



Review

Sensors and biosensors for analysis of bisphenol-A

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ABSTRACT

We discuss state-of-the-art sensing methods for the detection of bisphenol-A (BPA), a well-known and much studied contaminant causing a wide range of health problems to living beings especially the young. These methods are rapid, sensitive, inexpensive and suitable for on-site monitoring. We comprehensively review the principles, the mechanisms and the performances of chemical sensors and biosensors available in the literature. We also discuss future perspectives in developing sensors for the detection of BPA.

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Abbreviations: BPA, Bisphenol-A; PC, Polycarbonate; EDC, Endocrine disrupting compound; MIPs, Molecularly imprinted polymers; CNT, Carbon Nanotube; MWCNTs, Multi-walled carbon nanotube; SWCNTs, Single-walled carbon nanotubes; CoTe, Cobalt-Tellurium; PAMAM, Polyamidoamine; rGO, Reduced graphene oxide; SELEX, Systemic evolution of ligands by exponential enrichment; BHPVA, 4,4-Bis(4-hydroxyphenyl)valeric acid; ELISA, Enzyme-linked immunosorbent assay; HRP, Horse radish peroxidase; SPR, Surface-plasmon resonance; MAbs, Monoclonal antibodies; PABs, Polyclonal antibodies.

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1. Introduction

Bisphenol A (BPA) is scientifically known as 4,4'-(propane-2,2-diyl)diphenol. It is used as a monomer in the synthesis of polycarbonate (PC) and epoxy resins (Fig. 1a). It also finds application in the synthesis of polyacrylate, polysulfonate, unsaturated polyester resins and flame retardants. BPA is one of the most important chemicals synthesized globally in high volumes and is in high demand. A wide variety of food-storage or packaging materials are produced from PC, such as feeding bottles, water bottles and cans, tableware and microwave ovenware. Epoxy resins are also used as an internal coating material for lacquered cans and bottles used for the processed foods. BPA is a ubiquitous, well-known food-packaging migrant and contaminant, which raises concerns about food safety. BPA leaches into food products from the packaging material due to thermal treatment in processing (Fig. 1a) [1,2]. Apart from food-contact materials, it also finds many applications [e.g., production of currency notes, thermal printing paper, compact disks, adhesives, and powder paints [3,4]]. Recently, Geens et al. [3] reviewed the possible sources of BPA exposure to human beings. It is present in

a wide array of food and other items and pollutes the biotic and abiotic environments [5]. The exposure estimate for populations, primarily through food intake, is in the general range 0.1–1.5 $\mu\text{g}/\text{kg}$ body weight/day. It is roughly estimated that more than 2000 tonnes of BPA and its products are released into the environment annually due to domestic and industrial activities [6].

BPA is a potent endocrine-disrupting compound (EDC) and its toxicity is widely reported in literature [7]. The structure of BPA is analogous to endocrine hormones, namely estradiol and diethylstilbestrol, due to the presence of phenol groups in their structure [8] (Fig. 1b), so it has affinity to bind estrogen receptors. It has been demonstrated that low doses, even at sub-ng levels (0.23 ng/L) can affect human health [9]. Exposure to BPA is well known as affecting the functions of brain, thyroid, ovary and reproductive organs [10,11]. Generally conjugated forms of BPA (e.g., BPA-glucuronide, BPA-disulfate and BPA-chlorides) are found in biological samples [12]. Enhanced BPA levels in the urine of adults have led to increased incidence of sexual dysfunction in men. BPA is associated with cardiovascular diseases, obesity, carcinogenicity, neurotoxicity and developmental problems [13,14]. It also causes wheezing

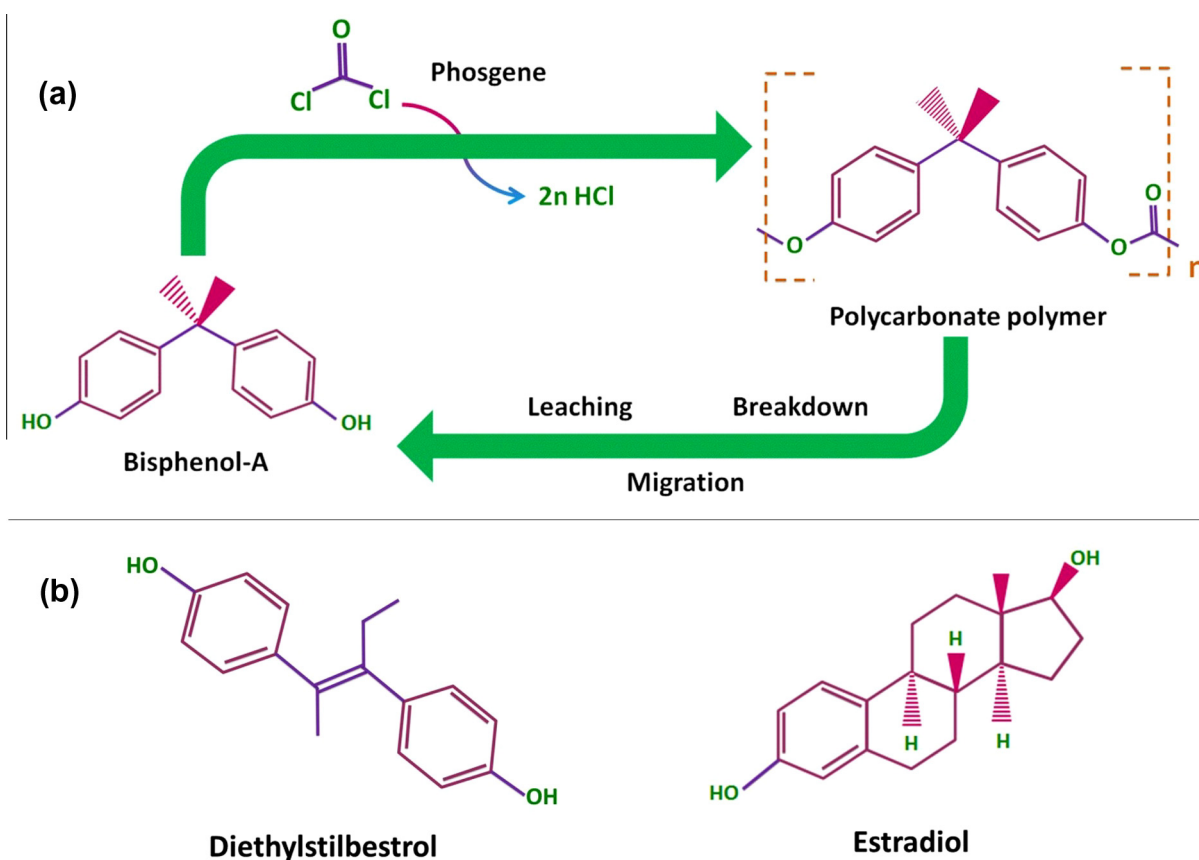


Fig. 1. (a) Synthesis of polycarbonate polymer from bisphenol-A and its breakdown to bisphenol-A. (b) Hormones structurally analogous to bisphenol-A.

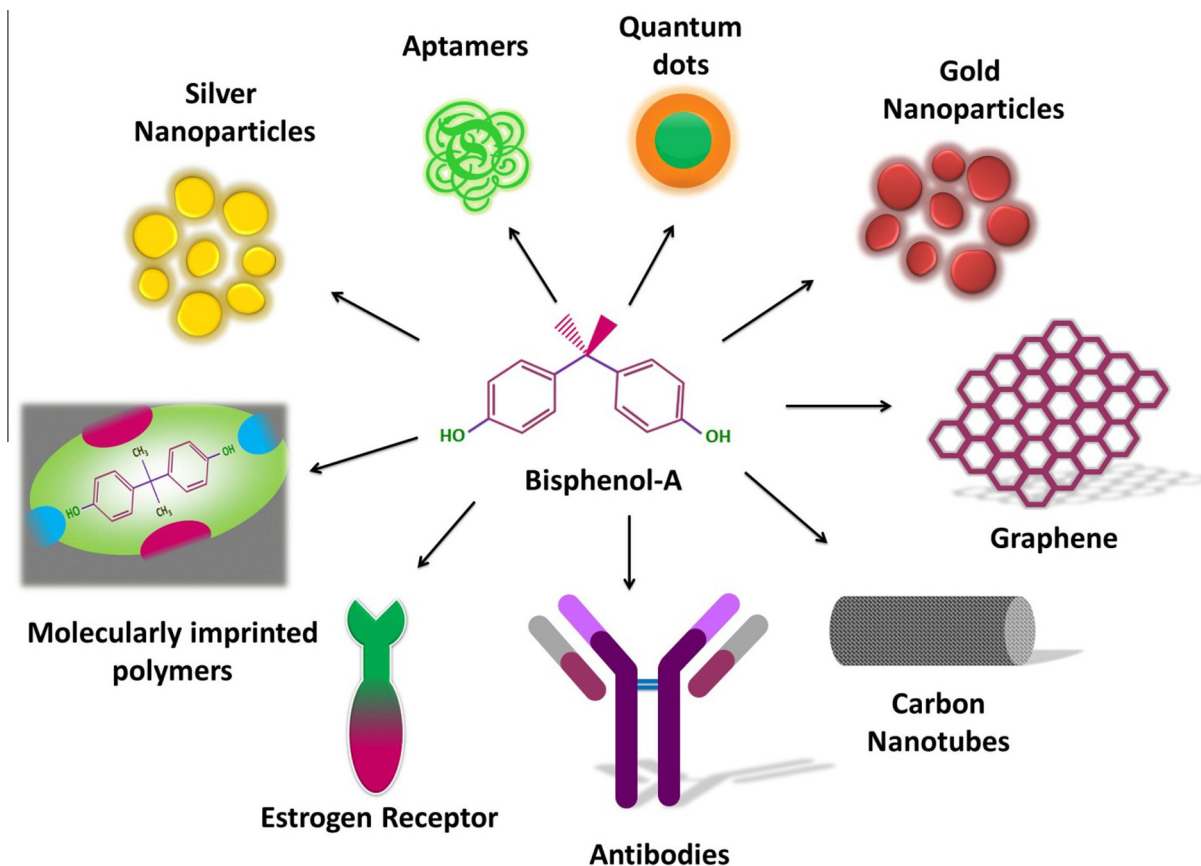


Fig. 2. Novel recognition and transducer components used for the fabrication of sensors.

[15], asthma and behavioral problems. BPA also causes health hazards among animals [16].

Regulatory agencies and health departments worldwide have shown their interest in possible exposure to BPA and its detrimental effect on health. It is vital to monitor and to control the harmful effects of BPA. A number of analytical methods for the analysis of BPA have been developed. Most of the analytical methods require cumbersome sample preparation and pretreatment, and they lack on-site applicability, whereas chromatography and mass spectroscopy-based methods need large capital investment, have high operating costs, require skilled personnel for analysis and interpretation, and are time consuming. Hence, many research groups have developed innovative methods for rapid, sensitive detection of BPA in various samples and matrices.

A number of published reports have discussed the use of analytical methods and sample preparation for detection of BPA using chromatographic techniques [17–19]. However, these reports failed to discuss the development of recent techniques, such as sensing and biosensing methods for BPA.

We comprehensively review several recent sensing and biosensing approaches developed for the detection of BPA (Fig. 2).

2. Chemical sensors for the detection of BPA

Chemical sensors are a major class of sensors, which have many applications, such as environmental and food analysis, process control, and medical diagnosis. A chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal [20,21]. In the following sections, we discuss various chemical-sensing systems developed for BPA, whose features are shown in Table 1.

2.1. Electrochemical sensors

Electrochemical sensors are widely accepted and employed due to their high sensitivity and simplicity. An electrochemical sensor consists of an electrochemical transducer (chemically-modified electrode) coated with a chemical or biochemical film as conducting material [22]. BPA is an electrochemically-active molecule due to phenolic groups but its direct determination is difficult because of weak response of BPA in conventional electrochemical sensors [23]. Various types of electrochemical sensor with advanced materials have been developed to increase the surface area of electrode to enhance oxidation signals.

2.1.1. Molecularly-imprinted polymer sensors

Molecularly-imprinted polymers (MIPs) are synthetic materials used as recognition elements in the design of sensors due to their higher thermal stability, reusability and selectivity compared to biological receptors. These polymeric materials bind with the target molecules, depending upon their shape, charge and functionality leading to variations in physical parameters, such as mass, absorbance or refractive index [24]. The specificity of MIPs against BPA depends on the choice of monomers and the method of synthesis. The binding of BPA to MIPs is a chemisorption phenomenon and involves the formation of two hydrogen bonds between BPA and 4-vinylpyridine in the imprinted cavities. The extent of binding to different kinds of MIPs is generally in the range ng– μ g, which results in highly-sensitive detection of BPA [25].

MIPs are used along with nanoparticles (NPs) to improve the sensitivity and specificity of the assay due to the large surface area of NPs. Kubo et al. [26] synthesized MIPs by polymerizing 4-vinylpyridine (functional monomer) using ethylene glycol dimethacrylate as a cross-linker and coated on the surface of a

Table 1
Features of various sensors developed for the analysis of bisphenol-A

Detection method	Linearity and limit of detection (LOD)	Real sample/Matrix	Ref.
<i>Molecularly-imprinted-polymer (MIP)-based sensors</i>			
2-aminothiophenol monomer/GNPs	8×10^{-6} – 2×10^{-2} M (1.38×10^{-7} M)	Aqueous extract of Plastic materials	[27]
Potentiometric method with BPA imprinted polymer	0.1 – 1×10^{-6} M (0.02×10^{-6} M)	Aqueous extract from PC bottles	[29]
MIPs and chitosan on acetylene black paste electrode	10×10^{-6} – 80×10^{-9} M (60×10^{-9} M)	Infant nursing bottles, water bottles	[30]
TiO ₂ nanotubes and MIPs (polypyrrole)	4.5 – 108×10^{-9} M (2×10^{-9} M)	Five different water samples	[31]
<i>Carbon-nanotube (CNT) sensors</i>			
MWCNT-GNPs/GCE	2.0×10^{-8} – 2×10^{-5} M (7.5×10^{-9} M)	Plastic wares	[35]
SWCNTs/ β -cyclodextrin	5.4×10^{-9} – 0.03×10^{-6} M (1×10^{-9} M)	Plastic samples	[36]
Fullerene – C60	74 – 0.23×10^{-5} M (3.7×10^{-9} M)	Waste water sample	[37]
<i>Graphene-based sensors</i>			
Graphene – Potassium ferricyanide	5×10^{-8} – 1×10^{-6} M (4.689×10^{-8} M)	Mineral water in plastic ware	[40]
Exfoliated graphene electrode	1.56 – 50×10^{-6} M ($0.76 \mu\text{M}$)	Water samples	[41]
Nitrogen-doped graphene sheets with chitosan	1.0×10^{-8} – 1.3×10^{-6} M (5.0×10^{-9} M)	Water samples	[42]
Graphene-CNTs nanocomposite	1×10^{-5} – 6×10^{-8} M (4.2×10^{-8} M)	Thermal printing paper	[43]
Graphene nanofibers and gold nanoparticles composite	0.08 – 250×10^{-6} M (3.5×10^{-8} M)	Baby bottles	[44]
<i>Quantum-dot-based sensors</i>			
CoTe QDs/PAMAM dendrimer	1.3×10^{-8} – 9.89×10^{-6} M (1×10^{-9} M)	Real water samples	[46]
<i>Metal composites</i>			
Cobalt phthalocyanine	8.75×10^{-8} – 1.25×10^{-5} M (1.0×10^{-8} M)	Plastic wares	[48]
Mesoporous silica MCM-41	2.2×10^{-7} – 8.8×10^{-6} M (3.8×10^{-8} M)	Water Samples	[49]
Mg–Al layered double hydroxide (LDH)	1×10^{-8} – 1.05×10^{-6} M (5.0×10^{-9} M)	Plastic wares	[50]
Amorphous hydroxy iron composites with β -cyclodextrin (BCD)	(0.2×10^{-6}) M	Beer Samples	[51]
Boron doped diamond	0.01 – 0.06×10^{-6} M (0.03×10^{-6} M)	Bottled drinking water	[52]
<i>Nanocomposite-based sensors</i>			
PAMAM–Fe ₃ O ₄	1×10^{-8} – 3.07×10^{-6} M (5×10^{-9} M)	Milk samples	[54]
Chitosan–Fe ₃ O ₄	5×10^{-8} – 3×10^{-5} M (8.0×10^{-9} M)	Plastic samples	[55]
MWCNTs–GNPs	1.13×10^{-7} – 8.2×10^{-3} M (3.6×10^{-9} M)	Honey, Tap water and Grape Juice	[56]
PAMAM–AuNPs–SF	1×10^{-9} – 1.3×10^{-6} M (0.5×10^{-9} M)	Water samples	[23]
Microfluidic Chip sensor	$11.1 \pm 1.8 \times 10^{-15}$ M	Tap water	[57]
Reduced Graphene oxide	6×10^{-8} – 1.1×10^{-5} M (1.7×10^{-8} M)	Plastic wares	[58]
<i>Chemiluminescence-based assays</i>			
Luminol and potassium hexacyanoferrate	8×10^{-7} – 1.2×10^{-5} M (3.1×10^{-7} M)	Aqueous extract from PC materials	[60]
Silver NPs	1×10^{-8} – 5×10^{-5} g/L (1×10^{-9} g/L)	Water samples	[62]
<i>Bioluminescence-based assays</i>			
BLYES assay	1.5×10^{-9} g/L	Drinking water	[73]
<i>ELISA</i>			
MAbs	0.22×10^{-9} M	Canned vegetables	[80]
<i>Nano-immunosensor</i>			
Mice-PAbs	0.3×10^{-9} g/mL	Human serum	[83]
Paramagnetic iron oxide nanoparticles	0.4×10^{-9} g/mL	Tap water	[84]
Lateral flow dipstick assay	5×10^{-6} g/L	Spiked water samples	[85]
<i>Quartz crystal microbalance immunosensors</i>			
MAB–Polymeric Nanoparticle conjugate	0.01×10^{-9} g/mL	Environment pollutant samples	[82]

(continued on next page)

Table 1 (continued)

Detection method	Linearity and limit of detection (LOD)	Real sample/Matrix	Ref.
<i>Surface-plasmon-resonance (SPR)-based sensors</i>			
2-aminoethanethiol /BPA conjugate	10×10^{-9} g/mL	–	[87]
MAB (Non-competitive and competitive immunoassay format)	0.4×10^{-9} g/mL	–	[88]
PAb	0.5×10^{-9} g/mL	–	
Binding inhibition format with PABs (IgY) conjugate	0.14×10^{-9} g /mL	Waste water	[89]
SAM – PABs	40×10^{-12} g/mL	Drinking water	[90]
<i>Fluorescence immunosensors</i>			
RIANA	14×10^{-9} g/mL	Water samples	[93]
<i>Aptamer-based sensors</i>			
SwCNT-FET capacitance based sensor	1×10^{-12} M	Binding buffer	[96]
Aptamer-biotin	10×10^{-15} M		
AAO-based capacitance sensor	100×10^{-12} M	Water samples from PC wares	[97]
Colorimetric aptasensor	0.1×10^{-9} g/L	Water samples	[98]
Competitive cDNA aptasensor	0.284×10^{-9} g/L	Drinking water	[99]
Functionalized aptasensor	0.01×10^{-9} g/L	Water samples	[100]
<i>Enzyme biosensor</i>			
Tyrosinase and SWCNTs	$0.1\text{--}12 \times 10^{-6}$ M (0.02×10^{-6} M)	Polluted surface water	[101]

gold-sputtered glassy-carbon electrode (GCE). The sensor was found to be more selective towards BPA and the electrochemical response was examined by cyclic voltammetry. Similarly, Huang et al. [27] used a gold-NP (AuNP)-modified GCE to graft 2-aminothiophenol with BPA as template. The oxidation of BPA was analyzed by relating it to the peak current. Apodaca et al. [28] showed that electro-polymerized MIPs could be used for the detection of BPA by electrochemical-impedance spectroscopy. Kou et al. [29] developed a potentiometric sensor using BPA-imprinted polymers as receptors coated on the electrode surface to aid specific and sensitive detection.

Chitosan forms excellent film, with good adhesion and high mechanical strength, so it is used with MIPs for the fabrication of electrochemical sensors. Acetylene-black electrodes have a large surface area, good electrical conductivity and adsorptive properties, so they are used instead of GCEs for the detection of BPA [30]. Lu et al. [31] designed a photo-electrochemical sensor using TiO₂ nanotubes and polypyrrole MIPs coated on the electrode surface. The sensor had a limit of detection (LOD) in the nanomolar range and was able to overcome the drawbacks of conventional electrodes.

Recently, Xue et al. [32] developed a sensor with an amine-rich MIP-capped core-shell AuNP as a substrate for surface-enhanced Raman scattering (SERS) for the detection of BPA. Bound and unbound MIPs gave signals, which were found to have a linear relation to different concentrations of BPA. Once the specificity of MIPs to BPA is improved, they should find potential applications as recognition elements in designing sensors (Fig. 3).

2.1.2. Carbon-nanotube (CNT) sensors

CNTs are one of the extensively studied nanomaterials for their wide gamut of intriguing physical properties, such as higher aspect ratios, larger surface area, better chemical and thermal stability, and electronic and optical properties that help in designing electrochemical sensors (Fig. 4a). Due to these properties, CNTs are increasingly used as transducer materials, especially as nano-scale electrodes for amperometric sensor fabrication [33,34]. The use of CNTs on a GCE greatly enhances the oxidation rate of BPA due to their inherently large surface area (Fig. 4b).

A multi-walled carbon nanotube (MWCNT)-AuNP hybrid film coated on a GCE has been used for the detection of BPA in the sub-micromolar range [35].

Single-walled carbon nanotubes (SWCNTs) were covalently conjugated with β -cyclodextrin to improve the performance of the amperometric sensor. The fabricated sensor displayed improved sensitivity in nanomolar range [36].

Fullerene (C60), a nanomaterial similar to CNT, with properties, such as large electroactive surface area, good electron conduction and biocompatibility, was also used to fabricate an electrochemical sensor. The sensor platform greatly enhanced the signal with an LOD of 3.7 nM, which was attributed to kinetic parameters of CNTs such as charge-transfer coefficient, electrode-surface area and diffusion coefficient [37]. CNTs have considerably improved the performance of electrochemical sensors in terms of electrochemical reactivity, electron-transfer efficiency, lowering anodic over potential, sensitivity and speed.

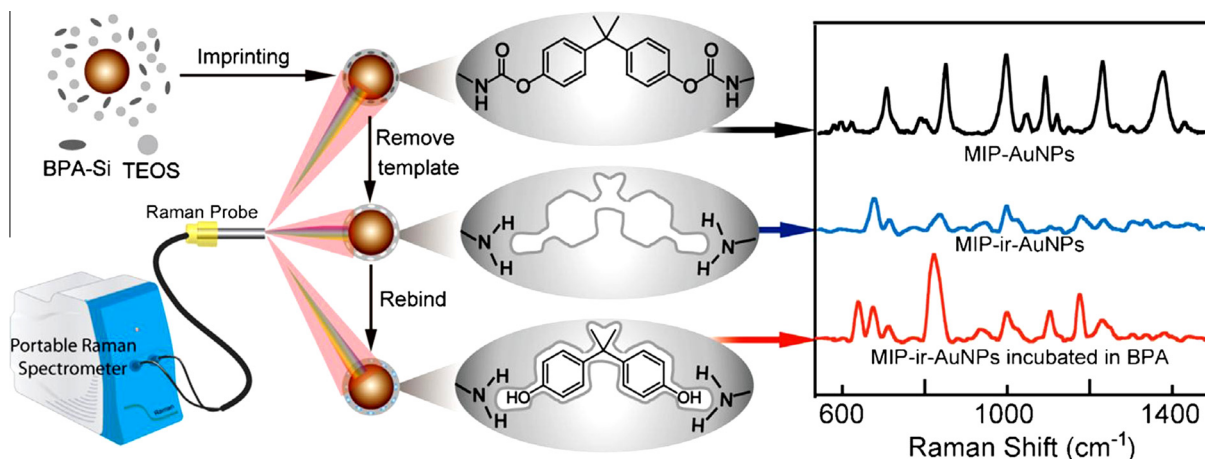


Fig. 3. Fabricating a MIP-core-shell gold-nanoparticle sensor for selective detection of bisphenol-A using a small portable Raman spectrometer [32].

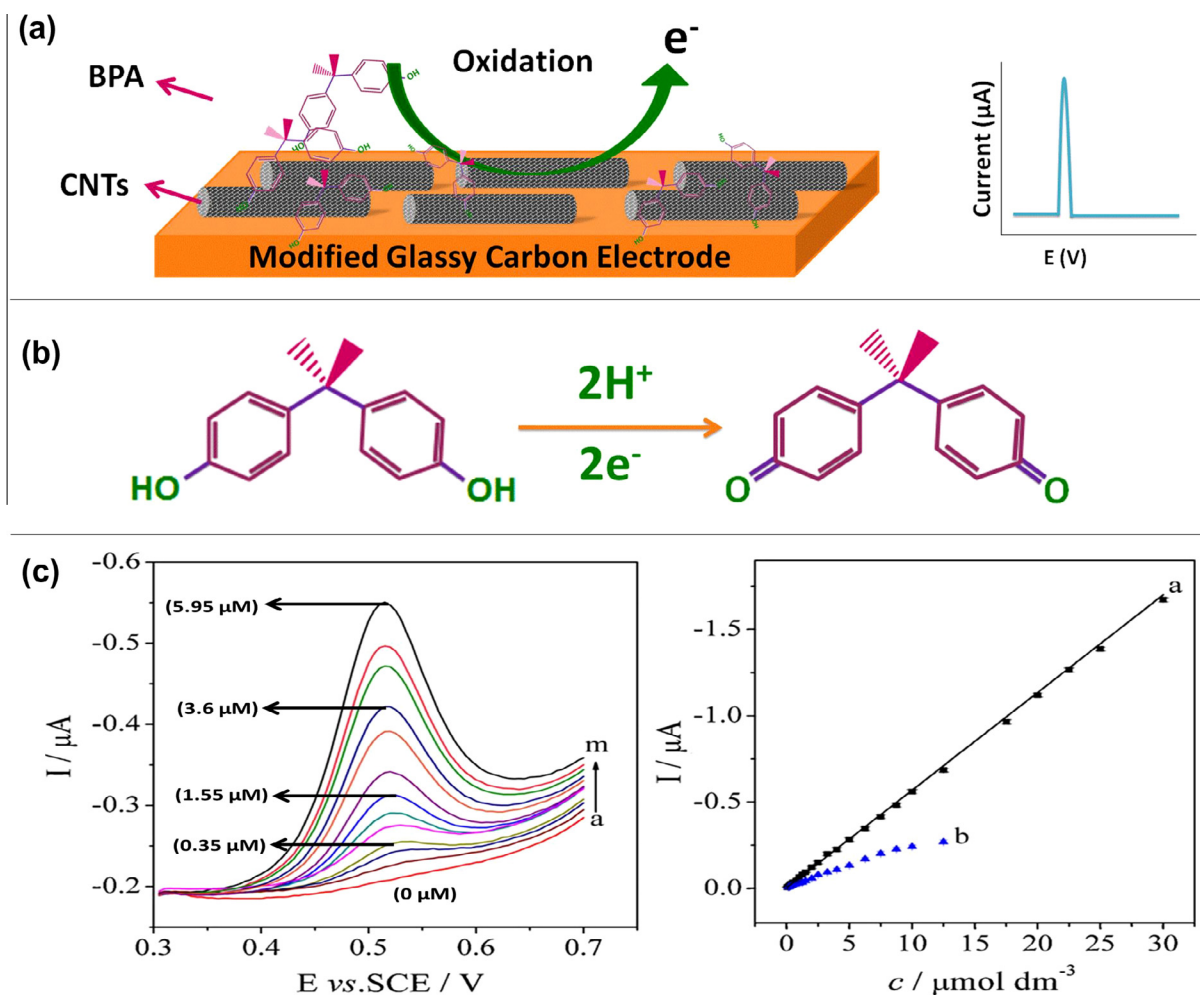


Fig. 4. (a) CNT-based electrochemical sensor for the detection of bisphenol-A. (b) Oxidation reaction of bisphenol-A on electrode surface during electrochemical sensing. (c) DPV curves of electrochemical sensor using CS-Fe₃O₄/GCE for different bisphenol-A concentrations [55].

2.1.3. Graphene-based sensors

Graphene is an exciting nanomaterial with two-dimensional layers of SP²-hybridized carbon. It is used for sensing due to its properties, such as higher electrical conductivity, large surface area, and fluorescence quenching, and the possibility of surface functionalization [38,39]. A graphene-modified GCE using potassium ferricyanide was developed and found to have an LOD in the sub-micromolar range [40]. Similarly, exfoliated graphene coated on the electrode surface was developed and applied to detection of BPA [41]. Nitrogen-doped graphene was found to have favorable electron-transfer ability and electro-catalytic properties compared to unmodified graphene.

Fan et al [42] used nitrogen-doped graphene sheets with a chitosan-based electrochemical sensor for detection of BPA in water samples with an LOD of 5 nM. A graphene-CNT nanocomposite synthesized by a simple, environment-friendly route was used with platinum NPs to fabricate an electrochemical sensor, which was applied to the detection of BPA in thermal printing papers [43]. The effective surface area of GCE increased by 1.7 times compared to bare electrode when a composite of graphene nanofibers and AuNPs was coated on the electrode surface. The composite actively took part in the electro-catalysis, which significantly reduced the oxidation over-potential of BPA and helped improve the oxidation peak current for the detection of BPA [44]. Graphene may increase the sensitivity of BPA detection if its prop-

erties other than electrical conductivity, such as fluorescence quenching and catalytic properties, are explored.

2.1.4. Quantum-dot-based sensors

Quantum dots (QDs) are nanoscale semiconductor structures having luminescent properties. QDs are one of the best candidates for designing nanoprobe, due to their size-controlled fluorescence, better fluorescence quantum yields than dyes, and stability against photobleaching [45]. Yin et al. [46] used an amperometric sensor comprising a GCE immobilized with cobalt-tellurium QDs, which were capped with polyamidoamine (PAMAM) dendrimer for the detection of BPA in water samples. The catalytic activity and the high adsorption capacity of CoTe QDs resulted in enhanced oxidation of BPA. At the same time, they observed enhanced conductivity of the solution, which was attributed to PAMAM dendrimers and resulted in better signal peaks.

2.1.5. Metal composites

Metal composites are hybrid materials of metal-metal or metal-polymer types. Metal-polymer composites have good conductivity and large surface area due to their mesoporous structures [47]. They enable enhanced binding of BPA and signal conduction from oxidation.

Yin et al. [48] determined BPA concentration using a cobalt-phthalocyanine-coated carbon-paste electrode and indicated that

the transfer of electrons and protons took place through an absorption-controlled process. With the help of different electrochemical techniques (such as cyclic voltammetry, differential pulse voltammetry, linear sweep voltammetry and chronocoulometry), the oxidation rate of BPA on the modified electrode surface was reported.

Mesoporous silica molecular-sieve materials, such as MCM-41 synthesized from cetyltrimethyl-ammonium bromide as a template, were used to design electrochemical electrodes. MCM-41 has a large active surface area and high accumulation efficiency compared to other materials, such as graphite, carbon nanotubes, activated carbon and silica gel. As a result, the sensor remarkably improved the oxidation signal of BPA [49].

Later, Yin et al. [50] studied the electrochemical behavior of BPA using a GCE coated with Mg-Al double-hydroxide layers and response signals were compared with different electrochemical techniques (such as cyclic voltammetry, differential pulse voltammetry, linear sweep voltammetry and chronocoulometry).

An amorphous hydroxy iron composite conjugated with β -cyclodextrin was coated on the GCE surface for detection of BPA. The linearity over a wide range was attributed to the stability of cyclodextrin against the BPA-oxidation products [51].

Boron-doped diamond was used as an electrode modifier and found to overcome the drawbacks of an unmodified bare-electrode sensor, such as background current and electrode-surface fouling [52].

Recently, Mazzotta et al. [53] used conductive polymer (poly(3,4-ethylenedioxythiophene)) to modify GCEs by an electro-polymerization process for the detection of BPA using cyclic voltammetry.

We can look to the catalytic property of the metal composites to improve the sensitivity of assays using electrochemical sensors.

2.1.6. Nanocomposites

Nanocomposites are increasingly used in fabricating electrochemical sensors due to the combined properties of nanomaterials and polymers, such as large surface area due to the branched structure of the polymers and good biocompatibility, which enhance the oxidation rates of BPA [54,55]. An amperometric sensor was fabricated using a PAMAM- Fe_3O_4 -modified electrode, which significantly reduced the oxidation over-potential resulting in detection of BPA at 5 nM concentration [54].

Similarly, a chitosan- Fe_3O_4 nanocomposite was used to fabricate an amperometric sensor for BPA (Fig. 4c), because of its desirable properties, such as the superparamagnetism of Fe_3O_4 . Chitosan is a polyaminosaccharide that provides stable, homogeneous suspension of NPs due to their chemical structure during sensor fabrication [55].

An electrochemical-imprinted sensor was fabricated by electrochemical deposition of MWCNTs and AuNPs onto the gold-electrode surface. Impregnated MIPs enhanced the signals and resulted in selective, sensitive detection of BPA [56]. In the same way, PAMAM dendrimers and a GNP-silk fibronin composite were also used for electrode modification. The enhanced oxidation peak current of BPA was attributed to the catalytic and conductive property of GNPs along with the high adsorption capacity and conductivity of positively-charged PAMAM [23].

Noh et al. [57] designed a microfluidic chip-based sensor for detection of EDCs, including BPA. Basically, it is an improved version of the electrochemical-detection system, which combines sample pre-concentration with a micellar electro-kinetic separation system. In the microfluidic chip sensor, the cellulose-dsDNA/AuNP-modified carbon-paste electrodes were used and detection was in femtomolar range for BPA in water samples. NPs improved the apparent mobility of the solutes due to additional interaction

sites on the surface, which resulted in enhanced separation and detection of EDCs.

Recently, Zhang et al. [58] fabricated an electrochemical sensor using reduced graphene oxide (rGO) conjugated with magnetic NPs. Graphene nanocomposite offered good adsorption capacity due to its large surface area and improved electrochemical conduction.

Justino et al. [59] have reviewed possible approaches to improving the analytical performance of sensors fabricated using nanomaterials. Nanocomposites may serve as potential candidates for fabricating electrochemical sensors if their physical and chemical properties, such as electrical conductivity, geometric symmetry and surface modification, are explored for developing ultrasensitive assays.

2.2. Chemiluminescence-based sensors

Chemiluminescence is the generation of light due to chemical reaction, in which a chemical species is excited to a higher energy state and spontaneous emission of light occurs when it returns to its ground state. Chemiluminescence is recognized as an effective and important technique in the analysis of molecules because of its high sensitivity, significant linear response up to a certain range and simple instrumentation (Table 1).

Wang et al. [60] used a flow-injection chemiluminescence-inhibition method for the detection of BPA in water samples using luminol and potassium hexacyanoferrate. Chemiluminescence can be induced by passing electric current instead of oxidation. The electric current-induced electrolysis of luminol-dissolved oxygen system (electro-chemiluminescence) was utilized for the detection of BPA. The electro-chemiluminescence method is simpler than the chemiluminescence method because it requires fewer reagents for analysis, and the electro-chemiluminescence reaction can be easily controlled and monitored [61].

Chen et al. [62] demonstrated that use of silver NPs enhanced the chemiluminescence of luminol and that it can be successfully used for the detection of BPA in water samples. The LOD was 1 ng/L and the method was found to be suitable for rapid on-site analysis.

3. Biosensors for the detection of BPA

Biosensors are modified chemical sensors, which use biological material as a recognition element. The biosensor is defined as a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles, microbes or whole cells to detect chemical compounds, usually by electrical, thermal or optical signals [63]. Fodey et al. [64] reviewed the properties and production of various types of synthetic and biological recognition elements having potential application for sensing purposes. These are broadly classified into various classes based on the mechanism of recognition and signal transduction [22], and play vital role in detection, monitoring and analysis.

We discuss various biosensing methods developed for detection of BPA in the following sections (Table 1).

3.1. Microbial biosensors

Microbial biosensors are devices that utilize microbes as the sensing element. Microbial sensors offer the advantage of studying the toxic effects along with quantification of the target compounds [65]. Generally, the microbes are genetically engineered by altering their pathways to sense and to report the target molecule and to serve as bio-reporters [66].

3.1.1. Microbial bio-reporters

Microbes, such as yeast and bacteria, are generally used to develop microbial bio-reporters. Hahn et al. [67] developed a yeast-cell-based estrogen-assay system (A-YES) for monitoring BPA using recombinant yeast strains of *Arxula adenivorans* LS3, capable of expressing human estrogen receptor. Based on the concept of human estrogen-receptor dimerization in the presence of estrogen and binding with estrogen-responsive elements, it led to activation of the phytase reporter gene in the yeast cells. The phytase activity of the strains in the presence of BPA and steroids was studied and expressed in terms of 17β -estradiol equivalent activity.

Gierach et al. [68] developed bacterial biosensors for monitoring of BPA and related EDCs using engineered *Escherichia coli* with ligand-binding domains of estrogen receptor. The growth phenotype of the bacteria was altered due to ligand-receptor binding and the strains responded to low doses of BPA in the μM range. These biosensors were reported to be able to accept ligand-binding domains from various species, assisting in exact identification of EDCs.

3.1.2. Bioluminescence-based assays

Bioluminescence is production and emission of light by bioluminescent proteins present in a living organism. Such proteins are broadly grouped into luciferases and photoproteins.

Bioluminescent emission from luciferase is due to an enzyme-substrate reaction, in which luciferin (substrate) is oxidized into an electronically-excited state by luciferase in the presence of oxygen, its subsequent relaxation causing the emission of a photon.

With photoproteins, the light emission is an inherent property and directly proportional to the concentration of the protein [69,70].

Bioluminescence is a versatile, sensitive tool, which has the ability to sense target biomolecules at low concentrations and is a potential candidate for detection of wide array of targets.

Gu et al. [71] used four different recombinant bioluminescent *E. coli* strains containing the *lux CDABE* gene from *Vibrio fischeri* to detect the genotoxicity caused by EDCs. They were able to monitor various toxic effects but not the estrogenic effect alone. The inhibition of specific bioluminescence by BPA was found at a concentration range of 0.01–10 mg/L.

Bioluminescent yeast assays for monitoring BPA with external addition of D-luciferin as a substrate for light emission was demonstrated by Leskinen et al. [72]. A bioluminescent yeast estrogen assay was developed for monitoring EDCs in surface and drinking water. The presence of EDCs in water produced light in the yeast cells, which was proportional to BPA concentration and had a limit of quantification (LOQ) of 1.5 ng/L. The presence of BPA activated the human estrogen receptor agonist complex, which expressed the light-emitting reporter gene. As a result, light was observed without the addition of exogenous substrates and the assay was found to be rapid and cheap in terms of analysis [73]. The sensitivity and the selectivity of the luciferase system towards the BPA have to be enhanced to detect BPA at sensitive levels in real samples.

3.2. Electrochemical-cell-based chip sensors

Electrochemical-cell-based chip sensors provide a novel sensing technique, in which variation in electro-dynamic and redox properties of the cells are utilized to detect target compounds. The electrochemical response of the sensor was measured through cyclic voltammetry or amperometric techniques. Choi et al. [74] developed electrochemical-cell-based chip sensors using neural cancer cells to monitor BPA.

Kafi et al. [75] developed electrochemical-cell-based chip sensors for the detection of BPA, which causes stimulatory and cytotoxic effects on neural cells at nanomolar concentrations. The electrode of the sensor was fabricated with layers of silicon,

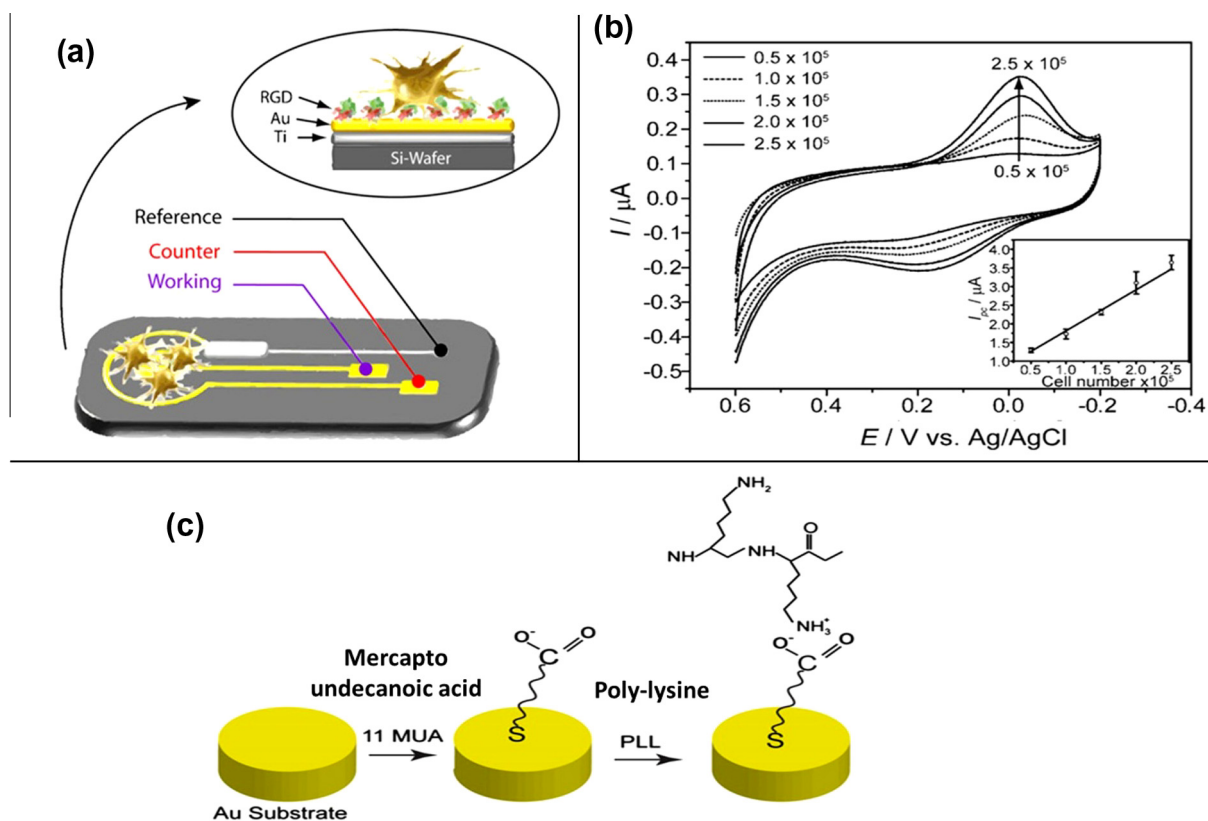


Fig. 5. Electrochemical-cell chip sensor for bisphenol-A. (a) Fabrication of electrochemical-cell chip. (b) Cyclic voltammogram with different cell numbers. (c) Chip-surface modification [75,77].

titanium and gold. The gold surface was coated with a cysteine-modified peptide as a bio-ligand, which helped in fixing the neuroblastoma cells on the electrode surface (Fig. 5). The dose response of the cells towards BPA was measured with the help of cyclic voltammetry, and morphological changes were evaluated using phase-contrast microscopy.

Similarly, Kafi et al. [76] developed a cell-chip sensor for the detection of BPA based on inhibition of the cell cycle. The electrochemical properties of the cell depended on specific nuclear changes during the cell-division stage of the cell cycle. Cells prepare for mitosis during the M-phase where cytokinesis occurs to form the daughter cells and, during the S-phase, the cells synthesize DNA. As a result, the electrochemical response (signals) will be high compared to other phases, which could be used for the detection of environmental toxicants.

A poly-lysine-based cell chip with neural cells in the G1/S and G2/M phases of the cell cycle was immobilized and subjected to various concentrations of BPA. The electrochemical behavior of the cells gave a good response greater than 300 nM of BPA [77].

Cell-chip-based sensors have been successful in monitoring drugs and toxicants at sensitive levels and served as a potential candidate for rapid on-site monitoring.

3.3. Immunosensors

Immunosensors are simple, specific and sensitive tools for detection and screening of a variety of analytes. These are fabricated using monoclonal (MAbs), polyclonal (PABs) or recombinant (rAbs) antibodies as biorecognition elements. The detection range of analytes depends upon the immunoaffinity of an antibody towards its antigen; the extent of binding can be converted to readable output signals using an appropriate transducer. Immunosensing is widely used as analytical technique for screening and detection of various environmental pollutants, toxins and biological compounds [78].

A novel immunosensor was designed for the detection of BPA by covalently conjugating the PABs on carboxylated polyvinylchloride polymer membrane coated on a gold-quartz crystal. Binding of BPA to PABs generated the potentiometric response, which was correlated with the quantity of BPA in solution [79].

3.3.1. Enzyme-linked immunosorbent assay (ELISA)

Enzyme-based immunoassays are widely-used analytical methods for screening target molecules, which offer signal amplification over immunoassays. ELISA methods for the detection of BPA have been reviewed elsewhere [17–19], so we discuss only recent advances here. High-affinity mAbs were generated by a hybridoma technique with four different haptens and the mAbs generated were used for various ELISA techniques. The methods developed were applied to detect BPA in canned food [80].

ELISA can be reliable for basic screening of BPA in simple matrices, but it has limited applicability in complex matrices.

3.3.2. Quartz-crystal-microbalance sensors

The quartz-crystal microbalance (QCMB) is a transducer, which works on the principle of the piezoelectric effect, whereby the electric charge of the crystal changes in response to applied stress. The QCMB precisely measures the changes in oscillation frequency due to changes in mass on the crystal surface [81].

A piezoelectric immunosensor for the detection of BPA was fabricated with polymeric NPs as signal enhancers. Park et al. [82] immobilized anti-BPA mAbs on the gold surface of a quartz crystal by covalent bonding between antibody and crystal surface. Since NPs add more mass to the mAb–polymeric NP conjugate, it results in enhanced signals and sensitive detection of BPA at the

0.01 ng/mL level. Labeling alters the structural and chemical properties of conjugates, which are complicated, and that increases the complexity of the process.

3.3.3. Nanoimmunosensor

Nanoimmunosensors exploit the unique properties of nanomaterials, such as large surface area, improved conductivity and magnetic properties to enhance the sensitivity of detection. Rahman et al. [83] designed a label-free impedance-based immunosensor using mouse PABs and polymeric NPs. Binding of BPA to the mouse PABs, which were covalently conjugated to the NPs gave the signal in the form of impedance. The method was found to be suitable for the detection of BPA in human serum.

A novel immunosensor for the detection of BPA has been based on the assembly of BPA-ovalbumin and superparamagnetic iron-oxide NPs with antibodies. NMR-relaxometry measurements showed that the presence of BPA in the sample reduced the transverse relaxation time compared to the sample without BPA. The method was used to determine BPA in tap water with an LOD of 0.4 ng/mL [84].

Mei et al. [85] developed lateral flow dipstick-based nanoimmunosensor by conjugating anti-BPA antibodies with AuNPs. In the lateral flow dipstick, the BPA–bovine serum albumin conjugate and anti-mouse antibodies were coated on the test line and control line, respectively. Based on the competitive immunoreaction between the BPA in solution and BPA-antigen led to variation in the color intensity. They achieved an LOD of 5 µg/L by visual observation, and the method was found suitable for rapid on-site detection of BPA. The dipstick is a simple form of sensor suitable for rapid, on-site monitoring.

3.4. Optical immunosensors

An optical immunosensor comprises a transducer, which converts the signals from antibody and antigen binding to light signals [20], and is classified into surface-plasmon resonance (SPR) and fluorescence biosensors (as below).

3.4.1. Surface-plasmon-resonance (SPR)-based sensors

SPR is an electromagnetic phenomenon resulting from the interaction of incident light with free electrons at a metal-dielectric interface. SPR sensors directly measure the changes in refractive index occurring at the surface of a metal film. Biorecognition elements are immobilized on the metal film supporting a surface plasmon. Adsorption of target species on the metal surface causes an increase in refractive index, which induces a shift in the wavelength of the refracted wave. Changes in the wave properties are measured using thin-film refractometers (Fig. 6). Advanced SPR sensor platforms have become a central tool for characterizing and quantifying biomolecular interactions due to their high specificity and rapidity [86]. Generally, bio-recognition elements, such as antibodies and receptors, are used to increase the specificity of sensors.

Soh et al. [87] reported an SPR sensor based on indirect competitive immunoassay by immobilizing 2-aminoethanethiol /BPA conjugate on a thin gold film. When a mixture of BPA and anti-BPA antibody was passed through the sensor, it resulted in binding of free antibodies to BPA on the thin film and led to the resonance-angle shift of the light wave.

Marchesini et al. [88] have generated both PAB and MAB against BPA and performed ELISA and biosensor immunoassays. In biosensor immunoassays, they used BIACORE 3000 equipment to obtain sensograms, which correlate with the BPA concentration in the sample. In non-competitive (direct) immunoassay format, they immobilized mAbs on the chip surface of the sensor, BPA in the sample bound to the MAB and the signal was recorded. In compet-

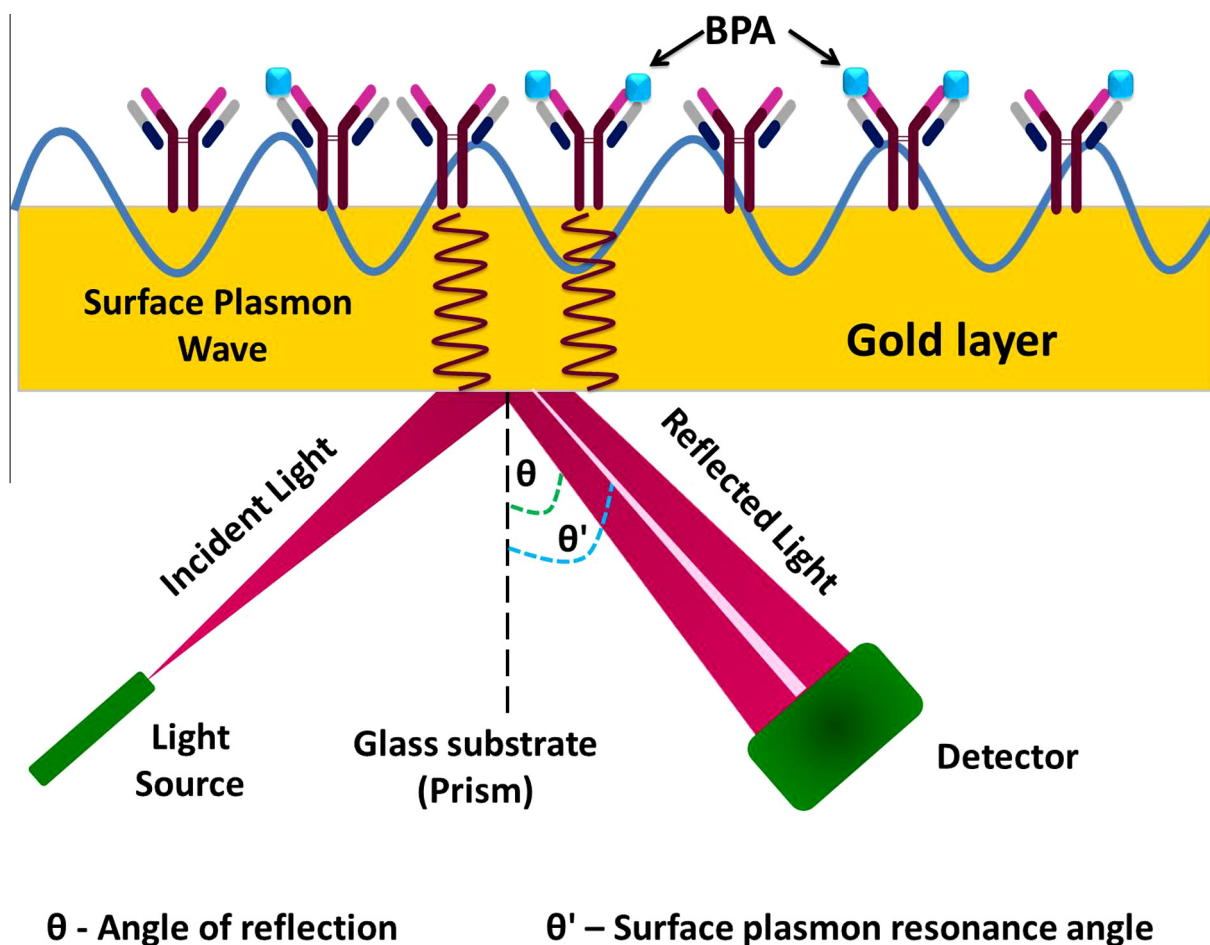


Fig. 6. Antibody-based surface-plasmon sensor for the detection of bisphenol-A.

itive inhibition (indirect) immunoassay format, they immobilized BHPVA on an activated chip surface, whereas they mixed the mAb with BPA in the sample, which then passed through the sensor. Free mAb present in the sample bound with the BHPVA on the chip surface and the signals were recorded and indirectly correlated with the BPA concentration in the sample.

Hegnerová et al. [89] indicated that the detection of BPA in wastewater (LOD 0.14 ng/mL) was done based on binding inhibition format in which known amount of antibody was mixed with the sample and then allowed to flow over the sensor surface. Free antibodies in solution will bind to the BSA-BPA conjugate immobilized on the surface and the obtained signals were proportional to the concentration to BPA. A similar principle to the binding-inhibition format was used to develop an SPR sensor with a self-assembled monolayer (organic thiol compounds)-functionalized chip surface with an LOD of 40 pg/mL [90].

Esterogen receptors selectively bind estrogens and are used as the biorecognition element for the development of analytical assays. Human recombinant estrogen receptor- α based SPR assay was developed and had a dissociation constant of 1.35 μ M towards BPA [91].

The dimerization property of the estrogen receptor was exploited for the detection of BPA by measuring changes in the refractive index during the binding of the analyte [92].

3.4.2. Fluorescence immunosensors

Rodriguez-Mozaz et al. [93] developed an optical immunosensor with a chemically-modified optical transducer chip, which worked on the principle of total internal reflection fluorescence.

Photodiodes detected the fluorescence of the labeled antibodies bound to analyte on the transducer surface, which correlated with the BPA concentration in the sample. The sensor had an LOD of 14 ng/L in water sample and had the advantage of being reusable.

3.5. Aptamer-based sensors

Aptamers are synthetic single-stranded oligonucleic-acid or peptide molecules with superior attributes, such as specificity and sensitivity compared to antibodies (Table 1). Aptamers are also called chemical antibodies due to *in-vitro* selection or synthesis through the combinatorial molecular technique known as SELEX (systemic evolution of ligands by exponential enrichment). Due to their exceptional chemical properties, they are quite helpful in the detection of a wide range of compounds [94]. Jo et al. [95] reported selection of an aptamer towards BPA through the SELEX procedure with a dissociation constant of 8.3 nM, which was much greater than that of antibodies used in detection.

A capacitive sensor was built by conjugating aptamers to SWCNTs coated on the electrode surface. Binding of BPA to the aptamer caused change in the capacitance, which was proportional to the amount of BPA bound to the aptamer. Based on real-time conductance measurement, an LOD of 1 pM concentration was obtained, which was further enhanced to the 10-fM level by tagging the aptamer with biotin and avidin [96].

Similarly, Kang et al. [97] also developed an aptamer-based capacitive sensor using anodized aluminum oxide, which resulted in a 3% change in capacitance per 100 pM of BPA in water samples.

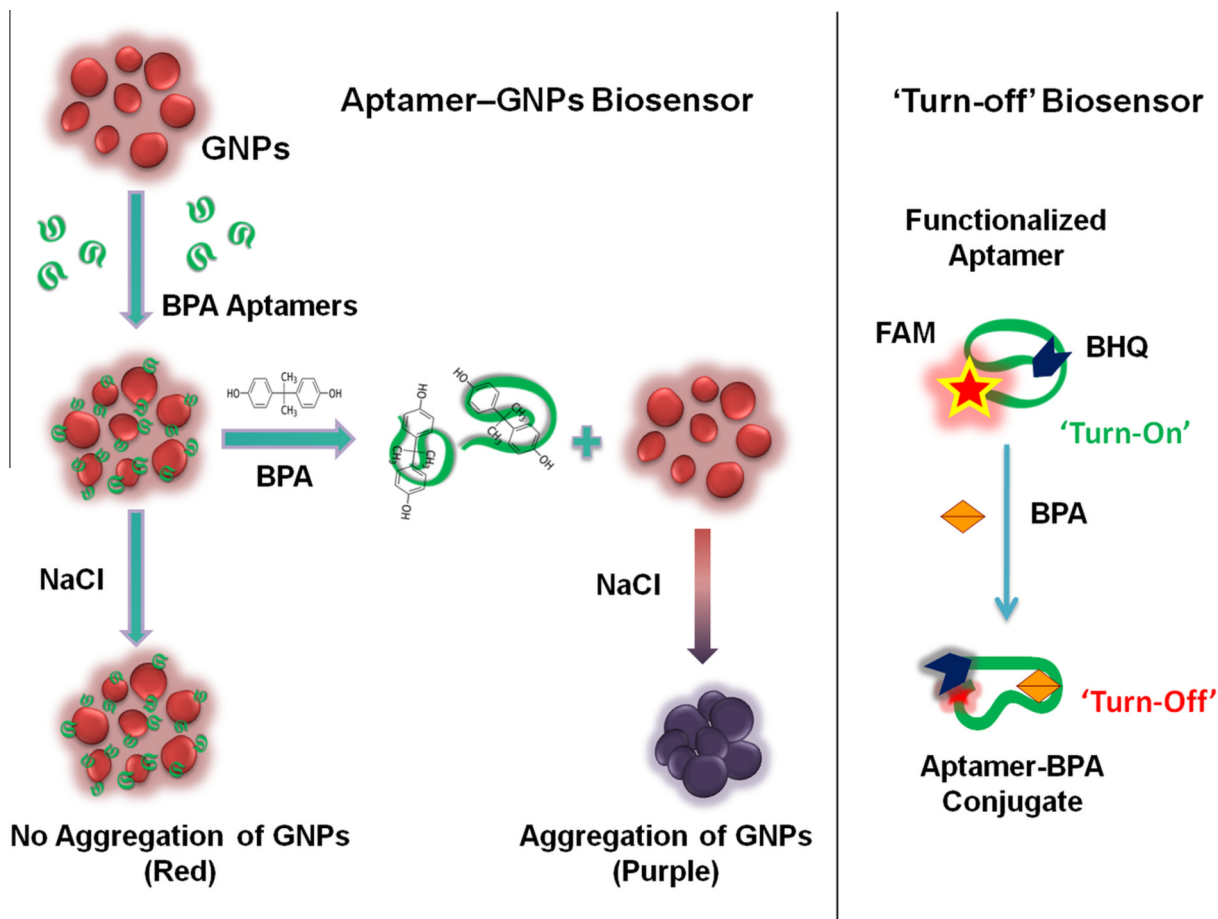


Fig. 7. Aptamer-gold nanoparticle-based colorimetric sensor and functionalized aptasensor for the detection of bisphenol-A [100].

An aptamer-AuNP-based colorimetric aptasensor for BPA was developed using salt-induced non-crosslinking aggregation of AuNPs, which resulted in a visible color change of the GNP solution from red to blue [98]. Xue et al. [99] developed an aptamer-based electrochemical sensor using methylene blue as an electrochemical redox label. In the absence of BPA, the complementary-DNA sequence binds with the aptamer; as a result, methylene blue will intercalate to the double-stranded DNA. In the presence of BPA, it preferably binds with aptamer and prevents the formation of double-stranded DNA, and prevents methylene blue from intercalating and enhances the signal.

Recently, Ragavan et al. [100] reported an aptamer-based “turn-off” fluorescent biosensor, in which the BPA aptamer was functionalized with fluorescent and quencher molecules at their ends. Change in conformation of the aptamer after binding with BPA led to change in the fluorescence emission, which was proportional to the amount of BPA (Fig. 7). Using the functionalized aptamer, an ultrasensitive LOD of 0.01 ng/L was achieved and it was found to be suitable for real sample analysis.

3.6. Enzyme-based and receptor-based biosensors

Biorecognition elements, such as enzymes and receptors, were used to improve the performance of the sensors. Enzymes being intrinsically selective towards the target compound, tyrosinase was used to fabricate an amperometric sensor involving a CNT-modified GCE for the detection of BPA. The authors observed an LOD of 20 nM of BPA with the biosensor developed and further improved the sensitivity by optimizing the assay parameters [101]. Human-estrogen receptor alpha belonging to the nuclear receptor

group has the affinity to bind BPA. A field-effect transistor was designed with a network of SWCNTs functionalized with estrogen-receptor alpha as the recognition element. They reported detection of BPA in picomolar concentrations within 2 min [102].

4. Perspective and conclusion

From the above discussion, it is evident that nanomaterials, such as graphene, CNTs and metal NPs, are promising materials for fabricating electrochemical sensors, chemiluminescence sensors and aptasensors by signal amplification, thereby improving the sensitivity of the assay. Nanotechnology is one of the likely areas to show encouraging prospects for developing sensors for detection of BPA by overcoming the shortcomings of currently-available analytical procedures. Similarly, biosensors have merit in terms of sensitivity and selectivity, due to their biorecognition elements.

Among biosensors, aptasensors are highly selective and increasingly replacing conventional immuno-based sensing systems. Stability is the major drawback of biorecognition elements, since they are sensitive to temperature, pH and degrading enzymes. Label-free sensing techniques are simple and selective for BPA detection, but sensitivity of the assay needs to be improved for it to become a principal technique.

Continuous monitoring of BPA in real samples will be advantageous compared to batch detection and efforts towards the development of continuous systems are encouraging. Most of the methods are employed for detection of BPA in simple matrices, such as water, but their performance in complex matrices has to be evaluated and improved for direct detection. In spite of the developments, sample preparation and pretreatment have major

roles in the extraction of BPA for exact quantitative detection. Since the preparative steps take a long time, advancements to reduce the time taken will considerably improve the speed of the assays.

Fundamental studies have to be carried with the aim of improving the features of sensing systems. Since the fabrication of sensors involve various streams of science, multidisciplinary effort will be helpful in designing ideal sensors. Even though the progress in developing sensors is convincing, improvements in real sample analysis and selectivity still need to be focused on designing and developing ideal sensing systems with better sensitivity and selectivity towards BPA. Further, validation of sensors and sensing systems is a decisive step to ensure accuracy and precision in quantification of BPA for widespread acceptance and use. Finally, novel sensors and sensing systems may help the regulatory agencies and other people to monitor and to screen real samples for the presence of BPA without much effort compared to conventional chromatography and mass spectrometry-based analytical methods.

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