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REVIEW ARTICLE

Fundamentals and commercial aspects of nanobiosensors in point-of-care clinical diagnostics

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Abstract

Among various problems faced by mankind, health-related concerns are prevailing since long which are commonly found in the form of infectious diseases and different metabolic disorders. The clinical cure and management of such abnormalities are greatly dependent on the availability of their diagnoses. The conventional diagnostics used for such purposes are extremely powerful; however, most of these are limited by time-consuming protocols and require higher volume of test sample, etc. A new evolving technology called "biosensor" in this context shows an enormous potential for an alternative diagnostic device, which constantly compliments the conventional diagnoses. In this review, we have summarized different kinds of biosensors and their fundamental understanding with various state-of-the-art examples. A critical examination of different types of biosensing mechanisms is also reported highlighting the advantages of electrochemical biosensors for its great potentials in next-generation commercially viable modules. In recent years, a number of nanomaterials are extensively used to enhance not only the performance of biosensing mechanism, but also obtain robust, cheap, and fabrication-friendly durable mechanism. Herein, we have summarized the importance of nanomaterials in biosensing mechanism, their syntheses as well as characterization techniques. Subsequently, we have discussed the probe fabrication processes along with various techniques for assessing its analytical performances and potentials for commercial viability.

Keywords Biosensor · Nanomaterial · Healthcare · Commercialization · Point-of-care detection

Introduction

Among various global challenges, health-related concerns (public as well as individual) are major threats faced by mankind. According to the World Health Organization (2015), millions of people are being victimized every year in some form of the illness, where more than half have been reported to develop severe conditions. Moreover, such sever conditions have eventually led to the lethal progression. Statistical analyses performed by various public as well as private agencies have revealed that the improper diagnoses not only impose cost burden to the patient but also increase the chances of developing severity (Snyderman 2012; Mahato et al. 2017). In a study by a group from Duke University, the correlation of disease progression with its severity, burden and extent of suffering of the patient has been summarized, where the progression increases exponentially after the infection (disease progression curve has been shown in Fig. 1) (Snyderman 2012). They have also elaborated the studies to the molecular level of disease progression and explained that the clinical symptoms appear way after the infection. In conventional settings, the diagnoses of diseased cases are done in the high end sophisticated instrumentation usually equipped in centralized laboratories, where the molecular- and microbiology-based protocols are majorly used (Chandra 2016). Thus, the patient develops a severe case by the time clinical diagnoses are completed in current scenarios. These strategies are very much powerful and precise, however, usually involves time-consuming process which makes them ineffective in various cases including emergency, ambulatory, and remote settings. To mitigate such constraints, extensive efforts have been employed for

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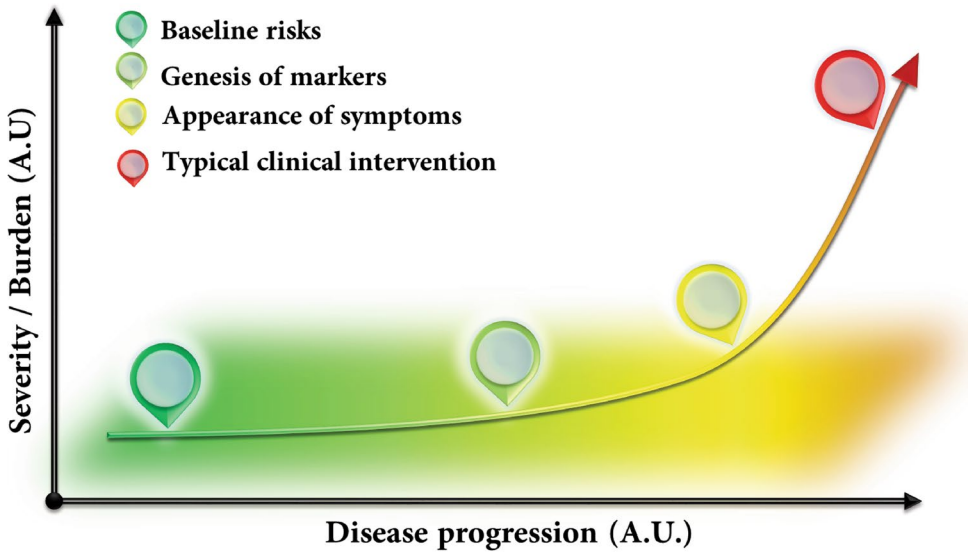

Fig. 1 Disease progression curve adapted from Snyderman et al. (2012); copyright John Wiley & Sons, Inc

establishing the alternate strategies for the diagnoses. Additionally, detecting the metabolic shift of symptom-less transition stage is very important phase to combat any disease or disorder as at this point the slight clinical immune booster can cure the disease, which otherwise is very difficult to treat in advance stages. In early stages, biomarkers are usually found in much lower concentrations, which not only limit the use of major conventional techniques and diagnostic devices but also open the door for various ultra-sensitive modules (Chandra 2016; Mahato et al. 2017). Among all options of detection in ultralow levels, biosensors have found an important place (Newman and Turner 1992; Turner 2013).

In last few decades, intervention of nanotechnology has revolutionized various fields of fundamental as well as applied sciences (Bainbridge and Roco 2016). In addition, recent past has also seen several advancements healthcare domain with the advent of nanomedicine and nano-diagnostics. These developments have attracted more attention of scientists, engineers, clinicians, and communities not only in terms of research and development but also from the commercial aspects due to their excellent performances over the conventional techniques (Kim and Jeong 2017). Low sample requirement, quick analysis, onsite detection, and robust nature of these nano-diagnostics prevalently give them dominance over lab-based techniques, which thereby making them more desirable for commercial acclaimation (Mahato et al. 2018). Historically, the first such module also known as "biosensors" was reported in 1962 by Clark and Lyon, which was based on the oxidase enzyme electrode to detect the glucose. A decade later, variant of this biosensor was commercialized by yellow spring instruments under the trade name "Model 23A YSI analyzer" in 1975 (Yoo and Lee 2010). The excellent commercial success of this module ignited the researchers and manufacturers for several new ventures. Down the timeline, various other achievements were also made, where first microbial biosensor (1975), first bedside artificial pancreas (1976), first plasmon resonance immunosensor (1984), etc. were the notable milestones in biosensing mechanisms. Later, blood glucose biosensor was launched by MediSense ExacTech Inc. in 1987 (Turner 2013; Bahadır and Sezgintürk 2015). After these path-defining products, a number of healthcare manufacturers have introduced several products including i-STAT, Glucocard, etc. (Mahato et al. 2017). In recent days, biosensors are extending their horizon by tackling various multitudinous clinical complexities for delivering precisely selective detections.

Biosensors: The fundamental understanding

Biosensor is a system which detect analyte with help of physicochemical detector coupled with the bio-recognition element (Kashish et al. 2017). In general, its major components include bio-recognition element, transducer, amplifier, and detector (as shown in Fig. 2a) (Mahato et al. 2016b). Bio-recognition element when comes in contact with target analyte generates stimulus for the transducer which converts it into a readable output (Yoo and Lee 2010; Baranwal et al. 2018). Depending on the type of transducer, the biosensing mechanism differs (Bahadır and Sezgintürk 2015) and is classified under optical, electrochemical, electromechanical, calorimetric types (Newman and Turner 1992). In addition, another classification is made based on the bio-recognition element, where these are further categorized in the broad classification as bio-catalytic (enzyme, cell, tissue-based catalysis), bio-complexing (antibody or aptamer-based modules) and receptor/antagonistic types

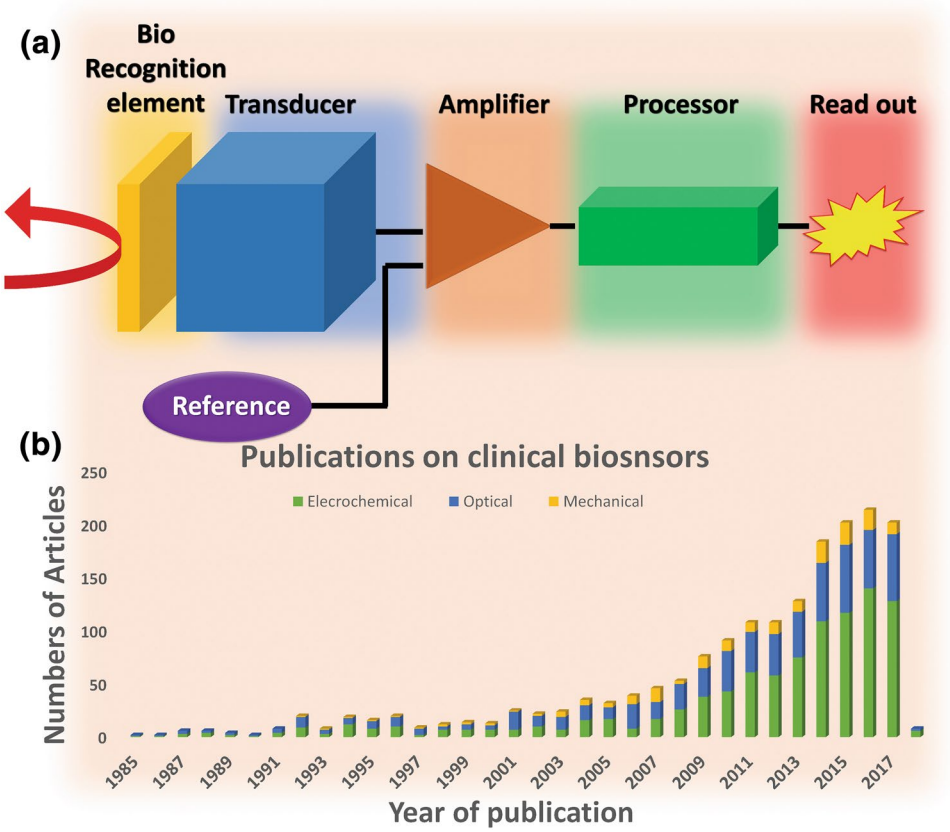

Fig. 2 **a** Components of biosensor. **b** The numbers of research articles published in subsequent years found in "Scopus" record for major classes of biosensor (strings searched with "biosensor" "clinical" and "electrochemical" using the "&" operator for electrochemical biosensors; "biosensor" "clinical" and "optical" using the "&" operator for optical biosensors; "biosensor" "clinical" and "MEMS/mechanical" using the "&" operator for electromechanical biosensors

viz. immunosensor (antibody), genosensor (ssDNA probe), aptasensor (Aptamer), etc. (Yadav et al. 2014; Chandra et al. 2015; Zhu et al. 2012a) are frequently reported. To explore the importance and expansion of various bio-sensing techniques, a short scientific survey was performed using the online database "Scopus". The trend of which clearly shows that enormous research thrusts have been given to miniaturize the conventional techniques down the years (as shown in Fig. 2b).

Optical biosensors

Optical biosensors are based on the changes in optical properties, where the transduction occurs in a phase, polarization, or frequency of input light in response to physical or chemical changes produced. These biosensors can be classified under absorption, fluorescence, luminescence modes on the basis of optical transduction, where absorption and fluorescence-based biosensors are amongst most explored for targeting various clinically important biomarkers (Kahveci et al. 2017; Mai et al. 2017). In absorption mode, when the light falls on the sample, biosensors absorb a particular energy level of the electromagnetic spectrum. In the presence of the target analyte and successful probe analyte complex formation, this absorption shifts either high or low energy levels which produces an output signal. The amplitude of these shifts can be correlated with the concentration of the analytes for quantification. The absorptive phenomena shown by analyte in response to the interacting electromagnetic radiations, when induces the absorption shift in visible frequency range, the sensor shows a color change in the presence of analyte is called as colorimetric biosensors. The correlational quantification of the analyte is based on Beer–Lambert's law Eq. (1).

$$\log\left(\frac{I_0}{I}\right) = \varepsilon C \Delta x, \tag{1}$$

where "I" is the final intensity of electromagnetic wave; "I_0" is incidence intensity of the electromagnetic wave; $\boldsymbol{\varepsilon}$ is molar extinction coefficient of the medium; "C" is concentration of the analyte; and "$\Delta \mathbf{x}$" is change in path length. In an example of uric acid colorimetric biosensors, the chromogenic agent 3,3′,5,5′-Tetramethylbenzidine (TMB) turns the blue color in the presence of gold nanoparticles. This blue color assembly is then decolorized by the uric acid, where the intensity of color change is dependent with concentration variation of uric acid. Figure 3a shows the scheme and the absorbance response (Kumar et al. 2015).

Another approach in optical biosensing is based on fluorescence phenomenon, where the fluorescent properties of

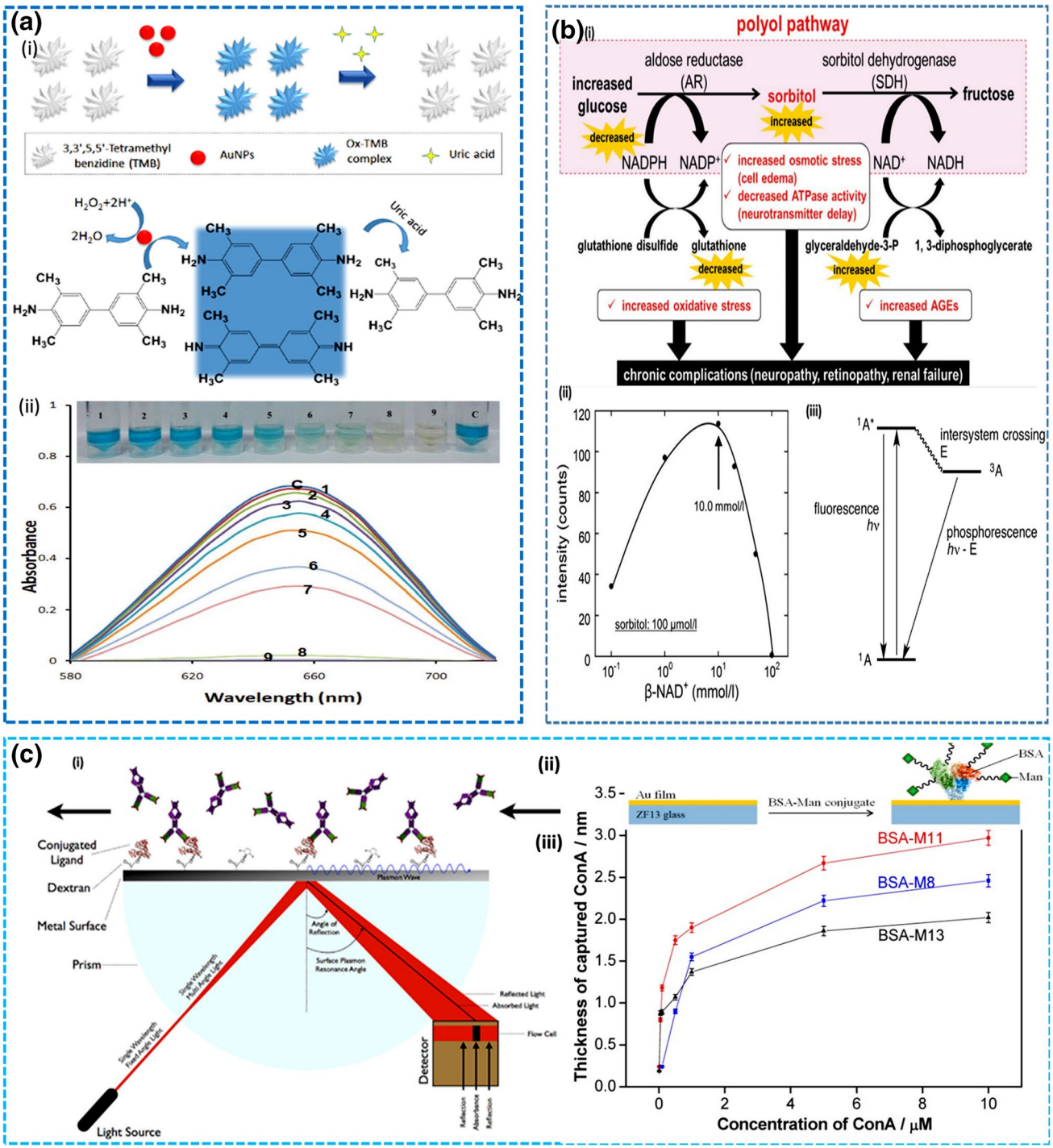

Fig. 3 **a** (i) The scheme of the reaction in colorimetric detection where the chromogenic agent TMB gets converted into oxidized form in presence of gold nanoparticles and thereby forms a complex with the unreacted TMB with thus forming Blue color. In a further step, the uric acid avails an electron tor blue colored complex thus the destabilization of colored complex occur thereby blue color vanishes. (ii) Shows the effects on the absorbance (λ max) on varying the concentration of uric acid [0 (1), 8.1 (2), 24.3 (3), 40.5 (4), 56.7 (5), 72.9 (6), 81.0 (7), 121.5 (8), 162.0 (9)] with the control (c) of AuNP–TMB–H_2O_2 (reprinted with the permission of Kumar et al. (2015) copyright Royal Society of Chemistry). **b** (i) Fluorescent biosensor for sorbitol detection, based on NAD+/NADH system. (ii) Fluorescence intensity on the varying concentration of the NADH (reprinted with Gessei et al. (2015), copyright Royal Society of Chemistry), (iii) shows the Jabłoński diagram, describing the phenomenon of molecular energy relaxation. **c** (i) Show the generalized schematic of SPR-based detection phenomena (image source: https://en.wikipedia.org), (ii) shows the schematic of SPR-based Biosensors for mannose detection (iii) comparison of the thickness of conA on different SPR chips consisting the BSA-M8, BSA-M11, and BSA-M13 reprinted with the permission of Tao et al. (2017), copyright American Chemical Society.

molecules are exploited for the detection of target analytes. In these biosensors, the absorbed energy fluoresces in lower energy states and is independent of the absorbance maxima, as described by Professor Aleksander Jabłoński (Jabaonski diagram is shown in Fig. 3b (iii)). Apart from imaging, several other fluorescence-based techniques have also been employed for bio-sensing approaches viz. fluorescence resonance energy transfer (FRET), fluorescence recovery after photobleaching (FRAP), etc. (Kuznetsova et al. 2006; Strianese et al. 2009). The major benefit offered by a fluorescence-based biosensors is their greater selectivity as every molecule shows its characteristic fingerprint spectrum (Strianese et al. 2012). For instance, the conversion of NAD^+ to NADH was employed to detect a diabetic biomarker sorbitol, where the fluorescence intensity of NADH is correlated with the quantification of sorbitol (Gessei et al. 2015) (The schematic representation has been shown in Fig. 3b).

In addition to these, a number of optical biosensors have also been reported based on the surface plasmon resonance (SPR) (Oliverio et al. 2017; Hoa et al. 2007; Haes and Van Duyne 2002). The SPR is a property by virtue of which conduction electrons of the surface of positive and negative permittivity show resonating oscillations with electromagnetic radiation of a particular frequency of white light resulting in the absorption of respective color (as shown in Fig. 3c) (Homola et al. 1999; Nguyen et al. 2015). Nanomaterials of various structures have been reported with the variable SPR properties (Nguyen et al. 2015). This phenomenon is exploited to design various biosensors, as the selective binding of target molecule changes the SPR significantly (Nguyen et al. 2015). For instance, SPR-based techniques have been employed for the detection of glycan using the protein–sugar composite probe, which includes the bovine serum albumin and glycan conjugate (Tao et al. 2017) (details has been shown in Fig. 3c).

Mechanical biosensors

Another major class is reported as mechanical biosensors, where mechano-physical properties of the probe materials are used to detect the analytes of chemical or biological origin. Commonly, three types of mechanical biosensors have been reported so far, viz. surface acoustic wave, quartz microbalance, and nano-mechanical systems. Among all mechanosensors, nano-mechanical system is widely accepted due to its high sensitivity and miniaturizability. These systems consist of cantilever probe, mechanical transducer and the processor where the probe is modified to obtain better selectivity (Reema et al. 2015; Hwang et al. 2009). The analytical performance of the system is majorly dependent on the material properties as well as the dimension of cantilever probe. For the biosensing, micro/nano cantilevers-based probe are commonly used where the probe dimension is in micro-nano range. Furthermore, these mechanical biosensors are operated under the basic modes which include deflection (static) and resonance (dynamic) mode (Mahato et al. 2016a; Dagdeviren et al. 2016). Static mode relies on the curvature change of cantilever probe due to the stress employed by the complex of analyte and receptor, whereas the dynamic mode of operation is based on the shift in resonating frequency change upon the adherence of analyte molecules onto the cantilever surface. Transducers are based on either displacement change or piezoelectricity generation. In displacement-based methods, the optical lever is widely employed, where the laser beam gets reflected off from the cantilever probe. Thereafter, the reflected beam is detected by position sensitive photodetector to obtain the signal (Tamayo et al. 2013). On the other hand, the probe cantilever coupled with piezoelectric crystal is used to generate the piezoelectricity for the response of the stimuli, and thereafter the motion-induced resistance of transducer is recorded for biosensing processes (Jun-Zheng et al. 2017; Su et al. 2017). The fundamental processes involved in mechanical biosensors are the change in mass, surface stress, young's modulus, and viscoelasticity after bio-molecular adsorption or coupling to the immobilized bioreceptor. All of these parameters collectively alter the curvature in static mode and resonance frequency in the dynamic mode of detection. Figure 4 shows the function of the typical nanocantilever based mechanical sensor (Tamayo et al. 2013). In addition to this, several other approaches have also been reported for the mechanical-based biosensors, where flexure-FET-based biosensors are appreciated globally for their high sensitivity (Jain et al. 2012).

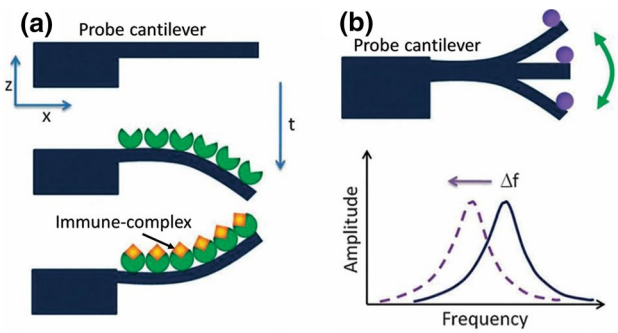

Fig. 4 Typical schematic representation of the mechanical biosensors (**a**) shows the deflection or static mode of operation based on the stress; (**b**) resonance or dynamic mode of operation which is based on the shifting of resonating frequency; adapted from Tamayo et al. (2013), copyright Royal Society of Chemistry.

Electrochemical biosensors

Electrochemical (EC) biosensors are another class of biosensors which employ various electrochemical techniques. Transducers in this genre of biosensors change chemical stimuli to readable electrical signals (Chandra et al. 2017). These biosensors have been widely explored due to their numerous advantages over other modes, which include better analytical performance, robustness, quick analysis, selectivity, and quantitation of analytes. Fundamentally, these biosensors work on the principle of electron flow from the chemical changes (particularly the redox processes), which directly generates the electrical signal (Grieshaber et al. 2008). Similar to other biosensors, electrochemical biosensors are further categorized into amperometric, potentiometric, and impedimetric types (Chandra et al. 2013). Electrodes are most important and integral part of electrochemical biosensing systems, which forms an electrochemical cell when assembled. Electrochemical biosensors are usually based on three-electrode cell systems. A three-electrode-based system includes working, counter, and reference electrode (Clark and Blaje-Coleman 1987) (shown in Fig. 5). For biosensing mechanisms, the working electrode surface is modified according to the scheme for obtaining signals of a specific target, while the counter electrode completes electrical circuit and reference electrode provides a stable and known potential for measurement (Eggins 2008).

Among all types of biosensors, EC biosensors have found extreme attention not only in the research but also in the commercial sectors (Mahato et al. 2018). These are preferred over the optical- and mechanical-based techniques because of its remarkable detectability, experimental simplicity, and low-cost fabrication. Apart from these, EC biosensors support the miniaturization of prototypes with uncompromised analytical performances. Since these systems are majorly based on electrodes and electrical circuits, they can be easily integrated in various electronic accessories for the regular monitoring. Not only this, EC biosensors deliver better performances in terms of the detection limits and ranges, where the detection limits have reported up to the sub-nanomolar level (sometimes in picomolar level) with wider detectable linear ranges from other types. However, constant research and development thrust have nowadays broken the barriers of these categorization in terms of performances. But, certainly, other benefits such as miniaturization and integration capabilities of EC-based prototypes make EC biosensors as a unique combination for the realization of high-performance commercial products (Nie et al. 2010).

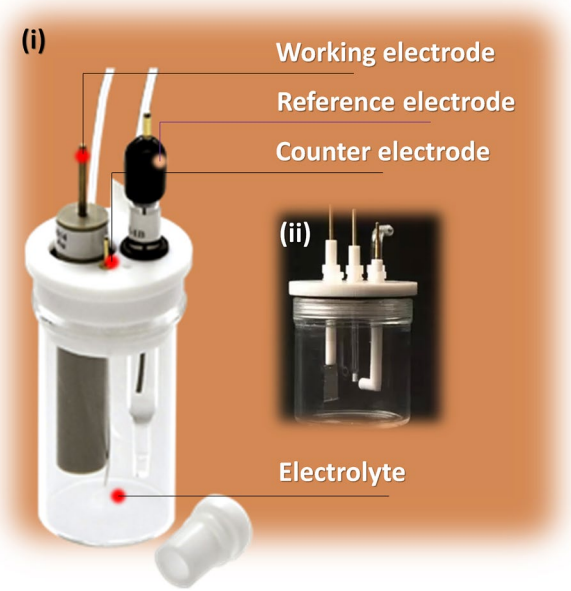

Fig. 5 (i) A typical three electrodes electrochemical used cell for biosensing applications; (ii) a commercially available electrochemical cell (Image sources: http://electrochem.ir and http://aliexpress.com)

Techniques used for electrochemical biosensing

For evaluating the electrochemical biosensing mechanisms, various techniques have been used, where the electron flow or charge formation during the redox reaction is measured. These techniques are described as follows:

Amperometry/voltammetry: Amperometry is the technique of electrochemical assessments, where the current generation with varying/static potential(s) is measured. In this technique, the applied potential across the electrodes (working and counter) initiates redox reaction process depending on the reduction/oxidation potentials of the analytes (Chandra 2016; Bard et al. 1980). The electrons generated by this process are then transferred into the electrochemical cell which eventually generates electric current. The amperometric biosensors are based on the aforementioned technique, where the generated current is calibrated for varying concentrations of the target analyte to obtain the analytical performance assuming that the presence of analyte contributes to more number of electrons. Another specialized amperometric method, also called voltammetry is a potentio-dynamic technique, where the current response is measured in varying potentials. Depending on the various ways for potential variation, voltammetry is practiced in different techniques including, cyclic, linear sweep, square wave, and differential pulse voltammetry. Among all variants of the voltammetry, cyclic voltammetry is the most explored technique and capable of giving the information of redox potential and electrochemical reaction rates of the analyte solution.

Potentiometry: Potentiometry is a technique which measures the charge potential at working electrode from the reference electrodes when no current flows in the

electrochemical cell. This technique provides the redox activities inside the EC cells. The mathematical modeling of the potential and the concentration of the analyte is governed by the Nernst Eq. (2).

$$E_{\text{cell}} = E^{0}_{\text{cell}} - \frac{RT}{nF} \ln Q \tag{2}$$

where E_{cell} is the potential of the electrochemical cell in zero current; E^{0}_{cell} is constant potential of the electrochemical cell; R is real gas constant; T is absolute temperature; n is number of electron transfer; F is Faraday constant; and Q is the ratio of ion concentrations at reduced state and oxidized state. Several potentiometric techniques have been used to detect the analytes including potentiometric titration, pH-based field-effect transistor, and light-addressable potentiometric sensor (Bard et al. 1980).

Impedometry/conductometry: Impedometry is the measurement of impedance in electrical or electrochemical systems. In impedometric biosensor, the impedance of EC cell is measured across the working and counter electrodes with reference to a known potential (usually provided by reference electrode) (Bard et al. 1980; Chandra 2016; Chandra et al. 2017). The specific attachment of non-conducting analyte over the conducting electrode surface hinders the flow of electrons, resulting in the impedance in the electrical circuit. Electrochemical impedance spectroscopy is amongst most widely used impedometric technique for assessing various biosensors. Since, this method requires no detection tags, it is mostly used for label-free detections and the current response is measured for a sinusoidal varying current. By varying the excitation frequency of sinusoidal potentials, the complex impedances can be obtained for a range of frequencies. Mathematical modeling of the impedance is shown in Eq. (3)

$$Z(j\omega) = \frac{U(j\omega)}{I(j\omega)}; \omega = 2\pi f, \tag{3}$$

where "Z" is impedance; "U" is potential; "I" is current flows through the circuit; and "ω" is angular frequency of sinusoidal potential and "f" is frequency in Hertz (Hz).

In electrochemical sensing, this technique has been very useful for monitoring the changes in electrical properties, resulting from various bio-recognition events over the surface of the modified electrode. For instance, the change in conduction on the electrode can be measured as a result of protein immobilization and antibody affinity binding reaction on the electrode. Conductometric techniques on the other hand are based on the strength of the ionic species in the EC cells. These types of biosensors are mostly associated with enzymes, where enzymatic species play an important role in obtaining the ionic strength after cleaving the electroactive agents.

Importance of nanomaterials in biosensors

Owing to the unique optical and electronic properties, nanomaterials have long been used in biosensing systems to enhance their capabilities particularly in the signal amplification. The other properties like miniscule size and high surface area have added additional advantage for immobilization of various recognition elements in greater extent. In this section, we briefly discuss about nanomaterials for various bio-sensing applications and their synthetic approaches. Nanomaterials can be synthesized by various ways: physical, chemical, and bio-mediated processes. Broadly these approaches are classified under the top–down and bottom–up approaches (Yadav et al. 2012). In top–down approaches, bulk materials are transformed into the nano-sized structures by means of mechanical attrition whereas, the bottom–up techniques follows the synthetic processes (Mahato et al. 2016a; Baranwal et al. 2016). These syntheses show the addition of atoms followed by nucleation and thereafter ripening of the structures. These techniques have their own pros and cons. The major limitation to the top–down approaches is that these generate a number of surface defects which significantly alter the surface chemistry, thereby making the nanostructures unsuitable for biosensing mechanisms which require rigorous surface modification (Baranwal et al. 2016). In the bottom–up strategies such limitations are not reported; however, the time of syntheses is of utmost concern. Based on the fundamental processes occurring in nanomaterial syntheses, methods are classified under physical, chemical and bio-mediated types. Physical methods consist of ion sputtering, high energy irradiation, colloidal lithography, mechanical milling and laser ablation, whereas electrochemical-, and photochemical-based chemical methods offer the nano-sized material syntheses. Another advantage of the chemical synthetic route is that these processes are capable of synthesizing the nanoparticles with various structures with the same ingredient by tuning the synthetic process, which is usually done by altering the pH, proportion, temperature, etc. Apart from these, biological routes are also reported where the reduction of ions are done by biological metabolites from different sources viz. plant, microbes, etc.; however, the reducing agents are mostly mysteriously unknown, which generally varies in the batches and hence this route is not always preferred. Nanomaterials are also obtained in the form of nanocomposites, quantum dots, dendrimers, etc. (Noh et al. 2012) Fig. 6 shows various types of the nanomaterials.

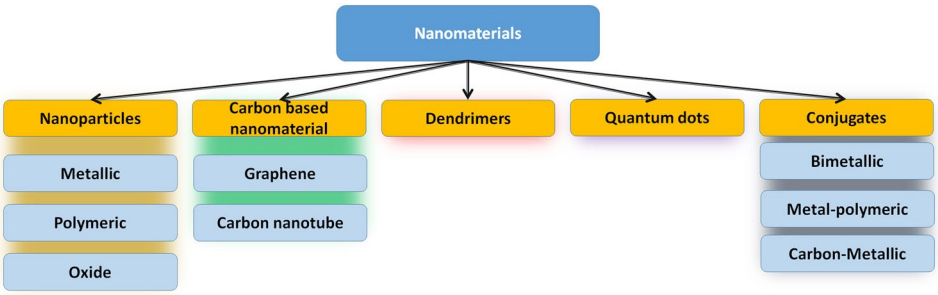

Fig. 6 Different types of nanomaterials used in biosensing mechanisms

Probe designing, development, and characterization

Probe design and development

In all biosensing systems, the detection probe plays an important role. Design of these probes are dependent on the types of biosensors. Commonly, the transducer materials are coupled with highly selective bio-recognition elements in all of the cases. For example, in electrochemical biosensors working electrode is functionalized for the selective detection of analytes, where the electrode surfaces are attached with bio-recognition elements such as antibodies, aptamers, enzymes, etc. (Chandra et al. 2017) The selection of the bio-recognition element is dependent on the nature of target molecules. For instance, if the target molecule is protein biomarker, antibodies are preferred as recognition element (Shan and Ma 2017; Ricci et al. 2007; Prasad et al. 2016). However, to introduce the temperature stability to the probe, aptamers can be used (Jarczewska et al. 2016). Similarly, enzymes are used if the target molecule can be catalyzed to give electroactive species, for example, glucose oxidase has been used for glucose detection (Kausaite-Minkstimiene et al. 2017; Shen et al. 2017). These bio-recognition elements immobilized onto the biosensing transducer usually is a modified electrode, where various strategies are employed for the modification including adsorption and covalent modification. In adsorption based technique, the bio-recognition moieties are adsorbed onto the electrode surface by means of physical forces (Banica 2012). Moreover, sometimes these are entrapped within the immobilization matrix, but such processes are not always preferred due to their tendency of leaching out during operation. To overcome such limitation, covalent modifications are adopted using various bio-conjugate techniques. The fundamental process of these techniques is the activation of bio-recognition element and electrode surface (Chandra 2016; Chandra et al. 2017). In the second step, covalent coupling process is employed building the probe. So far, various such techniques are employed based on coupling reaction using carbodiimides, carbonyldiimide, etc. (Arya et al. 2011; Wan et al. 2010). In addition to these, silane, biotin–avidin, streptavidin–biotin cross-linkers are extensively used for immobilizing the bio-recognition elements (preferably antibody or proteins) covalently over the probe surface (Shuai et al. 2017; Fu et al. 2011; Kim and Jeong 2017).

Characterization of the nanomaterials and developed probe

For the detailed characterization of nanomaterials, so far various techniques have been employed. UV–visible spectroscopy (UV–Vis) enables the preliminary determination of the particles or nanomaterial formation (Verma et al. 2014). The appearance of characteristics absorption confirms the preparation of the nano-material; however, in some cases, the poor dispersion of nanomaterials in solution restricts this technique for the characterization, such as graphene-based nanomaterials. Excellently dispersible nanomaterials show a characteristics absorption maxima depending upon the constituents and size of the grain or particle (Plascencia-Villa et al. 2016). Furthermore, the correlational size dependencies can be obtained using the UV–Vis characterization (Plascencia-Villa et al. 2016). However, the exact sizes of nanomaterial are confirmed by the scanning electron microscopy, atomic force microscopy or transmission electron microscopy (Kumar and Kumbhat 2016). With these characterization techniques, not only the dimension of nanomaterials is obtained, but also the topological features of the material are extracted (Kumar and Kumbhat 2016). The size distribution of dispersible engineered nanomaterials is characterized by dynamic light scattering (DLS), which categorizes the particles on the basis of their hydrodynamic sizes, where the hydrodynamic size is the equivalent size of the dispersed nanomaterial with the layer of other constituents along with water above it (Pecora 2000). This size depends on the physical properties of the colloidal solution including the viscosity, temperature, and diffusion coefficient. The surface charge on the nanostructured materials is another important property, which is determined by measuring the zeta potential measurement techniques (Berne and Pecora 2000). During the course of probe fabrication, these nanomaterials play an important role for covalent immobilization of the bio-recognition elements (Baranwal et al. 2016). For

instance, gold nanoparticle-based probe fabrication requires a strong adsorption forces to adhere the electrode in order to prevent the leaching out effects (Chandra et al. 2013). Alternatively, this has also been achieved by entrapping the particle inside the various immobilizing matrices. The confirmation of the presence and the adherence of nanomaterial on to the probe surface have been assured by various surface characterization techniques for dispersed nanomaterial in recent years, including Fourier transformed infrared spectroscopy, Raman spectroscopy, energy dispersive spectroscopy, elemental mapping, and x-ray photoelectron spectroscopy (XPS), where elemental and functional group details are obtained (Chung et al. 2018). Fundamentally, such techniques are based on identification of either chemical bond or elemental composition by exploiting various physical properties of the materials, which also help in characterizing the essential probe modification stages. In common practice, such modifications are employed by doping of conducing nanomaterials to the existing immobilizing matrices or by novel conducting nanocomposite materials. Furthermore, electrical, and optical properties of materials are dependent on the crystal structures which has been defined as the crystallinity and is obtained by X-ray diffraction (XRD), as well as the selective area electron diffraction (SAED) (Tang and Ouyang 2007). These are diffraction-based technique, where light beam gets diffracted when falls on the lattice plans depending on their distances.

During the probe fabrication process, changes in the functional groups occur after each steps; this modification is traced by surface modification techniques such as FTIR and Raman spectroscopy, while the verification of exclusively modified surfaces in every step of modifications is done with surface characterization techniques such as XPS and small angle XPS (Baranwal et al. 2016). Apart from these techniques, electrochemical characterization of the probe has also been employed, where the probes were assessed after each level of modification, using potentiometric, amperometric, voltammetric, impedance spectrometric based techniques. The significant change in the signal confirms the successful probe modification (Zhu et al. 2012b, 2013; Quan et al. 2006; Bollella et al. 2017). In recent years, a number of nanomaterial assisted bio-sensing mechanisms are reported (Lan et al. 2017; Li et al. 2015; Lu et al. 2017; Zhu et al. 2012b; Chandra et al. 2014; Choudhary et al. 2016). In context to this, a number of nanomaterials including nanoparticles and nanocomposites have been used (Lan et al. 2017; Li et al. 2015; Lu et al. 2017). For instance, gold, silver and platinum nanoparticles with/without surface modification have widely been explored to design biosensor for different clinically important analytes (Li et al. 2010; Wang et al. 2017; Kashish et al. 2017).

Analytical performance studies

Once the probe gets fabricated, biosensor is then evaluated for preliminary responses. These assessments are done for the probe stability in an electrochemical process, and when the probe passes it, analytical performances of biosensors are assessed for limit of detection, linear dynamic range, and limit of quantification (Mahato et al. 2016a). The mathematical modeling for these studies is usually done with regression plot (Armbruster and Pry 2008). In this model, the regression line is drawn for the different intensities of signals with varying concentration of the analyte (shown in Fig. 7). A biosensor should be judged on the basis of few parameters including the selectivity, sensitivity, range, accuracy, response time, recovery time, and working lifetime. These parameters are consciously taken care of while

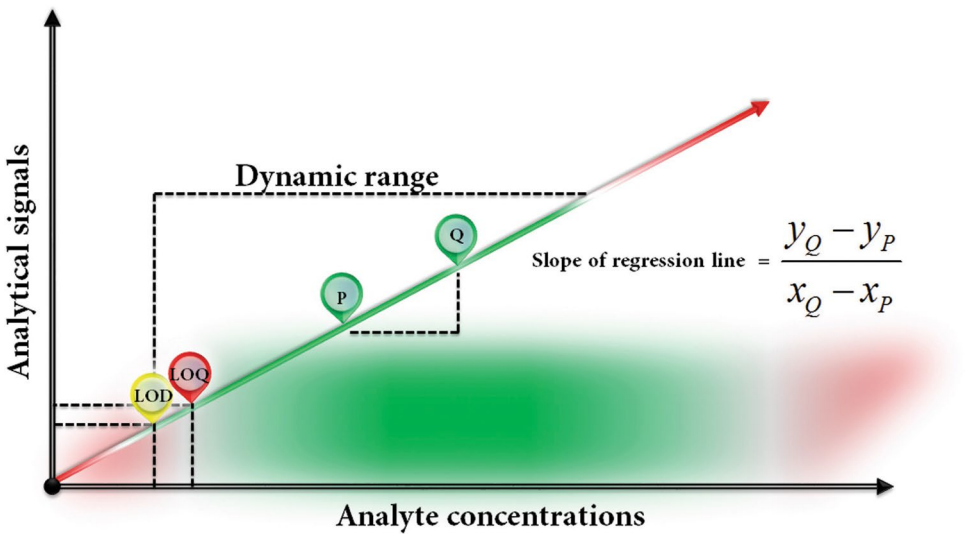

Fig. 7 Standard calibration plot used for calculating LOD, LOQ, Sensitivity and the dynamic range

fabricating any biosensor. Definitions are as follows (Eggins 2008).

Selectivity

It is the most important criterion for the biosensor evaluation. It is the ability of biosensor for discriminating out the non-specific targets from the sample of analysis.

Response time

It is the time interval when the probe generates quantifiable signal after sampling. Usually, it should be in seconds.

Recovery time

The time that is required to begin next run after the completion of ongoing process is called as recovery time.

Working lifetime

The working lifetime is related to the stability of biosensor; particularly, the bio-recognition elements and the coupled transducers lifetime in normal conditions.

Limit of detection (LOD)

The minimum amount of analyte that can give the signal in biosensing mechanism, which is generally calculated by using Eq. 4:

$$\mathrm{LOD} = \frac{3\mathrm{SD}_{\mathrm{Blank}}}{\mathrm{Slope}}, \tag{4}$$

where LOD is the limit of detection; $\mathrm{SD}_{\mathrm{Blank}}$ is the standard deviation of blank and the slope signifies the sensitivity of the probe for the particular analyte.

Limit of quantification (LOQ)

LOQ suggests that amount of analyte which is detectable by the biosensors.

$$\mathrm{LOQ} = \frac{10\mathrm{SD}_{\mathrm{Blank}}}{\mathrm{Slope}}, \tag{5}$$

where LOQ is the limit of quantification; $\mathrm{SD}_{\mathrm{Blank}}$ is the standard deviation of the blank and the slope signifies the sensitivity of the probe for the particular analyte.

Linear dynamic range

It is a range in the regression plot, where the signal is directly proportional to the concentration of analyte. The wider the dynamic range, the greater will be the clinical significance, as more number of concentration can be extrapolated by these values in quantitative detection.

Sensitivity

This is the property of a transducer by virtue of which it responses to the fluctuation of analyte. It is defined by the slope of regression line, where steeper slope signifies the relatively better sensitivity. This tells that the biosensor is capable of differentiating a small change very efficiently. The mathematical expression can be written as follows (Eq. 6).

$$\text{Sensitivity} = \text{Slope of the regression line} = \frac{y_Q - y_P}{x_Q - x_P}, \tag{6}$$

x_P, x_Q, y_P, y_Q are the coordinates of two points in the calibration plot, related to analyte concentrations and their corresponding signals.

These parameters tell about the analytical performances for the sensing of the clinically relevant target.

Real sample testing techniques

After the assessments of analytical performance, real sample analyses should be performed using various clinical samples. Sometimes, unavailability or complexity of clinical samples leads to inconsistencies in studies. To overcome such issues, spike-recovery and standard addition methods have been employed over the years. These methods test the analytical performances in mimicked real samples, where these samples are prepared with the native interfering constituent molecules. The selection of the interfering analytes in mimicked samples is usually the coexisting molecules in the environment or the similar structured molecules, which can potentially introduce interferences in detections.

Spike-recovery method

This technique assesses biosensors for various interferences in real sample. The significant differences in the recovery responses infer that strong interfering molecules are present in the sample, which are limiting the biosensor from proper functioning (Bhatnagar et al. 2017). If the recovery response is close to the spiked value, biosensing probe doesn't experience any hindrance from the matrices. This technique also tells the false responses of analyte. Here, if the recovery value is significantly greater than that of the spiked value, it clearly signifies false-positive signals. On the other side, the false negative results can also be assessed by this method, where the analyte molecule reacts with the other components of the real sample resulting in the depletion of analyte

molecules in native state. Thus, the recovery in this case gets significantly reduced from spiked value.

The mathematical calculation of the recovery and interpretation is given below in Eq. (7).

$$\%Recovery = \frac{\text{Observed} - \text{Neat}}{\text{Expected}} \times 100, \quad (7)$$

where "Observed" signifies the value of analyte concentration observed after the spiking of analyte; "Neat" signifies the value of analyte concentration present in sample before the spiking. The "Expected" is the exact concentration of the analyte spiked into the sample.

Standard addition method

In various real samples, intrinsic properties sometimes interfere biosensing mechanism called matrix effect. To avoid such matrix effects, another technique is employed called standard addition method, where a standard known concentration is added to the aliquots to acquire the calibration plot using biosensor responses (Bader 1980). In this method the aliquot of unknown concentration is treated with different known concentrations of the target analyte to obtain the signals. The calibration plot is then obtained by tracing the points of standard additions and unknown to zero concentration (Noh et al. 2012). Using this calibration plot, the unknown concentration of analyte can be evaluated.

Commercial biosensors: potential successors of conventional diagnostics

Once the biosensor passes the real sample tests with excellent performance, it is then translated into the commercial volumes, where the analytical abilities in real matrices decide the commercial viability of proposed biosensor. So far, a number of biosensors which include biosensing modules for blood glucose and cholesterol levels, malaria, HIV, uric acid, etc. have found a notable commercial success, globally (Bahadır and Sezgintürk 2015; Turner 2013). In addition to these, cancer and cardiac disease based biosensors have also found great attention for commercial volumes (Turner 2013). The low fabrication cost and the easy methodologies for mass manufacturing are the factors that play major role in such volumes. To reduce the cost, researchers have constantly been introducing advancements in biosensing technologies, including paper-based and chip-based microfluidic devices (Mahato et al. 2016a, b, 2017). These devices not only give the proper handling of sample but also provide precise estimation of the target analytes. Owing to the cheaper cost of paper, biosensors based on paper platform are affordable to the manufactures as well as the end-users. Figure 8 shows some of the commercially adapted clinical biosensors, which not only give better analytical performances but are also capable of delivering quick detections. Moreover, nowadays, various new technologies have been reported, where the

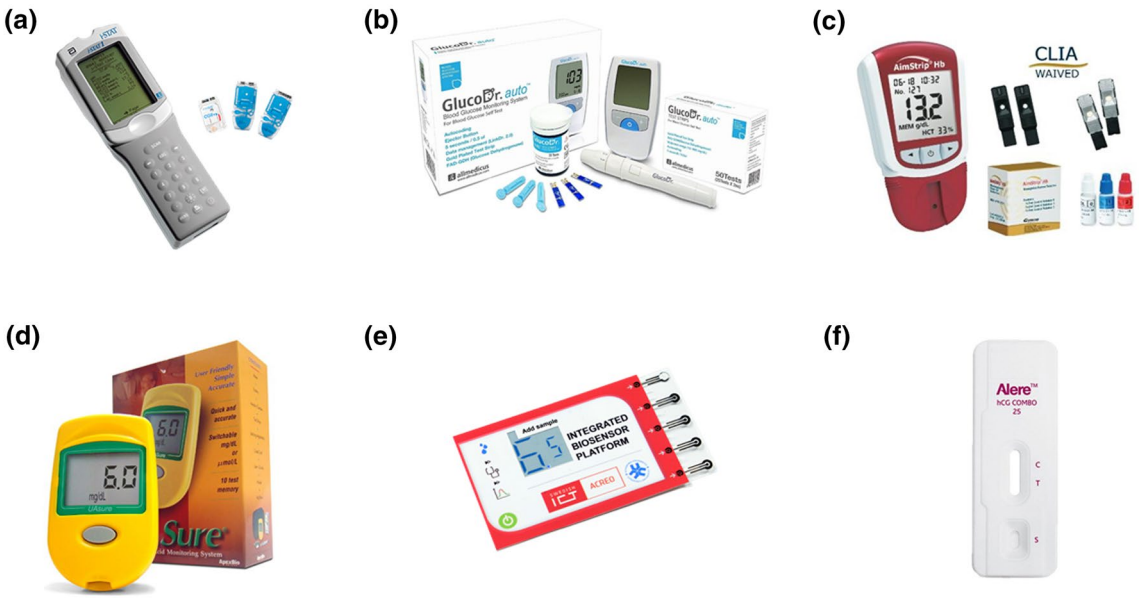

Fig. 8 Various miniaturized commercial biosensors are (**a**) a blood profiler from abbott (iSTAT) (https://www.pointofcare.abbott); (**b**) glucose monitoring system from allmedicus (GlucoDr) (https://www.lelong.com); (**c**) blood hemoglobin analyzer (AimStrip) (https://www.1cascade.com); (**d**) uric acid detector from ApexBio (UASure) (https://redmed.pl); (**e**) an integrated printed circuit biosensor from Acreo (https://www.acreo.se); (**f**) a pregnancy dipstick from alere (hCG combo) (https://www.alere.com)

low-cost simplistic prototypes are introduced by paper, elastomers and even the paper–elastomer hybrids-based platforms (Mahato et al. 2017; Liu et al. 2016). Not only these, a paper art form "origami" has tremendously been exploited for making various efficient low-cost microfluidic devices (Liu et al. 2016). The urgent need of rapid and effective diagnoses in emergency and remote settings has limited the use of conventional diagnostics as they follow time-taking protocols and usage of cumbersome instruments. Advanced biosensors of later generations are on the other hand mitigating such limitation by providing quick and point-of-care testing. The high demand of diagnostic volume in the endemics/pandemic affected demography again confines not only the conventional techniques but also the existing commercial biosensing devices for their outreach to end-users. Thus, there is an urgent need of commercially scalable low-cost prototypes to eradicate the potential endemic eruptions in future.

Concluding remark and future prospects

Clinical diagnostics have urgent need of the efficient and effective biosensors to address various clinical urgencies. An alarming situation has been anticipated by the various statisticians across the globe after seeing the trends of current health status, which is a critical concern for the clinicians, healthcare providers, planning commission and scientists across the world. In this review, we have summarized the ways of mitigating such cases by introducing the efficient diagnoses using biosensors, where these mechanisms are capable of biomarkers detection in pre-symptomatic phase of any disease. Apart from these, this review elaborates a discussion on the various aspects of biosensor fabrication and the characterization thereof. Furthermore, the impact of nanomaterials in biosensing prototypes has also been discussed. Authors anticipate that this review will provide a strong impact to the budding scientist to know about the fundamentals and state-of-the-art biosensors and its commercial viabilities in severe clinical contexts. This review inclined to address the adoption of new technology in existing systems. Not only these, it can also contribute to change the thought process of contemporary clinicians towards easy-to-use efficient diagnostics.

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Compliance with ethical standards

Conflict of interest Authors declared that there is no conflict of interest.

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