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A critical review on the use of potentiometric based biosensors for biomarkers detection

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ABSTRACT

Potentiometric-based biosensors have the potential to advance the detection of several biological compounds and help in early diagnosis of various diseases. They belong to the portable analytical class of biosensors for monitoring biomarkers in the human body. They contain ion-sensitive membranes sensors can be used to determine potassium, sodium, and chloride ions activity while being used as a biomarker to gauge human health. The potentiometric based ion-sensitive membrane systems can be coupled with various techniques to create a sensitive tool for the fast and early detection of cancer biomarkers and other critical biological compounds. This paper discusses the application of potentiometric-based biosensors and classifies them into four major categories: photoelectrochemical potentiometric biomarkers, potentiometric biosensors amplified with molecular imprinted polymer systems, wearable potentiometric biomarkers and light-addressable potentiometric biosensors. This review demonstrated the development of several innovative biosensor-based techniques that could potentially

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provide reliable tools to test biomarkers. Some challenges however remain, but these can be removed by coupling techniques to maximize the testing sensitivity.

1. Introduction

Biomarkers are an indicator device for control biological processes and sensing of human health.

Biomarkers can monitor and predict health states by monitoring biological fluids such as cholesterol, urine and blood pressure and can suggest appropriate (Feng and Pepe 2020; Moein et al., 2020; Strimbu and Tavel 2010). Extensive research has been done to use analytical methods to monitor biomarkers to create portable kits to control people's health (Karimi-Maleh and Arotiba 2020; Saad et al., 2020; Wang et al., 2020). Determining the activity and measuring the concentration of biomarkers in biological environments provides appropriate information to predict the progression of the disease or the proper treatment in clinical trials (Argiriadis et al., 2020; Ejeian et al., 2020; Karimi-Maleh et al. 2019, 2020b; Khodadadi et al., 2019). On the other hand, determining the dose of drugs and other biological compounds in biological samples provides the degree of effectiveness of the treatment process created by biomarker information (Alavi-Tabari et al., 2018; Karimi-Maleh et al. 2016, 2019b, 2020a; Miraki et al., 2019; Tahernejad-Javazmi et al., 2018). Accordingly, the practical view in the use of analytical methods based on the use of biomarkers has become a topic of interest for large companies and researchers in this field (Chai et al., 2017; Yousefpouran et al., 2020). Therefore, in recent years, many reports and applied research in using analytical tools to measure biomarkers to examine and control body activity in medical and sports research have been done (Orooji et al., 2020).

In potentiometry systems, potential of an electrochemical cell measure under static conditions. Potentiometry analytical systems is a useful quantitative strategy due to donot using of current—or only a insignificant current—flows through the electrochemical cell. This point helps to unchanged of analyte composition in determination process. The electrochemical cell in potentiometry systems involves of two half-cells. The potential in an electrochemical cell calculated by equation $E_{cell=}E_C - E_a$, where E_c and E_a are potentials for the redox reactions at the cathode and the anode, respectively. The selectivity of potentiometric systems for electrochemical determination of cations, anions or biomaterials is depend on the ability of a membrane material used in fabrication of potentiometric sensors. Potentiometric sensors are widely available in the market today (urea, uric acid, and glucose potentiometric sensors) and due to their kitability, it seems that there is a very bright future in the market of biomaterial measuring kits (Willander et al., 2017).

Potentiometry based on ion-selective electrodes (ISEs) has long been used as an old and inexpensive technique with the ability to convert portable kits (Coppedè et al., 2020). Fast response, wide dynamic range (3–5 orders of magnitude), easy operation, portable ability, easy modification and low cost are the main advantages of potentiometric based sensors (Ding and Qin 2020). Given the above points and the unique features of potentiometric membrane sensors as well as the high capability of biomarkers to assess the health of the body, it seems that the use of potentiometric methods to measure biomarkers and biological compounds can be a practical and quick approach in the treatment process or choose the right solution to treat people with chronic disease (Akl et al., 2020). Accordingly, the present review article examines various potentiometric methods that have been enhanced and selectable by modified methodologies to monitoring and sensing biomarkers. Although the variety of potentiometric biosensors is very diverse, our studies show that four main categories of potentiometric biosensors

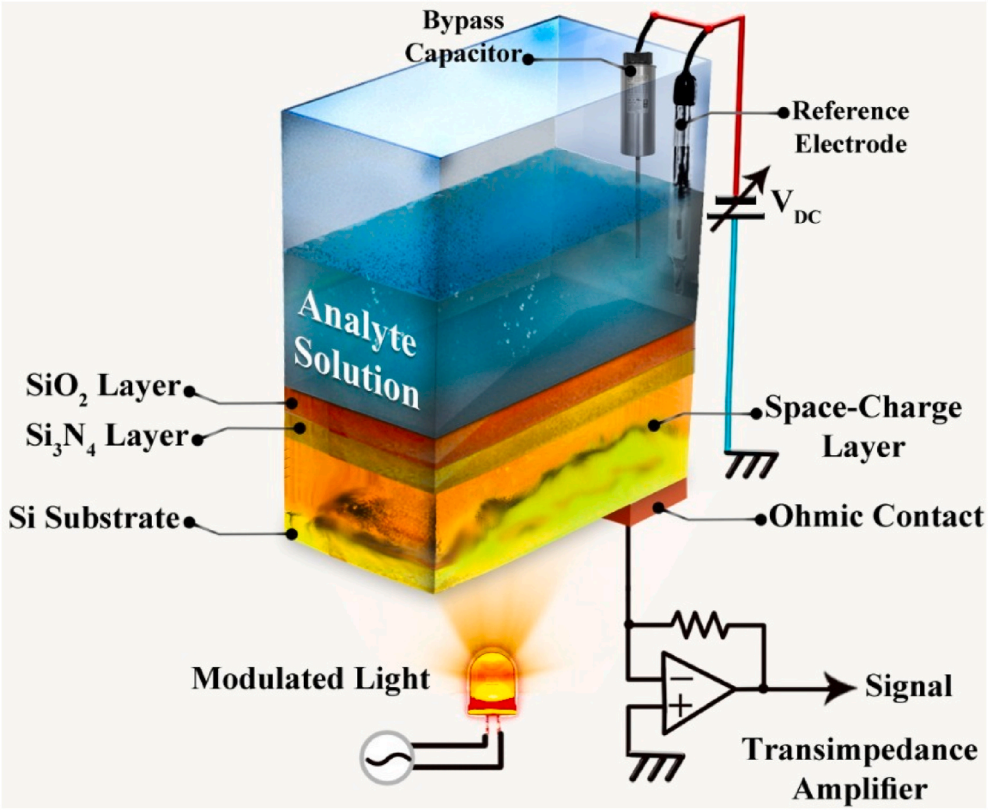

Fig. 1. General structure of LAPS sensor.

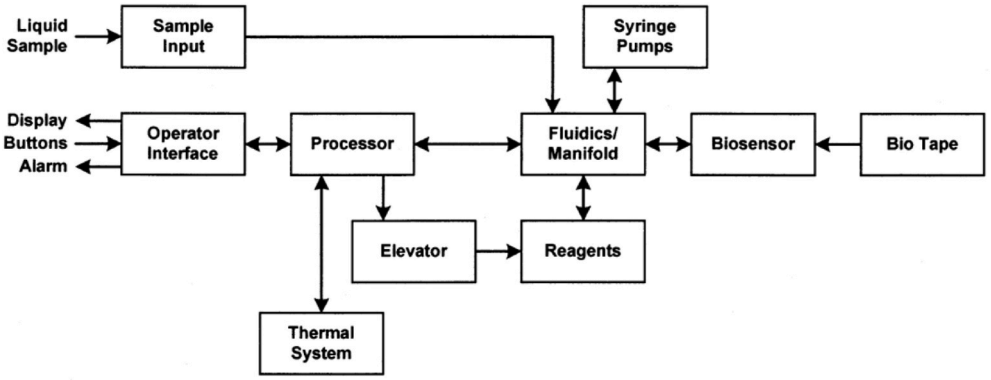

Fig. 2. Diagram of biological integrated detection system. Reproduced with copyright permission of Elsevier (Uithoven et al., 2000).

included photoelectrochemical potentiometric biomarkers, potentiometric biosensors amplified with molecular imprinted polymer systems, wearable potentiometric biomarkers and light-Addressable potentiometric biosensors have been used by researchers for bio-sensing systems that were review in this article as new approach of analytical systems for determination of biomarkers and other important biological compounds.

2. Light-addressable potentiometric biosensors

A light-addressable potentiometric sensor (LAPS) (Hafeman et al., 1988; Owicki et al., 1994) is a new attitude toe ion-sensitive field-effect transistor (ISFET) and work based on the field-effect in a semiconductor (Bergveld 1970). Fig. 1 showed the structure of LAPS for bio-sensing application. This type of potentiometric sensors consists of a semiconductor plate (usually silicon with resistivity of 1–10 Ωcm and thickness of 100–400 mm) cover with an insulating layer and also an ohmic contact on the bottom surface, respectively. In addition, LAPS systems is containing a measurement electronics and light source (light-emitting diode). The Si_3N_4), Aluminum oxide (Al_2O_3), or Tantalum pentoxide (Ta_2O_5), with thickness of 50–100 nm were used as insulating layer in some reported papers (Adami et al., 1995; Ismail et al., 2000; Yoshinobu et al., 2001b). The surface of this layer should be in contact of analyte for the determination of its concentration in

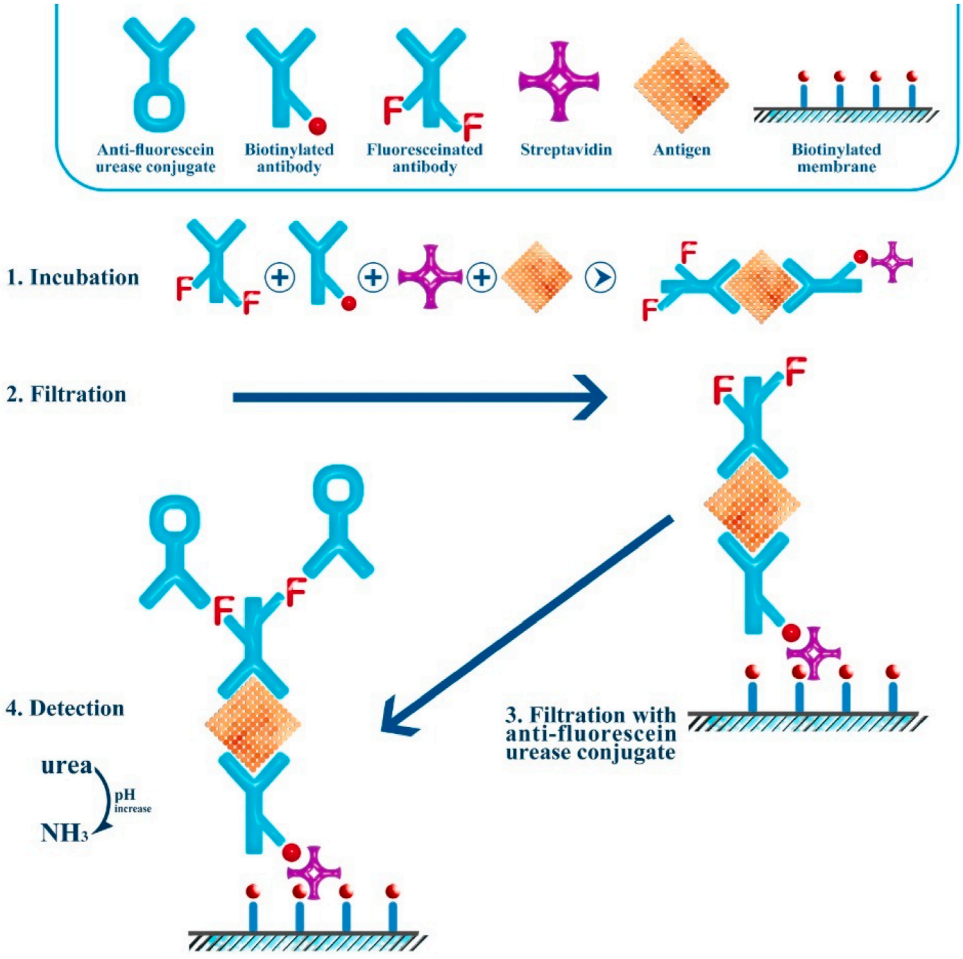

Fig. 3. Generally diagram of IFA/LAPS system for detection of VEE. Reproduced with copyright permission of Elsevier (Hu et al., 2004).

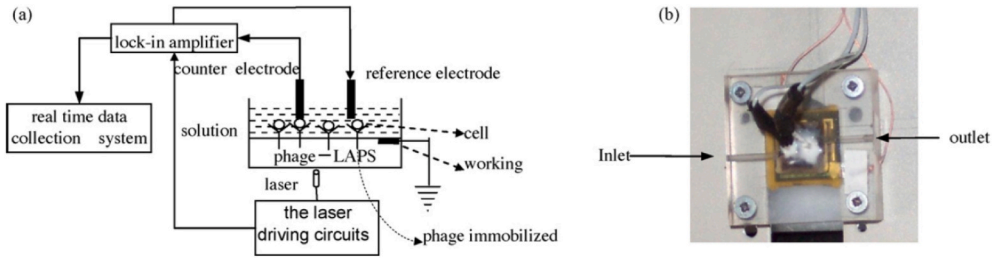

Fig. 4. a) General structure LAPS and b) phage-LAPS. Reproduced with copyright permission of Elsevier (Jia et al., 2007).

solution in the presence of a reference electrode (Adami et al., 1995; Ismail et al., 2000; Yoshinobu et al., 2001b). The application of bias voltage in the electrolyte–insulator–semiconductor organization as design system, results in a space-charge layer that is formed at the insulator–semiconductor interface. The light probe illuminate the semiconductor and then an alternating current (AC) photocurrent is formed in the range of 1–10 kHz. The conversion of current to voltage occurs by transimpedance amplifier.

Recently, many of researchers focused on the application of LAPS for the analysis of biological compounds. This type of potentiometric biosensors' light-addressability presented a powerful tool to explain the plurality of measurement spots on a single LAPS plate. This ability helps to measure (1) a plurality of analytes in a single matrix, (2) evaluate the same analyte in a plurality of matrixes, and (3) evaluating the spatial distribution of an analyte in the matrix. In this regard, Uithoven et al.) reported a LAPS as an analytical tool for identifying biological warfare agents (Uithoven et al., 2000). In their study, they coupled a light addressable potentiometric system with a flow-through immunofiltration-enzyme assay as a new biological integrated detection system and was suggested to detect *Bacillus subtilis* in the concentration range 10^4-10^6 cfu/mL. Fig. 2 shows a diagram for a biological integrated detection system (Uithoven et al., 2000).

Hu et al., (2004)have reported a LAPS for rapid and fast analysis of Venezuelan equine encephalitis virus. In their study, they used single-chain fragment variable antibody (scFv) against the Venezuelan equine encephalitis virus (VEE). Immunofiltration enzyme assay (IFA) was employed with LAPS in the detection process. The process involved a formation of an immunocomplex sandwich containing the VEE. After that, the change in the pH relative to the conversion of urea to NH_3 in the urease-containing antibody–antigen sandwiches system could be detected as the analytical response. The change of pH and the change in potential were monitored as a function of time. The rate of pH change was found to depend on the number of urease-containing antibody–antigens sandwich immobilized on the membrane during the filtration capture process.

Fig. 3 show the IFA/LAPS system for that design for this virus analysis. Results confirm that IFA/LAPS is a simple and highly selective method for detecting VEE in real samples.

Jia et al. conducted a study for the detection of small biomolecules and cancer cells (Jia et al., 2007). They designed a phage-LAPS biosensor and used it for the detection of human phosphatase of regenerating liver-3 (hPRL-3) and mammary adenocarcinoma cell (MDAMB231) as small bio-molecules. The results suggested that the system showed more advantages for detection of cancer cell compared to being cancer biomarker. The phage-LAPS biosensor response showed a linear dynamic relationship in the range 0.04–400 nM and 0–105 mL for the determination of hPRL-3 and MDAMB231, respectively. The results also showed that phage-LAPS is not suitable for the detection of small bio-molecules. Fig. 4 shows a design system by this group for selective detection of cancer cells.

The ability of LAPS to be modified in various ways has led to extensive research with changes in part of its analysis system. The different designs on these sensors have increased their selectivity and capability to an acceptable level. For example, Du et al. designed a new light-addressable microfluidic device as an analytical sensitive tool with unique properties for sensing bioengineered taste receptor cells (Du et al., 2019). They used a different design for this goal and fabricated this sensing system via stimulation chambers that integrate with LAPS in the presence of one cell culture microchamber. The combination of stimulation chambers and cell culture microchamber created a μ-Slide Chemotaxis 3D system that can be connected with LAPS then used for cell-based biosensors. The proposed system was successfully used for the sensing of bioengineered taste receptor cells in biological systems. The combination of LAPS system with this type of μ-Slide Chemotaxis 3D system have a great potential for single-cell level sensing with acceptable data in the future. This combination system with data and overall structure are shown in Figs. 5 and 6, respectively.

For the first time, LAPS offered great opportunities for the

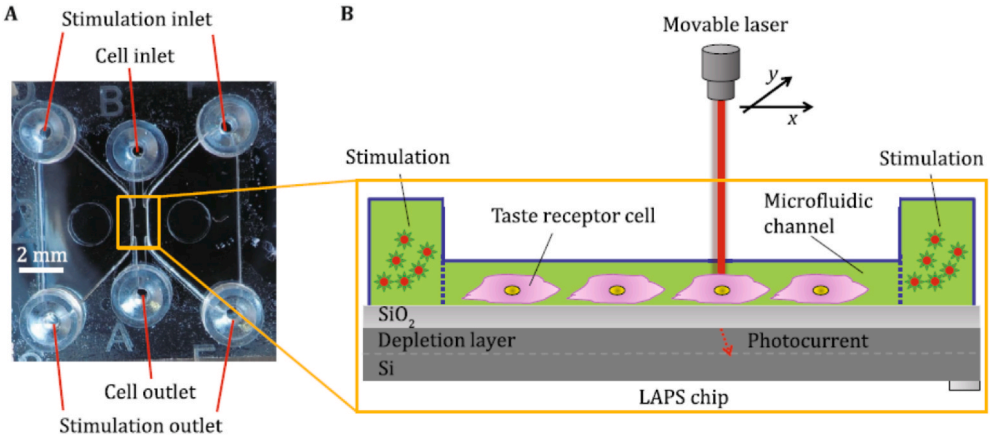

Fig. 5. A) Structure of using LAPS with detail in this work. B) Detail relative to the combination of LAPS with μ-Slide Chemotaxis 3D system using in Du et al. project. Reproduced with copyright permission of Springer (Du et al., 2019).

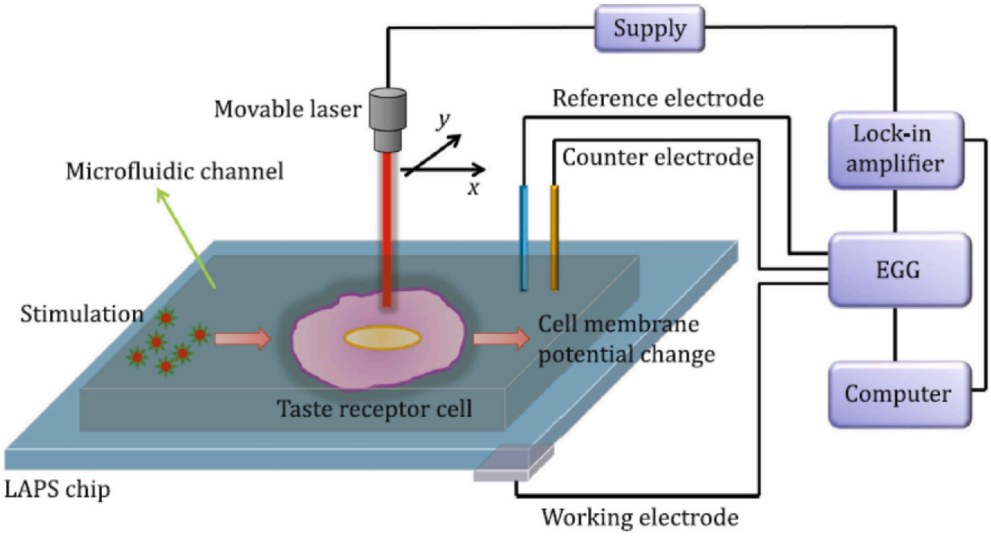

Fig. 6. Schematic of the setup system for cell culture reported by Du et al. Reproduced with copyright permission of Springer (Du et al., 2019).

Table 1
Reported papers for application of LAPS as an analytical tool for identification and measurement of biological samples.

Design LAPS system	Targets Intended	Time	Reference
Silicon plate decorated with oxynitride	Determination of the pH changing using urease as an enzyme	2 min	Hafeman et al. (1988)
Biotinylated acetylcholinesterase as biological part immobilized on cellulose nitrate	Anticholinesterases	1–5 min	Rogers et al. (1991)
eel acetylcholinesterase	Anticholinesterase	Not reported	Fernando et al. (1993)
Immunoligand assay coupled with LAPS	Escherichia coli O157: H7		Gehring et al. (1998)
n-type silicon substrates decorated with SiO_2 and/or Al_2O_3	urea, penicillin and glucose	15 min	(Seki et al, 1998)
LAPS amplified with Si_3N_4–SiO_2–Si	Carcinoembryonic antigen, cancer antigen and prostate-specific antigen	Not reported	Jia et al. (2012)
Goat anti-human immunoglobulin G antibody-coated at LAPS	human immunoglobulin G (hIgG)	5 min	Liang et al. (2016)
Pyranose oxidase enzyme decorated at Au nanoparticle coupled with LAPS	1,5-anhydroglucitol	20 min	Liang et al. (2017)
Penicillin modified LAPS	Determination of the pH changing	Not reported	Poghossian et al. (2017)
LAPS + Si_3N_4 as the H^+ sensitive material	Acidification of cells	Not reported	Liang et al. (2019)
AFP-aptamer + gold nanoparticles	Alpha-fetoprotein	Not reported	Li et al. (2020)

identification of various systems via coupling the spatial resolution of LAPS with the biological sensing mechanism. The change in pH values of the evaluated system can be a good indicator to gauge the activity of the cells under certain environmental conditions. The rapid change in pH values at a certain time indicates a high metabolic activity. On the other hand, minimal changes in pH values at a specific time confirms the low activity of the cells. It is essential to use electrolyte solutions with low-buffer capacities in LAPS-system measurement setups to determine the exact value of the acidification rate in cell systems. Acidification rate (pH/s) of the system can be calculated by decreasing the pH value over time in biological systems. By adding the compound to the investigation medium, the cell's metabolic activity under study would typically change (Wu et al., 2016). The cell's change in metabolic activity could alter the acidification rate (Owicki and Parce 1990). Based on the preceding observations, and the high-performance ability of LAPS, this type of systems were used to determine the metabolic activity of biomolecules such as visualization of *E. Coli colonies* (Nakao et al., 1995; Yoshinobu et al., 2001a) and the monitoring of the metabolic activity of unspecified bacteria (Libby 1993). Table 1 summarizes some studies that used LAPS as an analytical tool for identifying and measuring biological samples.

Different from the conventional arrangement of electrode/sensor array, there is the multi-pixel structure of LAPS systems where the pixel layout is defined by the scanning light in the sensing system. Therefore, high-resolution 2D imaging is one of the most exceptional features that can be achieved using LAPS systems (Tu et al., 2018). . Since LAPS systems are usually composed of acrylate and silicon matrix membranes, the fast and easy damage during transportation is one of the most important disadvantages of using LAPS systems (Wu et al., 2017). The high cost coupled with the complex surface treatment of LAPS system have been the main obstacles that stand in the way towards the development of portable kits. Hence, many of the reported studies in this context remained at the laboratory scale and never been commercialized. (Tu et al., 2018). Based on this, it is anticipated that more future efforts will focus on developing portable LAPS systems that offer rapid analysis of biological compounds.

3. MIP-based potentiometric biosensors

Measuring critical biological compounds accurately and examining the effect of drugs on the body as well as identifying cancer cells have been among the most important issues in the world that directly affects the survival of patients (Forouzanfar et al., 2020; Gouveia et al., 2019; Jia et al., 2019). Although analytical methods have long been used for this purpose, the selectivity of these methods to reduce errors in identification and measurement have been discussed in the literature (Filippo et al., 2020; Karimi-Maleh et al., 2019; Orooji et al., 2020). The modification in analytical procedures remains a fundamental area of interest (Karimi-Maleh and Arotiba 2020; Karimi-Maleh et al. 2016, 2019a, 2021; Tahernejad-Javazmi et al., 2018). Recently, molecularly imprinted polymer (MIP) was introduced as a new strategy for improving the performance of analytical sensors (Ibarra et al., 2020; Kubiak and Biesaga 2020; Mahmoudpour et al., 2020; Ndunda 2020). These sensors work according to the lock and key strategy. MIPs have specific cavities with a polymer structure designed for a particular target

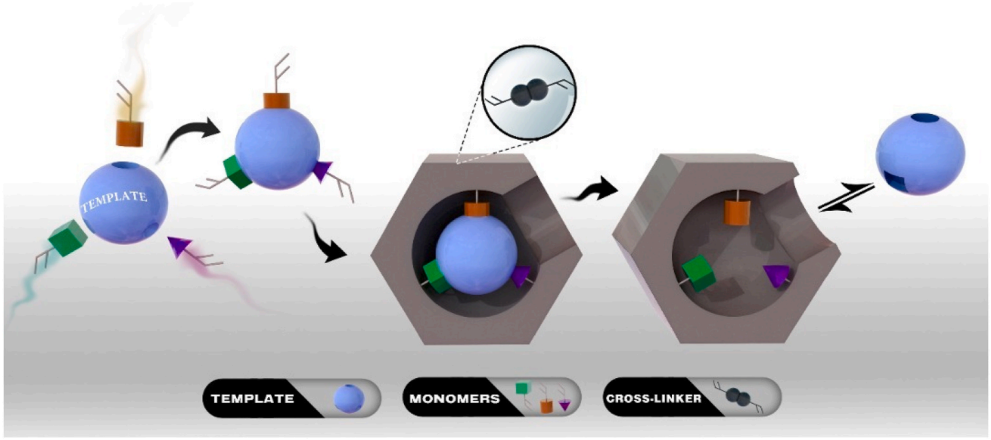

Fig. 7. Schematic of procedure for preparation of MIP.

Table 2
List of some reported sensors that used of MIP for amplification.

Analyte	Detection	LOD	Matrix	Ref.
Zearalenone	Optical	25.0 μM	acetonitrile	Navarro-Villoslada et al. (2007)
Volatile organic compounds (Toluene, xylene)	Acoustic	Not reported	Vapor	Fu and Finklea (2003)
TNT	Optical	5 ppb	Ambient air	Walker et al. (2007)
Atrazine	Electrochemical	0.1 ppm	Groundwater	Prasad et al. (2007)
Cu(II) ions	Quartz crystal microbalance (QCM)	0.08 μM	wastewater	Yang and Zhang (2009)
tenuazonic acid mycotoxin	Optical	0.5 μg mL^{-1}	Rice	Rico-Yuste et al. (2020)
prostate cancer biomarker	Electrochemical	0.96 μM	Buffer and blood	de Cássia Mendonça et al. (2020)
anticancer drug capecitabine	Electrochemical	0.324 nM	health human plasma and pharmaceutical samples	Afzali et al. (2020)
pyruvic acid as a cancer biomarker	Electrochemical	0.048	plasma and urine samples	Alizadeh and Nayeri (2020)

molecule with best fit strategy (Azizi and Bottaro 2020; Pandey et al., 2020; Zouaoui et al., 2020). Fig. 7 shows a schematic of MIP strategy and their use in bio sensing systems. Active sites in polymeric structures of MIP biosensors create specific interaction with target molecules and improve sensing systems' sensitivity (Dinc et al., 2019; Gui and Jin 2019).

Due to the creation of selective conditions and increasing the sensitivity of measurement in analysis systems, various sensors have used this technology to increase their selectivity. Table 2 summarizes some of the reported studies in the literature on MIPs.

Table 2 list some different types of using sensors amplified with MIP technology.

According to the aforementioned results and the role of the polymer in increasing the ability of sensors to measure important biological compounds, ion-selective membranes sensors were also used significantly. The MIP and especially MIP-proteins have been effectively integrated with potentiometric transduction for fabrication of MIP-based potentiometric biosensors. Usually, MIP with organic/inorganic mixtures within an ion-selective field-effect transistor (ISFET) is an important method of fabrication in MIP-based potentiometric biosensors. For example, Wang et al., (2010) used an ion-selective membranes sensor amplified with MIP technology that was designed to diagnose cancer biomarkers and viruses. In their work, the MIP structure was modified at the surface by gold (Au) layer via self-assembled technology and used for potentiometric determination of carcinoembryonic antigen. In the same study, the detection range 2.5–250 ng/mL (Wang et al., 2010). Nishitani and Sakata designed a new modified field-effect transistor (FET) potentiometric sensor with a MIP interface to detect small biomarkers (Nishitani and Sakata 2018). They used interaction of small biomarkers such as paromomycin and kanamycin with MIP coated surface of FET that created electrical signals as an analytical tool for the detection (Fig. 8).

As shown in Fig. 8, the Au film was coated at the end of the silicon-based n-channel FET and supported by the MIP system where Ag/Ag/Cl is the reference electrode for the fabrication potentiometric sensor. The theoretical investigation showed that the fabricated system can best fit by Langmuir adsorption isotherm.

Sharma et al. reported a selective ion-selective biosensor amplified with MIP synthesized by electrochemical procedures for sensing neopterin, as a cancer biomarker (Sharma et al., 2016). Atomic force microscopic (AFM) characterization clearly showed that the modification of the electrode surface with MIP can increase the active surface area and create a suitable place in the electrode surface for potentiometric sensing (Fig. 9).

Fig. 10 shows the schematic procedure and the creation of bonding between MIP and neopterin to fabricate this high sensitive biomarker. As shown in the same figure, 2,2-bithiophene-5-boronic acid (2,2BT,5,BA) created bonding via cross-linking with neopterin and could be suitable for the fabrication of MIP structure.

In another work, Moreira et al. was fabricated a potentiometric sensor for the determination of cardiac biomarker proteins by amplification the sensor with MIP (Moreira et al., 2015). In their study, they designed a myoglobin protein biomarker with MIP technology by polymerizing 2-aminoethyl methacrylate hydrochloride, 4-styrenesulfonic acid, and ethylene glycol dimethacrylate. The sensor was successfully implemented for the determination of myoglobin protein with a detection limit as low as 0.79 μg. Fig. 11 demonstrates the steps of synthesis of myoglobin protein-MIP sensor in the work of Moreira and co-workers (Moreira et al., 2015).

Furthermore, to obtain better and reproducible results, Moreira and

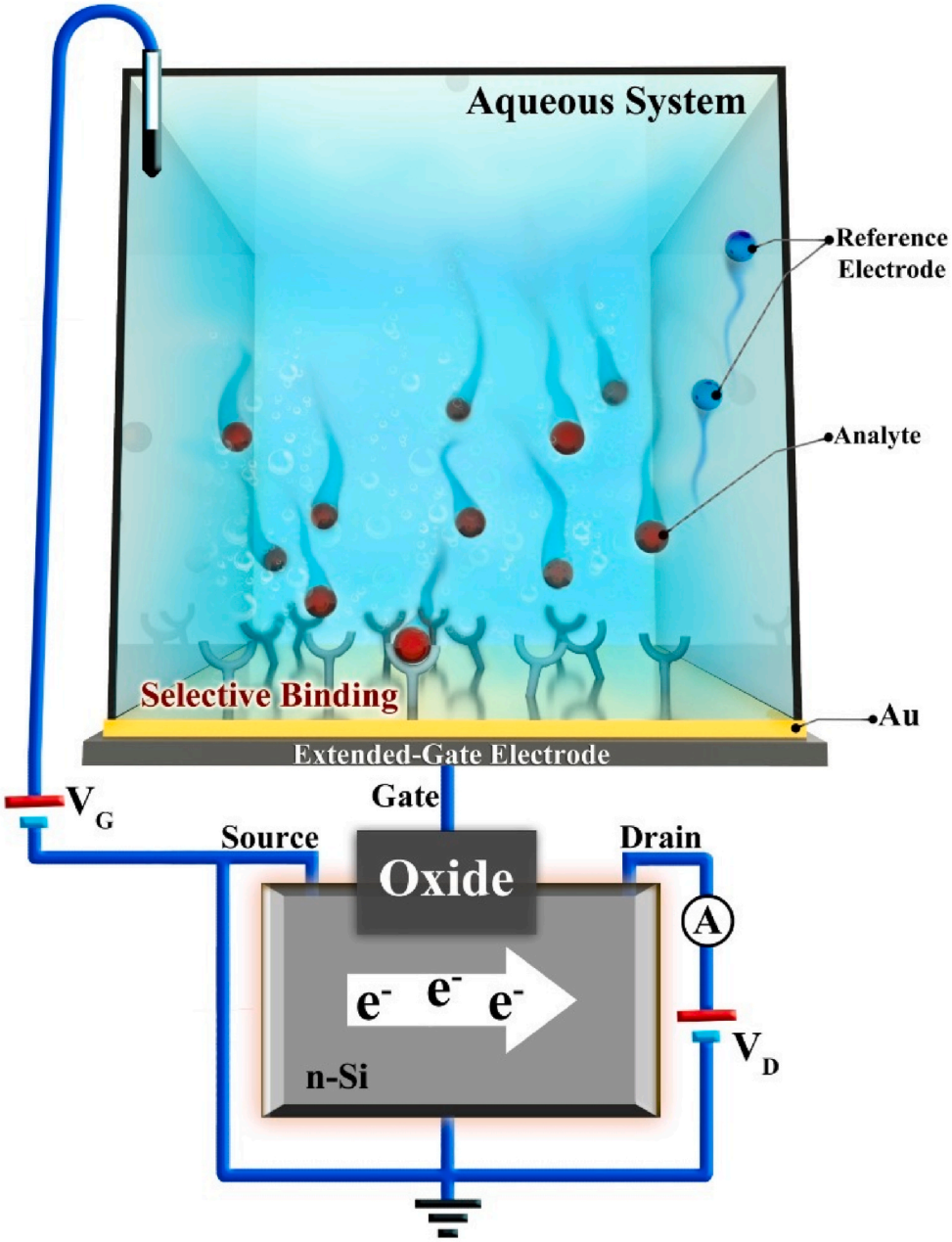

Fig. 8. Schematic of suggested system by Nishitani and Sakata for detection of small biomarkers. Permission of ACS (Nishitani and Sakata 2018).

co-workers (Moreira et al., 2015) grafted MIP onto graphite and used it to synthesize the sensor. The results confirmed that the synthesized protein-MIP sensor had more stability and accuracy results compared to the previous reported analytical sensors. The advantage of constructing selective potentiometric sensors offered via the MIP technique, allowed the fabrication of various ion-selective biosensors. Table 3 lists some of the different types of potentiometric biosensors amplified with the MIP technology.

Recently, MIP-based potentiometric biosensors were used as analytical tools for the detection of wide ranges of biomaterials such as drugs, inorganic ions, proteins and nucleic acids. Extensive use of MIP-based Potentiometric biosensors is considered as they showed many several promising features including low-cost, stable, specific, being easy to prepare and to miniaturize and their reasonable performance as bioreceptors for sensor technology. However, the most obvious challenge for the use of MIP-based potentiometric biosensors appears to be their application biosensing in real samples. The low conductivity of MIP-based sensors is another major problem for detection of biomaterials at low level concentration thus, it remains one of the research questions.

4. Wearable based potentiometric biomarkers

Wearable potentiometric sensors (WPISs) represent a different outlook at the physiological and clinical application of potentiometric sensors (Bandodkar et al., 2016a; Choi et al., 2018b; McCaul et al., 2017). They are receiving attention in research as they employ the chemical, material and electronic features to provide useful physiological information.

Despite the multiple efforts to develop wearable potentiometric sensors, a large gap still exists in meeting all the requirements for improving these systems (Jin et al., 2017; Wu and Haick 2018). More than 25% of published papers on the development wearable electrochemical sensors filed is related to wearable potentiometric ion sensors

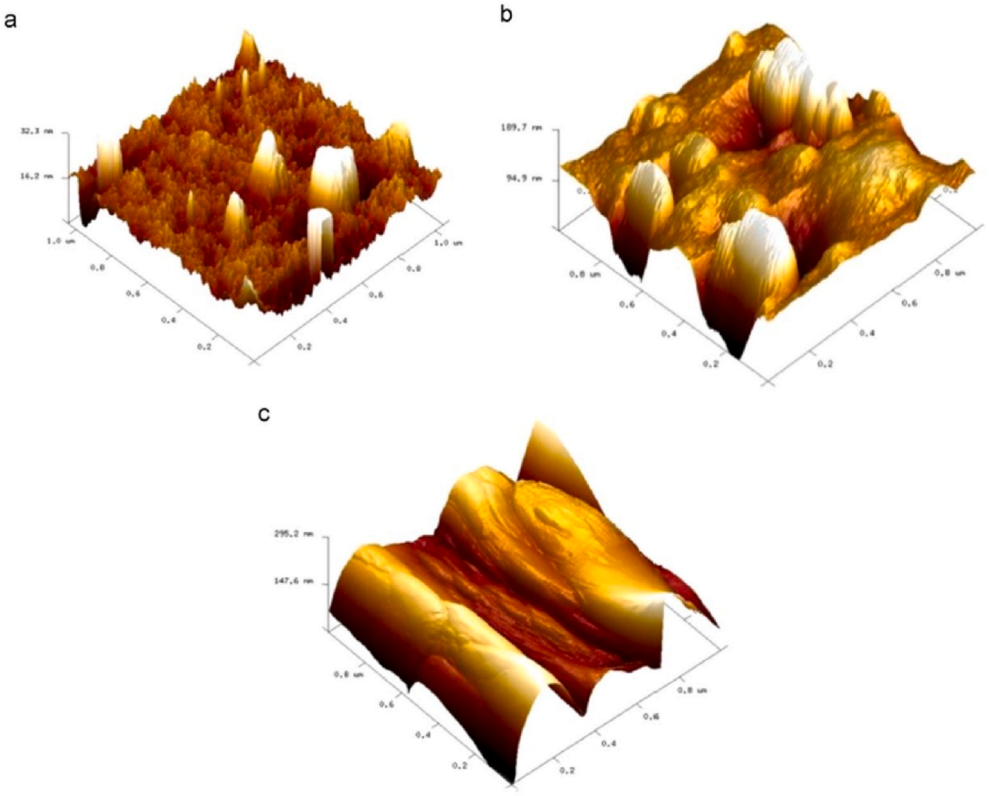

Fig. 9. AFM images of the neopterin-MIP sensor (a), AFM images of neopterin-MIP sensor after extraction of the neopterin template (b) and non-imprinted film (c). Reproduced with copyright permission of Springer. (Sharma et al., 2016).

(WPISs). This confirms the rapid movement of electrochemical sensors towards this new direction (Kim et al., 2017; Parrilla et al., 2019a). WPISs created a new perspective to biomarkers and pH monitoring measurement and evaluation in the human body (Cuartero and Crespo 2018; Liu et al., 2017). The monitoring of pH is a useful factor for managing chronic wounds and the measurement of crucial cations/anions help to understand and control some diseases. These diseases include heart disorders and cystic fibrosis, hypokalemia and hyperkalemia and hyponatremia and hypernatremia. The possibility of having analytical device taking diverse designs from sweatbands to patches without affecting the comfort level of the carrier has enabled the penetration of potentiometric ion sensors in many life aspects. WPISs are now involved in monitoring several critical biomarkers including sodium and potassium in sweat.

WPISs can be defined as electrochemical systems based on ion-selective electrode with materials and electronics integrated to allow on-body measurements (Hecht et al., 2009; Hu et al., 2016). This system is a biomarker detection tool to measure the concentration and activity of important ions in body fluids. It creates a complete information of the body's physiological activities in different configurations such as sweatbands, textiles, and epidermal patches (Fig. 12) (Parrilla et al., 2019a). Like all types of potentiometric sensors, electrodes, play an essential role in the measurement system's response and efficiency (Cuartero et al., 2016). The most commonly used electrodes in potentiometric sensors are gold (Au), carbon-based compounds (graphite, nanotubes or glassy carbon) onto polymeric substrates (e.g., PVC, poly (methyl methacrylate) (PMMA), polyethylene terephthalate (PET)), platinum, and silver (Bobacka and Ivaska 2010; Guzinski et al., 2017; Jarvis et al., 2018; Jaworska et al., 2018). On the other hand, $Ag/AgCl/KCl_{sat}$ is the conventional reference electrode in WPISs. Conducting polymers (CPs) and carbon (nano) materials are two major of indicator electrodes that were used many years ago in WPISs (Bandodkar et al., 2016b; Hernández et al., 2012). The dramatic growth of nanomaterials and the identification of their unique properties as well as the use of these materials to increase the measurements sensitivity of WPISs has resulted in many studies (Lee et al., 2016; Papp et al., 2018).

Parrilla et al. reported a biomarker detection tool for the sensing of ion patch in the human body (Sweat in this case) using WPISs technology (Parrilla et al., 2019b). As previously mentioned in this context, the Cl^-, K^+, Na^+ ions as well as the pH activity can be all detected by the proposed WPISs. Fig. 13 shows a schematic diagram for the proposed WPISs by Parrilla et al., (2019b).

Table 4 further summarizes different research efforts for the fabrication of WPISs in during the recent years.

Due to the use of all-solid-state ion-selective electrodes, the WPISs showed several advantages including the low sample volume requirements, miniaturization, reduced costs, versatility and simplicity for the in situ sensing of biomaterials. Although the use of WPISs as real tools for rapid analysis is growing, some of their disadvantages, such as skin contamination, low-sampling rates, and the existence of dried sweat on the glands thereby skewing analyte measurements, still exist. Thus, many studies aimed at focusing on solving these problems.

5. Potentiometric photoelectrochemical biomarkers

Photoelectrochemical (PEC) sensing has been proposed to improve the performance of potentiometric sensors for monitoring biomarkers (Pardo-Yissar et al., 2003; Shu and Tang 2019). The effect of light on photoactive materials (PAM) and detection an electrochemical response is based on PEC systems (Suresh et al., 2019). The absorption of photons with enough energy via PAM, electron−hole pair products are created. The photogenerated charge carriers' transferring to the sensor generate electrochemical response to the electrolyte, and thus, energy conversion occurs via the participating redox reactions. In PEC based sensors, the photoelectrodes play an important role in sensing systems. Compared to the methods aforementioned in the previous sections, few studies exist

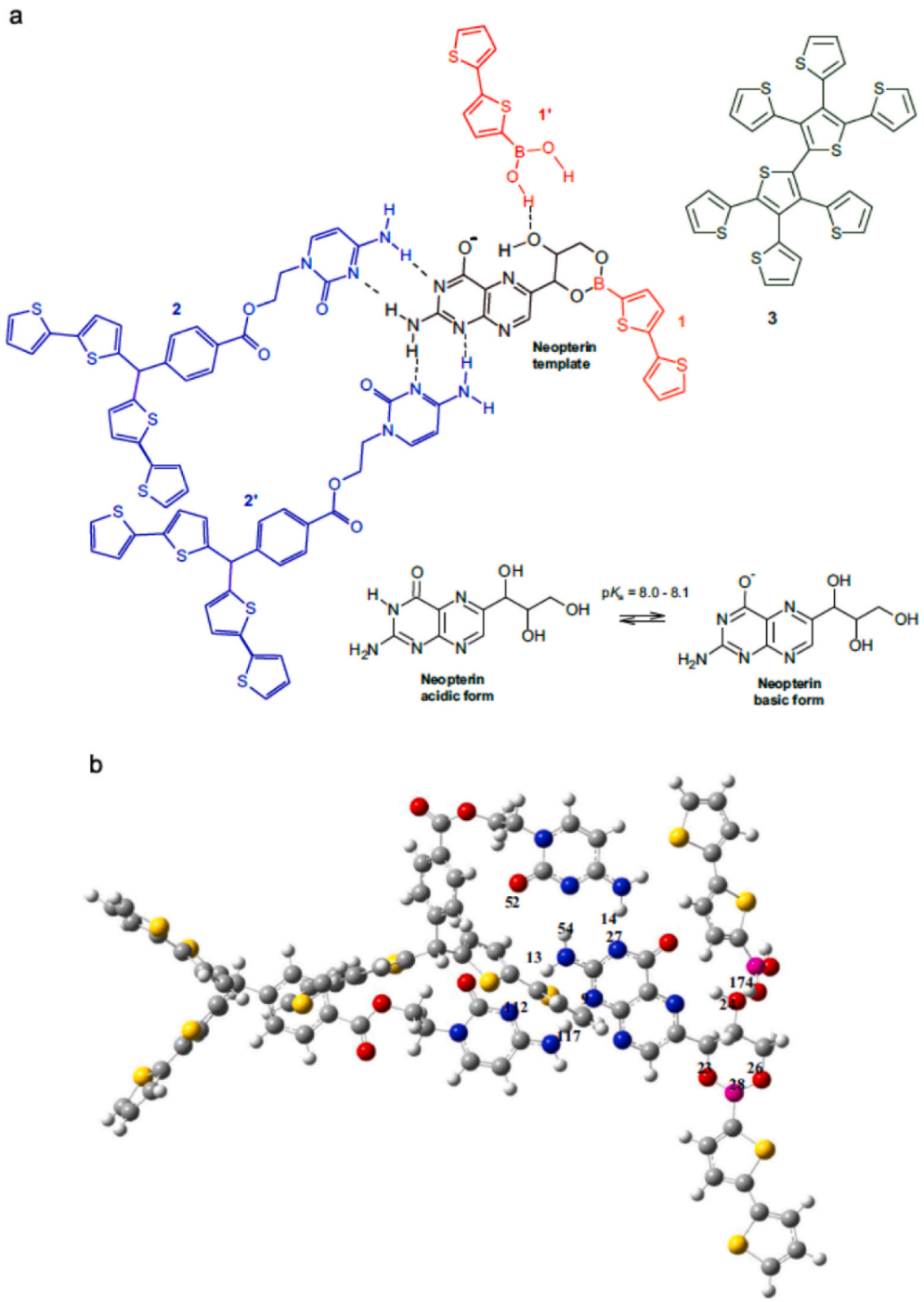

Fig. 10. a) Pre-polymer complex form of neopterin with 2,2BT,5,BA (1) and structure of 2,2BT,5,BA derivatized with cytosine (2) functional monomers as well as the cross-linking monomer (3). B) Optimize condition neopterin-MIP in this work. Reproduced with copyright permission of Springer (Sharma et al., 2016).

on the use of potentiometric photoelectrochemical as tools for biomarkers detection. This might be due to the limitation in selecting photoactive materials. Dai et al. reported a potentiometric addressable photoelectrochemical strategy as a new and selective sensor for monitoring and determining two prostate cancer biomarkers (Dai et al., 2016). In their study, a dual disk electrode (DDCE) modified with polyamidoamine dendrimers (PAAD) and cube anatase,TiO_2, mesocrystals (CAM) was proposed as robust and highly sensitive PEC sensing system for (human interleukin-6 (IL-6) and prostate specific antigen (PSA)). Two photo sensitizers namely, chitosan (CS) functionalized silver iodide, CS-AgI labeled different antibodies and carbon graphene nitride (g-C_3N_4) were coated at the surface of the electrode using the self-assembled technology for detecting the two preceding prostate cancers biomarkers. In this sensor, the g-C_3N_4 as anodic photocurrent and CS-AgI as cathodic photocurrent were selected to improve the sensor's sensitivity. Fig. 14 showed a schematic diagram for the fabricated potentiometric photoelectrochemical biomarker detection tool in this study.

A ratiometric photoelectrochemical aptasensor based on potentiometric response was fabricated for sensing Ochratoxin A (OTA) by Zhang group (Zhang et al., 2017). To fulfill this target, Bismuth phosphate ($BiPO_4$) nanoparticles (NPs) and $BiPO_4$- reduced graphene oxide (rGO) nano-composites (NCs) deposited onto Indium tin oxide (ITO) were used for recording anodic photocurrent and cathodic photocurrent,

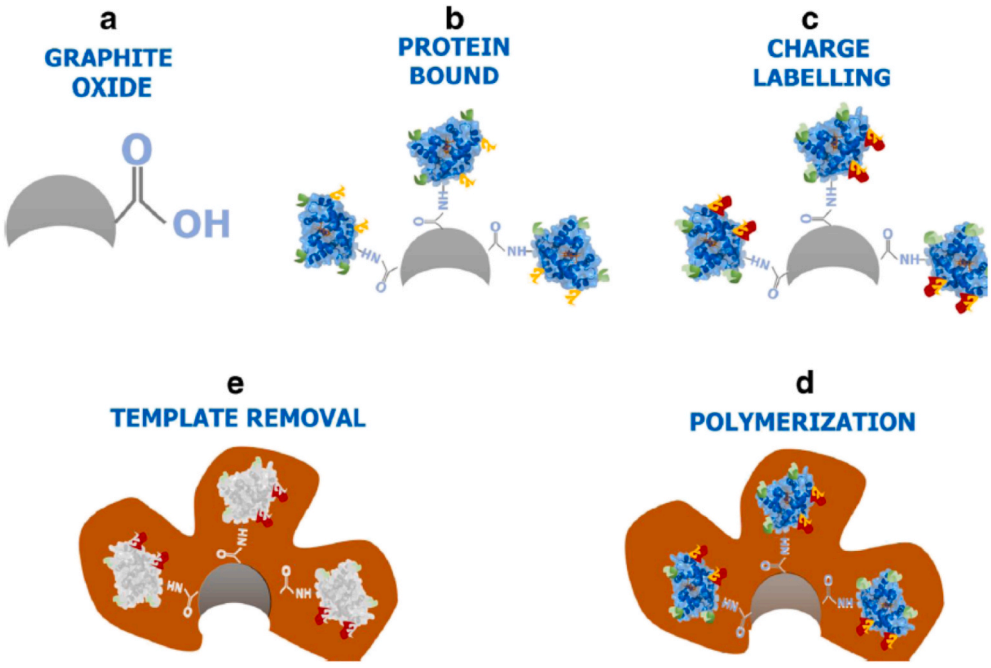

Fig. 11. Schematic of procedure for the synthesis of myoglobin protein-MIP sensor. Reproduced with copyright permission of Springer (Moreira et al., 2015).

Table 3
List of some potentiometric biosensors amplified with MIP technology.

Analyte	LOD	LDR	Matrix	Ref.
Carnitine	80 μM	Not report	urine samples	Moret et al. (2014)
Myoglobin	1.3 μM	linear response after 8.0×10^{-7} mol/L	Buffer solution	Moreira et al. (2011)
Metoprolol	1.26×10^{-7} M	2.0×10^{-7} -8.0×10^{-3} M	cough syrups	Al-Mustafa et al. (2014)
Phenylalanine	5×10^{-9} M	1×10^{-5} M - 1×10^{-4} M	Blood serum	Bangaleh et al. (2019)
Clarithromycin	8.0 × 10-7 M	1.0×10^{-6} M - 5.0×10^{-3} M	Buffer solution	Radi et al. (2019)
Sertraline Hydrochloride	0.8 μM	1.0 μM - 10 mM	urine and pharmaceutical samples	Mirzajani and Arefiyan (2019)
Dimethylamine	4.6×10^{-6} M	5.0×10^{-5} - 1.0×10^{-2} M	Soil Samples	SM Hassan et al. (2019)
Clonazepam	7.3×10^{-7} M	1.0×10^{-7} M - 1.0×10^{-1} M	Buffer solution	Babanejad et al. (2016)
Sarcosine as prostate cancer biomarker	0.38 μM	5.0 μM–1.1 mM	urine samples	Sheydaei et al. (2020)
Rosmarinic acid	0.085 μM	0.1–100 μM and 100–500 μM	plant extracts	Alipour et al. (2020)

respectively. Fig. 15 described the overall procedure for fabricated biosensors based on using of ratiometric photoelectrochemical aptasensor.

There have been numerous studies that have been reported in the literature on the use of potentiometric photoelectrochemical biomarker to monitor biological and medicinal compounds such as calcium, *Escherichia coli*, myoglobin and cardiac troponin I. (Cao et al., 2020; Hua et al., 2018; Hun et al., 2020). The use of potentiometric

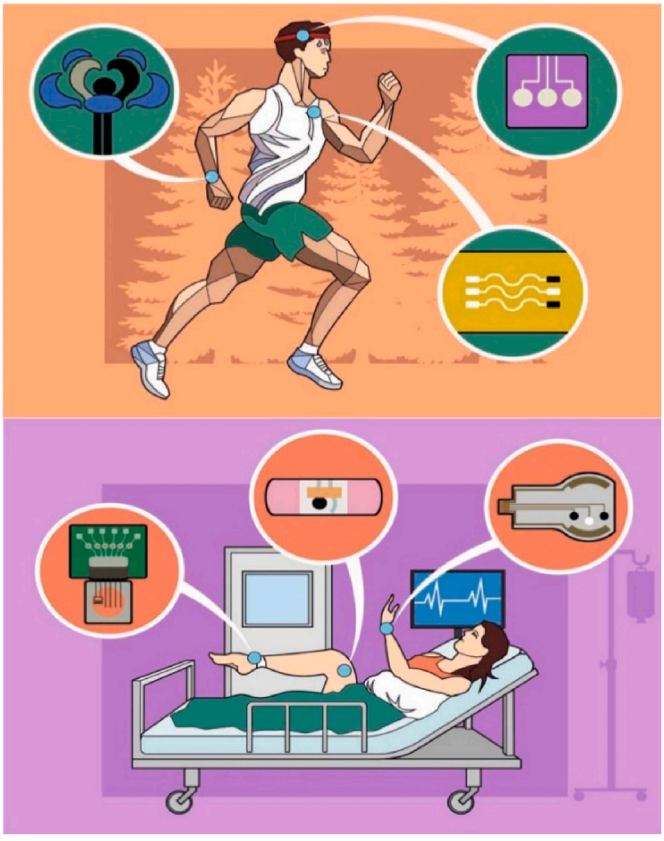

Fig. 12. WPISs biomarker in sport application; sensing based on textile-based, sweatband-based platforms and tattoo-based. WPISs biomarker is appropriate in clinical application. Reproduced with copyright permission of Springer. (Parrilla et al., 2019a).

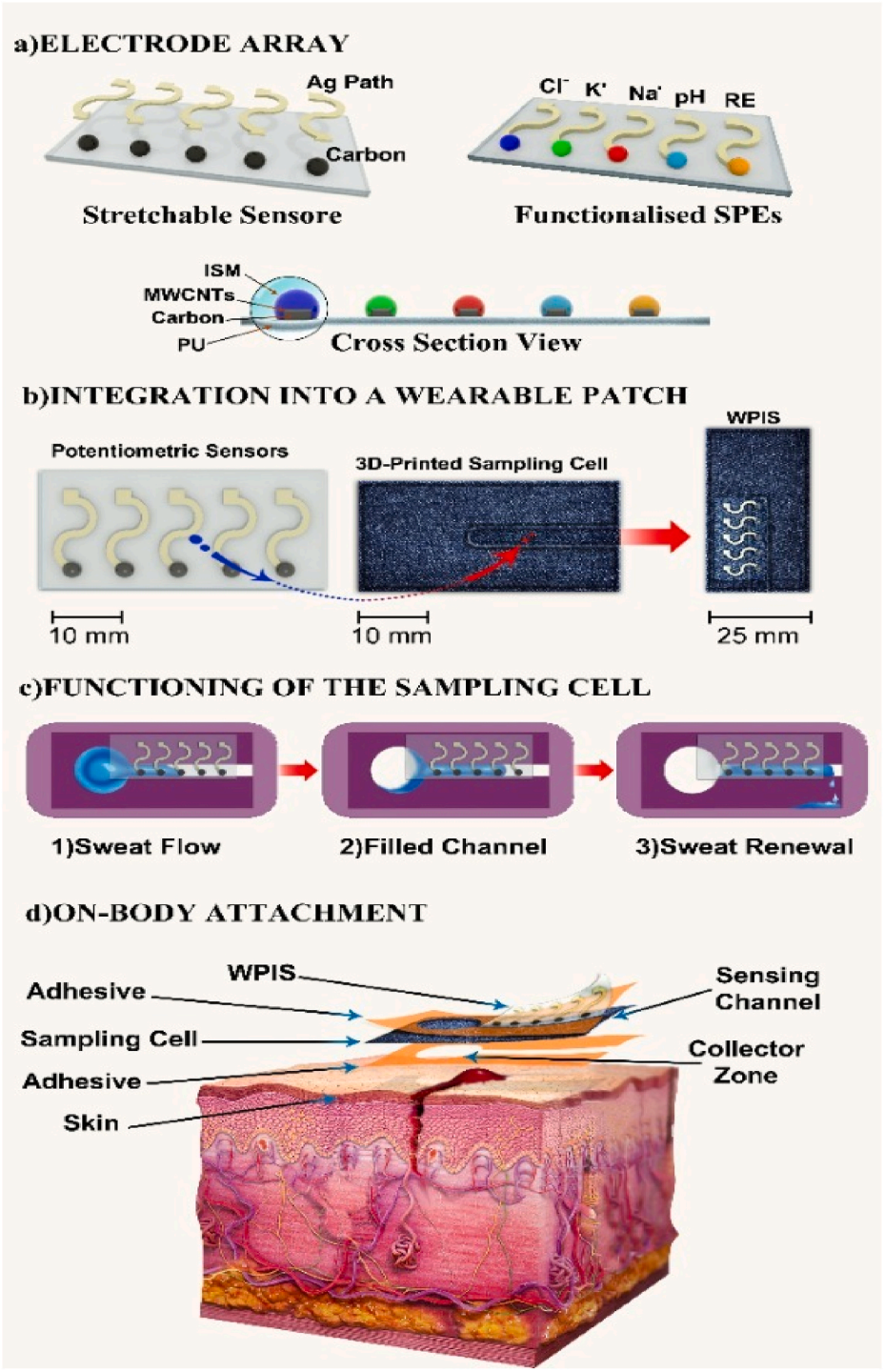

Fig. 13. A schematic of suggested WPISs as a biomarker for monitoring of Cl^-, K^+, Na^+ and pH activity. Reproduced with permission of ACS (Parrilla et al., 2019b).

photoelectrochemical technique as a biomarker sensing system has been receiving attention in research. However, the problems of designing photoelectrochemical systems such as hard signal generation conditions, the high cost and the difficulty of minimization compared to other methods represent the major obstacles against the use and implementation of these types of systems as portable kits.

6. Future outlook

The several features of the potentiometric methods summarized by the convenient operation, availability at a reasonable price, and ease of portable kits production, made them attractive methods for measuring biomarkers. However, they still suffer from various drawbacks including the stability, well established logistics of the biosensor, how to maintain optimum functionality, flexibility, as well as a timely detection of biomarkers.

Research efforts resulted in solutions to some of the existing issues by combining them with other technologies. In this regard, it seems that the use of potentiometric biomarkers based on photoelectrochemical, molecular imprinted polymer, wearable, and light-addressable technologies can create a new gateway to the world of decomposition kits in the future. Although the ability of these technologies to integrate with

Table 4
Recent research efforts for design and fabrication WPISs.

Type of wearable	Electrode fabrication	analyte	Sample	Time to start on-body recording	On-body tests (duration)	Ref.
Sweatband	Screen-printing	Na^+	Sweat	20 min	70 min	Matzeu et al. (2016)
Sweatband	Photolithography	Na^+/Cl^-	Sweat	20 min	25 min	Emaminejad et al. (2017)
Wristband	Screen-printing	Na^+	Sweat	8 min	60 min	McCaul et al. (2018)
Wristband	Roll-to-roll gravure printing	Na^+/K^+ and pH	Sweat	14 min	51 min	Bariya et al. (2018)
Epidermal patch	Lithography and electrodeposition	Na^+	Sweat	–	No	Rose et al. (2014)
Epidermal patch	Photolithography	pH	Buffer	10 min	60 min	Chung et al. (2014)
Epidermal patch	E-beam evaporation	Cl^-	Sweat	15 min	30 min	Choi et al. (2018a)
Bandage	Screen-printing	pH	Sweat	–	No	Guinovart et al. (2014)
Cotton yarn	Dip coating	K^+ and pH	Buffer	–	No	Guinovart et al. (2013)
Textile	Screen-printing	Na^+/K^+	Artificial sweat	–	No	Parrilla et al. (2016)
Microneedle	Dip coating and drop casting	K^+	Interstitial fluid	–	Ex vivo, 175 min	Parrilla et al. (2018)

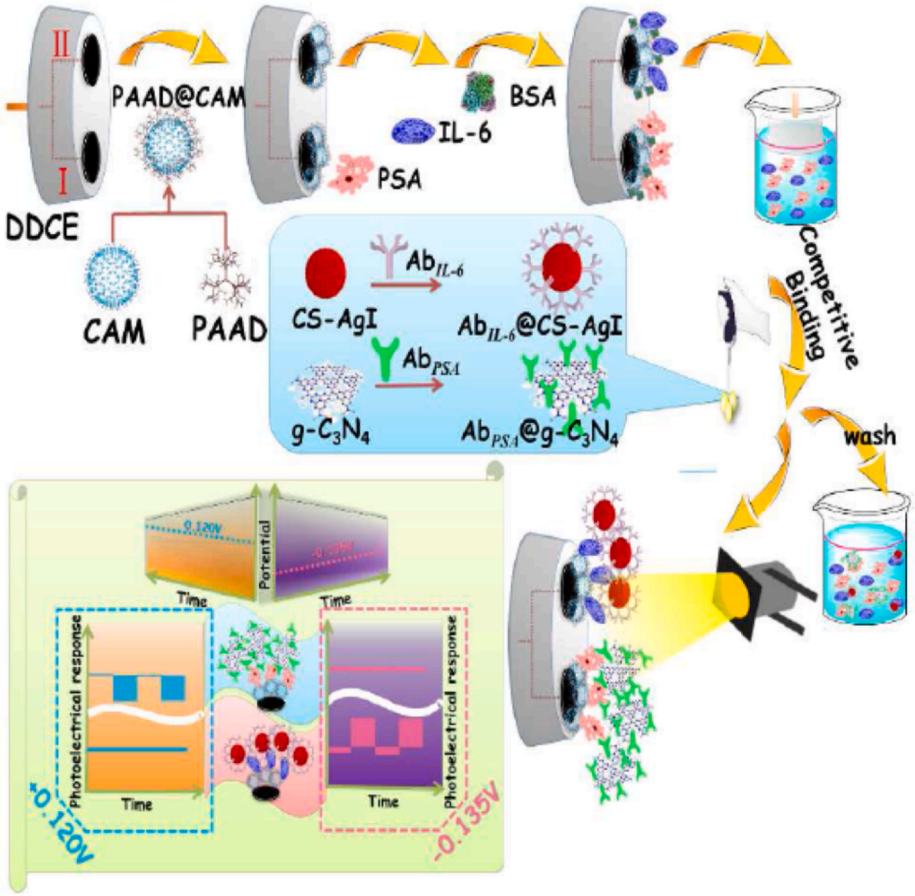

Fig. 14. Schematic of the suggested potentiometric photoelectrochemical biomarker for detection of two prostate cancers biomarkers. Reproduced with permission of ACS. (Dai et al., 2016).

potentiometric systems is not the same, it appears that in the future, portable sensor markets will be dedicated improve/develop wearable and light-addressable potentiometric systems. The detection of ions in sweat via wearable potentiometric biomarkers as well as monitoring human biological fluids have broadened the horizon for the implementation of potentiometric biosensor in clinical investigation. On-body sensors, surface regeneration and sensor stability are the key analytical challenges for developing of wearable potentiometric biomarkers without affecting the comfort level of the carrier. Despite their remarkable promise, but providing steady power supplies remain a challenge. (Bandodkar et al., 2016a). Securing the big data generated from measurements represents another important challenge for using of potentiometric biomarkers in a portable format. Therefore, it appears that solving the aforementioned problems will significantly increase the penetration of these potentiometric biosensors into the market.

7. Conclusions

Potentiometric monitoring of biomarkers and biological compounds using ion-selective electrodes (ISEs) is commonly applied in industrial

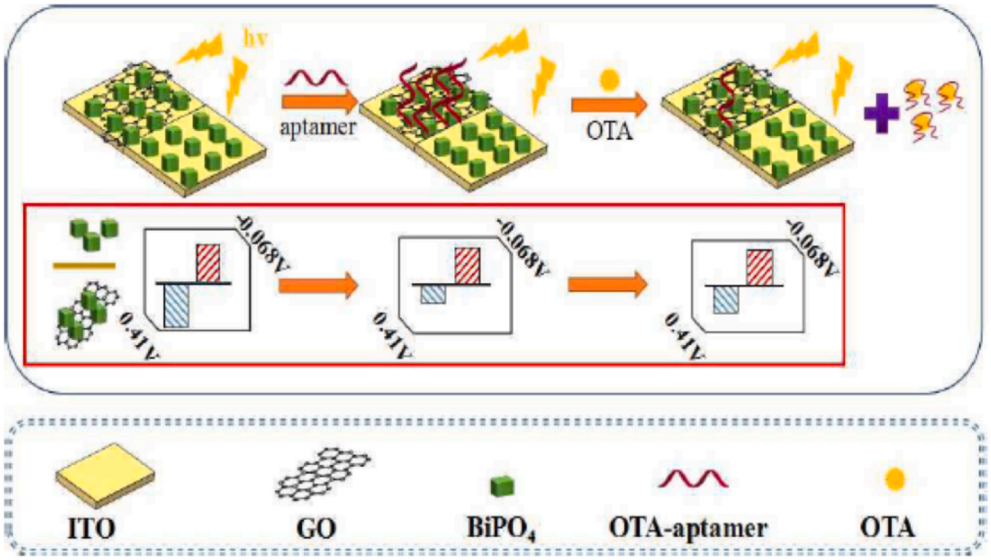

Fig. 15. Schematic of suggested potentiometric photoelectrochemical biomarker for detection of Ochratoxin A. Reproduced with permission of RSC (Zhang et al., 2017).

analysis, clinical diagnostics and environmental monitoring. Numerous studies have reported that the low detection limit as well as the low selectivity are the main disadvantages of potentiometric biosensors. Therefore, the combination of potentiometric sensors with other techniques such as photoelectrochemical, molecular imprinted systems, wearable and light-addressable technologies in recent years appeared to tackle many obstacles in this field. This article reviewed the fundamentals of these sensors and provided an evaluation for their potential as biomaterial monitoring methods. The reported studies in the literature showed that wearable based potentiometric sensors have been successfully used as biomarkers monitoring tools. The MIP-based potentiometric biosensors showed more selectivity for monitoring biomarkers compared to other strategies. In general, potentiometric sensors modified with a variety of techniques can be promising candidates for developing low-cost and accurate portable kits.

Declaration of competing interest

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

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