted due to their advantages for rapid inexpensive protein detection assay (Chen et al., 2011; Lee et al., 2009). Based on this view, various biomarkers such as kidney injury molecule-1 (KIM-1) and Cystatin C have been quantified by performing the magnetic immuno-sandwich assay and using miniaturized nuclear magnetic resonance device (μNMR) (Chung et al., 2015).

3.1.3. Gold magnetic nanocomposite-based POC

The hybrid nanocomposite concept emerged a decade ago and since then significant achievements have been made in this field (Jiang et al., 2013; Wybranska et al., 2015; Zhu and Diao, 2011). Gold magnetic nanocomposites (GMNCs) are among the most common hybrid materials used at nano-scale for fabricating POC devices (Ahmadi et al., 2014; Dadmehr et al., 2014; Shirazi et al., 2015). With the magnetic core and gold shell, these nanocomposites provide the collective improved properties that considerably upgrade the nanoparticle-based sensing settings. Inspired by the advantages of this genius nanocomposite, numerous LFIA strip test systems and printed electrode-based bioassays have been designed for analyzing various important biomarkers such as anti-Treponema pallidum (Yang et al., 2013b), epidermal growth factor receptor (EGFR) (Omidfar et al., 2015), thrombin (Zhao et al., 2011, 2013b.), human immunodeficiency virus p24 antigen (Ning et al., 2010), digoxin (Ahmadi et al., 2014), and nucleic acid (Fig. 4E) (Daneshpour et al., 2016). More details on these sensors and the structure of employed GMNCs can be found in Table 1.

3.2. Carbon nanomaterial-based POC

3.2.1. CNTs

Since the discovery of carbon nanotubes (CNTs) by Iijima in the early 1990s, they have attracted considerable attention due to their unique physical, chemical, and electrical properties. CNTs are mainly classified into two types: single-wall carbon nanotubes (SWCNTs) and multi-wall carbon nanotubes (MWCNTs), which are cylindrical tubes of sp^2 carbon. There are three methods commonly used to synthesize CNT: arc discharge, laser ablation, and chemical vapor deposition (CVD) (Gao et al., 2012; Sadegh and Shahryari-ghoshekandi, 2015; Zhu et al., 2011).

CNTs used in several modern technologies and devices as transducers, due to their high sensitivity, specificity, rapidity in analysis, low cost, and ease of use. Biosensors based on CNTs have been improved in their portability, functionality, reliability, and real-time diagnosis for POC analysis. The application of CNTs in POC systems has been under consideration for the analysis of biological analytes including DNA, glucose, proteins, and viruses (Justino et al., 2013). POC testing based on CNT biosensors can be classified into three types including CNT-based LFA, CNT-based printed electrode, and CNT-based LOC.

The coupling of CNTs with LFA strips can provide a rapid, feasible and sensitive method for detection of biomolecules such as DNA, and protein. Recently, Qiu et al. developed a MWCNT-based lateral flow biosensor (LFB) using streptavidin-biotinylated probe on nitrocellulose membrane and carboxylated MWCNT as a label. Amine-modified DNA detection probe was immobilized to the carboxylated MWCNT by covalent bonding between DNA amines and carboxylic acids of the CNT. This biosensor provided a rapid and sensitive detection of DNA sequence with a detection limit as low as 40 pM. In addition, this platform exhibited high reproducibility in the absence and presence of 5.0 nM and 50 nM target DNA. The combining of lateral flow with unique physical properties of MWCNT CNTs enhanced the sensitivity of the MWCNT-based LFB biosensor 12.5 times compared to the GNP-based LFB (Qiu et al., 2015).

In another study, a novel immunosensor has been fabricated based on CNT conductive paper and lateral flow immunostrip for the electrochemical and colorimetric detection of DNA oxidative damage biomarker (8-hydroxy-20-deoxyguanosine in both PBS and spiked urine samples. CNT conductive paper provided high reliability and accuracy sensing compared to the conventional strip test. The integrated device with dual detection methods (electrochemical and colorimetric) was able to detect 8-hydroxy-20-deoxyguanosine (8-OHdG) biomarker with a detection limit of 2.07 ng mL^{-1} for the colorimetric method and 3.11 ng mL-1 for the electrochemical method. Furthermore, the device was successfully applied for sensing of the 8-OHdG in urine with a detection limit of 5.76 ng mL^{-1} (colorimetric method) and 8.85 ng mL^{-1} (electrochemical method), respectively. This combined assay on one single strip provides a suitable platform for monitoring of 8-OHdG

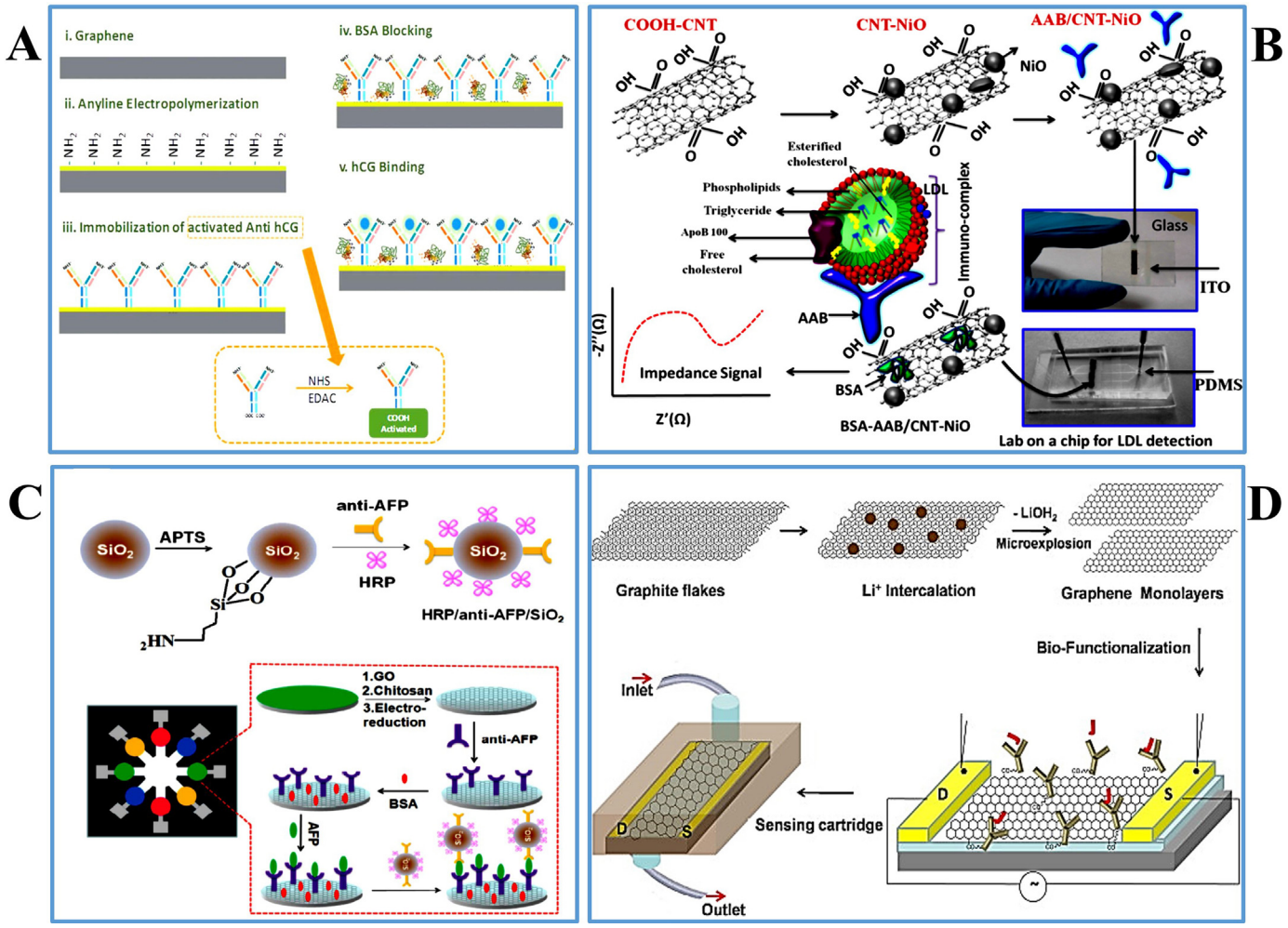

Fig. 5. Schematic diagrams illustrating the principle of operation of POC settings involving carbon nanomaterials. (A) hCG detection using oriented antibodies bound to graphene SPEs. (B) Preparation and assay procedure of a microfluidic paper-based electrochemical immuno-device using coimmobilization of HRP and antibody onto monodispersed SiO_2 nanoparticles. (C) Fabrication of the Lab-on-a-Chip for LDL detection. (D) Troponin detection via in-situ synthesis of intercalated graphene and subsequent functionalization for immunoassay development on electrode. Reprinted, with permission, from Ref. (Ali et al., 2015; Teixeira et al., 2014a; Tuteja et al., 2014; Wu et al., 2013a).

in medical diagnosis (Zhu et al., 2014).

During the past years, different efforts have been devoted to develop disposable biosensors by combining CNT with SPEs. Many versatile properties of CNTs such as adsorption capacity, the possibility of functionalization, their ability to promote the electron transfer reactions, and the possibility for miniaturization make them a very attractive material for sensitive and stable SPE-based electrochemical biosensors.

A novel CNT-SPE has been employed for the electrochemical detection of Human chorionic gonadotropin (hCG) (Fig. 5A). The CNT working electrode was modified with aminopropyl-triethoxysilane (APTES), in order to introduce amino groups onto CNT surface. These amino-modified CNTs were then attached to the antibody-target hCG by use of the cross-linking agents EDS and NHS. This modified electrode showed a high specificity, wide linear range (0.01×10^{-9}–100×10^{-9} g cm^{-3}) and low detection limit for hCG. The excellent detection capability and simplicity of this approach makes a convenient method for detecting hCG in a POC diagnostic (Teixeira et al., 2014b).

Khorsand et al. used carbon nanotube-modified screen printed electrode to develop two enzyme based biosensors for detecting 3-hydroxybutyrate (HB) in diabetic patients' serum samples. Both biosensors showed good stability and electrocatalytic activity and benefitted from the advantages of SPEs and SWCNTs. In the first study, HB dehydrogenase was physically immobilized on the functionalized SWCNTs modified electrode. SWCNT was used to facilitate electron transfer and reduce the oxidation potential of NADH to about −0.05 V. Electrochemical measurements showed that a good linearity in the range of 0.1–2 mM with a low detection limit of 0.009 mM (Khorsand et al., 2013b).

In the second study, SWCNT was used to help the maintenance of NAD^+ through the covalent attachment to CNT molecules. In this type of assay, only the first drop of NAD^+ conjugated with SWCNT would be sufficient for several electrochemical tests and the addition of NAD^+ is not required for each experiment. This biosensor can detect 3-hydroxybutyrate in the linear range from 0.01 to 0.1 mM with a detection limit of 0.009 mM (Khorsand et al., 2013a).

In addition, many desirable properties of CNTs allow them to be applied for microfluidic LOC applications (Fig. 5B). CNT integrated with microfluidic systems have been used for ultrasensitive detection of metabolites, proteins and nucleic acid (Ali et al., 2015; Choong et al., 2008; Moraes et al., 2012). For example, the detection of DNA concentration has been performed using an integrated microfluidic MWCNT biosensor. The MWCNT electrochemical sensor was fabricated using a combination of micro and nanolithography and then a microfluidic electrochemical cartridge including the counter and reference electrodes and a PDMS

microfluidic channel was assembled with the MWCNT chip. The complementary DNA targets delivered to the devices using the microfluidic channel and hybridized with DNA probes functionalized CNTs. This system offers a suitable and simple platform for developing portable and multiplexed assays (Kim et al., 2013).

Moreover, the integration of vertically aligned SWCNTs onto electrochemical microfluidic devices provided a promising platform for rapid, simple, and ultrasensitive determination of serotonin with detection limit of 0.2 nmol L^{-1} (Moraes et al., 2012).

In another study, an electrochemical aptamer-based microfluidic biosensor has been reported for vasopressin detection. The results exhibited high sensitivity, specificity in standard with a detection limit of 43 pM which is of the same order as the physiological level of vasopressin in the bloodstream. This miniaturized device offers a POC diagnostics tool for patients with excessive bleeding when standard medical infrastructure is not available (He et al., 2013).

Recently, Ordinario et al. developed a single microfluidic-encapsulated CNT-FET to electrical monitoring of protein–DNA interactions. The prototype sensor array was generated using macro-nano processing technologies including lithography and electron-beam evaporation and self-assembled films of DNA monolayers. In this approach, biosensing was accomplished by transducing the binding event between the DNA recognition element and the analyte into readable electrical signals that provided direct information of the sequence specific activity. The integrated platform was capable of detecting restriction enzymes concentration of 0.5 pM in a volume of 0.025 μL (corresponding to ~7500 proteins). This DNA modified CNT FETs showed promising tools for applications in multiplexed and/or portable LOC formats (Ordinario et al., 2014).

3.2.2. Graphene

Graphene, a one-atom thick and 2D closely packed honeycomb lattice, has attracted massive attention of the researchers in science and industry due to its very interesting electronic, mechanical, and thermal properties. There are various methods for the syntheses of graphene materials including mechanical exfoliation of graphite, chemical vapor deposition (CVD), electric arc discharge, epitaxial growth on electrically insulating surfaces, such as SiC, opening CNT and reduction of graphene oxide (GO) (Cai et al., 2014; Kuila et al., 2011; Pumera, 2011).

In recent years, graphene and its derivatives have provided a promising platform for sensitive clinical detection and POC diagnostics such as graphene-based printed electrode, and graphene based LOC.

Wu et al. reported the combination graphene-based amplification strategies with microfluidic paper-based electrochemical immuno-device for the multiplexed measurement of cancer biomarkers (Fig. 5C). The signal amplification was achieved by precipitation of RGO solution onto the working electrode as well as through the silica nanoparticles as label. This strategy provided accurate, rapid, simple, high-throughput, and inexpensive POC electrochemical immunoassays of cancer biomarkers (Wu et al., 2013b). Also, Batalla et al. developed an enzyme-based microfluidic chip coupled to graphene electrodes for the detection of D-amino acid (D-AAs) enantiomer-biomarkers that are involved in Vibrio cholera diseases. This simple and creative approach allows both the racemic resolution and detection of D-AAs on a single layout chip which is useful for the future development of POC devices to the detection of bacteria (Batalla et al., 2015).

In another approach, a functionalized graphene gated biochip has been fabricated to sense cardiac Troponin I (cTnI) biomarker (Fig. 5D). This label free biosensor could detect cTnI at pictogram concentrations (1 pg mL^{-1}) without any enzymatic amplification that leads to potential applications in routine monitoring of cTnI in blood samples (Tuteja et al., 2014).

The incorporation of graphene sheets into SPE presents another approach for developing POC tests. Teixeira et al. fabricated a new graphene-SPE for the electrochemical detection of hCG. The graphene-SPE modified with polyaniline (PANI) conducting polymer by electropolymerization of aniline. The graphene modified working electrode was then functionalized with anti hCG, by means of EDC/NHS chemistry that enabled oriented antibody binding to the PANI layer. The graphene–SPE– polyaniline devices showed a linear range from 0.001 to 50 ng mL^{-1} in real urine, a detection limit of 0.286 pg mL^{-1} and high selectivity even in the presence of the constituent components of urine (Teixeira et al., 2014a).

An ultrasensitive label free electrochemical immunosensor has been developed by covalent immobilizing antibody onto graphene oxide (GO) films for the detection lung cancer biomarker. The results exhibited high specificity, a wide linear range from 100 fg mL^{-1} to 50 ng mL^{-1}, and a detection limit as low as 10×10^{-18} g mL^{-1}. GO film can easily be integrated with MEMS technology for the development of miniaturized immunosensors towards POC diagnostics (Choudhary et al., 2013).

4. Conclusion and future outlook

Over the past decade, a number of innovative POC assays have been presented in both academic research and commercial products. By providing rapid and accurate analyses at patient's location, POC devices optimize diagnosis procedure, improve treatment management, and allow reaching efficient and cost effective clinical outcomes. It seems that the area of POC testing holds major potential for revolutionizing healthcare in both developed and developing countries. In developed areas, these tools are typically used in bedside diagnostic tests, in-home tests, and bioemergency response. In low and middle income countries, these systems are mostly utilized in clinical laboratories or isolated village health service providers.

The traditional POC approaches including LFA techniques provide quick and simple POC diagnostics which on the other hand have shown major limitations in accurate and sensitive analytical performance due to their simplicity and the need for sample pretreatment. Moreover, development of advance techniques in electrode printing and unique properties of electrical/electrochemical transducers has opened the door to widespread clinical applications of more sensitive sensing systems based on printed electrodes at micro/nano scale. As POC set ups, these screen printed disposable biochips have been considered as the state of art in in vitro and in vivo diagnosis applications. The cutting edge of PE-based POC assay studies has focused on the improvement of thick-film electrodes, immobilization strategy, and on nanomaterials to enhance electron transfer and finally detection sensitivity. On the other hand, integration of more components on a single SPE through miniaturization is necessary to make disposable and scalable SP micro electrode assays to move toward the cost-effective POC test systems.

Over the recent years, microfluidic technologies have significantly grown, especially in applications in the field of POC testing. Microfluidics allows the miniaturization of POC devices and automation of analysis processes which present considerable advantages including fabricating multiplex integrated systems called lab-on-a-chip platforms. In addition to fluidic transportation, sorting, mixing, or separation of liquid samples, microfluidic LOC devices are further developed in order to facilitate on-chip supramolecular chemistry, molecular motors and nanorobots, biomedical implants, biomimetics, and hybrid systems incorporated with blood vessels. Despite of all the advancements,

the POC tests are still far way to meet ultimate goal of an ideal diagnostic device which can find the extensive clinical application. One of the challenges in POC development is to prevent non-specific adsorption, leading to false response errors and decreased sensitivity. Another issue to be addressed is the integration and automation of the technology as well as development of appropriate sample preparation methods. The sampling procedures and readout analysis are required to be standardized and familiarized by the users. Smartphones are inexpensive, easy to use, and, widely available, and so they are very suitable for incorporation into microfluidic devices and PEs to create portable diagnostic and monitoring systems for POC testing. The upcoming generations of POC systems will be cabled or wirelessly interconnected in network-centric data links that will allow working together and be synchronized as terminal testers for the same or different patients remotely located. The main challenge in this regard is the development of integrated sensors and circuits on the same chip. The functionality of future POC platforms is expected to include more clinical tests and will be shifted from general-purpose laboratory equipment to personalized devices.

Undoubtedly, the rapid development of nanotechnology offers significant advancements in POC assays. The progress of bioanalytical assays will rely heavily on cutting edge innovations in nanotechnology including the use of nanoparticles and nanocomposites as well as nanomaterials such as CNTs and graphene. These innovations and developments will provide unique capabilities to enable the future generations of POC assay systems for non-invasive detection of trace amounts of molecular markers in biological fluids will eventually lead to considerable advancements in diagnostics and widespread use. It is predictable that in the near future, more and more nanostructures-based POC tests will become available in the ideal format of a diagnostic tool which provides reliable clinical analysis, particularly in low-resource, laboratory-free settings.

Declaration of interest

The authors report no declarations of interest.

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