Pranjal Chandra *Editor*

Biosensing and Micro-Nano Devices

Design Aspects and Implementation in Food Industries

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Preface

A healthy existence, an appropriate environment, high-quality food and cheap energy are inevitable components of human lives. The highest degree of health standards in the process 'from farm to fork' is essential in terms of food. As a result, in addition to other disciplines, food engineering and technology are also being altered by increasing automation levels. While the goal is simply to boost efficiency in food technology due to system theory and safety issues in other industries, a high level of automation is needed. Processes are complex, multifunctional control with feedback is frequently used, safety regulations permit a limited measurement tolerance and human error should be minimized as a risk factor. In recent decades, substantial technological developments have happened in the field of chemical sensors in general and biosensors in particular. It is driven by an increasing need for enhanced early detection sensors, which would allow remediation of biological, industrial, environmental and military applications within a shorter time frame. The success of biosensor technology is due so much to the fundamental research into new biorecognition mechanisms as to a number of constantly changing technology, such as sensor micro/nano-manufacturing and the production and immobilization of improved biorecognition components. A biorecognizing agent(s) and a physical transducer comprise two key components. The biological part of a biosensor is the single component of the 'instrument' which separates it from other sensors. The most commonly employed contacts in biodevelopment include enzyme–substrate, antibody–antigen, DNA–DNA and aptamer–target interactions. The transceivers rank in importance: electrical, optical, mass (piezoelectric), electrochemical/optical and calorimetric combinations (enzyme thermistor). This book provides a quick overview of the past, present and future of biosensors focusing on food technology. Although in future we will witness further progress with biosensors, I believe that this thorough and authoritative work will serve the intended users for many years to come. This book will be valuable for food and chemical engineers, food technologists and biochemists as well as graduates who work in biosensor-related

domains. It could also function as a reference book for colleges that provide graduate courses in food and biosensor technology. I am really glad to deliver this book to the audience with the cooperation of top experts.

Varanasi, Uttar Pradesh, India Pranjal Chandra

Contents

Editor and Contributors

About the Editor

Prof. Pranjal Chandra is an Assist/Professor at the School of Biochemical Engineering, Indian Institute of Technology (BHU), Varanasi, India. He earned his Ph.D. from Pusan National University, South Korea and did post-doctoral training at Technion-Israel Institute of Technology, Israel. His research focus is highly interdisciplinary, spanning a wide range in biotechnology, nanobiosensors, material engineering, and nanomedicine. He has designed several commercially viable biosensing prototypes that can be operated for onsite analysis for biomedical diagnostics. He is an associate editor/editorial board member of various international journals including Scientific Reports, Sensors International, Frontiers in Bioengineering and Biotechnology, Molecules, Frontiers in Sensors, Green Analytical Chemistry. He is an expert member/ reviewer of various national and international funding agencies. He has also been appointed as Advisor for the Biomedical Sensors Domain and Sensor Networks Systems at the Institution of Engineering and Technology (IET), Michael Faraday House, LONDON, United Kingdom. Prof. Chandra is author of over 120 high impact publications including research/reviews papers and invited book chapters. He has published 15 books on various aspects of biosensors/medical diagnostics/ material engineering. He has guided 5 Ph.D and currently he is supervisor of 8 Ph.D students. Prof. Chandra is the recipient of many prestigious awards, coveted honours, and fellowships such as: Fellow of Indian Chemical Society; Shakuntala Amirchand Award 2020 by Indian Council of Medical Research;

FSSAI: Eat Right Award-2022 (Government of India); DST Ramanujan fellowship (Government of India); Early Career Research Award (ECRA) (DST, Government of India); BK -21 and NRF fellowship, South Korea; Technion Post-Doctoral Fellowship, Israel; Nano Molecular Society India Young Scientist Award; Biotech Research Society India Young Scientist Award; Young Engineers Award 2018; Highly Cited Corresponding authors in The Royal Society of Chemistry (RSC), Cambridge, London; Top 10% cited article in the General Chemistry Section RSC Journal, Cambridge, London, Gandhian Young Technology Innovation Award (GYTI) 2020, etc. Dr. Chandra is also listed among the world's top 2% scientists in the year 2020 and 2021 by Stanford University, USA.

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1 Introduction to Nanobiosensing Technologies and Nanobioanalytical Systems

Behzad Rezaei and Marziyeh Poshteh Shirani

Abstract

Enormous improvements in the areas of material development, engineering, technology and such fields of application as medical, environmental, food, pharmaceutical, energy, and security have unavoidably led to nanobiosensing and nanobioanalytical systems. Nanobiosensoring and pure nanobioanalytical methods are different in that the former methods are self-contained integrated devices while the latter generally use biorecognition elements to determine the analyte. Nanobiosensors can be regarded as a special subclass of nanobioanalytical methods. An overview of the principles, main analytical players, and detection methods in the emerging areas of nanobiosensing and nanobioanalytical systems are provided in this chapter.

Keywords

Nanobiosensor · Nanobioanalytical system · Nanotechnology · Nanomaterial

1.1 Introduction

Nanobiosensing and nanobioanalytical systems are the certain results of important improvements in the development of nanotechnology and its areas of application such as pharmaceuticals, medicine, food, environment, and energy. Nanotechnology plays a significant part in the development and novelty, which improves the sensitivity and makes possible applications based on nanosensors and nanobiosensors (Momin et al. 2013).

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A chemical sensor, by definition, is an instrument, which converts chemical data, ranging from the concentration of a specific component in a sample to total composition analysis, into analytically useful signals (Hulanicki et al. 1991). Besides, a biosensor is an analytical instrument to incorporate a biologically active element such as enzyme, antibody, and DNA sequence with an appropriate physical transducer to provide a measurable signal, which is proportional to the concentration of a chemical compound in any sample (Rasooly and Herold 2008). Nanobiosensors, in particular, consist of nanomaterial-based transducers with physical nanoscale confinement, nanoparticles, or nanostructured surfaces (Malik et al. 2013). Nanobiosensing and nanobioanalysis detect and analyze target molecules by minuscule, frequently integrated, and multiplexed nanosensors to provide selective and extremely sensitive detection limits. The discovery, preparation, and application of materials for the fabrication of nanodevices the morphological features of which provide the desired sensitivity for detection in nanoscale have made this possible.

Biosensors cover conventional bioanalytical methods whereas nanobiosensors have fundamentally changed this area with potential alternatives via the minimization of standard laboratory practices as well as advantages such as fast response time, improved sensitivity, robustness, and portability (Srivastava et al. 2018).

1.2 Nanotechnology

Nanomaterials, which are a unique gift to mankind by nanotechnology, are compounds with dimensions in the 1–00 nm range. Given their superb mechanical, electrical and optical properties due to their nanoscale dimensions and the perfect combination of volume and surface properties with overall behavior, nanomaterials have been of great interest in the past few decades (Holzinger et al. 2014). Nanomaterials used for nanobiosensing and nanobioanalytical applications can be best categorized into two main groups: (1) carbon-based NPs including graphene, fullerene, carbon nanotubes, and carbon dots and (2) metal-based nanoparticles (NPs) including noble metals, nanorods, nanowires, oxide nanoparticles, and quantum dots (QDs).

1.2.1 Carbon Nanomaterial

Carbon-based nanomaterials have recently become attractive among researchers because of their exceptional electronic, optical, mechanical, chemical, and thermal properties. The essential features of zero-, one-, two-, and three-dimensional carbon nanomaterials have made them potentially applicable for the development of novel nanobiosensing and nanobioanalytical technologies. The use of carbon nanomaterials in biosensors has created new approaches and possibilities to detect and analyze target molecules. Biosensors based on carbon nanomaterials are reportedly biocompatible, sensitive, and selective and have lower detection limits for a broad range of chemicals to biological compounds (Kour et al. 2020). Table 1.1

Table 1.1 Comparison of various carbon nanomaterials properties

Carbon nanomaterials	Properties	Ref
Carbon nanotubes	Exceptional strength, resistance to fracture, flexibility, and good electrical properties	Sinha and Yeow (2005)
Graphene and derivatives	Large surface area, high thermal conductivity, high electrical conductivity, exceptional mechanical stiffness and adaptiveness to chemical modification	Kuila et al. (2011)
Fullerenes	Ferromagnetism, superconductivity, anti-HIV bioactivity, and optical limiting effects	Gibson (2010)
Nanodiamonds	Disperse uniformly and stably in water, high strength, high stability, excellent thermal conductivity, high refractive index, and enhanced resistivity	Zhang et al. (2018)
Carbon-quantum dots (CDs)	Excellent water solubility, low toxicity, good luminescence signals, chemical inertness, good electronic properties, and high resistance to photobleaching	Shirani et al. (2021)

shows the mechanical, thermal, electrical, optical, and chemical properties of different types of carbon nanomaterials. These compounds have a wide range of one photon properties (single photon adsorption), good biocompatibility, and are easily functionalized. In addition, carbon-based nanomaterials possess an intrinsic two photon fluorescence property in the long wavelength region (near-infrared II), which allows their application in deep tissue optical imaging. Moreover, they are extremely suitable for biosensing applications due to their high conductivity, chemical stability, and fast electron transfer rate (Shirani et al. 2018).

1.2.2 Metal Nanoparticle

Metal nanoparticles are a group of functional compounds with unique chemical and physical properties, which strongly depend on their shape, structure, composition, and size. Great improvements have been made in the preparation of metal nanoparticles and their applications in many areas such as electronics, sensors, catalysis, and medicine. Metal nanoparticles have played a significant part in the development of novel biosensors and/or improvement of current biosensing methods in order to meet the requirements for the detection of more specific and highly sensitive biomolecules. The outstanding physicochemical characteristics of such metals at the nanoscale have resulted in the development of a broad range of biosensors such as (1) nanobiosensors for point of care disease diagnosis, (2) nanoprobes for in vivo sensing/imaging, cell tracking, and monitoring disease pathogenesis or therapy monitoring, and (3) other tools based on nanotechnology, which is advantageous in basic biology research (Zhao et al. 2011; Baptista et al. 2011; Doria et al. 2012). Such noble metals as gold and silver provide extraordinary and strong optical properties in the field of biosensing (Špringer et al. 2017). They are extensively applied in many biosensing platforms as signaling or signal enhancing elements. The exceptional optical properties of noble metals are due to their

capability of maintaining surface-bound collective oscillation of electrons, which is referred to as surface plasmon, on their dielectric-metal interfaces at visible to near-infrared range of the spectrum. Through certain sizes, the surface-bound plasmon can be locally confined and resonantly excited at particular wavelengths of the incoming electromagnetic radiation. Localized surface plasmon resonance (LSPR) is extremely sensitive to the variations of refractive index in the dielectric medium and the changes in resonance wavelength are strongly limited in the vicinity of the nanoparticle surface. Depending on the corresponding application, LSPR response can be simply adjusted using different geometries of nanoparticle substrates or directly in the solution (Abkenar et al. 2017; Webb and Bardhan 2014). Plasmonic nanobiosensing is based on merging the unique optical properties of plasmonic nanomaterials with the target-specific nature of affinity probes (Jeong et al. 2016). Lim and Gao and Daraee et al. have recently reviewed the general working mechanisms of the plasmonic nanoparticles including Surface Plasmon Resonance (SPR), Localized Surface Plasmon Resonance (LSPR), Surface Enhanced Raman Scattering (SERS) and the recent applications of plasmonic nanoparticles in biosensing, cancer diagnosis, drug delivery, photodynamic, and photothermal therapy (Lim and Gao 2016; Daraee et al. 2016). Quantum dots are semiconducting nanocrystals, which have outstanding optical characteristics for nanobiosensing. When semiconducting quantum dots absorb light, they quickly re-emit it in a different color with a longer wavelength, which is fluorescent. The changes in the shape and size of nanocrystals can control the light wavelength (Ensafi et al. 2017; Li et al. 2018).

1.3 The Basic Concept of Biosensor

Understanding the concept of biosensing forms the basis for the study and development of nanobiosensors. Biosensors can be defined as sensing tools or measurement systems specifically designed to estimate a material using biological interactions and converting the data into a readable form via transduction and electromechanical interpretation. Each biosensor consists of three basic components: (1) bioreceptor, (2) transducer, (3) detector (Fig. 1.1). Bioreceptor is the exterior part of a biosensor, which is in direct contact with the target analyte during the operation. The major task of a bioreceptor is capturing the target analytes with high specificity and selectivity (Koyun et al. 2012). Some of the commonly used bioreceptors to prepare biosensors are enzymes (Zhao et al. 2017), aptamers (Kim et al. 2016), whole cells (Han et al. 2018), antibodies (Kim et al. 2008), and DNA (Li et al. 2010). The preparation is usually carried by the method of absorption/immobilization of the biorecognition element on the biosensor surface. Thus, the methods applied to attach the biorecognition element to the biosensor must preserve the sensitivity and selectivity. Adsorption, microencapsulation, entrapment, covalent bonding, and cross-linking are the most conventional methods to immobilize biorecognition elements (Sassolas et al. 2012; Luong et al. 2008; Datta et al. 2013). The objectives of immobilization are: (1) continuously monitoring the analytes in such flowing

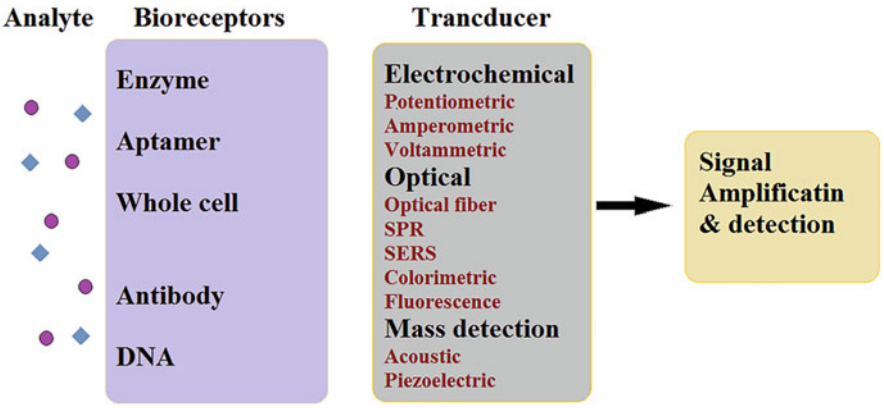

Fig. 1.1 General schematic of biosensors

samples as environmental samples, biological fluids containing low quantities of target molecules or bioreactor fluids, (2) repeatedly using the biosensor, (3) improving the performance of biosensors with respect to reproducibility and sensitivity by the development of the biorecognition unit, and (4) simplicity and flexibility of the immobilization method. The second component of a biosensor is the transducer system, which mainly converts the interaction of bioanalyte and its corresponding bioreceptor into an electrical form. As the name implies, ("trans" and "ducer" mean change and energy, respectively) transducer essentially converts one form of energy into another. The first form of energy is biochemical in nature since it is formed by the specific interaction between the bioanalyte and bioreceptor, but the second form is usually electrical. The third component of a biosensor is the detector, which receives the electrical signal from the transducer and appropriately amplifies it such that the corresponding response can be read and properly studied.

1.4 Biosensor Classification

Biosensors are generally categorized into two groups: direct recognition sensors, which directly measure the biological interaction, and indirect detection sensors, which are dependent on secondary elements (often catalytic) such as enzymes or fluorescent tags for measurements (Prasad 2014). The two types of biosensors are shown in Fig. 1.2. In each group, there are different kinds of optical, electrochemical, or mechanical transducers. The most usually used ligands are antibodies, but the development of other ligands including aptamers (protein binding nucleic acids) and peptides is also in progress. There are various kinds of direct and indirect recognition biosensors and selection of the right detector is complicated and depends on many parameters including the nature of the application, labeled molecule type (if used), required sensitivity, number of channels (or area) measured, cost, technical expertise, and detection rate.

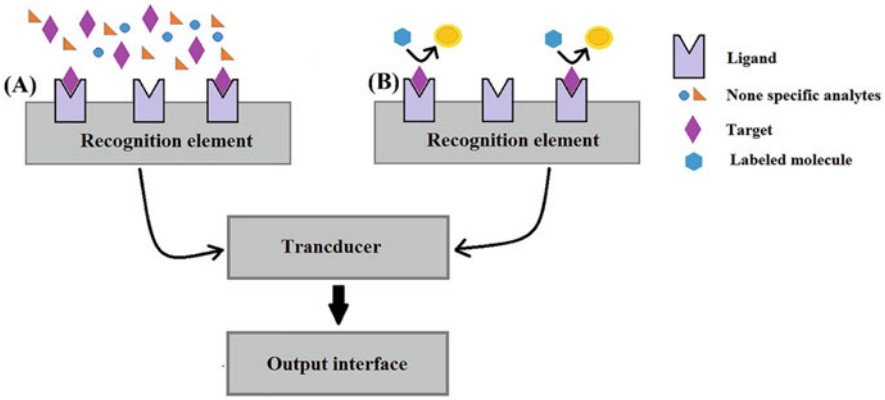

Fig. 1.2 General schematic of biosensors: (**a**) direct and (**b**) indirect detection biosensors

1.4.1 Direct Label-Free Detection Biosensors

Non-catalytic ligands such as cell receptors or antibodies are usually used in direct recognition sensors, which directly measure the biological interaction in real time. Such detectors commonly measure physical changes such as changes in optical, mechanical, or electrical properties induced by the biological interaction directly and do not need any additional labeled molecules for detection. Optical biosensors including those using evanescent waves generated by a beam of light incident on a surface at an angle yielding total reflection are the most common direct detection biosensors (Peltomaa et al. 2018). Conventional evanescent wave biosensors are surface plasmon resonance (SPR) or resonant mirror sensors. Interferometric sensors or grating couplers are other direct optical detectors. Non-optical direct detection sensors are quartz resonator transducers, which measure the variations of the resonant frequency of an oscillating piezoelectric crystal as a function of mass (e.g., analyte binding) on the crystal surface, microcantilevers used in microelectromechanical systems (MEMS), which measure bending induced by the biomolecular interactions, or field-effect transistor (FET) biosensors, which are transistors gated by biological molecules (Noi et al. 2019; Xu et al. 2018). Upon binding biological molecules to the FET gate, they can change the gate charge distribution leading to a change in the FET conductance.

1.4.2 Label-Based Detection Biosensors

Indirect detection sensors depend on the secondary elements to detect and utilize labeling or catalytic elements such as enzymes. Alkaline phosphatase enzyme and fluorescently tagged antibodies, which improve the detection of sandwich complexes, are examples of such secondary elements. Contrary to direct sensors, in which the changes induced through biological interaction is directly measured and

are "label-free," indirect sensors need a labeled molecule bound to the target. Most optical indirect sensors have been designed for the measurement of fluorescence. Nevertheless, densitometric and colorimetric changes and chemiluminescence can also be measured by such sensors, based on the type of label used (Saberi et al. 2019). Electrochemical transducers measure the oxidation or reduction of an electroactive compound on the secondary ligand and are common indirect detection sensors (Nasr-Esfahani et al. 2019). Many kinds of electrochemical biosensors including amperometric devices have been developed. These devices detect ions in a solution based on electric current or variations in electric current upon the oxidation or reduction of an analyte. Another common indirect detection biosensor uses optical fluorescence to detect the fluorescence of the secondary ligand by CCD, PMT, photodiode, and spectrofluorometric analyses. Furthermore, visual measurements such as color change or appearance of bands (e.g., lateral flow detection) can be applied for indirect detection.

1.5 Characteristics of a Biosensor

Biosensor performance and efficiency are assessed concerning well-defined technical and functional characteristics according to the IUPAC guidelines. Although the transducer type and sample characterization are used as factors, which determine the efficiency and applicability of a sensor in different fields, the performance of the sensor is dependent on such different parameters as linear dynamic range, linearity, sensitivity, detection limit, selectivity, reproducibility, and stability.

1.5.1 Linear Dynamic Range

The determination of the analyte concentration in a system depends on the knowledge of the maximum and minimum values measured by the biosensor in a test sample. Therefore, a calibration curve is plotted based on the results obtained. The analyte concentrations in test samples may be found by interpolation using this curve.

1.5.2 Linearity

The linearity of a sensor is determined based on the closeness of the calibration curve to a given straight line. In other words, the linearity system is measured by the degree of the resemblance of its calibration curve with a straight line.

1.5.3 Sensitivity

In analytical methods, sensitivity is defined as the slope of the calibration curve while sensitivity is the slope divided by the standard deviation. This means sensitivity is the slightest difference in quantity measured by an instrument. More accurate sensitivity results are often calculated using the linear portion of the calibration curve.

1.5.4 Detection Limit

The difference between the presence and absence of a substance (blank value) expressed at the confidence level is known as the limit of detection. In other words, detection limit is the lowest concentration of an analyte, accurately detected by a sensor with a low enough signal-to-noise (S/N) ratio. This parameter is usually calculated as three times the standard deviation of the baseline signal divided by sensitivity. Although a low signal-to-noise ratio limits the lower detection limit, it might increase sensitivity.

1.5.5 Selectivity

Selectivity is the capability of a biosensor to detect a specific target analyte from a sample collected containing a mixture of undesirable contaminants. The best classical example to illustrate selectivity is the interaction between a highly specific antigen and an immobilized antibody.

1.5.6 Reproducibility

Reproducibility, however, is the capability of a biosensor to yield the same final results irrespective of the number of times the experiment is repeated. The precision and accuracy of the transducer or electronic components in a biosensor mainly determine this. The reliability of biosensor output strongly depends on the reproducibility of the biosensor devices.

1.5.7 Stability

The ability of biosensors to give highly reproducible results depends on precision and accuracy. However, stability is another factor, which may undermine the performance of biosensors. In summary, stability corresponds to the ability of biosensors to get around ambient disturbances, which can change the desired output response during the measurement. This is more crucial in the fabrication of biosensors, which may need longer time or continuous monitoring to yield a final

result. The stability of biosensors may be affected by many parameters such as temperature, the affinity of the bioreceptor, and the fouling of membranes.

1.6 Bioanalyses System

Bioanalysis system is extensively applied in the sample preparation and detection. Sample preparation by a bioanalysis system includes (1) pre-treatment and/or modification of the recognition elements, (2) modification and/or treatment of the substrate surface prior to the introduction of the biological recognition element, and (3) the target analyte. For the detection, the type of instrumentation used and the pre-treatment or construction of each associated analytical component are covered by the bioanalysis system.

1.6.1 Nanomaterials in Sample Pre-treatment

The application of nanomaterials in the sample preparation has attracted the bioanalytical researchers' attention in the recent years. Various nanomaterials have been applied in extraction techniques such as solid-phase extraction, microextraction, and filtration. In section 1.2, nanomaterials were widely classified as metal-based NPs (including quantum dots (QDs); nanowires, nanorods, oxide nanoparticles, and noble metals), and carbon-based NPs (including carbon nanotubes, graphene, fullerene, and carbon dots).

Solid-phase extraction (SPE) is an alternative sample preparation technique to liquid–liquid extraction, which can decrease the volume of solvents required. SPE has been applied to pre-concentrate or remove target analytes from different matrices for many years. In this method, the sorbent is packed inside cartridges, syringe barrels, microcolumns, or disks. Common SPE sorbents are silica-based compounds such as C18 bonded silica. Different kinds of nanoparticles and nanocomposites including GO (Pourjavid et al. 2014), CNTs (Sun et al. 2015), G and RGO (Luo et al. 2013), MIPs (Moein et al. 2014), IIPs (Cui et al. 2013), LDHs (Abdolmohammad-Zadeh et al. 2014), TiO_2 (Baghban et al. 2013), and Al_2O_3 (Afkhami et al. 2011) are used as nanosorbents in SPE.

A new microextraction technique, referred to as microextraction by packed sorbent (MEPS), was introduced by the miniaturization of SPE cartridges (Abdel-Rehim 2004). In MEPS, microsyringes replace the SPE cartridges. Therefore, the amount of sorbent required is decreased to a few milligrams. The sorbent can be packed between the needle and the barrel of the syringe as a plug or a cartridge inside the needle. This method is particularly useful for online fully automated measurements. Also, the sample volume required is remarkably reduced to a few microliters. This method has an as high potential for online applications as other absorbents such as conventional SPE sorbents, and even more sophisticated sorbents can be packed and used for bioanalytical purposes.

1.6.2 Nanomaterials in Surface Modification

Considering their unique optical, and electrical properties, the surface modification of QDs for application in bioimaging and biomedicine will be discussed in this section. In general, the methods for the modification of QD surfaces are classified into two kinds; namely, covalent and non-covalent binding. In the non-covalent method, which involves electrostatic interactions, the QD surface carries a charge complementary to that of the biomolecule (Clapp et al. 2006). Electrostatic interactions have been successfully used to prepare CdSe/ZnS negatively charged QDs bioconjugated with organophosphorus hydrolase (OPH) with positively charged protein side chain and NH_2 ending groups (Ji et al. 2005). The non-covalent conjugation is also the interaction between the metal ions (Cd, Zn) present on the surface of QD and the active molecules. Proteins or polypeptides have amino acid sequences with an affinity to metallic cations. The adsorption of biomolecules is due to the formation of ionic bonds between the carboxylate group (COO−) of the ligand and Cd or Zn. Hydrogen bonding between the ligands and QD surface has also been reported (Shang et al. 2007). The immobilization of the biomolecules by the covalent bond often takes place by the condensation of the amine groups of the biomolecule and the carboxylic groups (from stabilizing agent) on the QD surface. The coupling is often carried out in the presence of N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC) chlorohydrate and N-hydroxysuccinimide (NHS). The coupling of the biomolecule is facilitated by the activated ester formed with NHS via the nucleophilic attack by the amine function at the electrophilic center of the carbonyl groups. This conjugation forms an amide linkage (Xing et al. 2007).

1.6.3 Nanomaterials in Target Analyte

QDs, which are metal-based NPs, have been used in the trace analysis of inorganic compounds, liquid- and solid-phase systems, and multiplexing analysis due to their extraordinary optical, and electrical properties. Several methods have been developed for the identification of Ag(I) based on the variations in the fluorescent property. Different fluorescence responses are observed depending on the Ag (I) concentration (Xia et al. 2008). Low Ag(I) concentrations reportedly enhance QD fluorescence and vice versa. Based on the results, particle size plays a significant part since most of the trapping defects in small particles form on the surface the passivation of which may enhance fluorescence. The most common methods to detect Pb(II) in QD-based systems are based on fluorescence quenching. For example, Wang et al. developed a novel CdTe-QD/AuNP assembly for the detection of Pb (II) based on the inhibition of the interaction between AuNPs and CdTe QDs (Wang and Guo 2009). One of the main disadvantages of this method is the rather poor selectivity. Therefore, the receptor–ligand composition must be enhanced. In addition, Wu et al. developed a novel system for Fe(II) and Fe(III) speciation and observed that both species quenched the fluorescence of GSH-CdTe QDs with

different quenching kinetics (Wu et al. 2009). However, to selectively determine Fe (II) in the presence of Fe(III), H_2O_2 was introduced to obtain a QD-Fenton hybrid system.

In general, there are two functional parts in a QD-based sensing material; namely, a recognition part for selective binding to the target metal ion (surface component) and an element for docking the recognition ligands (QD core), which is accountable for signaling the interaction. Selective and measurable interactions between the probe and the target ion are the essential requirements for an ion-specific probe. Selectivity for a QD-based probe can be achieved by several methods. The most common method is the application of small molecules with a strong binding affinity and selectivity to target ions as chelating ligands. For example, a high affinity is shown by N-acetyl-L-cysteine (NAC) for Hg^{2+} (Duan et al. 2011) while thioglycolic acid (TGA) and glutathione (GSH) have a higher affinity for Pb^{2+} (Mohamed Ali et al. 2007). Another method for ion selection involves supramolecular ligands such as crown ethers, calixarenes, and cryptands, the structures of which can be easily tuned to moderate their affinity towards different metal ions. For instance, 1,10-diaza-18-crown-6 ether derivative is selective towards Cd^{2+} (Banerjee et al. 2008). The applicability to multiplexing analysis is one of the most significant features of QDs in comparison with organic dyes. For example, Freeman et al. used CdSe/ZnS QDs functionalized with nucleic acids to develop a multiplexing system for detecting Hg(II) and Ag(I) (Freeman et al. 2009). T-rich and C-rich modified QDs were used for multiplex analysis using the affinity of Hg(II) and Ag(I) for thymine (T) and cytosine (C), respectively. Different QD sizes were chosen to separately determine each analyte. For example, QDs with a diameter and emission wavelength of 3.8 nm and 560 nm, respectively, were used for Hg(II) while QDs with a diameter and emission wavelength of 5.8 nm and 620 nm, respectively, were applied for Ag (I) detection. Luminescence was reduced by both ions due to an electron transfer process. Furthermore, Wu et al. used silanized QDs functionalized with DNAzymes (i.e., a novel type of enzyme with high specificity and sensitivity for metal ions) to develop a multiplexing system for Cu(II) and Pb(II) detection (Wu et al. 2010). QDs of 9.6 and 12.7 nm were used for this purpose, luminescence enhancement being monitored at 530 and 625 nm for Pb(II) and Cu(II), respectively, using a single excitation source set at 480 nm.

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Application of Nanotechnology in Food Analysis

2

Kenny Kai Ken Ting and Sook Mei Khor

Abstract

The research of nanotechnology practicality in food analytics is to innovate a cost-efficient and friendly platform while revolutionizing food safety and quality monitoring for the food conglomerates and the end-users. This chapter provides a methodical outline on the current quinquennial trends at the benchwork for nano-based analytics to benefit the food business, while summarizes the following: (1) the development of nanomaterials (organic, inorganic, composite) for determination of naturally occurred biological components and externally caused toxic compounds in food products, (2) the advantages of these nano-sensing technologies to rival the current commercial food analysis methods, and (3) the limitations and challenges faced by these methods to realize their real-life industrial applications. Future insights about the possible integration of information revolution (machine learning and big data) with nano-based food analysis will be briefly discussed as well.

Keywords

Nanotechnology · Food analysis · Nano-sensing · Food safety · Analytical chemistry · Nanomaterials

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2.1 Introduction

The advent of nanotechnology has introduced the capability to manipulate matter at a supramolecular or atomic level, resulting in numerous novel discoveries and applications of nanoscale materials. Thus, nanotechnology has contributed a gradual innovative leap in major global industries. The food and beverage industry, while being a multi-trillion dollar sector, fulfills the absolute necessity of the masses. Along with the arrival of the Industrial Revolution 4.0, the hastened pace towards an autonomous and efficient process is imminent. This attracts and prompts the food conglomerates to invest in nanotechnological research to utilize the great versatilities of nanoscience in improving the preparation, packaging, taste, safety, and quality control of their products (Jideani et al. 2020). As a result, in the recent years, there are already incredible amounts of nanotech products that are promoted and have been applied in the food supply chain. Most of the measures are designed for external use. These include but are not limited to, smart or active packaging that emits preservatives after the expiry date, nano-clays, plastic films, or containers with antimicrobial nanoparticles for barrier protection from microbes and oxidants, as well as biodegradable and eco-friendly nanomaterials. Some are designed for internal use, where the food products are infused with nanoparticles for purposes such as encapsulation of functional materials in supplements, titanium oxide, and iron oxide as food colorings, flavor carriers, and even unprecedented functional foods packed with nanoscale nutrients (Valdés et al. 2009) (Fig. 2.1).

For the general public, it is attractive for the rising trend of getting a fast, fresh, and reliable food supply chain. Food quality and safety have become the most crucial factor for consumers as the public demands for their products be free from

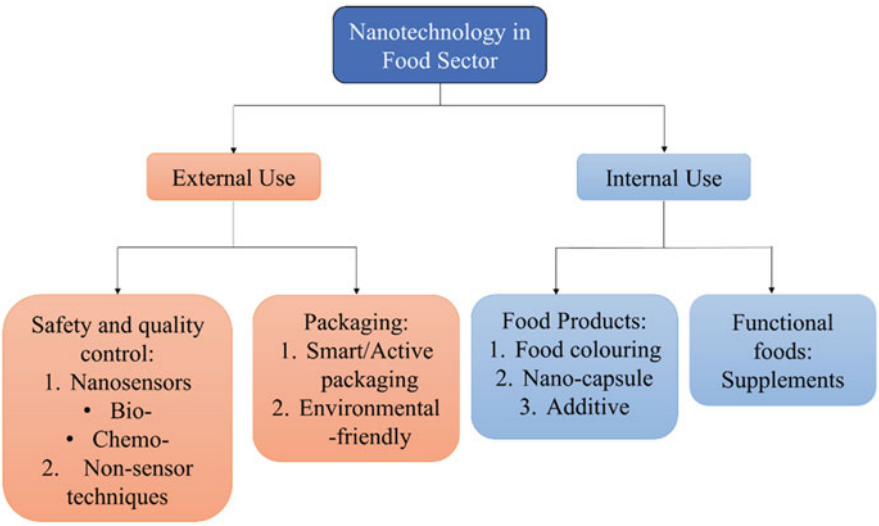

Fig. 2.1 Application of nanotechnology in the food and beverage industry

contaminants. Contaminants are foreign unwanted substances that may be present in the final products during the processing treatments. This covers chemical, biological, pathogenic, or even physical impurities. In this context, analytical techniques are extremely useful in the food business by ensuring the quality and safety of consumer products in the processing, packaging, and distribution, mainly by the detection of contaminants. Conventional methods in the current food production scenes are high-performance liquid chromatography and gas chromatography, both typically coupled with mass spectroscopy (HPLC-MS, GC-MS), infrared spectroscopy (IR), Raman spectroscopy (RS), nuclear mass spectroscopy (NMR), and capillary electrophoresis (EC). Besides the molecular interpretation routes, the food sector is also offered some biological-based approaches, such as enzyme-linked immunosorbent assays (ELISA) and polymerase chain reaction (PCR) (Nielsen 2017). However, those methods have limited use, due to the high cost of time and money, specialized eligibilities for operating personnel and environment, and the inability to conduct large-scale measurements of the complex food matrices. Typically, it should also be mentioned that most of the methods are used in complementary to each other in a hybrid system for accurate postmortem analysis. Thus, it lacks real-time evaluations.

For the past 10 years, the major division of analytical chemistry that is on the rise for its huge advantages in applied nanotechnology is the sensing aspect. Arrays such as ELISA and surface-enhanced Raman spectroscopy (SERS) have been advancing into the nanoscale territory with the potential birth of nano-ELISA and more novel SERS nanoprobes, in the hopes for early-stage detections of the contaminants in the resolution of the food safety and quality issues. Other nanomaterials-based methods such as nano-dipsticks and nanosensors are breakthroughs by integration and miniaturization from the complementary techniques. These have inspired an upsurge in the research and design of portable smartphone-based sensing arrays for laboratory and on-site deployments. Therefore, all prior mentions of nanotechnology are hugely beneficial for the food industry, which can fill the void as a promising approach to the unresolved food analysis problems. However, for developing countries that highly rely on food supplies, there exists a great transition barrier. The economic situations influence the local and non-domestic resources for research and development still in their infancy (Chaudhry and Castle 2011). Furthermore, due to the drastic change in physiochemical properties of nanomaterials from its macro-counterpart, the safety aspects are also a key challenge for its implementation. The potential toxicity of exposure to the human cell and the environment from poorly designed and unregulated nanotechnology is concerning for authorities to do a thorough risk assessment.

In this chapter, a general overview of the recent breakthroughs in the application of analytical nanotechnology in the food safety aspect for the past 5 years is described, with a focus on nano-sensing arrays while comparing to other analytical non-sensor nanomaterial-based methods. Case studies will be looked into on the types of analytes that have been successfully identified to date, along with examples of organic, inorganic, and hybrid composite nanosensors.

2.2 Current Trends of Nanomaterial-Based Sensors Developed for Nano-sensing of Analytes in Food Analysis

Nanomaterials are within dimensions from 1 to 100 nm (Ratner et al. 2003). The tested nanomaterial systems include the organic-based (mostly biosensors and some cases of organic product and biosynthesized nanoparticles) (Mustafa and Andreescu 2020), inorganic (metal, compounded metal, and oxides) (Choi and Lee 2020), and the hybrid composite of both organic and inorganic (metal-organic framework (MOF), clay, hybrid network) (Majeed et al. 2013). As for the working principles, a typical sensing array is based on either molecular pattern recognition with attuned selectivity (chemical or biological) (Mustafa and Andreescu 2020) or electrochemical transduction, which main targets are volatile species (Mustafa and Andreescu 2020). For the context of biosensors, it is mainly making use of biological receptors such as aptamers, proteins, DNA, antibodies, enzymes, etc. to provide an optimal amount of recognition and specification for the nanoparticle platforms. Then, the target analytes are detected by the underlying mechanisms aforementioned, i.e., via physical, electrochemical, chemical, or optical methods. Most up-to-date and ongoing innovations of sensors are in optical forms based on color change and surface plasmon resonance (SPR). In the context of nanomaterial-based optical biosensors, a more detailed overview of the history of their development, with an emphasis on the integration of refractomeric schemes into the sensors can be found in this critical topic here (Kobun 2021).

Nanotech analytical methods have been reported to identify and detect allergens, contaminants, foodborne pathogen, adulterants, nutrients, and other foreign substances that are deemed harmful for human consumptions. Common nanomaterials that are utilized in the system are gold nanoparticles (AuNPs) for their exceptional SPR properties and silver nanoparticles (AgNPs) for an additional antimicrobial quality. All the years of improvements in the field have strengthened the fine-tuning process of the nanoparticle properties, resulting in various shapes (e.g., hollow rod, stars, dendrites) and sizes of Au/AgNPs for a more efficient binding interaction towards target molecules. Metal oxides are also reported to be useful for analytics (e.g., Fe_2O_3 for its ferromagnetic and electromagnetic induction properties), however, they are more typically found in the current food industry as permitted additives (e.g., TiO_2 for food coloring) (He et al. 2019). Recent updates on carbon-based graphene and nanotubes have also brought forth an amplification in the electrical signal due to its great electrical and heat conductivity. The following sections will discuss the application of organic, inorganic, and composite nanomaterials into electrochemical and optical nanosensors for food monitoring and safety assurance as well as giving case studies for perusal.

2.2.1 Allergens

Food allergies are immunological reactions caused by ingestion or external contact of food allergens, which are biological compounds (mostly proteins) that can

involuntarily trigger immune responses and manifest symptoms with various threatening degrees (Flanagan 2014; Taylor 2006). Two major factors can contribute to the existence of food allergens in the final production stage: (1) the naturally occurring proteins in one of the raw ingredients, e.g., ovalbumin in eggs, glycinin in soybean and occasionally milk products, etc. (Koppelman and Hefle 2006; Wang et al. 2014); (2) trace amounts of allergens to come into contact with other food products in the same factory production line (Rai and Bai 2017). A lot of major regulatory bodies such as the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), as well as most regulatory authorities all over the world have classified food allergens into grades of increasing severity of symptomatic reactions. All food products are also strictly required to label any allergens for food safety purposes (Mainente et al. 2017). Even so, the current conventional method to test out allergens relies on the binding of IgE with the analytes, which has several drawbacks as follows (Yun et al. 2018):

1. The lack of binding interaction of some allergens with IgE.
2. The use of radioactive reagents (e.g., ^{3}H, ^{125}I) in cases of radioimmunometric assays.
3. The high costs of operation in cases of ELISA (~$60 per analysis).

While the majority of the reported studies (Table 2.1) are still in the early stages of development, there are a few examples of companies developing commercial smartphone-based assays for on-site testing, as reported in a review by Nelis et al. (2020) (Nelis et al. 2020).

Gluten allergies are triggered by gliadin, causing incurable Celiac disease, while the only way to prevent said reactions is through total avoidance (Chekin et al. 2016). A combination of fullerene nanoparticles and protease enzymes are used in a reported modified biosensor for a simplistic and rapid detection of gluten allergens in cereal grains (Ontiveros et al. 2017). The biosensor is coupled with electrochemical chronoamperometry. While the modification of fullerene nanoparticles in the sensor increases both selectivity and sensitivity, the protease enzymes are immobilized on carbon electrodes. Under optimal conditions of 0.6 U of protease enzymes, pH of 7.0, and potential of −0.7 V, the improved biosensor can detect gluten ranging from 1.7 to 8.3 mg/L, achieving a lower limit of detection (LoD) of up to 0.54 mg/L. Funari et al. (2017) also reported a quartz crystal microbalance-based immunosensor modified with a photonic immobilization array for effective spatial orientation of anti-gliadin antibodies. A low-cost strong signal is transmitted for a reliable, quantitative, and lower false positive reading confirmed by an ELISA control kit (Funari et al. 2017). The linear detection limit reaches the range between 7.5 and 15.0 pM, with a lower LoD of 4 pM and a faster detection time.

Peanuts have been of major interest for the detection of their allergens (e.g., arachin h 1, arachin h 2, and arachin h 6) for the protection of allergic consumers. In recent years, the detection of arachin h 1 becomes more refined with more nanosensors being reported. Peeters et al. (2014) investigated and designed aptamer-based sensors modified with gold nanoparticles, to successfully utilize

Table 2.1 Overview of reported allergen nano-sensing approaches

Allergen	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
Gluten	Electrochemical	Fullerene combined with protease enzyme	1.7–8.3 mg/L	0.54 mg/ L	n.a.	Cheaper and faster alternative for matrix complex detection	Difficulties to dissolve gluten in aqueous media	Ontiveros et al. (2017)
	Electrochemical	AuNPs on quartz crystal	7.5–15.0 pM	4 pM	15 s	Portable, user-friendly, cost-effective compared QCM	Challenge to reduce 3 hours of standard sample extraction process	Funari et al. (2017)
	Magnetic	Streptavidin magnetic NPs	1.5–4000 ng/ mL	1.5 ng/ mL	15–30 min	Highly sensitive multiplex analyte detection with little cross-reactivity, reducing cost	Requirement for trained staff to operate GMR data software with complex parameters	Ng et al. (2016)
Arachin h 1	Electrochemical	AuNPs	1–250 nM	1 nM	15 min	Real-time detection with lower cost and wide detection range (1–250 nM) for trace allergens	Quartz crystal microbalance measurements may still require trained personnel to operate	Peeters et al. (2014)
	Electrochemical	Au-graphene NPs	10^{-16}–10^{-13} M	0.041 fM	30 min	Higher selectivity for target DNA sequence than a mismatch sequence	Challenge to reduce cost for DNA probe synthesis	Sun et al. (2015)
	Optical	Aptamer-conjugated QDs	200–2000 ng/ mL	56 ng/ mL	10 min	Cost-effective with microfluidics, no probe immobilization	Real sample extraction process to be improved	
	Magnetic	Streptavidin magnetic NPs	7.0–2000 ng/ mL	7.0 ng/ mL	15–30 min	Highly sensitive multiplex analyte detection with little cross-reactivity, reducing cost	Requirement for trained staff to operate GMR data software with complex parameters	Ng et al. (2016)

Ara h 2	Magnetic	Streptavidin magnetic NPs	0.2–250 ng/mL	0.2 ng/mL	15–30 min	Highly sensitive multiplex analyte detection with little cross-reactivity, reducing cost	Requirement for trained staff to operate GMR data software with complex parameters	Ng et al. (2016)
Ara h 6	Electrochemical	AuNPs/enzymatic silver	1–100 ng/mL	0.27 ng/mL	n.a.	Low-cost screen-printed electrode for good reproducibility	Caution to optimize extraction process of allergens	Alves et al. (2015, 2017)
Parvalbumin	Magnetic	SPMNPs	0.01–100 μg/mL	0.046 μg/mL	20 min	Rapid lateral flow strip, larger scaled detection	Pork and white prawns induced false positive	Zheng et al. (2012)
	Electrochemical	Silicon dioxide coating on the Fe_3O_4 nanoparticles	0.5–4.5 ng/mL	0.16 ng/mL	10 min	Proposed convenient electrode renewal for easier handling	Cell-based sensors might require some training to operate	Jiang et al. (2015)
Tropomyosin	Electrochemical	Au-cysteine nanocomposite	0.25–0.5 μg/mL	0.15 μg/mL	n.a.	Label-free detection with simple building process	Challenges to improve regeneration and storage shelflife	Jiang et al. (2013)
	Electrochemical	Silicon dioxide coating on the Fe_3O_4 nanoparticles	0.1–1.5 μg/mL	0.03 μg/mL	10 min	Proposed convenient electrode renewal for easier handling	Cell-based sensors might require some training to operate	Jiang et al. (2015)

carbodiimide chemistry and covalent attachments for an organic chemistry-driven detection of arachin h 1. It is also reported that real-time monitoring of binding affinity of arachin h 1 is achieved with the assistance of impedance spectroscopy, with a detection range from 1 to 250 nM, LoD of 1 nM (Peeters et al. 2014).

With increased rapidity, sensitivity, and smaller dimensions, opportunities arise with microfluidics for advances into potential portable sensing devices for point-to-care (POC) innovations. Arachin h 1 is again detected with a composite of gold-graphene nanoparticles integrated on a stem-loop electrochemical genosensor, which primarily uses DNA sequence differentiation (Sun et al. 2015). Multilayers of immobilized biotin-conjugated thiolate DNA probe on a carbon glassy electrode are needed to improve electron conductivity, making it extremely sensitive in characterizing non-complementary sequences, with a linear detection range of 10^{-16}–10^{-13} M and a lower LoD up to the femto-scale.

Despite having similarities with its sister compound arachin h 2 in terms of molecular size, sequencing of amino acids, and molecular structure, arachin h 6 is disclosed in a recent study as the less dominant peanut allergen (Hemmings et al. 2020). Therefore, Alves et al. (2015) have reported a voltammetric biosensor fitted with gold nanoparticles and enzymatic silver deposits for detections of antibody and antigen sandwich complex of arachin h 6 (Alves et al. 2015). A follow-up study is carried out to understand more on the extraction of arachin h 6 from chocolate-based food matrices, i.e., a set of optimal conditions of time, temperature, additives (Alves et al. 2017). The immunosensor has reported a linear detection range of 1–100 ng/mL with a lower LoD of 0.27 ng/mL.

A multiplex sensor is beneficial in terms of convenient multianalyte detection and successful characterization for each of the target analytes. Wang et al. (2016) have reported a giant magnetoresistive immunosensing array that utilizes magnetic nanoparticles to generate a magnetic field required for the spin valve sensor. Real-time monitoring is achieved when an allergen is bound onto the ferromagnetic layer causing fluctuations in the resistance of the initial layer (Ng et al. 2016). Multiplex sensing is successful here to detect peanut allergens (arachin h 1 and arachin h 2) and gliadin, each with their distinctive linear detection range, and there is very little cross-reactivity for contaminated readings (Fig. 2.2). Streptavidin is conjugated with magnetic nanoparticles. The respective LoD ranges is 1.5 ng/mL for gliadin, 7.0 ng/mL for arachin h 1, and 0.2 ng/mL for arachin h 2.

Seafood, with the inclusion of finned fish, crustaceans, and mollusks, has been one leading cause of anaphylaxis. Although there are few studies to suggest the actual prevalence of fish and shellfish allergy (Moonesinghe et al. 2016), it is still crucial in developing a system for the screening of parvalbumin and tropomyosin in products. A magnetic nanoparticle probe-based immunoassay has been reported to detect fish parvalbumin through the lateral flow principle and antibody capture (Zheng et al. 2012). The superparamagnetic nanosurface (SMPNP) is conjugated with nitrocellulose and monoclonal anti-allergen antibodies. The calibration curve shows a linear relationship between allergen concentration and magnetic signals, with a quantitative LOD of 0.046 μg/mL and a qualitative LOD of 5 μg/mL, respectively. Recoveries in food matrices are within the acceptable levels of

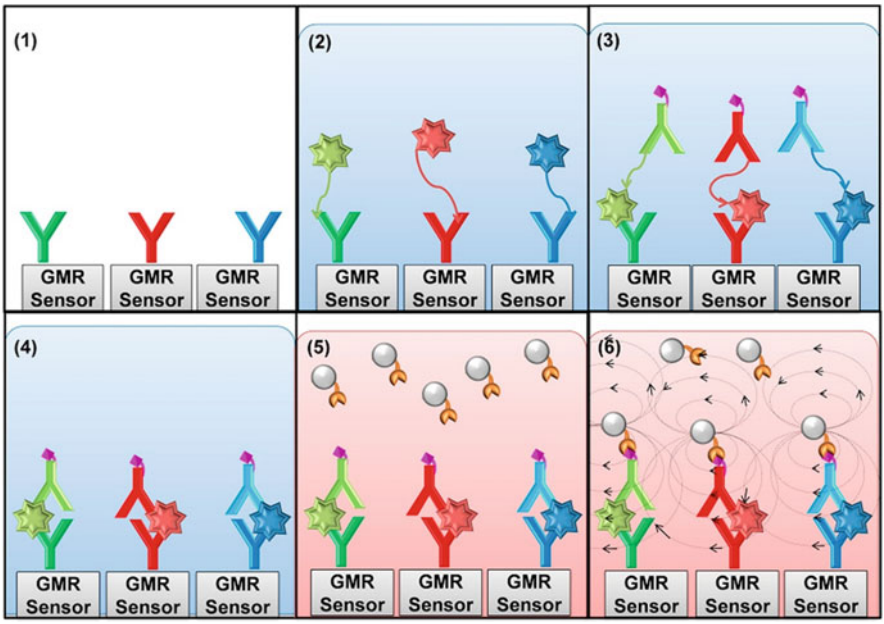

Fig. 2.2 Schematic illustration of GMR-based multiplex allergen nano-sensing assay for gliadin, Ara h 1, and Ara h 2. (Adapted with permission from Ng et al. (2016) from Elsevier, Copyright 2016)

80–120% (84.6–97.0%). Furthermore, it is shown that the nanoparticle-based assay has comparable and consistent results relative to the controlled Western Blot of 29 food samples (93.1%), with a fast detection time of 20 min.

Jiang et al. (2013) reported an electrochemical biosensor that utilizes self-assembled gold-cysteine nanoparticle composite as an immobilization unit for basophilic leukemia mast cells, enveloped in type I collagen to capture Pen a 1 via IgE antibodies (Jiang et al. 2013). Robust and stable signals can be processed and quantified via impedance spectroscopy, showing a great linearity range of 0.25–0.5 μg/mL, with a lower LOD of 0.15 μg/mL. The follow-up research was done on designed another nanoparticle modification for detecting both fish parvalbumin and Pen a 1(Jiang et al. 2015). Silicon dioxide coating on the Fe_3O_4 nanoparticles encased in lipidosome was adopted, to amplify the signal from the binding interactions of allergen-antibodies. The lower LOD for fish parvalbumin and shellfish Pen a 1 were 0.16 μg/mL and 0.03 μg/mL, respectively.

2.2.2 Heavy Metals and Toxic Dyes

Among contaminants, toxins such as heavy metals, residual pesticides, and toxic food dyes, pose a significant threat to public health. One possible route for such

contaminations of heavy metals in food often comes as the secondary pollution from the environment. It can also be caused by the food contracting trace amounts of heavy metal from the food processing lines, e.g., minerals used for aiding ultrafiltration system of beverages, writing and printing textures on the food packagings and labelings (Turner 2019). Examples of heavy metals include mercury (Hg^{+}), lead (Pb^{2+}), cadmium (Cd^{2+}), and arsenic (As^{3+}). The usual conventional analysis utilizes methods involving high-performance liquid chromatography (HPLC) with UV-vis spectra (Okano et al. 2015), colorimetry, gravimetry, normal, flame, or electrothermal atomic absorption spectroscopy (AAS), and inductively coupled plasma mass spectroscopy (ICP-MS). However, it is likewise laborious for the food analysis to proceed despite the conventional platforms provide fairly accurate results, which brings forth the inability for on-site performances. Hence, the nanotechnological approach (Table 2.2) could be developed as a cost-effective way to provide increased fieldwork analysis capabilities with the attuned adsorptive and even ferromagnetic natures of nanoparticles.

Surface-enhanced Raman spectroscopy (SERS) nanosensor was proposed for an increased selectivity for the detection of Hg^{2+} ions. Uniform dandelion-like gold-polyaniline (PANI) nanosphere was successfully synthesized through a one-step mono dispersion process of many short nanorods without neither templates and additives (Wang et al. 2011). Optimal morphology was achieved with adjustments on the ratio between aniline and $HAuCl_4$. The dendrite-covered structure provided an ultrasensitive reading as low as 10^{-11} M due to its larger contact surface area. The integration of PANI in the nanocomposite induces a more intense response for Hg^{2+} ions in comparison with Pb^{2+}, Zn^{2+}, and Cd^{2+} ions, showcasing the high selectivity and also good replicability. Similarly, a nanocomposite of gold/2-mercaptoisonicotinic acid (2MNA) was reported to multiplex detection of heavy metal ions in aqueous solutions (Tan et al. 2012). Relative SERS band intensity ratios were adopted as a more reliable way with reduced signal interference. The LODs were determined to be 3.4×10^{-8} M for Hg^{2+} and 1.0×10^{-7} M for Pb^{2+}, respectively. Masking reagents were not necessary for high selectivity towards mercury ions, while L-cysteine and sodium thiosulfate were beneficial for enhanced selectivity towards lead ions. Due to the simplicity, low-cost 2MNA, high sensitivity, and potential in situ use in aqueous environments, it could be a great monitoring system.

Nanoparticle-based optical sensors are developed for the ease of viewing results with our naked eyes. The hybrid of organic and inorganic components offers limitless combinations for a stable nanomaterial. The factors of uniformity for easier template reproduction, building cost, sterilization for the protection of the sensing receptors, detection selectivity range, and, most importantly, the firm immobilization of the receptors to avoid their accidental leakage into the testing solutions, thus causing sample contamination, are all technicalities that concern the development of optical sensors. Carbon-based nanomaterials such as graphene and its oxide are often chosen as substrates to load fluorophores. Pb^{2+} ions were reported to be detected through a fluorescent nanosensor using a hybrid of graphene-based quantum dots and graphene oxide by the working principle of ion-induced G-quadruplex

Table 2.2 Overview of reported heavy metals and toxic dyes nano-sensing approach

Heavy metals/ toxic dyes	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
Hg^{2+}	Optical	Dandelion-like gold-polyaniline (PANI) nanosphere	n.a.	10^{-11} M	n.a.	Greater sensitivity for Hg^{2+}, simple synthesis route	Challenge to improve stability	Wang et al. (2011)
	Optical	2MNA-modified AuNPs	1.0×10^{-7}–3.4×10^{-6} M	3.4×10^{-8} M	n.a.	Reduced cost for simultaneous detection	Possible unapparent selectivity towards other ions at 1.0×10^{-5} M	Tan et al. (2012)
Pb^{2+}	Optical	2MNA-modified AuNPs	3.4×10^{-7}–6.7×10^{-6} M	1.0×10^{-7} M	n.a.	Reduced cost for simultaneous detection	Some interference from Zn^{2+} ions on SERS	Tan et al. (2012)
	Optical	Graphene QDs/GO hybrid	9.9–435.0 nM	0.4 nM	2 min for quenching, 1 min for enhancement	Efficient biocompatibility for fast response time (1 min)	Caution for GO agglomeration for reduced surface area	Qian et al. (2015)
Cu^{2+}	Optical	GO modified Ag-In-Zn-S (AIZS) QDs	0–850 μM	0.18 μM	1 min response time	Great selective ion detection and high solubility in water	Fear of indium scarcity	Liu et al. (2016)
Metanil yellow	Electrochemical	AuNP/calix8	0.05–45 μM	9.8 nM	70 s accumulation time	Cost-saving for multiplex detection	High dependence on pH value	Shah (2020)

(continued)

Table 2.2 (continued)

Heavy metals/ toxic dyes	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
FCF	Electrochemical	AuNP/calix8	0.05–45 μM	19.7 nM	70 s accumulation time	Cost-saving for multiplex detection	High dependence on pH value	Shah (2020)
Allura Red	Electrochemical	ZnO NPs/chitosan/ MWCNTs	0.5–10 ppm	0.4 ppm	30 s	Hybrid with a faster and lower detection limit	Cost to operate differential pulse voltammetry	Kobun et al. (2015)

formation (Qian et al. 2015). The nanocomposite also achieved tunability in the fluorescence turn-on/off process. Therefore, the Pb^{2+} selectivity of the modified nanoprobe had greatly improved in fluorescence, biocompatibility, and resistance to photobleaching. Because of its rapid detection time, reproducibility, and high sensitivity towards Pb^{2+}, the LOD investigated was 0.6 nM, with a linear range up to 400.0 nM. Similarly, graphene oxide was also modified with additional to detect Cu^{2+} (Liu et al. 2016). This was accomplished via the aggregation of QDs upon the interaction with Cu^{2+}, followed by fluorescent quenching.

The accidental ingestion of synthetic food dyes in the human body poses a lethal threat. Some examples are metanil yellow which is prohibited by the World Health Organization (WHO) as a category II toxin (Srivastava et al. 1982), and fast green (FCF) which causes inhibition of neurotransmitter releases causing respiratory tract problems (Nayak and Shetti 2016). Recently, there was a report for a novel electrochemical nanosensor in detecting both metanil yellow and FCF simultaneously using AuNPs/calix (Majeed et al. 2013) arene (calix8) to modify the surface chemistry of a glassy carbon electrode (Shah 2020). The gold nanoparticles and calix8 hybrid served to significantly enhance the oxidation current signals of the analytes during cyclic voltammetry. Their contribution to further assist electron transfer between the dyes and the transducer was verified using differential pulse voltammetry. The designed sensor showed great merit in achieving maximum current within 2 min, broad linear range with LODs of 9.8 nM for metanil yellow and 19.7 nM for FCF, respectively, and stability when replication commenced in real water and juice samples. Similarly, azo dye such as Allura Red (E129) is reported to cause toxicity to humans for incessantly prolonged intake. Kobun et al. (2015) designed and developed an electrochemical sensor using zinc oxide nanoparticles, chitosan, and multiwall carbon nanotubes to modify gold electrodes, coupling with methylene blue as the redox indicators. A wide linear detection range of 0.5–10 ppm with a LOD of 0.4 ppm was reported when real food samples were tested on (Kobun et al. 2015).

2.2.3 Residual Pesticides

Pesticides are used frequently in agriculture to increase food production, but they are recognized as contaminants through leaching into raw food products, increasing toxicity towards human health. Chromatographic methods such as ultra HPLC (UHPLC)-mass spectroscopy (MS), ELISA, gas chromatography are expensive in pretreatment and contain many interference factors, resulting in the development of selective and effective analytical techniques (Table 2.3) in food sample matrices (Aktar et al. 2009).

Ferbam and thiabendazole (TBZ) are chemicals often used for their fungicidal effects. Furthermore, thiabendazoles are also used as veterinary drugs for antiparasitic and antimicrobial treatments in dairy livestock, such as tapeworms and gastrointestinal roundworms (Jedziniak et al. 2009). The residual chemicals can pose risks to human health with the build-up of antibody resistance from their

Table 2.3 Overview of nano-sensing approach for pesticide residue

Pesticide residue	Nano-sensing approach	Nanomateriais used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
TBZ	Optical	Molecularly imprinted polymers/Ag colloids	4–75 ppm	4 ppm in orange juice	23 min	Rapid, sensitive, MIPs can be easily functionalized	Laboratory required for SERS reading	Feng et al. (2018)
	Optical	Au nanorods	n.a.	0.06 ppm in apple juices	30 min	Rapid responses in real apples, highly reproducible results	Carbohydrates from apples might leach during sample extraction, decreasing signal intensity	Fu et al. (2019)
	Optical	Au nanorods	n.a.	149 in lemon, 179 in mango, and 216 μg/L in carrot juices	10 min	Fast sample preparation, high recovery rate (96–99%) of TBZ	Leaching of carbohydrates from food creating noises in SERS	Alsammarraie et al. (2018)
	Optical	Au@Ag-TGANPs	0.025–5 ppm	0.12 ppm in liquid milk	n.a.	Novel, fast and safe detection of analyte in liquid milk	Minor pretreatment, interference from other milk components (milk fats, casein) during SERS reading	Hussain et al. (2021)

	Optical	Ag-AuNPs with inositol hexaphosphate (IP6) and Mil-101 (Fe) MOF	1.5–75 ppm	50 ppb	8 s exposure	Improved SERS detection and high stability	In progress to finetune MOF shell thickness outside NPs for practicality	Xuan et al. (2019)
Ferbam	Optical	Au@Ag-TGANPs	0.025–5 ppm	0.003 ppm in liquid milk	n.a.	Novel, fast and safe detection of analyte in liquid milk	Minor pretreatment, interference from other milk components (milk fats, casein) during SERS reading	Hussain et al. (2021)
Paraoxon	Optical	Silicon-coated AgNPs/OPH/pyranine	1–100 ng mL^{-1}	1 ppb	30 min	Metal enhanced effect for higher signal	NPs need to be protected to prevent oxidation	Tuteja et al. (2014)
	Optical	AuNPs	4.5×10^{-8}–4.5×10^{-11} mol/L	75.5 pmol/L	30 min	Ultrasensitive, reduced cost for unmodified NPs	Caution for potential interference in real samples for false readings	Alami et al. (2020)
Parathion methyl	Electrochemical	Ag@graphene nanoribbons	5 nm–2780 μM	0.5 nM	n.a.	Easy fabrication, low cost, good reproducibility of electrodes	Challenges in signal attenuation (low sensitivity) and biofouling of electrodes when tested in real, highly complex matrix samples	Govindasamy et al. (2017)

(continued)

Table 2.3 (continued)

Pesticide residue	Nano-sensing approach	Nanomateriais used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
	Optical	AgNPs/ Graphene QDs	0.1–6 μg/L	0.017 μg/L	n.a.	Dual-mode sensing for more accuracy, low toxicity of QDs	Time-consuming (3 times filtering) in extraction from real samples	Li et al. (2020)

excessive uses. The most used platform has been integrating silver and gold nanoparticles into the detection of TBZ in various juice samples. Some utilized AgNPs with a LOD of 4.0 ppm (Feng et al. 2018), while some cases demonstrated the use of AuNPs/nanorods to detect TBZ in apples with a LOD of 0.06 ppm (Fu et al. 2019), as well as in lemon, mango, and carrot juices for up to 149, 179, and 216 μg/L (Alsammarraie et al. 2018). A SERS nanosensor was reported using silver-coated gold nanoparticles functionalized with thioglycolic acid (Au@Ag-TGANPs) (Fig. 2.3), and facile monitoring towards TBZ and ferbam in liquid milk were done for the first time (Hussain et al. 2021). Results showed the prepared nano-substrates could enhance the intensities of selected SERS bands by a factor up to 2.8×10^7. Despite requiring minor sample pretreatments, the nanosensor managed to detect TBZ and ferbam with LODs of 0.12 ppm and 0.003 ppm, respectively. Another study focusing on the metal-organic framework (MOF) approach had fabricated a composite of Ag-AuNPs with inositol hexaphosphate (IP6) and Mil-101 (Fe) MOF for ultrasensitive detection of TBZ in pear juices up to 50 ppb (Xuan et al. 2019).

Organophosphate compounds (OP) used in pesticides are easily decomposed via water or sunlight. Parathion and its neurotoxic metabolite, paraoxon, inhibit acetylcholinesterase (AChE), causing acetylcholine (Ach) to aggregate in cholinergic synapses and overstimulate the system (Valdés et al. 2009). Paraoxon was detected using silicon-coated AgNPs conjugated with organophosphate hydrolase (OPH) and fluorophore (pyranine) via metal enhanced fluorescence, producing a ten-fold increase in fluorescent intensity, with a linear range of 1–100 ng mL^{-1} and a LOD of 1 ppb (Tuteja et al. 2014). In another case, Alami et al. (2020) described an AuNPs-based nanosensor with dynamic light scattering to detect paraoxon via the aggregation of AuNPs due to choline, a hydrolysis product of ACh. A linear relationship between paraoxon concentration and the average diameter of AuNPs yielded a LOD of 75.5 pmol L^{-1} (Alami et al. 2020). Another derivative, parathion methyl, was detected using silver-supported graphene nanoribbons (Ag@GNRs) on screen-printed carbon electrodes (Govindasamy et al. 2017). They utilized the physiochemical advantages of GNRs to detect up to sub-nanomolar concentrations, i.e., large surface area, numerous catalytic sites for the reduction of parathion methyl, and high conductivity. Similarly, Li et al. (2020) designed a nanoprobe based on the reverse quenching principle of absorbers (AgNPs) and fluorophores (graphene QDs) to study dual-mode analysis of fluorescent and UV-vis spectrophotometry of OP with a LOD as low as 0.017 μg/L in water, carrot, and apple samples.

2.2.4 Pathogens (Foodborne) (Organic, Inorganic, Composite)

Foods and beverages contaminated with bacteria and parasites are notorious for vectoring foodborne and water-borne diseases. Statistics from the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) have shown that 48 million people have fallen ill from these microorganisms, e.g., *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Salmonella* (Havelaar et al. 2015).

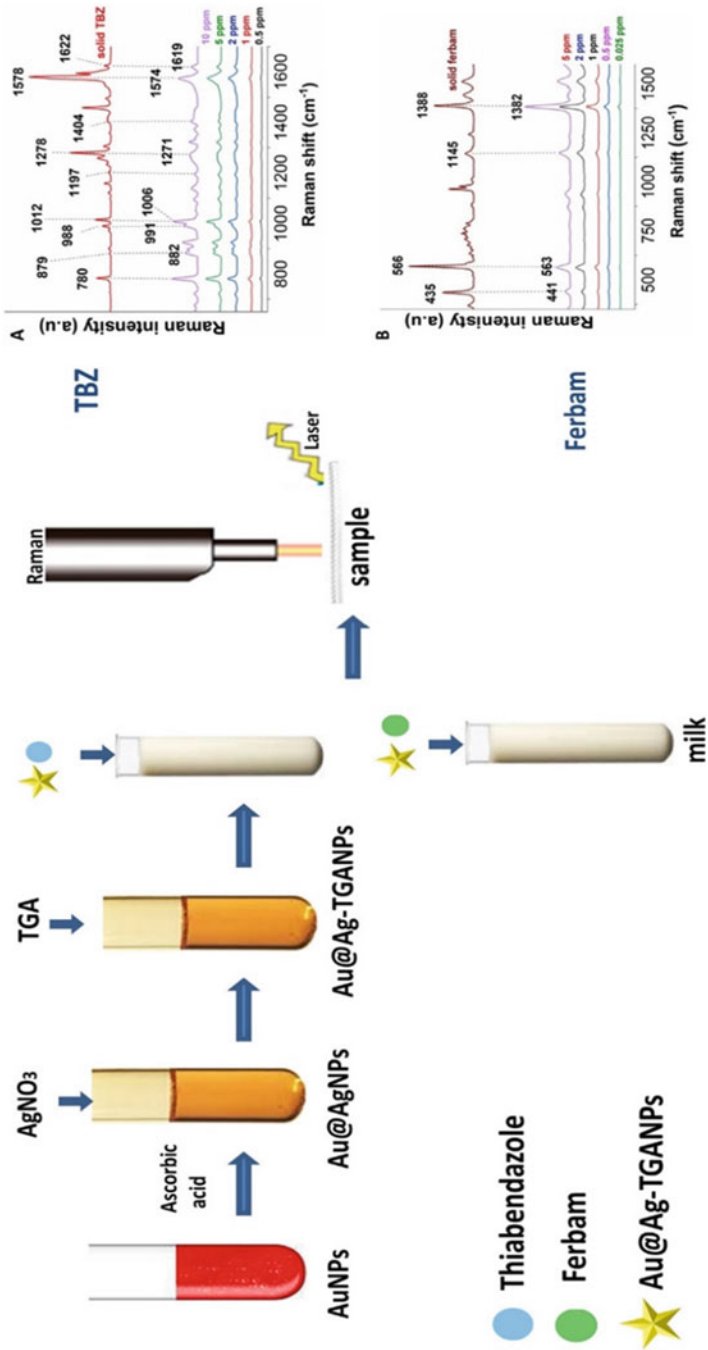

Fig. 2.3 Schematics for SERS-based facile screening of ferbam and TBZ in liquid milk samples. (Adapted from Hussain et al. (2021), open access)

Molecular genetic methods such as PCR revolve around microbiological control for the sample pretreatment, but it is complicated, cumbersome, and cost-extensive. Meanwhile, the challenges and limitations to standardizing recent nano-sensing of pathogenic contaminants into the current analysis climate are mainly divided into three categories: (1) sensitivity for identification of lowly concentrated pathogens using real-time PCR, (2) pretreatment steps to be integrated into the biosensing platforms for a vision of large-scale sensing in the future, and (3) the distinct differences between living and dead pathogens in the food products to prevent overestimation of the infection risk that can lead to serious consequences (Shen et al. 2021).

E. coli O157:H7 strain is one of the most caustic foodborne pathogens associated with gastrointestinal lining infections, causing near-fatal complications such as hemorrhagic colitis (HC) (Yu et al. 2001). Strategies to tackle the detection of *E. coli* include the integration of nanotubes, Au/AgNPs, graphene, and QDs into DNA-based fluorescence, magneto-fluorescence, and plasmonic resonance. Shelby et al. (2017) reported a multiparametric dual-mode nanosensor with the conjugation of capture antibodies on superparamagnetic iron oxide NPs, encapsulated with fluorophores (Dil dye). Monitoring the magnetic relaxation and fluorescence emission of the nano substrates with bacteria clustering, the study managed to detect as little as 1 colony-forming unit (CFU) (Shelby et al. 2017). High selectivity for O157:H7 strain was demonstrated when tested with nutrient broth solutions containing cross-contaminants. In another study, graphene oxide was used in tandem with the 6-carboxyfluorescein (6-FAM) labeled 3′ end of *eae* gene-specific sequence for a genosensing diagnosis of *E. coli* (Karimi et al. 2019). The detection range reached as little as 10 pg genomic DNA/1 mL Tris–HCl buffer, outperforming the usual polymerase chain reaction (PCR) platform. In the context of SPR-based sensors, Gür et al. (2019) reported the use of surface imprinted amine-functionalized AuNPs for the screening of *E. coli* found in urinary tract infections (UTIs) (Gür et al. 2019). This nanosensor could perform real-time detection in bacteria suspensions with a lower LOD of 1 CFU/mL. It showed high selectivity for *E. coli* not just in a nutrient broth mixture with other bacteria, but also in complex artificial urine samples.

A strategy for efficient *Salmonella* screening using immunomagnetic nanoparticles was used to develop an optical biosensor based on the coupled use of porous Au@Pt nanocatalysts (NCs) with a passive 3D fluidic chip to facilitate the sensitive detection of *Salmonella typhimurium* in spiked chicken samples (Zheng et al. 2020). The immuno nanocomposite was verified to possess effective enzymatic activity towards peroxidase compounds for robust signal output. The linear detection range spanned concentrations from 1.8×10^1 to 1.8×10^7 CFU/mL within a short time of 1 h, with a LOD of 17 CFU/mL. On the other hand, another facile biosensor for fast separation and detection of *S. typhimurium* was facilitated with an integrated nanochannel electrode modified based on magnetic NPs conjugated with target-specific antibodies (Zhu et al. 2020). The NPs aggregated onto the captured bacterium, and the complexes were trapped as they were funneled through the surface of the nanochannel electrode for electrochemical impedance spectroscopy. Cross-

reactivity tests revealed high specificity of the biosensor, with a LOD of 50 CFU/mL. In a similar principle, *Salmonella enterica*, another subspecies, has also been detected with the integration of AuNPs with a permanent magnet to amplify the magnetic signals of a screen-printed carbon electrode (Afonso et al. 2013). The conjugation of capture antibodies contributed to good separation and isolation of the bacteria, garnering a LOD of 143 cells/mL in skimmed milk. This detailed review (Shen et al. 2021) contains a more critical review that covers a wide range of the types of transducing mechanisms used in biosensors for rapid testing and analysis of Salmonella. The authors had elaborated on their perspectives on traversing and preparing the food industry for the implementation of in-field biosensing techniques, with a focus on the application of these novel biosensors on Salmonella surveillance for food safety purposes (Yu et al. 2001).

S. aureus and its toxins have been detected using $MnFe_2O_4$ magnetic NPs-AuNP shell composite (AuMNPs) (Wang et al. 2016). The magnetic NP cores were conjugated with polyethyleneimine layer and then subsequently with the adsorption of negatively charged AuNPs on the surface of the cores through electrostatic interaction. SERS readings had shown great band intensity with a LOD of 10 cells/mL. In another study, magnetic nanobeads were conjugated with a chosen *S. aureus* peptide sequence on a paper-based biosensor (Suaifan et al. 2017). Visual color changes from nanobead-peptide template dissociations were observed by the naked eye, and the results were reported to respond in minutes. The selectivity for *S. aureus* was evident in pure culture, contaminated food matrices, and environmental samples, with low LODs ranging from 7 to 100 CFU/mL. AuNPs hold advantages over carbon nanotubes (CNTs) with their lesser toxicity and their eliminations for shortening and acid functionalization. Table 2.4 outlines the examples of pathogen nano-sensing, while other exemplary nanotechnological strategies for pathogen sensing can be found in this dedicated review (Mustafa et al. 2017).

2.2.5 Adulterants (Organic, Inorganic, Composite)

Adulterations in foods and beverages pose a significant health risk for consumers, as it is done by either the removal of certain fundamental components or the admixture of inferior and cheap ingredients, causing degradation in food safety and quality (Jha 2016). Due to most of its toxic nature, almost all adulterants that are in use previously in the food industry have been classified and prohibited accordingly. Methods such as HPLC, ELISA, and RT-PCR are deemed expensive and complicated with pretreatments, limiting real-time uses. Therefore, research into new countermeasures with nanotechnology will bring great potential (Table 2.5).

Sudan dyes are subsequently banned for inducing health risks for their mutagenic and carcinogenic properties, which the International Agency for Research on Cancer (IARC) (Cheung et al. 2010) classified as Group 3 carcinogens. A study has reported a sensitive fluorescent nano-sensing approach based on inner filter effect (IFE) using upconversion nanoparticles (UCNPs) to facilitate the detection of Sudan dyes I–IV

Table 2.4 Overview of reported approach for pathogen nano-sensing

Pathogen	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
E. coli	Optical, Magnetic	Iron oxide SPMNPs@Dil dye	1–20 CFU	1 CFU	n.a.	Point-to-care user-friendly, cheap and stable NPs	High initial cost on benchtop magnetic relaxometer	Shelby et al. (2017)
	Optical	GO@6-FAM labeled 3′ end of *eae* sequence	0–20 pM	10 pg/mL	18 min	Easier than common PCR, higher selectivity	Difficulties when designing DNA primer and sequencing	Karimi et al. (2019)
Salmonella	Optical	Au@Pt NCs	1.8×10^1–1.8×10^7 CFU/mL	17 CFU/mL	1 h	Enzyme-free and microfluidic allows for cheaper fast detection	Fine-tuning of micromixers to increase mixing efficacy	Zheng et al. (2020)
	Electrochemical	Magnetic NPs@antibody	10^2–10^7 CFU/mL	50 CFU/mL	1 h	Reduced cost with no additional signal labels and large volume required	Newly ventured on integrated nanochannel, require more understanding	Zhu et al. (2020)
	Electrochemical	AuNPs	10^3–10^6 cells/mL	143 cells/mL	1 h 30 min	Easier modification of NPs and shorter analysis time	Preconcentration of bacteria required	Afonso et al. (2013)

(continued)

Table 2.4 (continued)

Pathogen	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
S. aureus	Optical	Au@$MnFe_2O_4$ NPs	10^1–10^5 cells/mL	10 cells/mL	n.a.	Strong magnetic responses for good SERS activity	Caution for smaller size AuMNPs that are unsuitable for fast bacteria separation	Junfeng Wang et al. (2016)
		Magnetic nanobeads@*S. aureus* peptide	7.5–7.5 × 10^6 CFU/mL	7 in pure broth, 40 in food, 100 CFU/mL in environmental samples	1 min incubation	Rapid color response, user-friendly, and reduced cost	Existence of random errors due to the manual threshold adjustment of the designated area	Suaifan et al. (2017)

in chili powders (Fang et al. 2016). The absorption band of target dye analytes was effective to quench the fluorescence emission band of the UCNPs. Optimal conditions of the nanosensor resulted in LODs ranging from 2.83 to 16.7 ng/mL across Sudan dyes I–IV. Sudan I have also been detected with an ionic liquid modified carbon paste electrode (ILCPE) decorated with Pt/CNTs nanocomposite (Elyasi et al. 2013). The modification on ILCPE greatly enhanced the electrical conductivity and biocompatibility of the sensor. No cross interferences from other substances disrupt the signal output, this sensitive electrochemical nanosensor has a LOD of 0.003 μmol L^{-1} (at 3σ). In another study, graphene oxide (GO) was functionalized with Au nanorods on the GCE surface to immobilize the anti-Sudan I antibodies (Wang et al. 2018). palladium/gold core-shell nanocrystallines (Pd/Au CSNs) with CdSe@CdS QDs created a signal bioprobe for the electrochemiluminescent (ECL) immunoassay for sensitive detections of Sudan I. It was implied that the synergistic effects between the GO/Au@GCE and the Pd/Au CSNs elevated the electronic transmission and thus the ECL intensity, making the nanomaterial combination highly selective and biocompatible with a low LOD of 0.3 pg mL^{-1}.

Processed meat products such as meatballs are common among the Asian and European food cultures. It is discovered that pork meat has been a potential adulterant in chicken or beef meatballs to reduce the cost of raw ingredients (Stephen Inbaraj and Chen 2016). From a healthcare standpoint, overconsumption of processed meat leads to high cholesterol and fat levels, resulting in chronic diseases, e.g., type I diabetes and myocardial infarction. Uncommon circumstances may lead to pork-related allergic reactions, due to ingestion and subsequent IgE-mediation towards swine serum albumins (Wilson and Platts-Mills 2018). On the other hand, the adulteration and consumption of pork meat pose controversy and anxiety from a religious view, such as the Halal food laws (Ali et al. 2014). Similarly, there are increasing cases of pork mixing into vegetarian and vegan foods. Kuswandi et al. (2017a, b) had utilized AuNPs in DNA-based colorimetric sensing of pork adulterants in processed food. The design demonstrated the benefit of AuNPs to couple with single-stranded DNA (ssDNA) for the differentiation of perfectly matched and mismatched nucleotides at 55 °C (Kuswandi et al. 2017a). This unique property allowed the label-free AuNPs to possess high selectivity for only matched swine DNA hybridizations to induce redshifted color changes visible to the naked eye, with a LOD of 6 μg/mL in mixed food matrices. The same group further developed a lateral flow immunostrip by the conjugation of anti-swine IgG polyclonal antibodies on AuNPs (Kuswandi et al. 2017b). The results showed that the response time was within 5 min, with a detection limit of 0.1% (w/w) of pork-in-beef meatballs, besides showing great replicability in test results in comparison to standard ELISA testings. Similarly, the AuNPs were coated with negatively charged citrate ions to ensure good dispersion with electrostatic repulsion (Ali et al. 2012). The ssDNA captured further stabilized the AuNPs via Van der Waals forces, preventing salt-induced aggregations while keeping a great selectivity towards swine ssDNA.

Table 2.5 Overview of the reported approach of adulterants and nutrients nano-sensing

Analytes	Nano-sensing approach	Nanomaterials used	Dynamic range	LOD	Analysis time	Advantages	Limitations/ challenges	Reference
Sudan I	Optical	UCNPs	0.05–40 μg/mL	15.1 ng/mL	8 min	Low toxicity, reduced light scattering, resisted photobleaching	Insolubility of UCNPs in water	Fang et al. (2016)
	Electrochemical	Pt/ CNTs@ILCPE	0.008–600 μmol/ L	0.003 μmol/L	n.a.	IL enhanced ionic conductivity for increased transfer rate in electrode, better than HPLC	Kinetic limitation might reduce sensitivity	Elyasi et al. (2013)
	Electrochemical	Pd/Au CSNs w/CdSe@CdS QDs	0.001–500 ng/ mL	0.3 pg/mL	1 h	Superior biocompatibility with high catalytic activity for electronic signal transfer	Fine-tuning of Pd/Au CSNs and PAMAM ratio to avoid probe preparation	Wang et al. (2018)
Sudan II	Optical	UCNPs	0.01–20 μg/mL	2.83 ng/mL	6 min	Low toxicity, reduced light scattering, resisted photobleaching	Insolubility of UCNPs in water	Fang et al. (2016)
Sudan III	Optical	UCNPs	0.01– μg/mL	3.52 ng/mL	8 min	Low toxicity, reduced light scattering, resisted photobleaching	Insolubility of UCNPs in water	Fang et al. (2016)
Sudan IV	Optical	UCNPs	0.05–40 μg/mL	16.7 ng/mL	5 min	Low toxicity, reduced light scattering, resisted photobleaching	Insolubility of UCNPs in water	Fang et al. (2016)

Porcine DNA	Optical	AuNPs	0.4–1.2 μg/mL	6 μg/mL	n.a.	Reduced cost and time for DNA sequence detection on-site	Visual confirmation provides no quantitative info firsthand	Kuswandi et al. (2017a, b)
	Optical	AuNPs@anti-swine IgG	0.1–100 (%w/w) pork	0.1 (%w/w) pork	5 min	Rapid immunostrip test for on-site testing	Challenges as lower reproducibility at 0.05 (% w/w)	Kuswandi et al. (2017a, b)
	Optical	AuNPs	0.4–6.0 μg/mL	4 μg/mL	10 min	Cheaper and more sensitive than RT-PCR test	Decreased sensitivity (<80%) at <5% pork	Ali et al. (2012)
Vitamin B12	Optical	Graphene oxide	25×10^{-8}–28.1×10^{-6} M	3.2×10^{-7} M	4 min	Improved GO optical properties for rapid and direct detection	Caution for GO agglomeration for reduced surface area	Gholami et al. (2015)
	Optical	Carbon dots	0–60 μM	0.1 μM	n.a.	Easy functionalization, enabling photostability	Fine-tuning of spectral due to IFE	Ding et al. (2018)
Folic Acid	Optical	CdTe QDs	0.23–113 μM	48 nM	5 min	Simple synthesis of QDs and increased sensitivity	Caution of Cd and Te leaching	Li et al. (2020)
Malic Acid	Electrochemical	Carboxylated MCNTs	0–0.25 mM	0.01 nM	2 min	Improved electron transfer and high surface area	High cost of CNT production	Dalal et al. (2017)

2.2.6 Nutrients

Vitamin B12 or cyanocobalamin contains a cobalt ion in the center of a tetrapyrrole-derived macrocyclic ring, similarly found in hemes and chlorophylls (Smith et al. 2018). HPLC and AAS are conventional B12 detection methods but they are time-consuming and less specific. Photoluminescence (fluorescence quenching) is preferred over chemiluminescence due to its inability to distinguish B12 cobalt ion from free cobalt. Monolayers of graphene oxide (GO) were synthesized for the label-free screening of B12 in acidic media (Gholami et al. 2015). The non-covalent interaction between GO nanolayers and vitamin B12 was in high affinity, showing great specificity compared to other vitamins and nutrients in the samples. The efficient quenching effects led to obtaining a LOD of 3.2×10^{-7} M. In another example, carbon dots were directly utilized as fluorophores in this IFE-based fluorescent nanosensor for their low cytotoxicity, convenient synthesis and functionalization, and unique optical and electrochemical affinities compared to conventional QDs (Ding et al. 2018). The overlapping of the B12 absorption peak and the emission peak of carbon dots at 360 nm facilitated the quenching effect of B12 on carbon dots, leading to a LOD of 0.1 μM.

Conventional methods to detect folic acid (FA) require tedious preparations (HPLC) and difficult designs (fluorimetric). Folate is also a water-soluble vitamin B-complex compound. Excess intake may lead to inhibit the absorption of vitamin B12, while deficiency contributes to cardiovascular exacerbation and neural tube defect during pregnancy. FA is the synthetic analog of folate typically used in supplementary and fortified foods (Li et al. 2020). An FA-molecularly imprinted polymer shell was attached to silica nanoparticles, followed by embedding cadmium telluride (CdTe) QDs capped with mercaptoacetic acid (TGA)/3-mercaptopropionic acid (MPA)/glutathione (GSH) into the imprinted shell for the design of an FA-dependent fluorescent nanosensor via the sol-gel method (Li et al. 2020). Visual detection for FA was determined with a blueshifted color change from the initial color red, LOD to be 48 nM. Real sample testing yielded rapid and precise responses, detecting FA up to 265.8 μg/100 g.

Malic acid detection is quite limited currently to using enzymes, which required designation. An enzymatic electrochemical nanosensor for malic acid was developed using immobilized NADP-malate dehydrogenase on a carboxylated-multiwall CNT working electrode (Dalal et al. 2017). Screen printing of the CNT electrode allows for low-cost production, while the functionalized CNT electrode promotes electron bindings and mediates its transfer with a larger surface area. These have led to a responsive sensor with high specificity and sensitivity for the amperometric detection of L-malic acid in tomatoes with a LOD of 0.01 nM. Table 2.5 summarizes the aforementioned nano-sensing approaches of nutrients.

2.3 Conclusion and Future Perspectives

Nanotechnology advances in the cornerstone of real-time food monitoring as it allows early insights and error intervention in the manufacturing line at an accelerated pace with real sample trials from the twenty-first century onwards. Alternatively, the current trend shows there is more focus on carbon-based and hybrid nanocomposites (GO, GQDs), miniaturization for on-site citizen testing, and 3D chip/electrode imprinting as its way forward. This is due to more convergence of data handling, data processing, automation, and data accessibility. The ubiquitous amount of data has evolved beyond the conventional relational databases, i.e., big data. As such, food safety monitoring must be able to accommodate a higher velocity, volume, and variety, leading to a high efficacy to process, record, and generate the information overload with low latency in real time. Nano-sensing can intersect with the Internet of Things (IoT) to collect massive databases through interconnected devices, while implementing suitable algorithms through the help of machine learning neural networks and artificial intelligence (AI) to gain insights and achieving some degree of automation in big data and predictive analytics. Fortunately, breakthroughs in smartphone-based devices (SBD) for global food analysis are progressing greatly with the potential to bringing this innovation to not just large plants, but also small farms and in-house analysis. However, challenges to utilize social media and cloud services to transmit food data in real time from sensors to sensors, devices to devices must be considered for easier accessibility. On the other hand, there are also limits of SBD hindering data trend interpretation with false positives that should be looked into to ensure an end-user-friendly interface. In the context of societal concerns, the R&D departments need to consider the factors of acceptance for both the food industry and the consumers to migrate the applications of nanotechnology into foods, while attracting stakeholders into a willing potential investment.

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Nanoengineered Aptamer Assisted Strategies for the Detection of Foodborne Pathogens

3

Maryam Mousavizadegan, Amirreza Roshani, and Morteza Hosseini

Abstract

This chapter focuses on the detection of pathogens in food samples using novel aptamer-based assays. Aptamers, defined as oligonucleotide sequences with high affinity toward various targets, provide a less expensive alternative to antibodies and can specifically differentiate between various microbial strains. The emergence of nanomaterials has revolutionized the route to detecting and monitoring pathogens in an efficient, rapid, and cost-effective manner. The incorporation of these two fields combines the merits of nanomaterials and aptamers to create rapid and highly sensitive sensing platforms for a multitude of targets which can be used to replace the existing conventional approaches in food safety monitoring. In this chapter, we will first present an introduction on the topic followed by a brief summary of common foodborne pathogens. Aptamer engineering and SELEX will then be elaborated. In the next section, various aptamer-based sensing approaches will be discussed along with the recent examples in foodborne pathogen recognition.

Keywords

Aptamer · SELEX · Biosensors · SPR · Foodborne pathogen

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3.1 Introduction

Food contamination by pathogenic microorganisms is a global health concern as it can lead to serious and often fatal diseases and burdens the food industry with heavy economic consequences. The annual number of foodborne diseases according to the World Health Organization (WHO) is about 600 million with 420,000 deaths. The burden of contaminated food is much heavier in developing countries. Foodborne pathogens can be divided into bacteria, parasites, and viruses. Norovirus infections and bacterial infections, especially *Salmonella* species, *Clostridium perfringens*, *Escherichia coli, Staphylococcus aureus,* and *Campylobacter* species are the leading cause of foodborne illnesses and hospitalizations (Bintsis 2017).

Common detection methods, which include PCR techniques or cell culture-based approaches, are generally time-consuming and require intricate instrumentation and several complex steps and reagents. Furthermore, many of these approaches, especially culture methods, suffer from low sensitivity and selectivity. Thus, cost-effective, sensitive, and efficient techniques for rapid foodborne pathogen detection are required, especially in remote, developing areas in which laboratories and professional technicians might not be available. Owing to the importance of rapid, efficient food analysis, ample research has been devoted to the development of sensing platforms with high sensitivity, portability, and real-time quantification (Majdinasab et al. 2018).

Nanomaterials possess unique optical and electrical properties as a result of their high surface-to-volume ratio, and can bestow enhanced performance when incorporated with a biosensor. They also provide a more effective surface for biomolecule immobilization such as antibodies and aptamers, which can further raise the selectivity of a sensing platform. These advantageous characteristics have led to an increased desire for the implementation of nanomaterials in analytical devices (Sanvicens et al. 2009).

Aptamers are defined as oligonucleotides, either RNA or DNA, which can selectively bind to a range of target molecules including proteins, drugs, inorganic molecules, etc. The affinity of aptamers is comparable to or even higher than that of monoclonal antibodies, with dissociation constants generally ranging from the picomolar to low micromolar range (Jayasena 1999). Aptamers can be used as a more efficient alternative to antibodies for diagnostic purposes as they are more stable in a range of temperatures, pH, and ionic strengths, do not show toxicity and are less prone to denaturation. Their production is simpler and more cost-effective and has a longer shelf-life compared to antibodies (Lim et al. 2010). Owing to all the numerous merits, aptamer-based sensors, more commonly known as aptasensors, have become a point of focus among many researchers with the aim of generating precise sensing devices.

In this chapter, novel aptamer-based sensing approaches will be discussed. We will first elaborate on various foodborne pathogens, followed by a brief description of aptamer screening methods. An explanation and novel examples of optical, including colorimetric, fluorescence, chemiluminescence, surface-enhanced Raman scattering and surface plasmon resonance based aptasensors, and electrochemical,

including impedimetric, potentiometric, and amperometric aptasensors will also be provided.

3.2 Common Food Pathogens

Approximately 40% of the estimated 50 million global annual deaths are caused by infectious diseases. In the USA alone, foodborne pathogens lead to about 76 million cases of illness each year, and around 300,000 hospitalizations and 5000 fatalities (Sharma and Mutharasan 2013). This situation is much direr in developing regions of the world, as detection and therapeutic facilities are limited.

Foodborne pathogens consist of mostly bacteria and fungi, and also viruses, prions, and protozoa. Food contamination during either the production and processing stages, storage, or transportation before reaching the consumer. Many microorganisms, secret toxins or other substances, for instance, bacterial spores, in the extracellular environment during their growth, much of which are resistant to the various inactivation treatments undergone during food processing. These molecules each have distinct mechanisms of activation and pathogenesis, gaining an understanding of which can be beneficial to tackle these illnesses.

In Table 3.1, common foodborne pathogens have been summarized.

3.3 Aptamer Engineering

For a long time, nucleic acids (NAs) were regarded as biomolecules whose role was either hereditary information storage (DNA) or the transfer of the information to proteins (RNA). Further investigations in the world of NAs led to the discovery of a diverse array of functions for these biomolecules including enzymatic catalysis (deoxyribozymes and ribozymes), transcription regulation (miRNAs), and specific targeting.

Aptamers are short (usually 20–60 nucleotides), single-stranded DNA or RNA molecules with distinct secondary structures which allows them to specifically bind to a target with high affinity. Most aptamers have been seen to fold into spiral, hairpin, stem ring, convex ring, clover, or pseudo knots structures (Lin and Patei 1997). With comparable affinities, aptamers are considered appropriate substitutes for antibodies with numerous advantages including significantly lower toxicity and immunogenicity, higher stabilities, and notably cheaper and simpler generation process. Owing to all these merits, aptamers have become favorable candidates for targeted drug delivery (Chen et al. 2017a), molecule purification (Forier et al. 2017), and sensing (Fakhri et al. 2018). To this day, numerous specific aptamers for a range of targets including cells, viruses, proteins, vitamins, toxins, heavy metals, etc. have been generated.

Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is the process of aptamer selection first developed independently by Tuerk and Gold (1990) and Ellington and Szostak (1990) in 1990. It generally consists of two

Table 3.1 Common foodborne pathogens, along with their detection methods and associated products

Pathogen	Standard detection methods	Food sources
Bacteria		
Brucella spp.	Conventional bacterial cell culture and biochemical methods	Direct or indirect exposure to infected animals or consumption of their contaminated products
Campylobacter spp.	Conventional bacterial cell culture and biochemical methods	Chicken and bovine flesh
Clostridium botulinum	ELISA for toxin detection	Improperly prepared home-canned food
	PCR	
	Conventional bacterial cell culture and biochemical methods	
Mycobacterium bovis	Conventional bacterial cell culture and biochemical methods	Milk
		Water
		Feedstocks
Listeria monocytogenes	PCR	Beef
	Conventional bacterial cell culture and biochemical methods	
Mycobacterium tuberculosis	Conventional bacterial cell culture and biochemical methods	Meat and dairy products
	PCR	
Salmonella spp.	Bacterial assays	Meat, dairy, vegetable, fruit
Shigella spp.	Conventional bacterial cell culture and biochemical methods	Polluted water
		Vegetables (salads)
Staphylococcus aureus	PCR	Meat and poultry
	Conventional bacterial cell culture and biochemical methods	Cold salads
		Vegetables
		Dairy products
Streptococcus spp.	Conventional bacterial cell culture and biochemical methods	Dairy products
		Water
Vibrio spp.	Conventional bacterial cell culture and biochemical methods	Fruit and vegetables
		Water
Parasites		
Cryptosporidium spp.	Direct fluorescence assay	Soil, food, water, or surfaces that have been contaminated with the feces from infected humans or animals
Cyclospora cayetanensis	Microscopic examination of wet smears	Fruit and vegetable
	Staining tests	
	Serological testing	

(continued)

Table 3.1 (continued)

Pathogen	Standard detection methods	Food sources
	DNA testing for oocysts in the stool	
Giardia intestinalis	Microscopic analysis for cysts in stool samples	Soil, food, or water that has been contaminated with feces from infected humans or animals
Toxoplasma gondii	Serological testing	Meat
		Goat milk
		Infected soil or sand
Viruses		
Astrovirus	Electron microscopy (EM)	Contaminated food and water
		Fruit and vegetables
Hepatitis A virus	Detection of HAV-specific antibodies	Water, shellfish, frozen vegetables, and fruit (berries), and salads
Norovirus	RT-PCR	Any food contaminated by norovirus affect person
Rotavirus	Electron microscopy	Drinking water
	Polyacrylamide gel electrophoresis (PAGE) RT-PCR	
Fungi		
Aspergillus spp.	Galactomannan testing	Various sources
Fusarium spp.	Fungal cell culture	Soil and polluted agricultural products
Penicillium spp.	Fungal cell culture	Various sources

alternating stages: first the original oligonucleotides are amplified through a polymerase chain reaction (PCR) and in the second stage the target is incubated with the oligonucleotide pool, and the ones which have interacted with the target are separated to be amplified for the second round (Fig. 3.1). Usually the process is repeated for 15–120 rounds in order to attain a specific aptamer with high affinity and low dissociation rates (Lakhin et al. 2013).

Since the introduction of SELEX, it has undergone numerous improvements which have both reduced the time required for aptamer selection and increased the affinity of the aptamers selected for the desired target. In this section, a brief description of some of the most common SELEX approaches will be presented.

1. Conventional SELEX: The conventional SELEX, as described in (Tuerk and Gold 1990), is a time-consuming method lasting from a few weeks to a month. A chemically synthesized library including about 60 oligonucleotides, all of which contain a random, varying region flanked by constant regions for PCR primer annealing is incubated with target molecules. After 20 rounds of selections, during which oligonucleotides with low affinity are removed, aptamers with high affinity are enriched and selected. Although this approach is highly effective

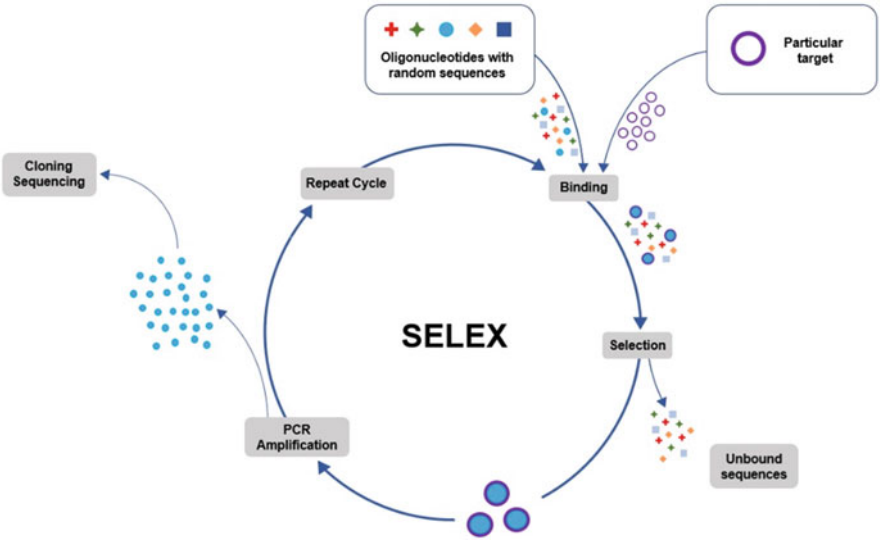

Fig. 3.1 Schematic representation of the SELEX process for specific aptamer selection

and well-established, the time-consuming and laborious nature of this approach has led to the search for alternate techniques.

2. Capillary electrophoresis-SELEX: CE-SELEX is among the most frequently used variations of the SELEX method. As first described by (Mendonsa and Bowser 2004), this method manages to reduce the necessary rounds for aptamer selection from 20 to 4 without losing the affinity of the aptamer to its target. In this method, the target bound oligonucleotides, which have a lower mobility compared to free oligonucleotides, are separated based on the electrophoretic mobility.
3. Magnetic bead-based SELEX: In this method, which was first published in 1997 (Bruno 1997), the target proteins are immobilized on magnetic beads and then, incubated with an oligonucleotide library. Using a magnetic separator, the target-aptamer complex is separated from the unbound oligonucleotides.
4. Cell –SELEX: This technique is mainly used when there is not enough prior knowledge about the target. In this approach, whole prokaryotic and eukaryotic cells are incubated with an oligonucleotide library and several rounds of separation, similar to that in conventional SELEX, are performed (Ninomiya et al. 2013).
5. *In silico* selection: Numerous programs have been developed to aid the in silico approaches for aptamer selection through computational docking, oligonucleotide tertiary structure prediction, and target interaction modeling. Among these programs Rosetta (Das et al. 2010), FR3D (Sarver et al. 2008), R3D Align (Rahrig et al. 2010), AutoDock (Detering and Varani 2004), DOVIS (Zhang et al. 2008), Aptamotif (Hoinka et al. 2012), and MPBind (Jiang et al. 2014) can be mentioned.

Given the many merits of aptamers in target detection, research studies are continuously working on developing more efficient methods for aptamer selection by combining computational methods, high-throughput sequencing techniques, nanotechnology, etc. with conventional SELEX to boost the efficiency and reduce the time and cost required for aptamer generation.

3.4 Aptamer-Based Assays in Foodborne Pathogen Detection

Although the aptamer-based sensing devices which can be used for public health and food safety monitoring are currently limited, numerous studies have been carried out for the development of aptasensors in the recent years. In this section, we will introduce optical and electrochemical aptasensors for the recognition of foodborne pathogens. Optical detection approaches include colorimetric, fluorescence, chemiluminescence, surface-enhanced Raman scattering (SERS), and surface plasmon resonance techniques, whereas electrochemical methods can be divided in impedimetric, potentiometric, and amperometric sensing techniques. For each section, the role of specific nanomaterials for signal enhancement will be discussed.

3.4.1 Optical Detection

In an optical sensor, the detection of the analyte or group of analytes is transduced to an optical signal, which can be classified to colorimetric, fluorescence, chemiluminescence, surface-enhanced Raman scattering (SERS), and surface plasmon resonance based sensors. Aptamer-based optical sensors (optical aptasensors) are a class of optical detection methods in which target recognition is achieved through an aptamer. The biochemical signal is then converted to visible, ultraviolet or infrared (IR) radiations which can be detected with the naked eye or using spectroscopy methods. As a result of their simplicity, sensitivity, and stability, optical assays have recently gained prominent interest for disease, environmental, and food safety control (Damborský et al. 2016).

Conventional optical approaches based on organic materials are complex, require large sample volumes, and further suffer from low sensitivity which limit their use (Choi et al. 2018). Nanomaterials (NMs), including nanoparticles (NPs), nanorods, quantum dots, nanoclusters, and other nanostructures, possess excellent physicochemical properties due to their high surface-to-volume ratio which results in desirable optical, electronic, and plasmonic characteristics and thus can help overcome these limitations (Ajay Piriya et al. 2017). Various NMs including gold NPs, silver NPs, cadmium sulfide quantum dots, carbon dots, magnetic NPs, etc. have been used for signal enhancement, labeling and separation purposes in the optical detection of pathogens.

In this section, we will briefly discuss various aptamer-based optical sensors used for the detection of foodborne pathogens.

3.4.1.1 Colorimetric Aptamer-Based Assays

In a colorimetric assay, the presence and concentration of an analyte is determined with the help of a reagent that undergoes color change upon target attachment. Because of their simplicity and since results can be immediately detected with the naked eye, colorimetric assays are quite favorable among researchers (Lee et al. 2006). In a colorimetric aptasensor, the attachment of the target to the aptamer is converted into detectable color change. For this purpose, organic dyes or nanomaterials might be employed in either an enzymatic or non-enzymatic approach (Hao et al. 2017a).

Limitations such as low sensitivity and complexity in colorimetric systems can be overcome using various NMs, in particular gold and silver NMs which through aggregation or chemical reactions can induce distinct color change (Fakhri et al. 2020; Naderi et al. 2018). NMs strategies in colorimetric detection system can be generally divided in three ways: color change caused by the aggregation of NMs, color change caused by the destabilization of NM structures, and color change resulting from oxidation reaction by peroxidase-mimicking NMs.

Electrostatic interactions lead to the aggregation of some NMs, especially AuNPs, which induces a color chance in the solution within the visible light range, so it can be detected by the naked eye. Taking advantage of the color change induced in AuNPs upon aggregation, Feng et al. developed a specific aptasensor for the detection of *Shigella flexneri* in food samples. Specific aptamers which were immobilized on the surface of AuNPs stabilized the nanoparticles and prevented their aggregation. In the presence of the target bacteria which bind to the aptamers,

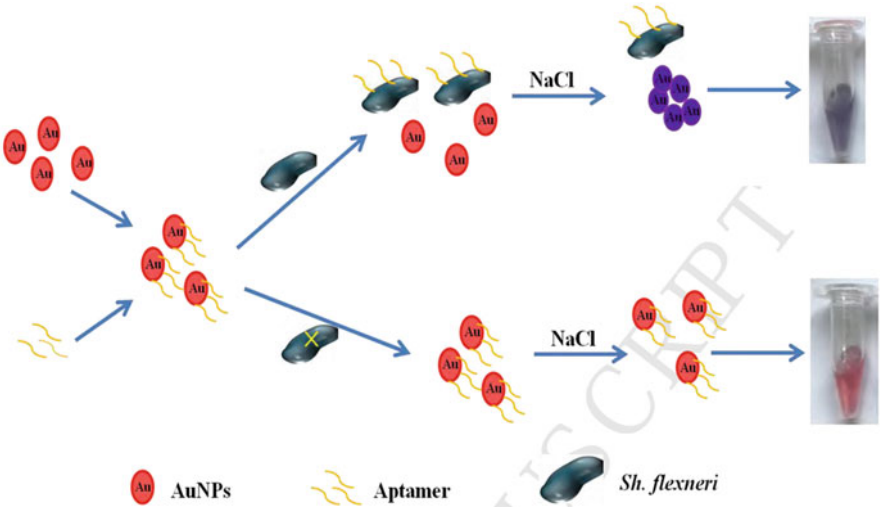

Fig. 3.2 A schematic representation of a AuNP-based colorimetric aptasensor for the detection of *Shigella flexneri* in food samples. A blue color change reflects the presence of the target bacteria (Feng et al. 2019)

AuNPs aggregate leading to a color change in the solution from red to blue (Fig. 3.2) (Feng et al. 2019).

Enzyme mimics have recently attracted ample attention in the development of colorimetric aptasensors as they are cost-effective and do not have the disadvantages that enzymes possess such as short lifetime and limited operational conditions. In one study, researchers developed a specific aptasensor for the detection of *Campylobacter jejuni* based on the peroxidase-mimicking activity of Au@Pd NPs. In the presence of H_2O_2, Au@Pd NPs can oxidase TMB, generating a blue colored solution. The absence of the target bacteria lead to the interaction of free aptamers with the NPs, blocking its surface and inhibiting its catalytic activity (Dehghani et al. 2018).

3.4.1.2 Fluorescence Aptamer-Based Assays

Fluorescence is the process in which an excited molecule, dye or nanomaterial emits light as it returns to its ground state. Due to their high sensitivity and efficiency, fluorescent assays are among the most prominent optical approaches which can generally be classified into labeled and label-free sensors. Since very few aptamers and biomolecules display intrinsic fluorescent behavior, most aptasensors are developed using a label which can consist of a fluorescent dye or nanomaterials (Feng et al. 2014). Label-free aptasensors are mainly based on molecular beacons in which the dye's fluorescence intensity is enhanced by the aptamer and quenched upon the binding of the target (Rhouati et al. 2016). Fluorescence resonance energy (FRET) is defined as the energy transfer between two fluorescent materials, a donor and an acceptor, with overlapping emission and absorption spectra, respectively (Borghei et al. 2017). Labeled and label-free FRET-based aptasensors have also frequently been used for foodborne pathogen recognition.

Albeit the many advantages of fluorescence sensing including simplicity and outstanding sensitivity, their use can be limited because of the disadvantages of organic dyes, which suffer from low extinction coefficients or quantum yields. Hence obtaining a fluorescent aptasensor with a low limit of detection using such dyes can be difficult. However, with the discovery of numerous nanomaterials with unique optical properties, new horizons in fluorescence detection have opened (Zhong 2009). Semiconductor quantum dots (QDs) are among the most commonly used fluorescent NPs, in which with the reduction of their size and as a result of the quantum confinement effect, their band gap widens leading to a range of size dependent luminescence peaks. QDs have numerous advantages including high photo-stability, tunable absorption and emission peaks, and bright emission which has led to the development of many QD-based aptasensors (Kurt et al. 2016; Renuka et al. 2018; Mohamadi et al. 2017).

Carbon dots (CDs), graphene quantum dots (GQDs), and graphene oxide quantum dots (GOQDs) are another group of nanomaterials with superior fluorescence behavior. Other than displaying strong photoluminescence, chemical inertness, biocompatibility, these NMs have low toxicity as compared to semiconductor QDs (Nemati et al. 2018a, b). GO and GOQDs have other merits such as its ability to interact with DNA through π–π stacking and also to act as a quencher for many

fluorescent dyes. In one study, GOQDs were used as quenchers for 5-carboxyfluorescein-labeled complementary DNA (FAM-cDNA) for the development of a fluorescent aptasensor based in FRET for the detection of *P. aeruginosa*. In the presence of the target bacteria and upon its binding to its specific aptamers, FAM-cDNA disassociated from the GOQDs, thus recovering the fluorescence of FAM (Gao et al. 2018). In another study, FRET between carbon quantum dots (CQDs) and gold nanoparticles (AuNPs) were exploited for the specific detection of *S. aureus* with a detection limit of 10 CFU/mL (Pebdeni et al. 2020).

Lanthanide-doped upconversion nanoparticles (UCNPs) are another class of NMs with fluorescence emission with excitation peaks in the near infrared (NIR) region. Their outstanding features including high photo-stability, multi-color tenability, low background noise, and narrow emission spectrum have led to their increasing application to fluorescence sensing systems (Duan et al. 2012; Li et al. 2020). These nanoparticles were used in a FRET-based aptasensor for the detection of pathogenic bacteria in which AuNPs (acceptors) were attached to the specific aptamers and UCNPs (donors) were attached to a complementary DNA sequence. The absence of target bacteria led to the occurrence of FRET, whereas in the presence of the target, the emission recovery of the UCNPs (Fig. 3.3) (Jin et al. 2017).

3.4.1.3 Chemiluminescence Aptamer-Based Assays

In chemiluminescence, a chemical reaction leads to the generation of excited molecules which emit light upon their return to the ground state. Various types of chemiluminescence, including bio-chemiluminescence, thermos-chemiluminescence, and electrogenerated chemiluminescence, are being employed for the detection of analytes. As there is no external light required for excitation, chemiluminescent signals are highly detectable thus leading to the outstanding sensitivity and proficiency of the sensors (Roda et al. 2016). Luminol or its derivatives are typically used as substrates which undergo many oxidations until they reach the excited state. From there, they emit blue light (425 nm) while returning to the ground state. The main disadvantage of chemiluminescent reactions is their low quantum yield, which researchers are attempting to improve using enzymes such as horse-radish peroxidase (HRP) or various nanomaterials with catalytic behavior (Ragavan and Neethirajan 2019). AuNPs have been proven to possess catalytic activity and thus are great candidates to incorporate with CL reagents as they lead to signal enhancement, unique optical features, and higher stability, as used in one study for the development of an aptasensor to detect *Salmonella typhimurium* (Hao et al. 2017b). Other nanostructures including ones containing silver or cobalt particles have also been explored for the catalytic behavior toward luminol or other CL substrates (Beigi et al. 2019; Salehnia et al. 2018).

Chemiluminescent resonance energy transfer (CRET) in the non-radiative energy transfer from a CL donor to an acceptor such as a dye or fluorescence NMs. As in this process, an external excitation energy source is eliminated, problems regarding autofluorescence or fluorescence bleaching are significantly reduced compared to

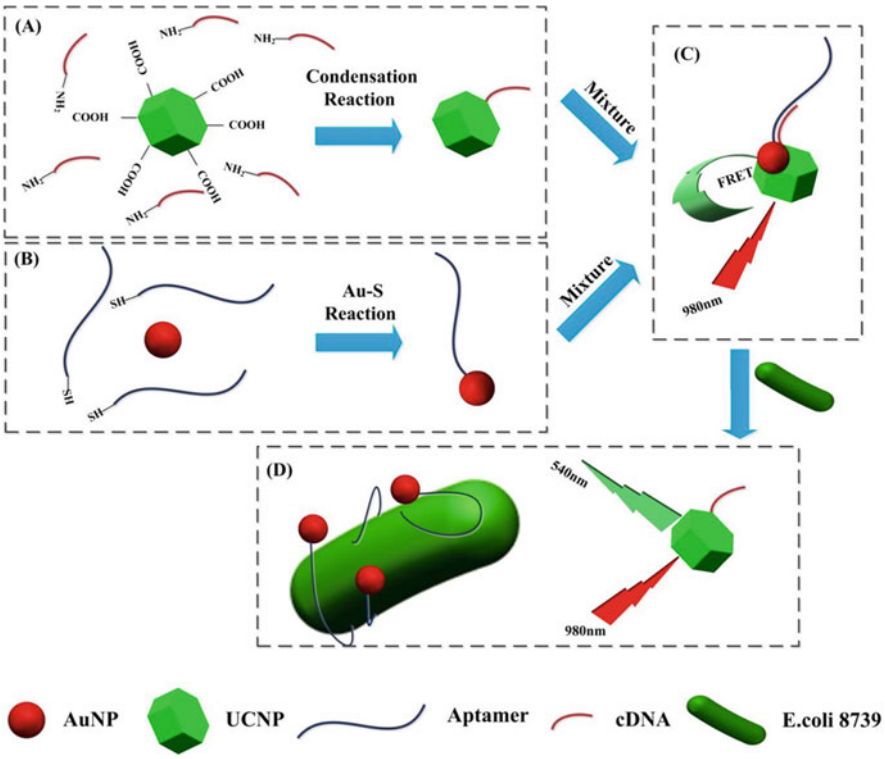

Fig. 3.3 A schematic representation of a FRET-based aptasensor with AuNPs and UCNPs for the detection of pathogenic bacteria (Jin et al. 2017)

FRET. A CRET-based aptasensor was proposed by Hao et. al. for the detection of *S. aureus* using rolling circle amplification (RCA) for further signal enhancement. In this method, Co^{2+} enhanced *N*-(aminobutyl)-*N*-(ethylisoluminol) (ABEI) functional flowerlike gold nanoparticles (Co^{2+}/ABEI-AuNFs) acted as the donor and WS_2 nanosheets were used as the acceptor. In the absence of target bacteria, the aptamers hybridized with the primers and inhibited the RCA reaction, which led to the quenching of the CL signal. The presence of the target bacteria freed up the primers for the initiation of the RCA reaction. The products of the RCA reaction interacted with the Co^{2+}/ABEI-AuNFs, thus freeing them from the nanosheets and attenuating the quenching effect they had (Hao et al. 2017a).

3.4.1.4 Surface-Enhanced Raman Scattering Aptamer-Based Assays

Raman scattering is an inelastic scattering of photons in which the energy of the light is decreased by the vibrational modes of the chemical bonds of matter. Surface-enhanced Raman scattering (SERS), also known as surface-enhanced Raman spectroscopy, is a surface-sensitive method that employs absorbed molecules on rough metal surfaces or specific nanomaterials to enhance the Raman scattering of the

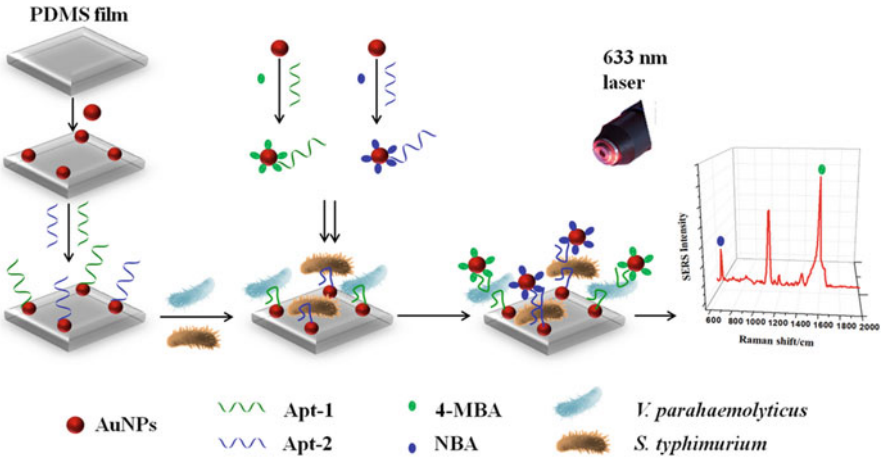

Fig. 3.4 A schematic representation of a SERS aptasensor for the simultaneous detection of two foodborne pathogenic bacteria (Duan et al. 2020)

specimen by 10^8–10^{12} times (Yi-Xian et al. 2012). Noble metal nanostructures, such as AuNPs and AgNPs, are among the commonly used NMs for signal enhancement in SERS-based sensors, although copper and aluminum NMs, and also mono- and bimetallic nanostructures such as Au@AgNPs, Au@ SiO_2NPs, Ag@SiO_2NPs, MNPs@Ag@Silica, MNPs@Silica@ Ag@Silica, Fe_3O_4@TiO_2@AuNPs, have recently been reported.

Compared to molecular-based methods, pre-treatment is not required in SERS-based detection. Furthermore, this approach can be achieved without the need for external labels such as fluorophores. All these, along with the outstanding sensitivity of SERS which enable single molecule detection have led to the vast application of this method, coupled with aptamer targeting, in foodborne pathogen identification including the detection of *Salmonella typhimurium* (Chen et al. 2017b), *Salmonella enterica* (Gao and He 2019), *E. coli* (Díaz-Amaya et al. 2019), *Vibrio parahaemolyticus* (Shen et al. 2019), etc.

As this approach is highly sensitive and selective, it is quite efficient for multiplexed detection of more than one pathogen for food safety control. In one study, a SERS aptasensor was developed for the simultaneous quantification of *V. parahaemolyticus* and *S. typhimurium* in a food matrix. To fabricate this sensor, as shown in Fig. 3.4, polydimethylsiloxane (PDMS), which is a widely used polymer as support material for SERS substrates since it shows high optical transparency and stability, was coated with AuNPs. Specific aptamers against the target bacteria were coated with two Raman reporters (4-MBA and NBA) and immobilized on the AuNPs, thus enabling the specific sensing of the two aforementioned bacterial cells (Duan et al. 2020).

3.4.1.5 Surface Plasmon Resonance Aptamer-Based Assays

Surface plasmon resonance (SPR) is a phenomenon defined as the resonant oscillation of certain materials' conductive electrons when stimulated by light of certain wavelengths. Using SPR, many optical analytical tools have been generated based on the detection of the interaction of two different molecules, one of which is mobile and the other fixed of a gold or silver film. Any variations in mass due to molecular binding lead to the change in the refraction index at the surface. As the SPR signal is solely based on changes in mass, the need for labeling is omitted in this technique. Besides being label-free, SPR is highly sensitive and provides rapid, real-time target quantification (Linman et al. 2010). SPR has been combined with aptamers for the specific detection of several foodborne pathogens including *Salmonella* (Lei et al. 2015) and *Vibrio parahaemolyticus* (Ahn et al. 2018).

Local surface plasmon resonance (LSPR) is an alternate method to SPR, in which instead of a continuous gold film, metal nanoparticles (prominently AuNPs or AgNPs) are used, which can lead to heightened sensitivity and more cost-effective sensing platforms. Compared to SPR, LSPR has gained more attention recently (Oh et al. 2017). Taking advantage of this approach, a multiplexed aptasensor was developed for the simultaneous detection of up to three pathogenic bacteria (Yoo et al. 2015). This aptasensor was developed using silica NPs (SiNPs) covered with a thin layer of Au absorbed on a glass slide and functionalized with specific aptamers. Using this method, a sensitive and reproducible aptasensor for pathogen identification was developed.

3.4.2 Electrochemical Detection

In an electrochemical sensor, the detection process is based on electronic current change caused by oxidation/reduction reactions that occur on the electrode surfaces. To create an electrochemical aptasensor, the aptamers are generally immobilized on conductive electrodes. Aptamer immobilization is prominently carried out on the basis of the chemical interaction of sulfhydryl-modified oligonucleotide sequences with gold electrode surfaces, although other techniques such as biotin-avidin modifications have been employed for aptamer immobilization (Radi 2011).

Electrochemical aptasensors (E-aptasensors) have been extensively used for the detection of various analytes as they are highly selective and sensitive and enable real-time analysis. Compared to optical techniques, electrochemical sensors require fewer reagents and thus are more cost-effective, and are also more feasible for on-site detection. Furthermore, quantitative measurements can be more precisely acquired with electrochemical approaches (Hayat and Marty 2014). E-aptasensors are usually classified with regard to the signal being measured, either impedance, current or potential, into impedimetric, amperometric/voltammetric, and potentiometric detectors, respectively.

3.4.2.1 Impedimetric Aptamer-Based Assays

These sensors measure the change in electrical impedance which occurs in the electrode/electrolyte interface when biorecognition occurs on the surface of a modified electrode (Wang et al. 2012). The ration of the system voltage phasor to the current phasor is known as impedance. As these electrochemical sensors do not require special reagents, and also because of their high stability and wide measurable range, impedimetric sensors are among the main detection approach used in E-aptasensors (Hayat et al. 2012), and have frequently been applied to detect foodborne pathogens including *Salmonella typhimurium* (Bagheryan et al. 2016), *Staphylococcus aureus* (Reich et al. 2017), and *Shigella dysenteriae* (Zarei et al. 2018).

Nanomaterials, especially AuNPS, are widely employed for electron transfer enhancement in electrochemical sensors, as they are able to improve the conductivity and increase the effective area of the electrode for biomolecule immobilization. In one study, an impedimetric aptasensor was developed for the rapid detection of *S. aureus* in food samples (Jia et al. 2014). In this approach, reduced GO (rGO), for their superior electron transporting property, and AuNPs, for the immobilization of thiolated aptamers, were decorated on the electrode for signal amplification and to reduce the detection limit (Fig. 3.5).

3.4.2.2 Potentiometric Aptamer-Based Assays

In these electrochemical biosensors, ion selective electrodes are used for analyte analysis. A two-electrode (WE (working electrode) and RE (reference electrode)) system or a three-electrode (WE, RE, and CE (counter electrode)) system are employed where target detection is done through measuring the potential variations

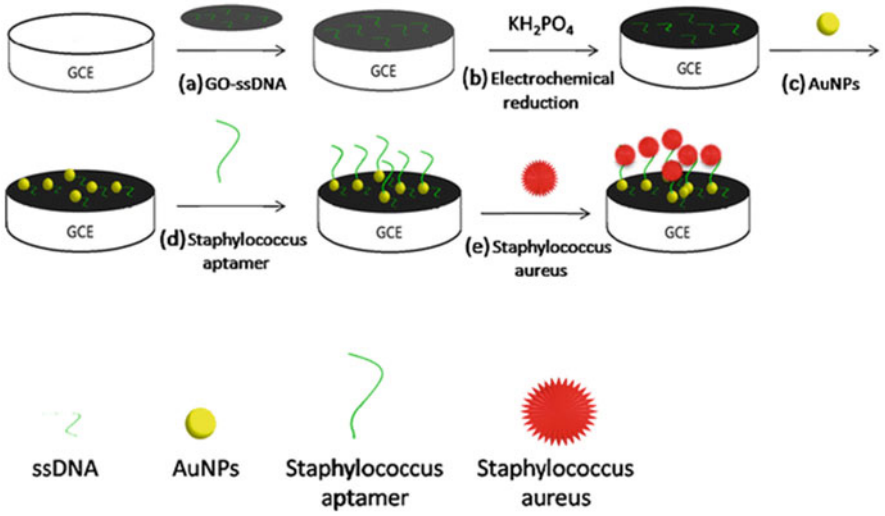

Fig. 3.5 A schematic representation of an impedimetric aptasensor based on rGO and AuNPs for the detection of *S. aureus* in food samples (Jia et al. 2014)

between WE and RE (Perumal and Hashim 2014). Although this technique has outstanding sensitivity and selectivity, it requires a highly stable and precise reference electrode which can hinder its application (Su et al. 2011). Potentiometric E-aptasensors have been used for the detection of several pathogens including *Salmonella typhimurium* (Silva et al. 2019), *Staphylococcus aureus* (Zelada-Guillén et al. 2012), *Listeria monocytogenes* (Ding et al. 2014), and *E. coli* (Hua et al. 2018).

Single-walled carbon nanotubes (SWCNTs) display significant charge-transfer capabilities and can be used as efficient ion-to-electron transducers in potentiometric sensing (Crespo et al. 2008). They are also feasibly deposited on many surfaces and can easily interact with the nucleic acid bases of the aptamers through π–π stacking interactions (Zelada-Guillén et al. 2009). In one study, a potentiometric aptasensor based on SWCNTs was developed for real-time analysis of *S. aureus* contamination in food samples (Zelada-Guillén et al. 2012).

3.4.2.3 Amperometric Aptamer-Based Assays

A two- or three-electrode system is also used in this class of electrochemical sensors. In these biosensors, analyte recognition is enabled through the measurement of the current flow between two electrodes when a redox reaction takes place as a result of the immobilized electroactive species on the surface of the working electrode after the application of an appropriate potential. Inert metals, such as Au and Pt, or carbon derivatives, such as graphite are commonly used to design the working electrode (WE). The simplicity and low-cost nature of these sensors has led to their vast application for biorecognition purposes (Hammond et al. 2016). Although regeneration problems between measurements are their main disadvantage (Ricci et al. 2007).

This method was used to generate a hetero-sandwich aptamer/immune amperometric sensor for *V. parahaemolyticus* detection. Specific antibodies were immobilized on the electrode as capture probes for the target bacteria, whereas aptamers induced RCA reaction for signal enhancement. This sensor was highly successful in the detection of *V. parahaemolyticus* in fish samples (Teng et al. 2017).

3.5 Aptamer-Regulated DNAzymes

Recent advances in molecular biology have shed light on the various functions of nucleic acids besides simply being hereditary biomolecules for the storage and transfer of genetic information. It has been proven that, similar to proteins, nucleic acids can function as ligand binding materials (DNA or RNA aptamers) or as catalytic molecules (ribozymes or DNAzymes) (Liu et al. 2009). As DNA is generally more stable than RNA, more focus has been devoted to DNA aptamers and DNAzymes.

Deoxyribozymes, more commonly known as DNAzymes, are defined as DNA sequences with the capability to perform chemical reactions. Numerous DNAzymes have been discovered with the ability to catalyze various reactions such as RNA cleaving (Santoro et al. 2000), DNA cleaving (Carmi et al. 1998), ligation (Purtha et al. 2005), phosphorylation reactions (Li and Breaker 1999), or peroxidase-

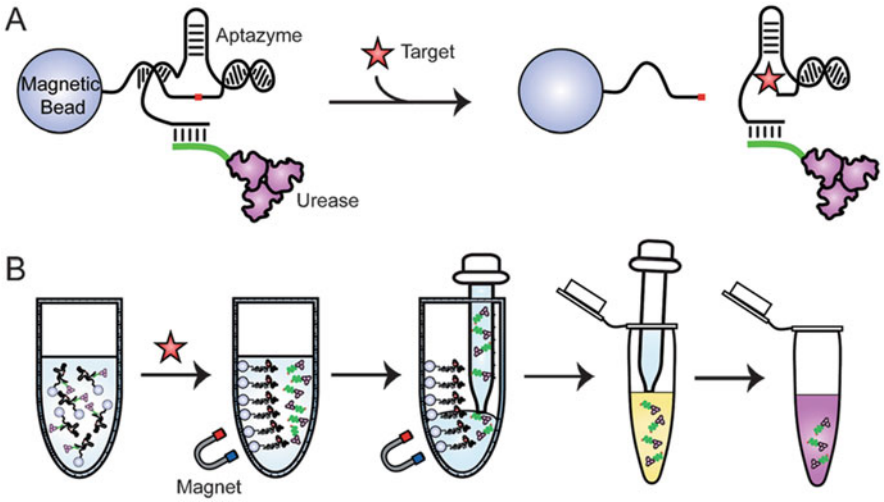

Fig. 3.6 Schematic representation of a biosensor based on RNA-cleaving DNAzymes and urease for the specific detection of pathogenic bacteria (Tram et al. 2014)

mimicking (Kosman and Juskowiak 2011). Among these, RNA-cleaving DNAzymes are most widely employed DNAzymes for sensing and therapeutic purposes. These DNAzymes are made of a substrate strand, containing a single RNA linkage (rA) which is the cleavage site, and an enzyme strand, which is composed of a catalytic core and two arms with distinct secondary structures. In the presence of specific cofactors, usually metal ions or amino acids, the substrate is cleaved in two parts (Liu et al. 2009).

Aptamer-regulated DNAzymes, also known as aptazymes, combine the recognition capabilities of aptamers with the catalytic activity of DNAzymes for highly selective molecular recognition. Many aptazymes have been generated using RNA-cleaving DNAzymes, as used by a group of researchers to develop a simple litmus test for the detection of pathogenic bacteria. In this method, RNA-cleaving DNAzymes were linked to urease and connected to magnetic beads. As can be seen in Fig. 3.6, the detection of the target bacteria leads to the release of the urease-DNAzyme complex, which can elevate the pH levels through the hydrolysis of urea into carbon dioxide and ammonia, thus enabling detection using litmus dye or a pH paper (Tram et al. 2014). In another study, RNA-cleaving DNAzymes were used to develop a fluorescence sensor for the detection of *E. coli*. The DNAzyme included an RNA linkage, which was flanked by nucleotides labeled with a fluorophore and a quencher, named RNA-cleaving fluorescent DNAzyme. The presence of the target bacteria led to the activation of the DNAzyme, which cleaved the chain, thus freeing the quencher and recovering the fluorescence emission of the fluorophore (Ali et al. 2011).

Peroxidase-mimicking DNAzymes have also been coupled with aptasensors for the detection of numerous analytes including the identification of foodborne

pathogens. G-quadruplex (G4)-hemin complex is a well-established peroxidase-mimicking DNAzyme. In one study, rolling circle amplification (RCA) was coupled with G4 DNAzymes to develop an electrochemical sensor for the detection of *E. coli*. In this assay, a probe containing anti-*E. coli* aptamers and a primer sequence for RCA with two G4 units was used. The presence of the target bacteria led to the formation of numerous G4 structures as a result of RCA. In the presence of hemin and K^+, the catalysis of H_2O_2 occurred leading to a significant electrochemical signal (Guo et al. 2016). G4 DNAzymes were also employed in a colorimetric sensor for the detection of *Vibrio parahemolyticus* (Sun et al. 2019). In this assay, aptamer-conjugated magnetic nanoparticles were employed as the capture probes, and G4 DNAzymes served as signal amplifying elements. The presence of the bacteria led to the oxidation of TMB by the G4-hemin complex, generating a blue solution.

3.6 Current Limitations

Albeit the promising merits and rapid advances of aptamer-based detection assays, aptasensors are still fairly immature compared to immunoassay. This is partially due to the limited availability of aptamers with high specificity and affinity toward the target. Furthermore, surface immobilization technologies are still not fully understood for aptamers, although the incorporation of nanotechnology with aptasensors have helped to tackle this problem to some extent. Another problem which can hinder the vast use of aptamers is that configuration change has been reported for some as a result of certain temperatures, pH, or other experimental factors, which can interfere with their ability to capture the target. Owing to the aforementioned problem, many aptamers have not been successfully applied to real samples, despite being able to achieve excellent results in the buffer. Actual samples also have a complex composition which can lead to nonspecific interactions and unselective targeting by the aptamers. These problems need to be thoroughly investigated in order for aptamers to be able to find their way in the biosensor market.

3.7 Conclusion

In this chapter, a brief overview of aptamer-based sensors and their application for foodborne pathogen detection was presented. Food safety and foodborne pathogens are a major concern which can have tremendous health and economic repercussions for societies. Conventional detection techniques, including cell culture methods and PCR, are time-consuming and require complex laboratory facilities and professional technicians, therefore their application is limited especially in remote, developing areas. Thus, rapid, simple detection techniques are highly in demand for foodborne pathogen screening and food safety monitoring.

It has been predicted that aptamer-based sensors will soon dominate the sensing field in biomedicine and food safety control due to being cost-effective, sensitive, reproducible, and stable for real-sample analysis. The incorporation of

nanotechnology has further helped generate simple aptasensors with superior performance by providing signal enhancement approaches and facilitating biomolecule immobilization. It can be expected that in the near future simpler, more efficient, and faster nanoengineered aptasensors will be available for food safety control.

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Electrochemical Sensors for Food Adulterants

4

Neda Irannejad and Behzad Rezaei

Abstract

Most foods that are consumed daily are prone to food adulterant. Food adulterants are classified into several main groups. One of the most important cases of food adulterants is to increase the quality of raw or prepared foods by intentionally or accidentally adding non-food to them. The removal or replacement of valuable food components with relatively cheaper ones that significantly affect the original nutritional value and the addition of any poisonous or deleterious substances that are hazardous to the health of the consumer are also cases of food adulterants. In the recent years, food adulterations have steadily increased and become a major challenge for consumers, taking into account all economic, social, health, and religious aspects. Due to the importance of recognizing the authenticity of each food before it becomes available for public consumption, various methods including physical, chemical, biochemical, etc., are used to evaluate them. Meanwhile, electrochemical sensors, with their unique features such as simplicity, ease of operation, high sensitivity, and selectivity, have become a promising choice for evaluating food authenticity.

Keywords

Food adulterant · Biosensors · Electrochemical methods

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4.1 Introduction

Food in a variety of raw, processed, or semi-processed forms is consumed as a basic necessity of life to support various biochemical and physiological activities. Plant or animal foods are prone to food fraud and adulteration, which directly affects the health of consumers. Synonyms like admixture and substitution help to better define the word adulteration (He et al. 2020a, b; dos Santos et al. 2020). The term food fraud and adulteration mean a reduction in the quality of food following intentional or unintentional substitution, as well as the removal of some value-added substitutes from the main food items, the manipulation or misrepresentation of food, and the packaging of food for economic gains (Fikselová et al. 2020; Gizaw 2019).

Therefore, one of the most influential issues in the food supply chain that has attracted the attention of researchers, government, and regulatory bodies is the quality and safety of food. The term adulteration is used legally when a food product fails to meet federal or state standards (Choudhary et al. 2020). Foods that fall into one or more of the following categories are considered adulterated foods under Federal Food, Drug, and Cosmetics Regulations (FFDCA) and the Food and Drug Administration (FDA) (Wallace and Oria 2010).

- Adding a substance that is harmful to health.
- Add cheap or low-quality items that affect the ultimate nutritional value.
- Remove any valuable constituents from the main food.
- Decreased food quality to some extent below defined standards.
- Add any substance that increases the volume or weight of the food.
- Add any substance that appears the food more valuable.

Given the importance of food health and its effect on the quality of consumer's life, comprehensive knowledge of food adulterations, and the various consequences of these frauds are very important and decisive.

4.2 Intentional Adulteration

Intentional adulterations are additives of inferior substances with similar food properties that are used to obtain financial gain. One of the most common types of adulteration is color adulteration (Fiorino et al. 2019a, b). Types of intentional adulterations can be summarized as follows:

- Adding water and/or urea to liquid milk and removing and/or substituting milk solids from a natural product affects the quality and nutritional value of the product.
- Adding extraneous matters to the ground spices that affect the quality and health of the final product.

- Adding non-food ingredients to foods such as washing powder to ice cream, chalk to sugar, chicory to coffee, powered stone to common salt, etc., all of which severely affect the health of the final product.

Given the direct connection between intentional adulteration with quality, nutritional value, and health of food products, as well as its overall impact on consumer health, their diagnosis is very important (Banti 2020).

4.3 Unintentional Adulteration

Unintentional food adulteration (Incidental adulteration), as its name implies, is the result of ignorance or lack of proper facilities, and hygiene which affects the quality of food. This type of unintentional adulteration can occur at any stage from production to consumption. Therefore, all processes of product production, processing, storage, transportation, and marketing can be identified as food adulterations (Esteki et al. 2019; Osman et al. 2019). Types of unintentional adulterations can be summarized as follows:

- Leakage of pesticide residues, rodent droppings, fertilizers, and larvae into vegetables, fruits, etc.
- Leakage of industrial pollutants such as heavy metals to vegetables, plants, etc.
- Contamination is caused by bacteria and fungi during the production, transportation to consumption stages.
- Dust or harmful residues of packaging materials enter the food.

Given the direct impact of unintentional food adulteration on consumer health, the detection and measurement of this type of food adulteration are very crucial (Oliveira et al. 2019; Wang et al. 2020).

4.4 Natural Adulteration

The presence of various chemicals, organic compounds, or radicals naturally occurring in foods cause another type of food adulteration called natural adulteration. This type of adulteration is more commonly reported in pulses, mushrooms, vegetables, fish, and seafood that contain toxic substances (Okpala 2019; Services H 2001).

4.5 Adulteration in Organic Foods

According to the standards set by the relevant organizations in each country, if the food is claimed to be organic, it is necessary to follow certain protocols to sure the product has unique characteristics. In a typical agricultural product, none of the synthetic pesticides are used. Therefore, any food that does not meet the existing

standards is in the category of food adulterations (van Ruth and de Pagter-de Witte 2020).

4.6 Adulteration During Irradiating the Foods and Production of Genetically Modified

In the preparation process of some foods, ionizing radiation is applied to destroy and check the multiplication of microorganisms, bacteria, viruses, or insects. Due to the possibility of disturbances in the internal metabolism of cells, DNA cleavage, disruption of chemical bonds, and the formation of free radicals during the irradiation process, the dosage of radiation are very important. If the use of ionizing radiation dosage is outside the specified standard range, this activity without consumer awareness is considered as food adulteration. Modern technology, or gene technology, refers to the Genetically Modified Organisms (GMOs), for genetic (DNA) modification that does not happen in nature. Producing transgenic foods is known as food adulteration when it violates food nutrients and health standards (Bansal et al. 2017; Banti 2020).

4.7 Importance and Necessity of Detecting Food Adulterations

Human health is highly affected by food adulterations. Food adulteration can have both short-term and long-term health consequences leading to many mild to life-threatening conditions. Diarrhea, dysentery, vomiting, and skin diseases are immediate side effects of eating foods with adulterations. Long-term side effects include gastrointestinal problems, peptic ulcers, and stomach dysfunction, liver disease, kidney damage, heart disease, bone marrow abnormalities, and cancer (Gizaw 2019; Kumar et al. 2019). Given the necessity of food adulteration detection, it is essential to achieve methods with high accuracy and precision that can provide reliable results in the shortest time. To date, a variety of methods have been developed based on morphological/anatomical characteristics, organoleptic markers (odor, color, texture), and chemical/electrochemical testing to authenticate traded food and to check for adulterants (Hong et al. 2017; Jiménez-Carvelo et al. 2019). Physical (based on microscopic/macroscopic analysis of food structure), chemical, and biochemical (based on common chromatographic methods, spectroscopies, immunologic and electrophoretic techniques), and molecular transductions (based on DNA analysis) are the main studied techniques (He et al. 2020a, b; Meenu et al. 2019).

4.7.1 Electrochemical Detection Techniques

Electrochemical sensors have found a special place as a promising tool for examining food frauds and adulterations. The dramatic revolution in the use of

electrochemical methods can be attributed to the special detection mechanism based on the conversion of the input signal (analyte detection) into an electrical output signal appropriate to the concentration of the target molecule. An electrochemical cell consists of a working or indicator electrode (as a converter in electrochemical and bioelectrochemical reactions), counter (as a controlling element for monitoring the possibility of applying currents to the working electrode), and reference (to stabilize the potential applied to the system) (Cesewski and Johnson 2020; Kurbanoglu et al. 2020; Riu and Giussani 2020; Sharifi and Pirsa 2020; Ye et al. 2020). Electrochemical methods are classified into potentiometric, amperometric, and impedimetric sensors depending on the output signal.

4.7.1.1 Potentiometric Biosensors

Potentiometry is an efficient method under zero or no significant flow currents through the indicator and reference electrodes. Potentiometry is a process in which the changes in indicator electrode potential are measured concerning a reference electrode. The response generated in this method is proportional to the number of electroactive species present in the sample (Banica 2012; Rezaei and Irannejad 2019). The potentiometric method has the following characteristics:

- Simple cell design and measurement method, and the possibility of managing the examined signal.
- Ability to measure without interfering with dissolved oxygen.
- Lack of the influence of the eluent flow rate on the electrode potential, in the presence of certain types of indicator electrodes.
- Lack of indicator electrode participation in electrolysis reactions and, consequently, reduced contamination of the electrode surface.
- The possibility of using the reference electrode at greater distances from the indicator electrode if the electrical contact between them is maintained through the flowing solution, which is due to the non-critical ohmic resistance.

In potentiometric methods, the Walther Nernst equation can attribute the measured potential difference (between the indicator, and the reference electrode) to the analyte concentration (Eq. 4.1).

$$E = E^{\circ} - \frac{RT}{nF} \times \mathrm{Ln} \frac{\propto \mathrm{Red}}{\propto \mathrm{Ox}}. \tag{4.1}$$

In this equation, "E°" is equivalent to the standard potential of the electrode (V), "R" is the gas constant (8.314 $\mathrm{J.K^{-1}}$), "T" is the constant temperature in Kelvin degrees, "F" is Faraday's constant (96,500 $\mathrm{C.mol^{-1}}$), and "$\propto$ Red/$\propto$ Ox" is attributed to the activity ratio of the species in the sample. In potentiometric methods, due to the sensitivity dependence on temperature, it is necessary to keep the temperature constant. Potentiometry is chemically ineffective on the sample. This feature makes this method effective in measuring very low concentrations (Cifrić et al. 2020; Ding and Qin 2020).

Potentiometric electronic-tongues (E-tongue) are one of the most widely used biosensors. E-tongues are multi-sensory systems based on biological mechanisms used to analyze liquids (Peris and Escuder-Gilabert 2016). In the gustatory system, the taste information (such as salts, acids, sugars, bitter, and astringent compounds) are converted into an electrical signal by the biological membrane of gustatory cells in non-specific taste buds of the tongue. Then the taste is detected by being transmitted to the brain. An E-tongue includes parts for automatic sampling, chemical sensors with different selectivity, signal recording equipment, and signal processing software. This method has many advantages, the most important of which is no requirements of special sample pre-treatment. The most important and sensitive component in E-tongue is the membrane. In the design of a typical E-tongue, the Ag/AgCl reference electrode and connection of a conductive resin (such as silver epoxy resin) to electrical wires (such as copper, silver) are used. The membrane in this system must be non-porous, water-soluble, and mechanically stable. Selective binding of ions leads to membrane potential (Rodríguez-Méndez et al. 2016; Wadehra and Patil 2016; Wasilewski et al. 2019).

4.7.1.2 Amperometric Biosensors

Electrochemical amperometric systems are based on measuring the current due to oxidation or reduction of electroactive species at the electrode surface. Amperometry represents methods in which current changes occur over time, while the potential in the cell is kept constant. In this method, the current is measured while maintaining the potential at the desired value. The peak intensity of the measured current is directly related to the bulk concentration of the analyte in the solution. Due to the distinguishing feature of the potential due to oxidation or reduction of biological species, biosensors have a high selectivity (Dias et al. 2017; Kucherenko et al. 2020; Sahin and Kaya 2019).

4.7.1.3 Voltammetric Biosensors

Voltammetry refers to methods in which analytical evidence is evaluated following potential change and determination of the resulting current. Different potential change methods have led to the appearance of various voltammetric methods, such as cyclic voltammetry (CV), linear sweep voltammetry (LSV), normal pulse voltammetry (NPV), and differential pulse (DPV), square wave voltammetry (SWV) (Fischer and Fischerová 1995; Rezaei and Irannejad 2019; Uslu and Ozkan 2011). Among these, cyclic voltammetry, with the possibility of investigating the mechanisms involved in the reaction, parameters affecting kinetic such as electrochemical rate constant, an analyte concentration, has attracted much interest. The CV method is based on tracking the current between the working and the counter electrodes, while the potential changes of the working electrode relative to the reference electrode are controlled. In this method, the potential sweep is performed from an initial value (V_1) to a predetermined value (V_2) and then returned to its original or another specified potential one. Reverse scanning provides very valuable information regarding the reversibility of the reaction. Due to the effective role of time in performing chemical and biochemical reactions, the speed of potential

sweeping over time is very decisive (Chooto 2019; Pellitero et al. 2020; Puthongkham and Venton 2020).

Electronic-tongues (E-tongue) based on voltammetric methods are another type of these systems. In the design of voltammetric E-tongue typically an array of noble metal networks such as gold, palladium, platinum, and silver, or electrodes embedded in a polymer and epoxy graphite coating membrane are commonly used. The use of engraved arrays including working, counter, and reference on screen-printed electrodes is another type of arrangement of E-tongue (Atta-ur-Rahman 2020; Pérez-Ràfols et al. 2019; Shimizu et al. 2020). Voltammetric E-tongue, potentiometry E-tongue, or even hybridization have created a dramatic revolution in food analysis, biomedical, and pharmaceutical researches (Hosnedlova et al. 2020; Magro et al. 2019; Tan and Xu 2020; Titova and Nachev 2020).

4.7.1.4 Electrochemical Impedance Spectroscopy (EIS)

In biological systems, the use of simple, inexpensive, fast, and non-invasive methods is very important. Meanwhile, the electrochemical impedance (EIS) technique, with the ability to evaluate the properties of inherent materials and to investigate specific processes involved in the conductivity/resistance or capacity of the electrochemical system, has created a huge revolution in biological measurement and analysis systems. "Impedance" represents the resistance of an electrical circuit in the presence of alternating current (AC) scanned between electrodes. In this method, the current response is measured by applying a small sinusoidal potential, along with extensive changes in the frequency range. The impedance response results in the Nyquist plot which consists of two components, real (Z_{re}) and imaginary ($-Z_{im}$) ($-Z_{im}$ versus Z_{re}), as a function of frequency (He et al. 2020a, b; Malvano et al. 2020; Preuß et al. 2020). In analyzing the Nyquist plots of any particular system, the corresponding equivalent circuit is used to investigate the possible presence of ohmic resistance (R), capacitance (C), constant phase element (CPE), and Warburg impedance (W). In Table 4.1, further introduction of each component, frequency dependence, and phase shift of impedance components are discussed.

Using the obtained equivalent circuit and the interpretation of the Nyquist plot, useful information is obtained from biological systems, foods, proteins, microorganisms, nucleic acids, antigens, and antibodies (Chai and Oh 2020; Reich et al. 2020; Xu and Yadavalli 2019).

Table 4.1 Define each component of the impedance

Impedance component	Definition	Phase angle (°)	Frequency dependence
R	$Z = R$	0	No
C	$Z_C = 1/j\omega C$	90	Yes
CPE	$Z_{CPE} = 1/A(j\omega)$	0–90	Yes
W (infinite)	$Z_W = \sigma/\sqrt{\omega}\,(1-j)$	45	Yes
	$\sigma = RT/n^2F^2\,\sqrt{2}\,(1/\sqrt{D_0c_0} + 1/\sqrt{D_Rc_R})$		

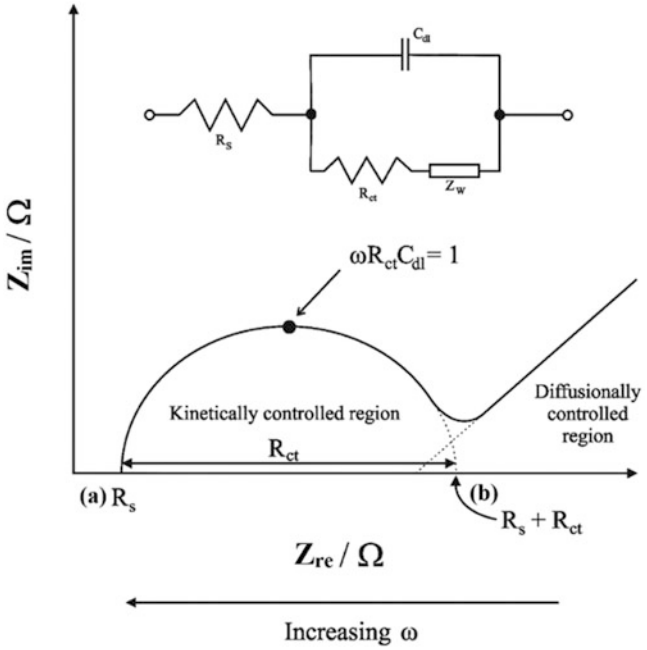

Fig. 4.1 Nyquist plot of the Randles circuit (Rezaei and Irannejad 2019)

One of the most common Nyquist plots is the Randles circuit. According to the equivalent circuit (Fig. 4.1), Randles circuit consists of a solution resistance (R_s), located in series concerning the double layer (C_{dl}), and charge (electron) transfer resistance (R_{ct}), which located in parallel to each other. Warburg impedance (W) located in series with the R_{ct}. As can be seen in Fig. 4.1, R_s and R_{ct} can be calculated directly from points (a) and (b), respectively (Randviir and Banks 2013).

4.7.2 Overview of Electrochemical Detection Methods for Food Adulterants (In Recent Years)

In the following, some applications of electrochemical detection methods for analyzing food adulteration are reviewed and summarized in Table 4.2. Honey is considered a valuable natural food. Honey is rich in vitamins, carotenoids, proteins, mineral salts, sugars, and phenolic compounds, which in addition to high nutritional value, also has antioxidant properties. One of the effective parameters in honey quality control is measuring the amount of phenol and flavonoid content in it. Given that any change in the standard concentration of these compounds has a direct impact on the nutritional value of honey and can be considered as food adulteration, their measurements are very important (Bogdanov et al. 2008; Damto 2019).

Table 4.2 Summary of some of the electrochemical sensors for food adulterants (2019–2021)

Adulterant	Food	Electrochemical	Biosensor	LOD[a]/LOQ[b]	Linear range	Ref
Amphetamine	Natural over-the-counter weight-loss products	SWV	Batch injection analysis	LOD: 0.13 mg L^{-1}	5.0–40 mg L^{-1}	Freitas et al. (2021)
Coumarin	Milk	DPV	Carbon-based electrode	LOD: 1.3 μM	2–34 μM	Krishnan and Saraswathyamma (2021)
Corn syrup	Honey	CV	Cu/CuO electrode	—	—	Guellis et al. (2020)
Melamine	Infant formula	DPV	Molecularly imprinted composite	LOQ: 0.0172 nM	0.1–180 nM	Regasa et al. (2020a, b)
Formaldehyde	Milk	DPV	Polypyrrole (PPy)-reduced gold	LOD: 0.4 mM	—	Xi et al. (2020)
Porcine DNA	Meat	DPV	SiNWs/PtNPs[c] on SPCE[d]	LOD: 2.4×10^{-9} M	3×10^{-9}–3×10^{-5} M	Kusnin et al. (2020)
Melamine	Infant formula	CV, SWV	MICPs[e]	LOD: 4.47×10^{-10} M	$0.6–16 \times 10^{-9}$ M	Regasa et al. (2020a, b)
Formaldehyde	Mango juice	CV	α-Fe_2O_3	—	0.01–0.3 mg/L	Kundu et al. (2019b)
Chloramphenicol	Milk	CV, DPV	Co_3O_4@rGO	LOQ: 0.55 μM	1–2000 μM	Yadav et al. (2019)
Sus scrofa mtDNA	Raw and processed meat	CV, DPV	SPCE-gold	LOQ: 0.58 μg/mL	—	Hartati et al. (2019)

(continued)

Table 4.2 (continued)

Adulterant	Food	Electrochemical	Biosensor	LOD[a]/LOQ[b]	Linear range	Ref
Saccharide	Commercial juice	CV	Inv-GOx[f]-MWCNTs[g]-AgNPs	LOD: 1×10^{-9} M	1×10^{-4}–1×10^{-9} M	Bagal-Kestwal and Chiang (2019)
H_2O_2	Beer	CV, EIS	2D MOF[h]/MWCNT films	—	0.001–8.159 mM	Wang et al. (2019)

[a]Limit of detection
[b]Limit of quantification
[c]Silicon nanowires/platinum nanoparticles
[d]Screen-printed carbon electrode
[e]Molecularly imprinted conducting polymers
[f]Invertase and glucose oxidase
[g]Multiwalled carbon nanotube
[h]Two-dimension metal-organic framework

Draghi et al. used a potentiometric biosensor as a simple, fast, and available method for determining phenol compounds (Draghi and Fernandes 2017). The proposed biosensor is label-free which stabilized on the surface by forming covalent bonds using tyrosinase extracted from Musa acuminata. The designed two-layer transducer consists of the first layer, a combination of poly(vinyl) chloride carboxylate (PVC-COOH), graphite, and potassium permanganate, and the second layer, a mixture of poly(vinyl) chloride carboxylate and graphite. The results showed that the designed potentiometric biosensor has a low detection limit of 7.3×10^{-7} M and a wide linear range of 9.3×10^{-7} and 8.3×10^{-2} M.

One of the most common food adulterations in developing countries is formaldehyde adulteration. Formaldehyde (as formalin, 37% formaldehyde), has a wide range of applications as a preservative in biological samples, cosmetics, and food such as milk, seafood, fruits, vegetables. Formaldehyde is identified in the group of carcinogens with long-term negative effects on human health (Biswas et al. 2020; Mohanty et al. 2018). The Kundu research team designed an efficient electrochemical biosensor to detect formaldehyde adulteration in citrus juice (Kundu et al. 2019a). The response of the designed biosensor was evaluated using cyclic voltammetry. The results of this study showed that nanocomposite based biosensor (CNT-Fe_3O_4) as an available, fast, and in time method has high sensitivity (527 μA mg/L cm^2), low detection limit (0.05 mg/L) in the linear detection range of 0.05–0.5 mg/L. The introduced method is a highly stable, reproducible, efficient, and selective biosensor for formaldehyde determination in orange juice.

Meat is marketed as one of the most valuable foods, in various forms (raw or processed). Given the importance of this food, the meat must be free of harmful bacteria and unwanted chemicals. The purity of the meat and the accuracy of the meat products composition percentage are other essential parameters for consumers. Therefore, determining the exact composition and analyzing the quality of meat to confirm its free from any food adulteration is essential (Böhme et al. 2019; Han et al. 2020; Martuscelli et al. 2020).

Due to the importance of using inexpensive, rapid, and available techniques to assess meat quality, in the Flauzino research group, a sensitive sensor using a graphite electrode modified with graphene oxide/poly(3-hydroxybenzoic acid) nanocomposite with specific DNA was designed to detect bovine mitochondrial DNA (Flauzino et al. 2020). Figure 4.2 shows the scheme of the designed genosensor construction. The results of this study showed that the designed sensor has high selectivity and repeatability that can be used five consecutive times without losing the current signal.

In a valuable study to detect processed sausage adulteration, Mansouri et al. used a unique sequence probe (Mansouri et al. 2020). Figure 4.3 shows the schematic of genosensor preparation. For this purpose, a species-specific electrochemical DNA probe (locked nucleic acid, LNA) was designed and used as a DNA-based electrochemical genosensor. The results of this study showed that the proposed genosensor as a sensitive, inexpensive, fast, and reliable system has a high sensitivity of 148 pM lower limit of quantification (LLOQ) and optimal accuracy with a standard deviation (RSD) of 0.16%.

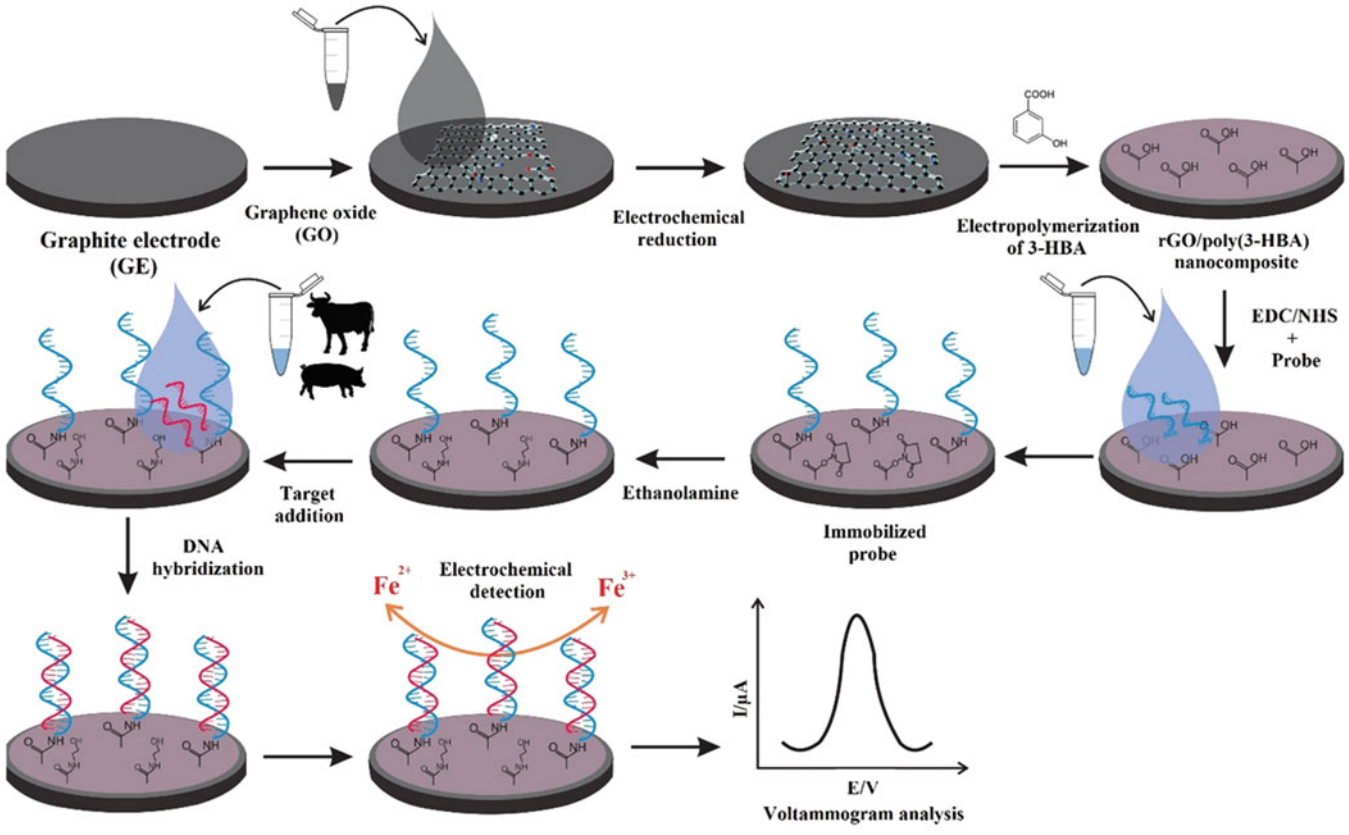

Fig. 4.2 Schematic preparation of designed electrode on a graphite surface modified with rGO/ poly 3-hydroxybenzoic acid (3-HBA) nanocomposite for covalent binding of the single-stranded DNA molecule, to bovine mitochondrial DNA, to confirm the purity of beef. Initially, according to a specific mechanism, an amine-terminated single-stranded probe of DNA BOSNH using *N*-(3-dimethyl aminopropyl)-*N′*-ethyl carbodiimide hydrochloride (EDC), *N*-hydroxy succinimide (NHS) was attached into graphite surface carboxylic groups/rGO/poly (3-HBA). Then the oligonucleotide solution of BOSNH was added to the electrodes under certain conditions. Ethanolamine was used to remove the EDC/NHS reactive groups. Finally, the prepared electrode was washed with PBS and dried with nitrogen gas (Flauzino et al. 2020)

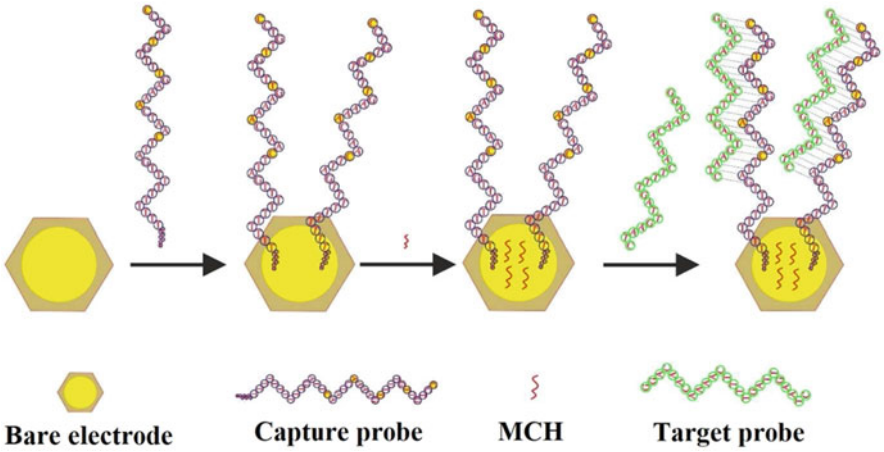

Fig. 4.3 Schematic of the designed electrode. Initially, the surface of the gold electrode was well polished and washed. Then, the dried electrode was modified with a locked nucleic acid (LNA). After ensuring the absence of any unabsorbed LNA probes, non-specific binding sites were blocked using mercaptohexanol solution (MCH). Finally, after contact of the electrode with the DNA target solution for a certain time, a specific genosensor was designed (Mansouri et al. 2020)

The level of glucose and fructose in honey is an influential factor in its nutritional value. Revenga-Parra et al. used an efficient electrochemical sensor based on a new Schiff–Nickel-based complex (Ni(II)-2,3dhS) on carbon nanotube-modified screen-printed electrodes (CNTSPE) to determine and quantify saccharides in honey (Revenga-Parra et al. 2020). Figure 4.4 shows the preparation of the Ni(II)-2,3dhS/CNTSPE sensor. The use of this sensor has created the conditions for direct measurement of saccharides in honey, without the need for any pre-preparation or initial separation. The results of this study provide a clear overview of saccharide analysis in food.

Electrochemical impedimetric biosensors (EIBs), with the rapid, sensitive, and non-destructive detection ability, have revolutionized measurement systems. These sensors detect target molecules by generating responses in the form of electrical signals to an input sinusoidal electrical signal (Brosel-Oliu et al. 2019; Chinnadayyala et al. 2019; Leva-Bueno et al. 2020; Tanak et al. 2019). As shown in Fig. 4.5a an electrochemical impedimetric biosensor (EIBs) consists of a signal transducer, an electrically conductive electrode substrate, and biological recognition elements (Chai and Oh 2020). Electrically conductive electrode substrate is made of platinum, graphite, gold, stainless steel, silicon, and aluminum. Nano-porous metal oxide compounds and carbon composites have also been used in the design of electrically conductive electrode substrates. Antibodies, aptamers, and receptors are elements of biological recognition elements. To achieve the desired results in biosensors, it is necessary to use appropriate methods to immobilize the biological recognition elements, on the electrode surface. The proper selection of methods that

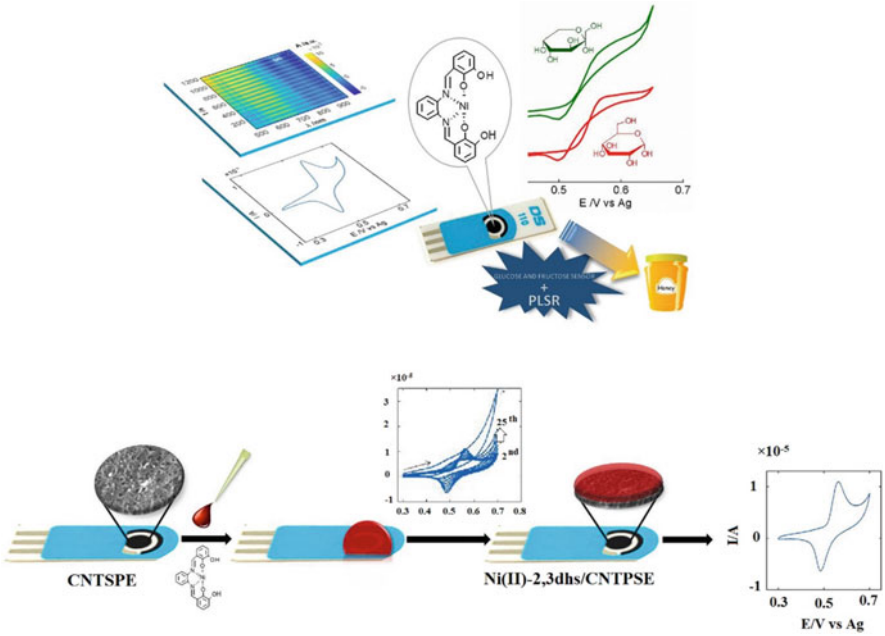

Fig. 4.4 Schematic of the Ni(II)-2,3dhS/CNTSPE sensor. The CNTSPE electrode was immersed in a solution of Ni (II)-2,3dhS at a certain concentration. Then, by applying the appropriate potential, the modified electrode (Ni(II)-2,3dhS/CNTSPE) was designed and washed (Revenga-Parra et al. 2020)

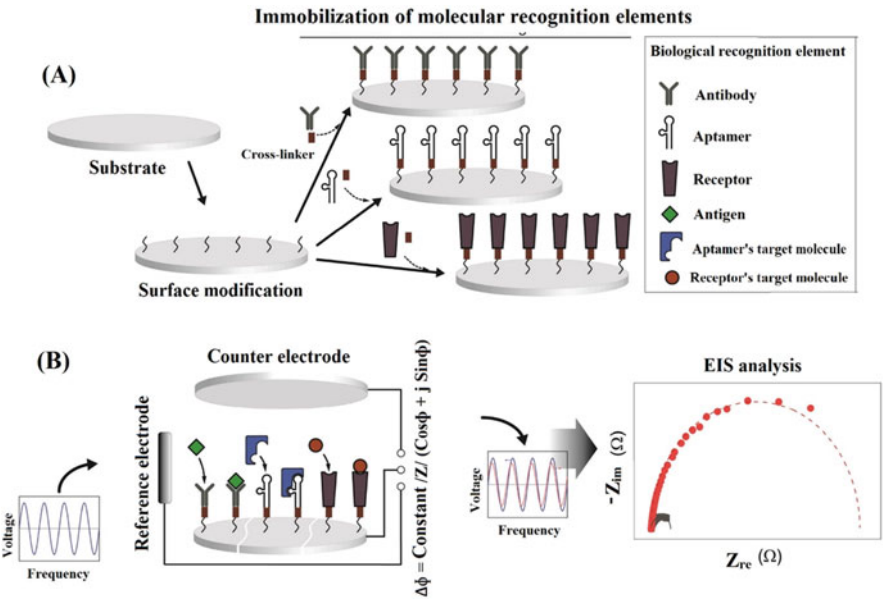

Fig. 4.5 Schematic illustration of (**a**) the structure and construction, and (**b**) detection and measurement process, of EIB (Chai and Oh 2020)

do not damage the active center of the biological recognition elements during the immobilization process on the surface is crucial.

Vegetable oils, as an energy source with essential fatty acids, are an important part of a balanced and healthy diet. The nutritional value of vegetable oils is highly evaluated during the production process, correct labeling, and quantification of quality factors (Salah and Nofal 2020). Semenov et al. used an E-tongue-based potentiometric sensor to evaluate important indicators of edible oil quality, such as peroxide value, panisidine value, and concentration of total tocopherols (Semenov et al. 2019). The results showed that the proposed method with simplicity, relatively low cost, very short analysis time, and "green" characteristics can be very effective in identifying edible oil.

Cheese is one of the most important dairy products, which the concentration of ions in it is very important in determining its nutritional values (Lei and Sun 2019). Torabi et al. have introduced a potentiometric E-tongue for the simultaneous evaluation of ions in commercial cheeses (Torabi et al. 2020). The proposed method is a very promising option for traditional methods.

Oroian et al. used an E-tongue-based voltammetry technique to verify the authorization of honey (Oroian et al. 2018; Oroian and Ropciuc 2019). Designed electrodes based on silver and gold have the potential to measure validation parameters honey according to the botanical authentication. The results of this study showed that the introduced system is a promising method in the honey industry.

Coffee is known as one of the most consumed beverages in the world. Due to the commercial importance of this valuable beverage, adulterant samples have also become widespread. Adding toasted beans such as soybeans and rice corn are one of the most common examples of coffee adulteration (Burns and Walker 2020; Wang et al. 2020). Arrieta's research team used a voltammetry system designed based on E-tongue to assess the authentication of coffee samples (Arrieta et al. 2019). The results of this study confirm the optimal performance of a designed sensor to evaluate the presence or absence of adulteration in coffee samples.

Antibiotics and compounds with antimicrobial activity with a wide range of applications in medicine, agriculture, and animal husbandry have been one of the fundamental successes to improve human health benefits. Today, the uncontrolled use of antibiotics has raised many concerns. Improper release and disposal of these compounds in the environment can have irreversible effects on health and the environment. These emerging contaminants accumulate in soil and water ecosystems and enter the food cycle while increasing their antibiotic resistance with maintaining their antimicrobial effects. All of these concerns have led to the development of techniques for detecting very small amounts of antibiotics (Pollap and Kochana 2019; Sachi et al. 2019).

Murilo Henrique et al. used a powerful impedimetric E-tongue designed based on molybdenum disulfide and graphene oxide to successfully identify distinct antibiotics (Facure et al. 2020). The designed sensor, with the ability to quickly detect, high sensitivity, the ability to distinguish infected samples from samples without antibiotic contamination, is a promising method of monitoring and detecting

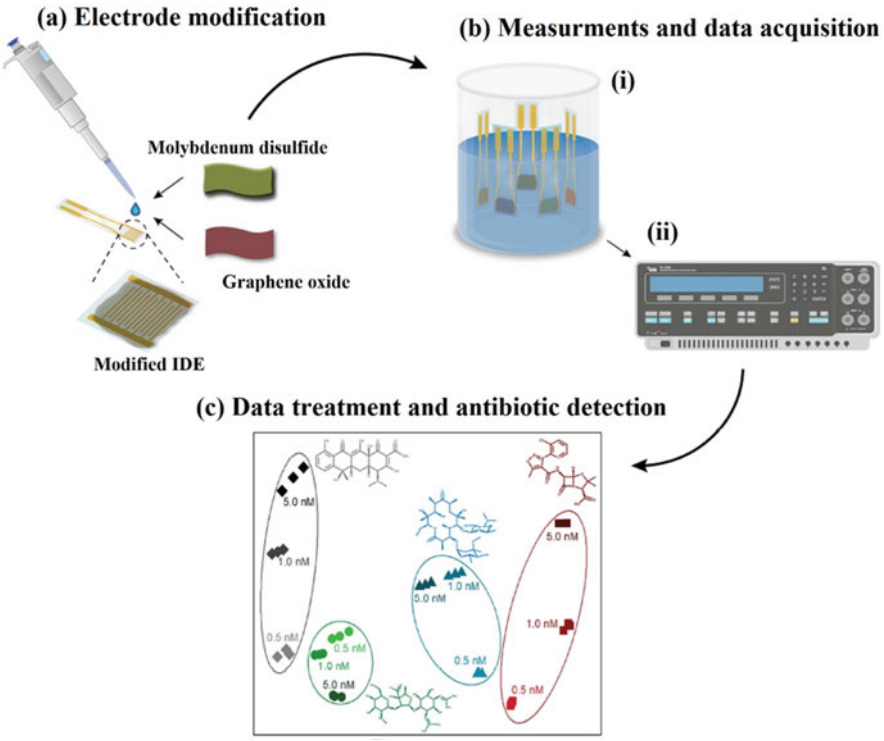

Fig. 4.6 Schematic of E-tongue impedimetric system. (**a**) electrode modification, (**b**) design of a synthetic E-tongue impedimetric system consisting of five modified electrodes (*i*) and impedance analyzer (*ii*). (**c**) Diagnosis of antibiotics (Cloxacillin benzathine, Erythromycin, Streptomycin sulfate, and Tetracycline hydrochloride) (Facure et al. 2020)

antibiotics in highly sensitive liquid environments. Figure 4.6 shows the schematic of fabricated impedimetric E-tongue designed based on molybdenum disulfide and graphene oxide.

Elamine et al. designed an E-tongue-based impedance system to detect honey sugar (Elamine et al. 2019). The designed system is stable, reliable, and reusable. E-tongue-based impedance system has a good ability to analyze the authentication of honey. Figure 4.7 represents the fabricated impedimetric E-tongue.

4.8 Conclusion and Perspective

Due to the increasing importance of using foods with high nutritional value, achieving fast, accurate and simple methods to evaluate the safety, quality, and microbial and physicochemical properties of food are very sensitive and necessary. Currently, the world is witnessing the various types of new methods and technologies in this field. Among these, methods based on electrochemical sensors and biosensors, with

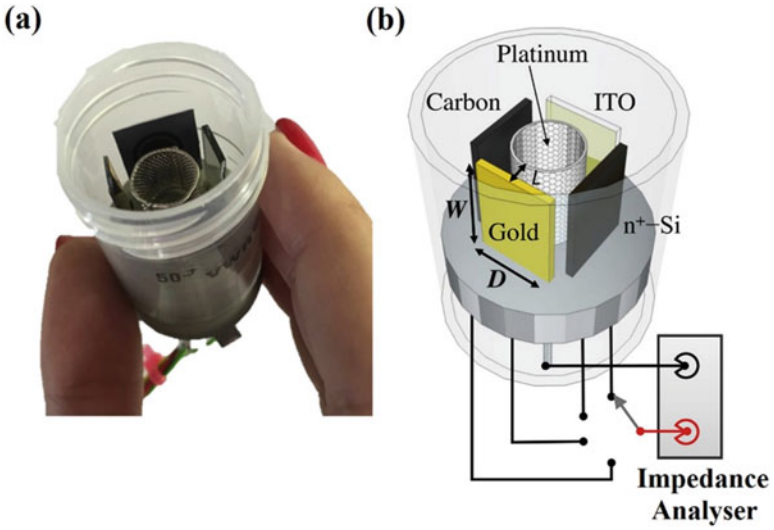

Fig. 4.7 (**a**) Photograph of a designed system based on E-tongue; (**b**) Schematic of the spatial distribution of electrodes and electrical connections in the design of an E-tongue-based impedimetric system (Elamine et al. 2019)

their unique features such as simplicity, ease of operation, high sensitivity, and good selectivity, have attracted much attention. Table 4.2 is a summary of recent research work (2019–2021) on the use of electrochemical methods to detect food adulterations. Considering the effective potential of electrochemical methods, and their compatibility, high detection power, and very good sensitivity in measuring a wide range of food adulterations, there are clear aspects in the advancement of these techniques.

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Fluorescent Biosensing and Chemosensing Strategies for Food Quality Assessment

5

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Abstract

In developing countries like India the population scale has been gradually increasing year by year and hence the need to supply healthy or hygienic food stuffs to them is a crucial factor. Though serious monitoring protocols are there, to till date food adulteration is a menace to people's health as it adjoined with serious issues. Pre-identification or detection of particular food adulterants will assist to ensure the safety of people. In recent decades, fluorescent based biosensors and chemosensors are put forwarded to detect various food adulterants in different sort of sources because of their high sensitivity, selectivity, quick response, cost-effective, naked eye qualitative detection, etc., This chapter has explained with a detailed note on food quality strategy which covers all the basic and essential facts needed, and various optical fluorescent biosensors for accidental adulterants such as pathogens, chemosensors for pesticides, bio and chemo sensors for food toxins, chemosensors for heavy metals, and phenolic contents, and also for some optical sensors for intentional adulterants such as melamine, urea, formaldehyde, and veterinary drugs. Also, we have precisely represented the merits of the reported fluorescent sensors, and also we mentioned the improvements further needed in this particular field to deliver its application to each people to ensure their health safety.

Shenbagavalli Kathiravan and Karthika Lakshmi Servarayan contributed equally with themselves. Ellairaja Sundaram is contributed equally with corresponding Author.

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Keywords

Adulteration · Food safety · Fluorescent biosensors · Chemosensors · Quantum dots

5.1 Introduction

Food safety is a scientific discipline which includes handling, storage, and preparation of food products to ensure their safety (Trienekens and Zuurbier 2008). Analysis of food quality is considered as important factor because of serious health issues via either by incidental or accidental contaminations (Pardeshi 2019). According to the World Health Organization (WHO), higher than 200 diseases, starting from diarrhea to cancers are mainly originated from natural toxins, harmful bacteria, viruses, allergens, pathogens, and parasites (Peltomaa et al. 2021) (Fig. 5.1).

In general, adulteration is defined as the process by which the quality or the nature of a given substance is reduced through the addition of a foreign or an inferior substance (Lakshmi 2012). There are two types of adulteration reported such as incident and accident adulteration. Intentional adulterants are those substances that

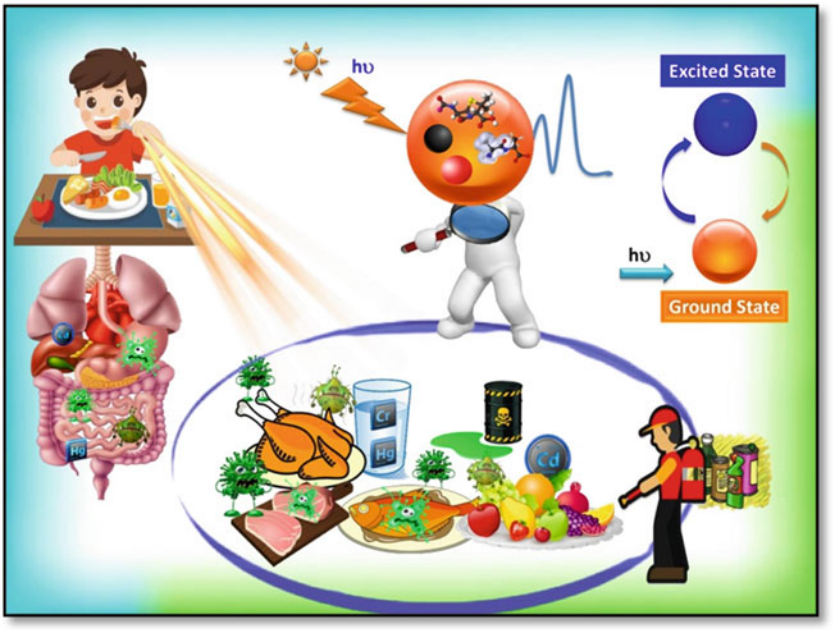

Fig. 5.1 General schematic representation for the fluorescent sensors for various food adulterants using various fluorophores

added as a deliberate act, for example, sand, marble chips, stones, mud, chalk powder, water, dyes, and so on (Bansal et al. 2017). Unintentional adulterants are incidentally found in the food substances, for example, pesticides, pathogens, droppings of rodents, larvae in food (Ayza and Belete 2015). In 2008, significant amount of melamine was mixed with China's milk supply to increase protein content which killed at least six children and harmed thousands of others (Zhou and Wang 2011). Due to those adulterants, peoples are suffering from various diseases such as heart disease, kidney failure, skin diseases, asthma, and other chronic diseases (Agarwal et al. 2019). Hence, food adulteration should be treated as a major issue and they should be detected qualitatively and quantitatively.

Sensor is an analytical device which detects various analytes such as metal ions, biomolecules, pathogens, pesticides, etc., based on their changes in physical/chemical phenomenon such as light, temperature, mass, and current as output signal. Based on the transducer, sensor can mainly classify into two types such as biosensor and chemosensor. Biosensors are categorized based on the transducers such as optical sensors, electrochemical sensors, thermoelectric sensors, and piezoelectric sensors and based on bio-recognition elements like enzymatic sensors, whole-cell sensors, immunosensors, microbial biosensors, and DNA or RNA biosensors (Justino et al. 2017). Among sensors, optical biosensor has greater advantages over conventional analytical techniques so far reported for food samples, because they are high sensitive, selective, rapid, reproducible, reliable, and miniaturizeable (Chen and Wang 2020). Fluorescence based biosensor is the current emerging optical tool for food adulterants or toxins detection, because of its simplicity, ultrasensitivity, and selectivity while comparing with other sophisticated technologies (Strianese et al. 2012).

5.2 Fluorescent Based Sensors for Accidental Food Adulterants

5.2.1 Biosensors for Pathogens in Food Stuffs

Foodborne pathogens are generally causing food poisoning which has been acting as a major threat factor to the human health because of their rapid growth, ability to surviving, and the possibility of cross-contamination (Athmar et al. 2020; Adetunji et al. 2018; Prakitchaiwattana and Det-udom 2017). The characteristics of the most common pathogens are bacteria, viruses, and parasites (Bintsis 2017). The most important pathogens reported in foods are *Salmonella spp.*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus cereus*, and *Escherichia coli* (Sağlam and Şeker 2016). Viruses like Hepatitis A and Noroviruses and parasites like Cyclospora cayetanensis, Toxoplasma gondii and Trichinella spiralis are also causing the foodborne diseases. Therefore, it is necessary to detect these foodborne pathogens to prevent foodborne diseases.

Fluorescence biosensors can detect foodborne pathogens and their toxins within a short period of time. For example, *Staphylococcus aureus* has detected by using

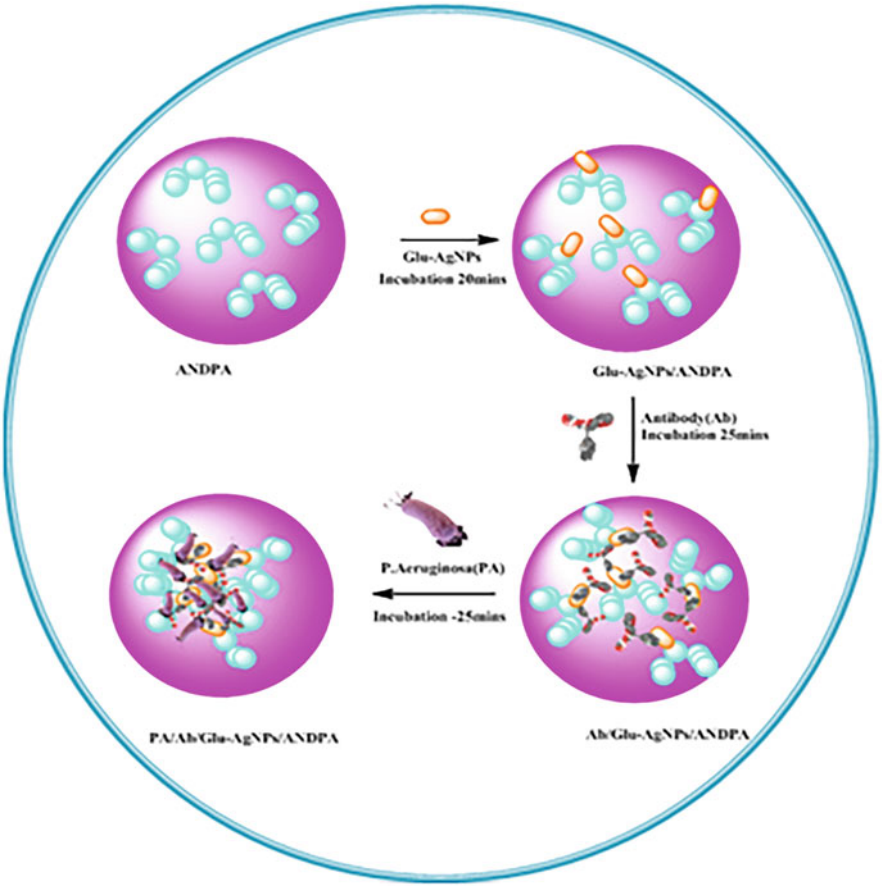

Fig. 5.2 Designing of pyrimidine glucose stabilized-AgNPs based immunosensor for *Pseudomonas aeruginosa* detection in food samples. (Reprinted with permission from {*Journal of Agricultural and Food Chemistry*, 2017,65(8), 1802–1812}. Copyright {2021} American Chemical Society)

monoclonal antibody (anti TNase) conjugated with CdTe quantum dots through streptavidin coupling. This sandwich type immunoassay has showed 3 ng/mL of LOD (Venkataramana and Kurkuri 2016). Based on the aggregation induce phenomenon, *Pseudomonas aeruginosa* and *E. Coli* have been detected by using an organic pyrimidine fluorescent probe tagged Glucose stabilized-AgNPs conjugates and glucose based acrylamides (Glc-acryl and Glc-bis), respectively, in water, soil, and food products such as milk, sugarcane, and orange juices (Ellairaja et al. 2017; Ajish et al. 2018) (Fig. 5.2).

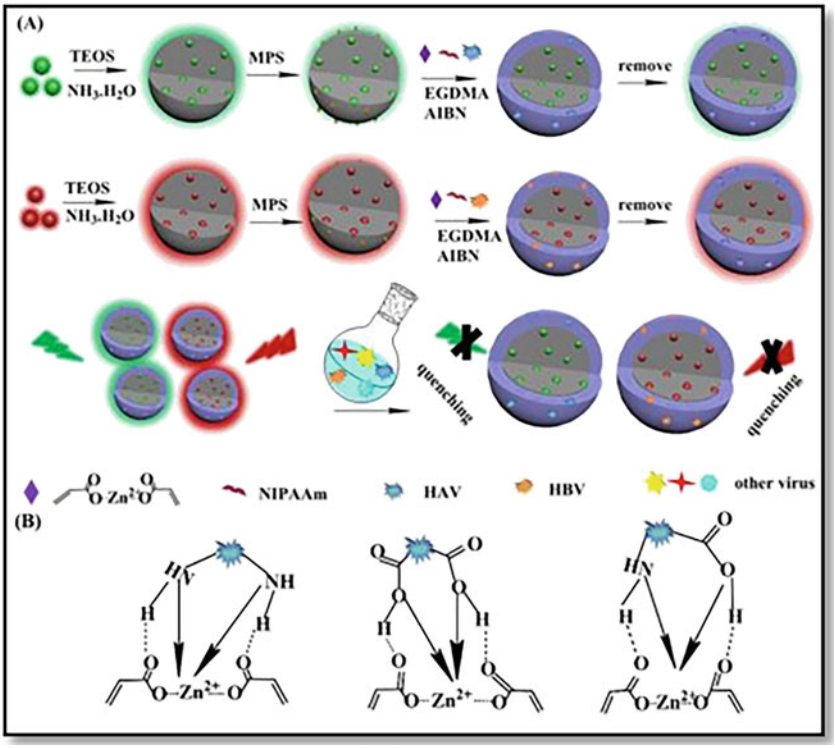

Fig. 5.3 Schematic representation for the simultaneous determination of hepatitis A virus and hepatitis B virus using imprinted polymer. (Reprinted with permission from {*Analytical Chemistry*, 2019, 91(24), 15748–15756}. Copyright{2021} American Chemical Society)

The two-label free fluorescence aptasensors have detected *Salmonella Typhimurium* bacteria. In turn off method, aptamer is first intercalated with SYBR green leading to enhanced fluorescence signal with limit of detection 733 CFU/mL. In turn on method, the Forster resonance energy transfer (FRET) occurred between Rhodamine B and gold nanoparticles which showed the LOD 464 CFU/mL (Srinivasan et al. 2018). Using one-pot greener methodology, a fluorescent based immunosensor has reported for the specific and ultrasensitive detection of *Aeromonas hydrophila* in fish samples and the LOD is found as 2 CFU/mL in fish organs (Ellairaja et al. 2017). Multifunctional molecularly imprinted hybrid polymer prepared by using zinc acrylate as a functional monomer, used as sensing platform for the simultaneous determination of hepatitis A and B virus and limit of detection is found as 3.4 and 5.3 pmol/L, respectively (Luo et al. 2019) (Fig. 5.3).

Based on carbon based fluorescent quantum dots, immunosensors have been reported for the detection of *Bacillus anthracis and Campylaobacterjejuni* bacteria, using CQDs-Eu and Graphene Quantum Dots (GQD)-antibody in tap water, fish pond water, and poultry liver sample (Zhou et al. 2019; Dehghani et al. 2020). A

fluorescence sandwich immunoassay reported for the detection of *Listeria monocytogenes* using chitosan-cellulose nanocrystal (CNC) membrane with limit of detection of 10^2 CFU/mL (Capo et al. 2020). A Multiplex immunosensor has been successfully reported for the simultaneous detection of *E. coli O157:H7, S. aureus,* and *V. parahaemolyticus* using peptide-mediated immunomagnetic separation technique and an immunofluorescence quantum dots in milk (Wang et al. 2020a, b, c).

DNA enzyme-based fluorescent probes have been widely used for various food bacterial detection. Using printing DNA enzyme probes a novel sensor was fabricated using covalently attaching picoliter-sized microarrays of an *E. coli*-specific RNA-cleaving fluorogenic DNAzyme probe (RFD-EC1) on cyclo-olefin polymer (COP) film. This designed immunosensor has detected E. coli in meat and apple juice with LOD of 10^3 CFU/mL and also demonstrated in food packages (Hanie et al. 2018). Another *E coli* based immunosensor has developed by Meng et al. (2018) using a new DNAzyme/graphene hybrid material. This specific sensing material platform has offers a general and attractive approach in real-time analysis, and also shown sensitive, and highly selective detection of E. coli pathogenic bacteria. Recently a novel immunosensor based on a DNAzyme has designed to rapidly detect the *pseudomonas aeruginosa* in the field and the detection limit of 1.2 cfu/mL was achieved. In addition to that, the target protein molecular weight was also determined as 10–50 kDa using proteases and filtration method (Mingcan et al. 2021).

5.2.2 Chemosensors for Pesticides in Food Samples

Pesticides play an important role in improving agricultural productivity and eliminate as well as control the pests, insects, and weeds (Saleh et al. 2020). It is considered as a critical health parameter when it is mixed with food stuffs (Jia et al. 2020). Pesticides can be classified into insecticides, fungicides, rodenticides, fumigants, herbicides, and insect repellents (Capoferri et al. 2018). Among the different types of pesticides, chemical insecticides like carbamates, dinitrocompounds, organochlorines, organophosphates, pyrethroids, and neonicotinoids are used in the most pest control due it's cheap and effecti(Pérez-Fernández et al. 2020). Pesticides are widely distributed in water, soil, sewage sludge, sediments, and the aquatic region (Reynoso et al. 2019). The accumulation of pesticide residues from agriculture practices can lead to serious adverse effect in human like neurological disorder, hepatic and reproductive problems, cancer, psychiatric, endocrine-disrupting disorders, bone marrow disorders, mimic the hormones and lead to death in severe cases (Nsibande and Forbes 2016; Bakirhan et al. 2018; Nicolopoulou-Stamati et al. 2016; Campos and Freire 2016). The World Health Organization and Food and Agriculture Organization of the United Nations have established maximum residue limits for pesticide residues in food 2018 (FAO and WHO 2019). Thus, a number of traditional methods are available for the detection pesticide which includes HPLC (Rajput et al. 2018), mass spectrometry (Kailasa et al. 2013), immunoassay (Ji et al. 2020), liquid chromatography-mass

spectrometry (Masiá et al. 2014) in food samples. The above mentioned methods have some limitations like intensive sample purification and preparation, solvent substitution, time consuming, requirement of sophisticated and expensive instruments, highly skilled operator, and inability to perform on-site detection (Van Dyk and Pletschke 2011). On this regard, fluorescent based biosensors for the detection of pesticides involve as a powerful potential application for sensitivity, simplicity, rapidity, specificity, and cost-effective features (Jia et al. 2017).

In agricultural pest control, organophosphorus pesticides are used about 38% of the total pesticides used worldwide (Pundir and Malik 2019). Based on the literature survey, it is clearly revealed that quantum dots have been widely used as a fluorescent probe for various pesticides detection. Specifically, cadmium based quantum dots have been widely used along with metal nanoparticles or fluorescent probes. For example, CdTe/ Au NPs, and TGA-CdTe-QDs/Au NPs, composite materials based fluorescent sensors have been reported for organophosphorus pesticides, glyphosate, and carbamate, respectively, based on aggregation induced emission and FRET mechanism with the LOD of 0.008 mg/L, 9.8 ng/kg, and 0.011 mg/mL in lake water, apples, and vegetable (Cai et al. 2019; Guo et al. 2013; Guo et al. 2013). Another highly sensitive fluorescent based biosensor has been developed for the quantification of organ phosphorus pesticides (OPs) using acetyl cholinesterase (AChE) modulated upper conversion nanoparticles with Cu^{2+} ions based on OFF-ON-OFF sensing strategy. Developed sensor has shown a linear range of detection from 0.1 to 50 ng/mL and the LOD was reported as 0.05 ng/mL. It is also tested in adulterated environmental and agricultural samples and obtained satisfactory results ($p > 0.05$) with traditional GC-MS technique (Wang et al. 2019a, b). Based on carbon dots two fluorescent based sensors have been designed for the detection of herbicide atrazine and paraoxon-ethyl pesticide with the calculated LOD of 3 pM and 0.22 ± 0.02 μM, respectively, in vegetables, fruits, and grains (Mohapatra et al. 2018, Chang et al. 2017a, b). Simultaneous detection of Atrazine, Chlorpyrifos, Lindane, Tetradifon, and Imidacloprid pesticides was done by using fluorescence based carbon dots and the LOD was found to be 0.013 and 0.04 μM in river water samples (Mandal et al. 2019). By using methylammonium lead halide perovskite quantum dots (MAPB-QDs), simple fluorescent sensor has been developed for the detection of polar organochlorine pesticides in apple and grape samples along with LOD of 0.04 μM (Yang et al. 2020a, b). Walia and Acharya (2014) has used glutathione-coated CdS nanoparticles for the detection of dicofol pesticide with the maximum LOD of $\approx 55 \pm 11$ ppb. Fan et al. (2016) has prepared ZnCdSe and CdSe quantum dots for the multiple detection of pesticides like dursban, dipterex, paraquat, methyl thiophanate, and cartap pesticides with LOD of 2.0×10^{-8} mol/L, 5.0×10^{-8} mol/L, 2.0×10^{-8} mol/L, 5.0×10^{-8} mol/L, and 2.0×10^{-8} mol/L, respectively, in black tea, and wastewater samples.

5.2.3 Bio and Chemosensors for Food Toxins

The analysis of toxins is one of the most important areas in food quality and safety (Hajslova et al. 2004). In general, toxin is a macrobiochemical substance which is mainly derived from protein origin. When it binds with the host receptor cites of the specific human organs, it causes severe diarrhea, toxic shock syndrome, debilitating infections such as meningitis and even death (Iriarte et al. 2001). Toxins produced by microorganisms are called microbial toxins; these include the fungi and bacteria. In general the microbial toxins are commonly contaminated in food materials. The microbial toxins present in food matrices can be classified into three types: bacterial toxins (e.g., cholera, ricin, Staphylococcal enterotoxin (SE) B, and Shiga-like toxin), mycotoxins (e.g., aflatoxins, zearalenone, citrinin, fumonisins, and patulin), and algal toxins (e.g. microcystins (MCs), nodularins (NODs), motopurinemicrocystins (MCs) motopurine, anatoxins (ANTXs), and saxitoxins (STXs)). The conventional methods mentioned above are used in the detection of food toxins (Omar et al. 2020; Nolan et al. 2021). Although these methods show high sensitivity and selectivity but they often suffer from limitations such as lack of portability, time consuming, less stable, cost-effective, and the requirement for skilled operators.

In biosensor development, nanomaterials are incorporated to enhance sensitivity and selectivity and applicable for the rapid and on-site analyses (Malhotra et al. 2014). Plenty of sensors have been reported for toxin detection based on nanoparticles incorporated quantum dots, for example, the ricin, ochratoxin A (OTA), saxitoxin (STX), and fumonisin mycotoxins have been detected fluorimetrically by using zinc coordinated CdSe-ZnS core–shell QDs, ZnCdSe quantum dots (ZnCdSe QDs), molecularly imprinted silica layers appended to quantum dots (MIP-QDs), and CdSe/ZnS quantum dots (QDs)/silver nanoparticles (SNPs) with LOD of 16 ng/mL, 0.33 ng/mL, 0.3 g/kg, and 62.5 μg/kg, respectively, in milk, coffee, shellfish samples (Anderson et al. 2013, Liu et al. 2020a, b, c, Sun et al. 2018, Anfossi et al. 2018). By using carbon quantum dots (CQDs)/gold nanoparticles (AuNPs), and 5-carboxyfluorescein (FAM)/palladium nanoparticles (PdNPs), fluorescent sensors have been fabricated for the detection of Maitotoxin and Aflatoxin M1, respectively, by FRET mechanism, and showed a LOD of 0.3 pmol/L, 1.5 pg/mL, respectively, in fish and milk samples (Gholami et al. 2020; Li et al. 2017). Recently, Sadi et al. (2018) reported a fluorescent sensor for citrinin based on FRET mechanism by using the anti-citrinin antibody immobilized on the surface of magnetic/silica core–shell (MSCS) and the citrinin–Rho123–BSA conjugate with linear range from 1 to 6 pM and the limit of detection is 0.1 pM in maize flour samples. Based on optical immunoassay, Botulinum neurotoxin type F was detected by using organic fluorophore attached with monoclonal antibody through EDC/NHS coupling. Under this condition the linear and the detection limit of this sensor was found as 50–500 fg/mL and 34.4 fg/mL in milk, juice, meat, etc. (Shenbagavalli et al. 2020).

Rasooly et al. 2015 proposed the detection of shiga toxin using charge coupled device (CCD) and light-emitting diode with linear range from 100 ng/mL to 0.01 pg/mL. Aptasensors have been designed for AflatoxinB1 (AFB1) and patulin using

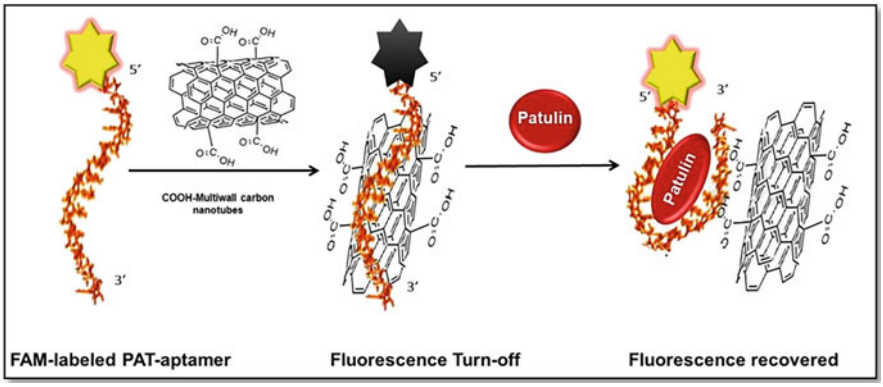

Fig. 5.4 Schematic representation for the quantification of Patulin using MWCNT-Aptamer conjugates. (Reprinted with permission from {*Food Chemistry, 312, 126048,* 2020 Copyright {2021} Elsevier)

fluorescein-labeled AFB1aptamer and carboxyfluorescein (CFL) functionalized multiwall carbon nanotubes (MWCNTs) with LOD of 1.6 ng/mL,0.13 μg/L, and 0.41 μg/L, respectively, in rice cereals and apple juice (Chen et al. 2019, Khan et al. 2020) (Fig. 5.4).

5.2.4 Chemosensors for Heavy Metals, and Phenolic Contents in Food Sources

In general heavy metals possess density higher than 5 g/cm^{3}are accident adulterants in food samples (Zeng et al. 2019a, b), for example, Mercury (Hg), Arsenic (As), Lead (Pb), Cadmium (Cd), Chromium (Cr), and Tin (Sb) (Rai et al. 2019). These metals have shown potential carcinogenicity and cause headache, irritability, memory deterioration, kidney bladder problems, and skin cancer. In particular, hypertension and cardiovascular diseases are strongly related to Arsenic exposure (Lee et al. 2019).

Among toxic heavy metals, arsenic (As) is considered as a major accidental adulterant in drinking water. As per World Health Organization (WHO), the optimal level of arsenic in drinking water is around 10 μg/L (Yogarajah and Tsai 2015). In 1984, Bangladesh has faced a very serious incident associated with arsenic contamination in ground water (Hezbullah et al. 2016). In recent years various detection methods have been developed such as Atomic absorption spectroscopy (Afrasiab et al. 2014), nanosensors (Vaishanav et al. 2017), aptamer sensor (Zeng et al. 2019a, b, Mao et al. 2020), Nanobionic Sensors (Lew et al. 2021), and fluorescence sensor (Devi et al. 2019) for heavy metal detection in food samples. Using fluorophores, carbon dots, nanomaterials, nanoclusters quantum dots, and aptamers, different type of fluorescent sensors have been reported for arsenic detection. Very recently, Liu et al. (2020a, b, c) has reported a miniaturized smartphone integrated

paper-based fluorescence sensor with Cu nanoclusters for the selective detection of As (III) in groundwater along with detection limit of 2.93 nM (0.22 ppb).

Moreover, the mercury metal (Hg) also shows serious toxicity, including damage to the nervous system and it cannot be degraded (Yeom et al. 2021). Liu et al. (2020a, b, c) have developed a mercury sensor using boron and nitrogen co-doped graphene quantum dots (B/N-GQDs) with the LOD of 6.4 nM. Chromium (VI) ions are highly toxic industrial pollutant and causes irritating mucous membranes, pulmonary sensitivity, dental erosion, and renal damage (Xiang et al. 2007). Lin et al. (2019) have developed a fluorescent sensor for the detection of chromium in water using copper nanoclusters (Cu NCs), with a linear range from 0.1 to 1000 mM, and LOD of 0.03 mM.

Cadmium (Cd) also acts as extremely toxic, bioaccumulations species which produces cancer. WHO provides standard drinking water level of Cd from 3 to 5 ppb which recommends kidney damaging diseases (Xue et al. 2011). Recently, a paper strip based colorimetric smartphone platform has developed by Wang et al. (2020a, b, c) for the quantitative detection of cadmium ions from 0.10 to 60.00 μM with the LOD of 0.1 μM in rice samples using glutathione stabilized gold nanoclusters (AuNCs) (orange emission) with ethylene diamine functionalized graphene oxide [EDAGO] (blue emission). Lead is also one of the most toxic heavy metals and even below 5 μg/dL[10] leads to health issues (Kim et al. 2012). Xu et al. (2014) group was reported a Pb sensor using NaYF4:Yb^{3+}/Tm^{3+} nanoparticles and the LOD were found as 80 nM in biological and analytical samples. For Pb^{2+} ions detection in food material, a new DNAzyme-functionalized R-phycoerythrin (DNAzyme-R-PE) based sensor was developed by Jikui et al. (2019) and the limit of detection was achieved as 0.16 nM along with a linear range from 0.5 to 75 nM toward Pb^{2+} ions. Furthermore, it was demonstrated to detect Pb^{2+} ions in spiked lake water samples.

Third trace most abundant and nutrition metal is copper and excess of copper may lead to copper homeostasis, Alzheimer's disease, amyotrophic lateral sclerosis, Menkes disease, Parkinson's disease, and Wilson's disease (Carter et al. 2014). Li et al. (2020) have recently developed an optical sensor for Cu detection by using glutathione stabilized Au/Histidine complex, which results high blue emission, and it was quenched while adding Cu ions from 0.5 to 300 μM (Fig. 5.5).

For the first time, a sensitive chemiluminescence (CL) based microfluidic device was fabricated for the simultaneous quantification of total flavonoids and total phenolic acids by the utilization of magnetic zinc-imidazole frameworks (ZIF-4). This fabricated device can detect these phenolic contents ranging from 0.04 to 0.10 μg/mL and it was applied to detect total flavonoids and phenolic acids which is present in tea and honey samples (Nafiseh et al. 2021). Novel paper-based analytical device (PAD) was designed for the simultaneous detection of Bisphenol A and its toxic analogs using metal-organic framework of UiO-66-NH_2 coated molecularly imprinted polymers (MIPs). This method was used to detect the BPA and its halogenated analogs in real samples like dust in a simultaneous manner from 0.14 to 0.30 ng/g (Lingshuai et al. 2021) and results were compared with standard LC-MS/MS methods and also this is a greener and low cost device for BPA

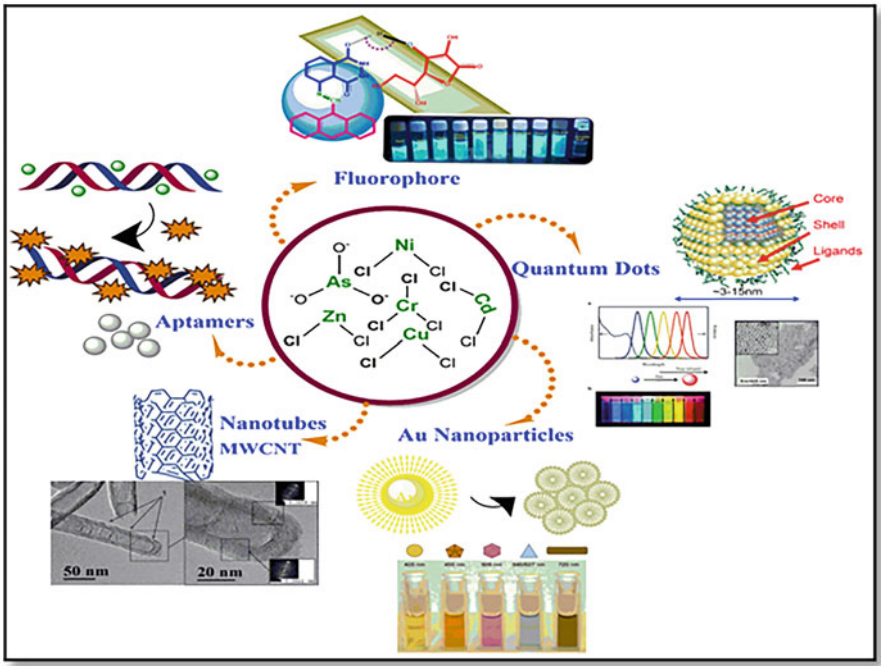

Fig. 5.5 Schematic representation for detection of heavy metal ions using various fluorescent materials

detection. Though it is novel approach, developed device is not tested in real samples like water that has been addressed as main BPA contaminant source for aquatic living species so far reported.

5.3 Detection of Intentional Adulterants in Food Stuffs

5.3.1 Fluorescent Sensors for the Detection of Melamine, Urea, and Formaldehyde

Generally, health risks to consumers by milk adulteration is depend on the toxic nature of the adulterants intentionally added into the milk, such as formaldehyde, hydrogen peroxide, hypochlorite, dichromate, salicylic acid, melamine, and urea (Nascimento et al. 2017). Due to its serious health issues of melamine adulterant present in the milk, different methods are being used to detect melamine, namely HPLC, UPLC-MS/MS (Li et al. 2018; 2019), differential pulse voltammetry (Tsai et al. 2010), electrophoresis (Wen et al. 2010), colorimetric (Chang et al. 2017a, b), near mid-IR (Mauer et al. 2009), and fluorescence methods (Tang et al. 2018).

Recently, very sensitive and low cost melamine sensors are reported using fluorimetric technique. Most of the research groups have utilized fluorescent nanomaterials like carbon dots and fluorescent organic molecules for the detection of melamine in milk (Du et al. 2016). Lu et al. (2015) group have synthesized a 7-(benzylamino)-9,9-dibutyl-9H-fluorene-2-carbaldehyde (BDFC) attached with gold nanoparticles and used for melamine sensing based on aggregation mechanism. After the addition of melamine, strong emission intensity is noted from released probe. From the emission intensity, the linear response is calculated from 1.0×10^{-8} to 4.0×10^{-6} mol/L with LOD of 3.0 nmol/L in milk and milk based products. Similarly using AS1411(DNA sequence)-templated copper nanomaterials Ga et al. (2020) have designed a fluorescent sensor for the detection of melamine based on quenching mechanism with correlation coefficient of 0.9823 in milk samples. Using graphene quantum dots (GQDs)/Hg^{2+} ions, Li et al. (2014) have developed a melamine sensor based on charge transfer quenching mechanism with LOD of 0.12 μM in raw milk.

Indian Council of Medicine reported that illegally added urea to milk causes kidney failure and death. Different analytical techniques have been already used for the determination of urea in milk including enzyme-based sensor (Renny et al. 2005), near IR methods (Khan et al. 2014) crystal optical sensor (Kasture et al. 2015). Due to simplicity and sensitivity, fluorescent sensors have been used for the detection of urea in milk. Soni et al. (2018) have applied phenol red/urease enzyme for the detection of urea in saliva samples with the LOD of 10.4 mg/dL based on pH change and finally fabricated a filter paper-based strip.

Another pH sensing based urea detection has designed by Zhang et al. (2019) using MoS_2 quantum dots (MQDs)/2,3-diaminophenazine (DAP)/Urease enzyme and the LOD was calculated as 1.8 mM and finally tested in water samples. Stable fluorescent lipid polymer/urease enzyme conjugates were prepared and applied for the detection of urea in milk samples based on switching OFF–ON mechanism in the presence and absence of urease enzyme (Nikoleli et al. 2010). Using perylenediimide functionalized with imidazoles (PDI-Hm), (PDI-Hm), a fast fluorescence sensor has designed by Cho et al. (2020) for urea sensing based on aggregation fluorescence quenching mechanism and the LOD is found as 0.4 mM and applied in urea containing real samples like urine.

5.3.2 Fluorescent Biosensors for Intentionally Adulterated Meats

Formaldehyde(FA), amine, enrofloxacin, and fluoroquinolone residues are intentionally added to the food materials such as meat, fish, fruits, and vegetables to keep them fresh (Bi et al. 2017). The increasing level of formaldehyde in the food products causes heart disease, liver diseases, diabetes, and neurodegenerative diseases for human beings (Cao et al. 2020). Mostly organic fluorescent probes and some of their metal complexes have been utilized for sensing of these adulterants in food products.

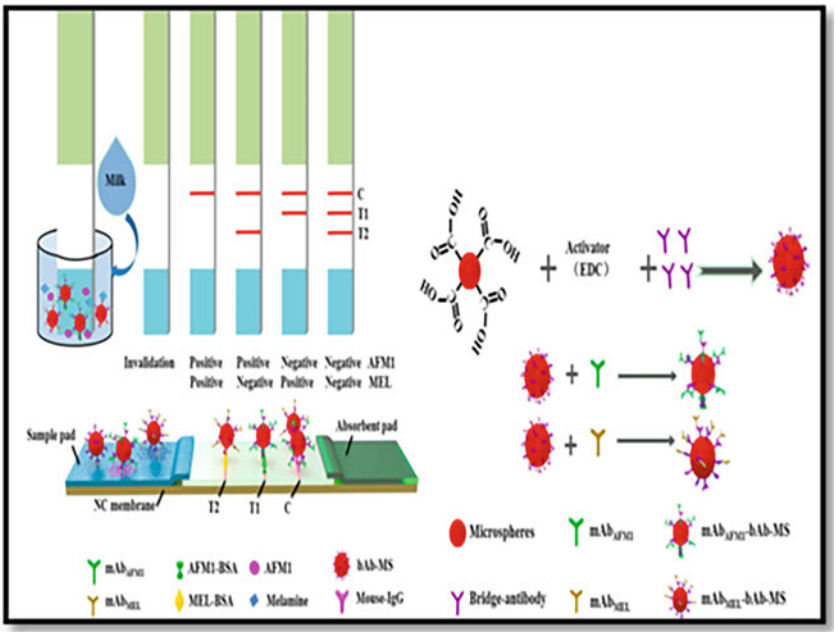

Fig. 5.6 Schematic representation for the working principle of Mycotoxin Immunosensor in milk samples using Eu nanoparticles. (Reprinted with permission from {*Analytical Chemistry*, 2019, 91, 1968–1973}. Copyright{2021} American Chemical Society)

Ding et al. (2020) synthesized a reliable and specific fluorescent organic probe CmNp-CHO, for detecting FA from 0 to 20 μM and LOD is found as 8.3 ± 0.3 nM in food samples, living cells, onion tissues, and zebra fish. Hu et al. (2016) have developed a sensor for the detection of amine in meat spoilage using perylenediimide molecules (PDIs) and the LOD is found as 2.6 and 1.2 ppb, respectively. Huang et al. (2013) have detected enrofloxacin (ENR) residues in chicken meat using fluorescent Ru $(phen)_3^{2+}$ complexes and the linear range has been detected from 0.025 to 3.5 ng/mL with LOD of 0.22 ± 0.02 ng/mL. First time, a fluorescent protein (serum albumin) has been used as model protein to detect fluoroquinolone in fish meat (Li et al. 2012).

Because of their attractive red color, Sudan I, II, and III synthetic dyes are used as colorants in chilly soups, sauce, beverages, and other sweet items and causing cancers (Schummer et al. 2013). From the previous reports, it is understood that Sudan dyes have been detected using carbon dots and heteroatom doped carbon dots as sensing materials in various food stuffs like soft drinks (Yang et al. 2020a, b; Hu et al. 2016; Yuan et al. 2016). Jose et al. (2016) prepared the hexadecylamine capped silicon nanoparticles (Si NPs) used for the detection of Sudan I and with LOD of 3.90×10^{-8} M in chili powder samples (Fig. 5.6).

To reduce production costs, most of the manufactures in global market use pork instead of beef and therefore among other edible meat contaminations, pork contamination is considered as a serious concern. An ultrasensitive biosensor has designed for pork DNA detection by using sandwich type sensing assay consists dual sensing platforms including graphene oxide-gold nanorod (GO-AuNR) functionalized capture probe (CP) and SP-conjugated gold nanoparticles (AuNPs). Designed biosensing assay has shown excellent sensitivity with a limit of detection (LOD) of 100 aM and it was validated with extracted pork sample DNA sample with LOD of 1 fM. It has also exhibited a selectivity and specificity to differentiate the DNA sequences of six closely related non-target species (Ibrahim et al. 2020). But the aggregation of these sensing materials, costly DNA reagents may be considered as important facts in this particular sensor. Using fluorescent molecularly imprinted polymer nanogel (F-MIP-NG) another biosensor was developed for rapid detection of porcine serum albumin (PSA) detection in halal meat extracts and it has exhibited high sensitivity with a LOD of 40 pM, and a linear range of 0.25–5 nM (Chehasan et al. 2021).

5.3.3 Fluorescent Biosensors for Veterinary Drugs (VD)

In this part, veterinary drugs and their role as an intentional adulterant, and their detection by fluorescent sensors in food samples are completely discussed (Falowo and Akimoladun 2019). Veterinary drugs are classified into the antimicrobials, antiparasitics, β-agonists, and antimicrobials (Nie et al. 2019). They are commonly used to kill the bacteria, internal parasites, fleas, lice, mites, and ticks. Continuous exposure of these drugs may cause major threats such as heart and respiratory diseases in live stocks and finally with humans (Vidic et al. 2017). Their abnormal levels may lead to various health issues and the Maximum Residue Limit (MRL) for chlortetracycline VD in muscle, liver, and kidney is found as 100 μg/kg, 300 μg/kg, and 500 μg/kg, respectively. Hence, their detection in food items has been playing a vital role. For VD detection concern, different methods are available such as Liquid chromatography (Wang et al. 2020a, b, c), printed polymer methods (Ibarra et al. 2020), and immunoassay colorimetric sensor (Yu et al. 2018). Among various analytical detection tools, fluorimetric based sensing tool are noted as most sensitive, selective, smart operating tool and also low cost method for various VD samples detection (Jayalakshmi et al. 2017).

Recently, Jin et al. (2006) have developed an enzyme-linked immunosorbent assay (ELISA) based immunoassays methods for the detection of protein, small molecules, and food quality analysis. Most of the reported fluorescent immunoassays are often used microplate reader, which is not being available in resource-limited areas. Very recently cost-effective 3D-printed attachment based light-emitting diode has used for detection of amantadine (Yu et al. 2020). Bennett et al. (2020) have developed nanomechanical cantilever based sensors for antimicrobial resistance (AMR) and phenotypic antibiotic resistance within ∼45 min of detection time, by using the laser detector in clinical samples. Using aqueous gold

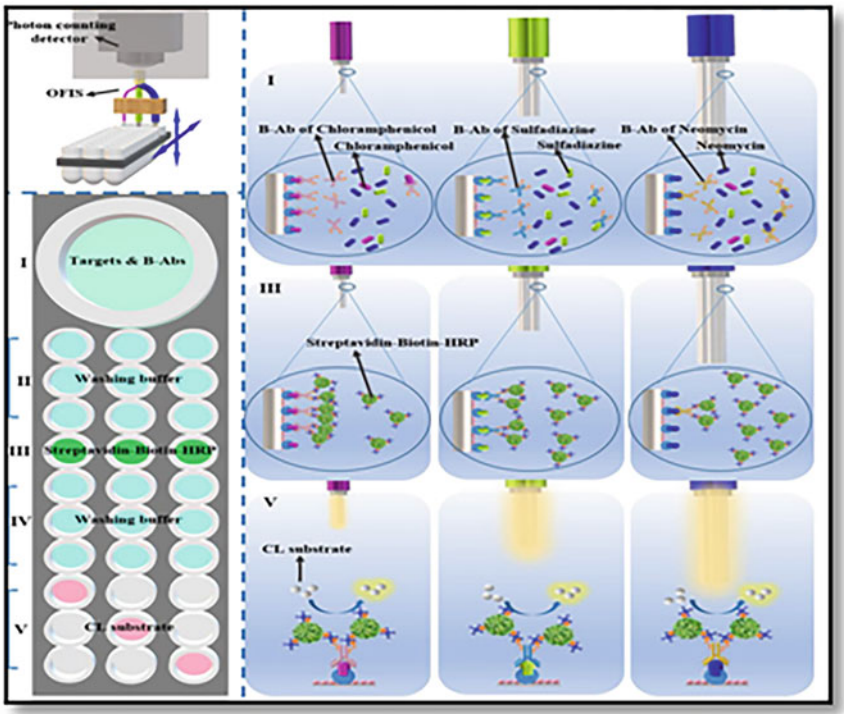

Fig. 5.7 Pictorial representation for the detection of veterinary drug residues using optical fibers. (Reprinted with permission from {*ACS Sens.*, 2019, 4, 1864–1872}.Copyright{2021} American Chemical Society)

nanoparticles (AuNPs) and double-stranded DNA (dsDNA), a colorimetric cum fluorescence aptasensor has been designed by Emrani et al. (2016) for the detection of streptomycin VD, based on aggregation induced quenching mechanism and the LOD were found as 73.1 and 47.6 nM in real samples like milk and serum, respectively. Jia et al. (2019) have reported a chemiluminescence based sensor for the detection of chloramphenicol in meat by using synthesized luminol-H_2O_2-4-(imidazole-1-yl)phenol and the LOD was found as 2.0 pg/g in meat samples. Another research crew has designed an immunosensor for toltrazuril (Tol) detection using monoclonal antibody (mAb) and the detection range was achieved from 2.19 ng/mL to 4.21 ng/mL along with the LOD of 2.60 μg/kg) and a strip was also designed to demonstrated in real samples like feed, egg, and chicken (Wang et al. 2019a, b) (Fig. 5.7, Table 5.1).

Sensitivity selectivity and stability of these sensors are mainly depending on the sensing and signalling materials used in the development of fluorescent sensors. Upon the keen observation above different sorts of fluorescent sensors so far reported for various food adulterants, we are furnishing the following reports about the merits and demerits of the fluorescent sensors. Quantum dots, synthetic

Table 5.1 Selected fluorescent based biosensors for various food adulterants detection

Types of fluorescence detection	Basic sensing material	Analytical Characteristics (LR & LOD[a])	Adulterants	References
Quantum dots based detection	CdTe QDs-streptavidin	3 ng/mL	*Staphylococcus aureus*	Venkataramana and Kurkuri (2016)
	CQDs-Eu film	LR: 1–45 μM LOD: 0.17 μM	Bacillus anthracis	Zhou et al. (2019)
	Quantum dot probes	LR: 10–10^7 CFU/mL LOD: 2.460, 5.407, and 3.770 CFU/mL	Escherichia coli O157:H7, Staphylococcus aureus, and Vibrio parahaemolyticus.	Wang et al. (2020a, b, c)
	G-MIP (Green-QDs@MIP) and R-MIP (Red-QDs@MIP)	LOD: 3.4 pmol/L and 5.3 pmol/L	Hepatitis A virus (HAV) and hepatitis B virus (HBV)	Luo et al. (2019)
	ZnCdSe quantum dots (ZnCdSe QDs)	LR: 0.5–80 ng/mL LOD: 0.33 ng/mL	Ochratoxin A	Liu et al. (2020a, b, c)
	CdSe/ZnS quantum dots	62.5 μg/kg	Fumonisin mycotoxins	Anfossi et al. (2018)
	Carbon quantum dots (CQDs) and gold nanoparticles (AuNPs)	LR: 1–600 pmol/L LOD:0.3 pmol/L	Maitotoxin	Gholami et al. (2020)
	CdTe QDs	LR:0.017–0.5 mg/mL LOD: 0.011 mg/mL	Carbamate	Guo et al. (2013)
	Nitrogen-doped carbon quantum dot	LOD: 3 pM	Atrazine	Mohapatra et al. (2018)
	Carbonization of sucrose	LOD:0.22 ± 0.02 μM	Paraoxon-ethyl	Chang et al. (2017a, b)
	Methylammonium lead halide perovskite quantum dots	LR: 0–110 μM LOD:0.04 μM	Organochlorine pesticides	Yang et al. (2020a, b)
	Gelatin	LR: 0.013 μM LOD:0.04 μM	Imidacloprid Tetradifon	Mandal et al. (2019)

	TGA-CdTe-QDs and CS-AuNPs	LR: 0.02–2.0 μg/kg LOD: 9.8 ng/kg	Glyphosate	Guo et al. (2013)
	ZnCdSe and CdSe QDs	LOD: 2.0×10^{-8} mol/L^{-1}, 5.0×10^{-8} mol/L, 2.0×10^{-8}mol/L, 5.0×10^{-8} mol/L, 2.0×10^{-8} mol/L	Dursban, dipterex, Paraquat, methyl thiophanate, Cartap	Fan et al. (2016)
	CdTeQDs, rhodamine Glutothiamine	LR: 0.02–2 μmol/L LOD: 0.006 μmol/L	As^{3+}	Tang et al. (2018)
	Dual emissive carbon dots (DECDs)	LR: 2–300 Mm LOD: 0.4 μM	Cr^{6+}	Yunxia et al. (2018)
	Nitrogen-doped carbon quantum dots (C-dots)	LR: 0.08–1 mm LOD: 0.14 mM	Cr^{6+}	Kun Ha et al. (2019)
	Glutathione capped CdTe QDs (GSH-QDs) were	LR: 0–2.0 μm LOD:3.0 nM	Cr^{3+}	Peng et al. (2018)
	Amino-functionalized carbon dots (C-dots) and gold nanoparticles (AuNPs)	LR: 50 nM and 500 nM LOD: 36 nM	Melamine	Dai et al. (2014)
	Graphene quantum dots (GQDs)/Hg^{2+}	LR: 0.15–20 μM LOD: 0.12 μM	Melamine	Li et al. (2014)
	Sulfur doped carbon quantum dots	LR: 0–40 μM LOD: 0.12 μM	Sudan I	Yang et al. (2020a, b)
	Fluorescent carbon dots (CDs)	LR: 0.5–60, 0.5–60, 1–70, and 1–70 μM LOD: 0.17, 0.21, 0.53 and 0.62 μM	Sudan I, II, III & IV	Hu and Gao (2020)
	CdSe@SiO_2@CdTe quantum dots hybrid-based immunosensor	LOD: 0.37 ng/mL LOD: 0.057 ng/mL	Amantadine (AMD)	Yu et al. (2020)
	MoS_2 quantum dots and 2, 3-diaminophenazine	LR: 5–700 μM LOD: 1. 8 μM	Urea	Zhang et al. (2019)

(continued)

Table 5.1 (continued)

Types of fluorescence detection	Basic sensing material	Analytical Characteristics (LR & LOD[a])	Adulterants	References
Aptamers based detection	Aptamer-AuNPs-RB complexes	733 CFU/mL	*Salmonella typhimurium*	Srinivasan et al. (2018)
	Aptamer/cDNA duplex	5–100 ng/mL 1.6 ng/mL	Aflatoxin B1	Chen et al. (2019)
	5-carboxyfluorescein (FAM) and palladiumnanoparticles (PdNPs)	5–150 pg/ML 1.5 pg/mL	Aflatoxin M1	Li et al. (2017)
	Carboxyfluorescein (CFL) and multiwall carbon nanotubes (MWCNTs)	LOD:0.13 μg/L	Patulin	Khan et al. (2020)
	Biotin and FAM-labeled complementary strand of Aptamer (CS1) modified SNPs-Streptavidin complex	LR: 2–500 nM LOD: 0.45 nM	As^{3+}	Taghdisi et al. (2017)
	ATTO 647N/Aptamer-SWNT	LOD: 0.42 nM	Pb^{2+}	Taghdisi et al. (2014)
	6-Hydrazino-1,3,5-triazine-2,4-diamine (HTD)polyclonal antibody and as the immobilized antigen	LOD: <0.5 μg/mL	Melamine	Fodey et al. (2011)
	Gold nanoparticles (AuNPs) and double-stranded DNA (dsDNA)	LOD: 73.1 and 47.6 nM	Streptomycin	Emrani et al. (2016)
	Monoclonal antibody (mAb)hapten	LR: 2.19 ng/mL to 4.21 ng/mL LOD: <2.60 μg/kg	Toltrazuril (Tol)	Wang et al. (2019a, b)
Nanomaterials based detection	Chitosan-cellulose nanocrystal (CNC) membrane	LOD: 10^2 CFU/mL	*Listeria monocytogenes*	Capo et al. (2020)
	Carbon quantum dots (CQDs) and gold nanoparticles (AuNPs)	LR: 1–600 pmol/L LOD:0.3 pmol/L	Maitotoxin	Gholami et al. (2020)
	Molecularly imprinted silica layers appended to quantum dots (MIP-QDs)	20–100 g/L 0.3 g/kg	Saxitoxin	Sun et al. (2018)

	Glutathione coated CdS nanoparticles	LOD: ≈55 ± 11 ppb	Dicofol	Walia and Acharya (2014)
	Silicon oxide-coated copper nanoclusters	LR: 0.010 mg/L to 2.0 mg/L LD: 1.1 µg/L (2.75 µg/kg)	Cd^{2+}	Li et al. (2020)
	Pyrene modified nanocrystalline cellulose (NP-1) was	LOD: 0.09 µM (10.70 µg/L)	Cd^{2+}	Tümay et al. (2020)
	Cu nanoclusters (CuNCs) capped by tannic acid (TA) (CuNCs@TA	LR: 0.03–60 µM LOD: 5 nM	Cr^{6+}	Cao et al. (2020)
	Graphitic carbon nitride (g-C_3N_4) nanosheets	LR: 0.6 µM–300 µM LOD:0.15 µM	Cr^{6+}	Rong et al. (2015)
	Gold nanoparticles (Au NPs)	LR: 6.25 ng/mL−800 ng/mL	Cr^{3+}	Qiang et al. (2013)
	Catechin synthesized gold nanoparticles (C−Au NPs).	LR:10 nM−1.0 µM LOD: 1.5 nM	Pb^{2+}	Wu et al. (2013)
	Lysozyme type VI-stabilized gold nanoclusters (Lys VIAuNCs)	LOD: 3 pM	Hg^{2+}	Lin et al. (2010)
	Hg^{2+} and carbon nanodots	LOD: 0.3 µM	Melamine	Lei et al. (2016)
	Gold nanoparticles (AuNPs)	LR: 1.0×10^{-8}– 4.0×10^{-6} Mol L^{-1}	Melamine	Lu et al. 2015
	AS1411-templated fluorescent Cu Nanomaterial's	LR: 50 µmol/L–120 µmol/L	Melamine	Lu et al. 2019
	Hexadecylamine capped silicon nanoparticles (Si NPs)	LR: 2.91×10^{-5} to 4.97×10^{-7} M LOD of 3.90×10^{-8} M	Sudan I	Jose et al. 2016
	Biotin-Ab and Streptavidin−Biotin−HRP Nanocomplex	LR: $10 - (2 \times 10^{4})$ pg/mL LR: 0.5–500 ng/mL LR: 0.1–300 µg/mL	Veterinary drug residues in chloramphenicol, Ulfadiazine and neomycin	Nie et al. (2019)
	Gold nanoparticles	LOD: 0.51 nM 0.095 ng/mL	Amantadine	Yu et al. (2018)

(continued)

Table 5.1 (continued)

Types of fluorescence detection	Basic sensing material	Analytical Characteristics (LR & LOD[a])	Adulterants	References
Synthetic fluorophores based detection	Glycoacrylamides	LR:1.0 × 10^6 to 1.70 × 10^8 cells/mL LOD:7.30 × 10^5 cells/mL	*E. coli*	Ajish et al. (2018)
	2-Amino-4-(anthracen-9-yl)-7-hydroxy-4H-chromene-3-carbonitrile	LR: 4–736 CFU/mL LOD: 2 CFU/mL	Aeromonas hydrophila	Sundaram et al. (2019)
	4-(anthracen-9-yl)-6-(naphthalen-1-yl)-1,6-dihydropyrimidine-2-amine	LR: 8–10^{-1} CFU/mL LOD: 1.5 CFU/mL	Pseudomonas aeruginosa	Ellairaja et al. (2017)
	2-amino-4-(4-formylphenyl)-4H-chromene-3-carbonitrile (AFC)	50–500 fg/mL 34.4 fg/mL	Botulinum neurotoxin type F	Shenbagavalli et al. (2020)
	Tetraphenylethene (TPE) derivatives	LR: 0.009 and 22.5 mg/L LOD: 0.008 mg/L	Organophosphorus pesticides	Cai et al. (2019)
	Coumarin-6-CF_3	LOD: 10 ppb	As^{3+}	Ezeh and Harrop (2012)
	Acriflavine and rhodamine	LR: 0.04–0.09 mg/L LOD: 10 μg/L	As^{3+}	Saha et al. (2016)
	Norbornene derived 8-hydroxyquinoline (N_8HQ)	LOD: 1.6 nM	Cd^{2+}	Sarkar and Shunmugam (2013)
	2-aminoanthracene, and 2-thiophenecarboxaldehyde (ANT-Th)	LOD: 0.4 μM	Cr^{3+}	Karaku (2020)
	Rhodamine AR/H_2O_2	LOD: 1.0 nM	Cu^{2+}	Gao et al. (2018)
	N,N′-dioctadecylthiacyanine perchlorate (NK) and Octadecyl rhodamine B chloride (RhB)	LOD: 9.13 ppb	Hg^{2+}	Saha et al. (2020)

	Manganese probepentaaza macrocycle conjugated to a hemicyanine dye (q CHM)	LOD: 10 ppb	Hg^{2+}	Sayani et al. (2018)
	Fluorescein functionalized Fe_3O_4 nanoparticles	LOD: 0.83 nM	Ni^{2+}	Shah et al. (2013)
	Chalconepyrene-conjugated pyridine	LR: 0–18 equiv	Ni^{2+}	Prabhu et al. (2017)
	Perylenediimide functionalized with imidazoles (PDI-Hm)	LOD: 0.4 mM	Urea	Cho et al. (2020)
	CmNp-CHO	LR: 0–20 μM LOD: LOD of 8.3 ± 0.3 nM	Formaldehyde	Ding et al. (2020)
	Perylenediimide molecules (PDIs)	LOD: 2.6 and 1.2 ppb	Amine	Hu et al. (2016)
	Fluorescent Ru (phen)32+ complexes	LR: 0.025–3.500 ng/mL LOD: 0.22 ± 0.02 ng/mL	Enrofloxacin (ENR)	Huang et al. (2013)
	N-(2-hydroxyethyl)ethylene diaminetriacetic acid	LR: 0.3–8.0 μmol/L LOD: 79.6 nmol/L	Sunset yellow	Yuana et al. (2016)
	Luminole H_2O_2 4-(imidazole-1-yl) phenol	LOD: 2.0 pg/g	Chloramphenicol	Jia et al. (2019)

[a]*LR* linear range, *LOD* limit of detection

organic molecules, Nanomaterials, Nanoclusters, and Aptamers have been primarily used as fluorescent probes for adulterants detection.

- Quantum dots have been mainly addressed by various researchers for the detection heavy metal ions, toxins and bacteria in food stuffs. Furthermore, Bi/Tri metallic quantum dots have often shown better fluorescent stability compared to single quantum dots.
- Fluorophores are predominantly applied for the development of chemosensors for food toxins like organ phosphorus pesticides, formaldehyde, amine, enrofloxacin, etc. and also for some heavy metal ions. Functional groups of the fluorophores are tunable based on the properties of the adulterants and better linear range cum LOD has been achieved in than fluorescent quantum dots based sensors.
- Pathogen and pathogenic microbial toxins can be detected using the immunoassays Aptamers/DNA/nanomaterials or nanoclusters with fluorescent labels have been exploited for the fabrication of sensing platforms of the above toxins.
- These kinds of platforms widely used for the designing of biosensor kits in miniaturized form.

Challenges to be addressed

- Quantum dots based sensors are mainly used conjugate with Au Nanoparticles and hence they are not cost-effective.
- Despite fluorescent based organic molecules are easy to synthesis, their stability and solubility in aqueous medium are major issues during sensor development.
- Nanoparticles or nanoclusters based fluorescent sensors are commonly suffering from aggregation issues.
- Even though, the Aptamers or DNA or Antibodies are essential elements for development of fluorescent immunoassay, they are not cost-effective and also need labeling and special storage procedures.
- Most of the developed sensors are demonstrated for toxins in spiked real samples and not tested in real conditions.

5.4 Future Recommendation

- Since the food is playing an essential role for the survival of human beings, the quality of the food stuffs are considered as a crucial factor for human life and hence the portable, affordable, and reliable analytical devices for food toxins are very much essential for their healthy and wealthy life.
- The above mentioned disadvantages or challenges of the fluorescent sensors like insolubility in aqueous medium stability and reproducibility have to be take care during the designing of the sensing platforms in future.
- Most remarkably, based on above reports, no research group has attempted to fabricate a sensor strips to apply for the societal usage.

- Hence these above research findings have to be transformed as sensor tool or Kit and it will reach even people in the rural areas.
- Since maximum people are having their own smart phones, development of mobile based spot test will offer speed, simplicity, portability, and affordability for them.

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Optical Detection of Targets for Food Quality Assessment

6

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Abstract

Food safety and quality is one of the scientific disciplines that have gained the concern and attention of people. For the most part, food safety tends to be considered by end consumers first before the nutrients provided by the food, as food contaminants can have a significant, direct and often irreversible health effect. There is, therefore, a need for rapid and on-site sensing technologies or devices to be established to rapidly identify and sort contaminated foods. The inability to rapidly identify and isolate infected food from the food supply chain will lead to foodborne disease outbreaks. After consuming these contaminated foods, about 10% of the world's population gets sick, according to the WHO. Consequently, this issue promotes the design and development of miniaturized (portable), cost-effective and, at the same time, sensitive, precise, and reliable technologies and methods for the identification of food contaminants such as acrylamides, microbes, heavy metals, food preservatives, toxins, pesticides, and antibiotics. These food contaminants are foreign substances commonly contained in consumable food products that, after their absorption into the human body, could potentially cause short- and long-term health effects. Different detection technologies and instruments for food quality assessment, such as chromatography, spectroscopy, magnetic, electrochemical, and optical methods, are available to date. Optical methods of detection that have been developed in recent years to identify targeted food contaminants have been studied in this chapter. Analytical performance such as LOD, LOQ, linear range and time of analysis, detection cost, advantages, disadvantages, and limitations of different approaches to optical

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sensing are presented. The comparison between different types of optical sensing approaches are outlined as well.

Keywords

Carcinogens · Preservatives · Toxin · Antibiotics · Heavy metals · Pesticides

6.1 Introduction

The rise in living standards has led to the need to develop rapid and on-site advanced sensing technologies to ensure food safety and quality, beginning from the production line, packaging and distribution to the end consumer. Food safety and quality have become the criteria for consumers to think about before making any purchases in the last few decades. It has also been one of the variables to be checked before making decisions by the food manufacturers and policymakers. To assess our level of health, the amount and types of food we eat are essential factors. It impacts the development and function of our body's hormones, enzymes, and other metabolic process regulators. Food safety and quality has since been a concern of scientists and the public until today, as food quality is closely related to health quality and unsafe food poses global threats to health.

Carcinogens, dangerous pathogens (bacteria, viruses, parasites), heavy metals, chemical compounds, toxins, pesticides, and other substances that could cause various diseases ranging from diarrhea to cancer are found in unsafe or contaminated foods. Nearly 1 in 10 individuals in the world get sick after eating contaminated food, according to the World Health Organization (WHO), and about 42,000 die every year (WHO 2020). The most common foodborne disease is diarrheal disease, which causes 550 million people to fall sick and about 230,000 die each year (WHO 2020). Foodborne disease has created a problem for health care and creates an economic burden worldwide. As the world's population is growing exponentially, the growing demand for food could pose a challenge to food safety due to the escalation of industrialization in agriculture and meat production. Food can become contaminated at all of these points in the food supply chain, beginning from the food production line, the transport and distribution of food, the storage of food up to the handling of food in the kitchen, if no precautionary measures have been taken.

People have been grappling with food safety problems dating back three decades, including the appearance of novel foodborne illnesses, uncertain long-term effects of genetically modified foods (GMOs), adulterated foods, the presence of food contaminants, and food spoilage. A consistent and efficient quality management approach, or regular screening, should be developed and enforced to ensure food safety and food quality for customers. There are several up-to-date methods for detecting target contaminants in foods, ranging from laborious and time-consuming traditional bacterial detection methods based on culture, colony counting, chromatography and immunoassay, amplification based on nuclear acid sequence, polymerase chain reaction (PCR) to non-destructive instrumental imaging techniques such as

optical biosensors, electrochemical biosensors, and spectroscopy (Bhardwaj et al. 2017; Hameed et al. 2018).

The emphasis of this chapter will be on the occurrence of these different target contaminants in food and an overview of available optical detection methods, including attractive optical biosensors, certain optical detection methods based on spectroscopy, and other advanced techniques used in optical detection to trace the existence of target contaminants in food and reduce the incidence of foodborne diseases. Optical detection can be defined as a non-destructive, automated technique focused on the interaction of light and matter for food quality evaluation, resulting in the conversion of incoming light rays (optical energy) into electronic signals. Eventually, the presence of contaminants in food can be determined and quantified through examination, analysis, and interpretation of the visual images and spectral characteristics provided by an integrated measuring system. The operating theory of an optical detector is that the targets from an emitting diode will reflect or disrupt the coming light beam. A measuring system responds to the changes to the light beam and interprets them for information. For food safety and quality assurance, because of its sensitivity, precision, and performance, optical detection is often a better option than sensory evaluation or traditional bacterial detection.

The contaminated food issue, following the alarming statistics announced by the WHO, prompts the production and design of compact, cost-effective, responsive, quick and shortest-time-as-possible technologies and methods for detecting these food contaminants as the rise in population year by year will exacerbate the condition if the speed of contaminant detection and separation could not be preserved. There are many up-to-date techniques available for detecting food contaminants, such as chromatography, spectroscopy, magnetic, and electrochemical methods. This chapter studies optical detection methods for food contaminants (carcinogens, microbes, heavy metals, food preservatives, toxins, pesticides, and antibiotics) that have been established in recent years. Carefully discussed are the analytical performance (LOD, LOQ, linear range, analysis time), cost, advantages, disadvantages, and limitations of different optical detection methods for the food contaminants mentioned above. The comparison between different types of methods of optical detection as a whole is also outlined.

6.2 Food Contaminants: Sources, Removal Problems, and Effective Corrective Approaches

Carcinogenic substances in food can be classified into two classes, genotoxic and non-genotoxic. Genotoxic carcinogens are chemicals that can cause DNA damage, lead to cell mutation, and thus increase the risk of tumors. It is dangerous and presents a risk of cancer even when exposed to a very low dose, so there is no threshold value or dose deemed safe for exposure to genotoxic carcinogens. Natural food constituents such as ethyl carbamate, phytotoxins or contaminants such as acrylamide (AA), heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and products of cholesterol oxidation (COPs) may be genotoxic

carcinogens found in the diet (Cuevas-González et al. 2020). On the contrary, non-genotoxic carcinogens is assumed to have a threshold dose at which concentration surpass the threshold value would induce cancers through diverse underlying mechanisms including cell proliferation, tumor promoters, cytotoxicity, endocrine modifiers, receptor mediators, or immunosuppressants other than mutation in the previous case (Hartwig et al. 2020; Hernández et al. 2009; Nohmi 2018). Phenobarbital, carbon tetrachloride, diethylstilbestrol, and others are the examples of non-genotoxic carcinogens (Nohmi 2018).

Most of the dietary carcinogens evolved during the process of food storage, preparation or processing, while some of the dietary carcinogens may be the natural constituents of the food (Cuevas-González et al. 2020). Food thermal treatment is known to produce carcinogens by accelerating lipid and protein oxidative reactions due to increased production of free radicals that react rapidly with atmospheric oxygen and decreased protection of food antioxidants. It is important to note that in addition to giving the desirable aromas, colors, and flavors to the food, different carcinogenic compounds could be produced in the single thermal treatment of food. Therefore, decreasing dietary carcinogens while preserving the organoleptic properties and palatability of food is a significant challenge for the food industry (Koszucka and Nowak 2018).

Food serves as a medium for microbes' growth, but not all of it is harmful. For fermentation, some microbes such as fungi and probiotic bacteria are beneficial, giving the food stronger organoleptic properties. Yet certain bacteria, such as *Escherichia coli (E. coli)* O157:H7*, Staphylococcus aureus (S. aureus), Salmonella* sp.*, Listeria monocytogenes, Clostridium perfringens, Campylobacter jejuni, Vibrio* sp.*, Clostridium botulinum, Bacillus* sp.*, Shigella* sp. and *Streptococcus pyogenes* are responsible for food poisoning (Bhardwaj et al. 2017; Mukama et al. 2017). Various food bacteria, including both Gram-positive and Gram-negative, can secrete toxins that cause foodborne infection, from less severe gastrointestinal disorder to more severe paralysis and even death (Abebe et al. 2020).

The high survivability and adaptability characteristics of microbes allow them to grow and reproduce in different environments, so the eradication of microbes is a challenge to the food industry. Since at different stages and phases the microbes can reach the food chain and food distribution line, it poses a new food safety problem. Some foodborne microbial pathogens manifest diseases within a few days, while others, in some cases, remain latent in the body after consumption of microbial-contaminated foods prior to disease manifestation. Although rigorously heat-sterilizing the food could kill the microbial environment, the taste and texture of the food could likely alternate at the same time. Nevertheless, some pathogens, especially in microbial-contaminated pork or bacon, are not killed even after being subjected to high-temperature cooking. Those three *S. typhimurium* (ATCC 14028, I33, and I116 strain), *S. derby* B4373, *S. Potsdam* I133, *S. Menston* I79, *S. eppendorf* I66, and *S. kingston* I124 are examples of these high heat resistant pathogen strains that could be contained in pork meat (Quintavalla et al. 2001). That is why Muslims refuse to consider non-halal pork. In addition, the emergence of antibiotic resistance bacteria is also one of the global threats that contributes to prolonged hospitalization

and increased mortality that should not be undermined. Therefore, the growth of multi-drug resistant bacteria has also contributed to the development of rapid and efficient bacteria detection techniques (Locke et al. 2020).

One of the commonly debated concerns is also the inclusion of heavy metals in food because heavy metals are non-biodegradable, toxic even at small concentrations and do not fully excrete from the human body (Sharma et al. 2018). The source of heavy metals in food may be heavy metal accumulation in the soil where crops are grown (Sharma et al. 2018), or contamination of the abiotic ecosystem in which the animal origins are produced, causing bioaccumulation across various tropical levels along the food chain (Ali and Khan 2018), or the leaching of heavy metals from cookware and foodstuffs during food preparation and storage (Aderemi et al. 2017). Long-term health problems such as improper function of endocrine glands, hypertension, neurological disorders, respiratory diseases, immunological disorders, and others could be caused by the ingestion of food containing heavy metals (Sharma et al. 2018).

Heavy metal transmission from soil-food crops is the contributing factor for the presence of heavy metals in food. The presence of heavy metals in the soil matrix has a few sources; it may be due to atmospheric deposition, animal manure, irrigation with wastewater or polluted sewage, and pesticides and herbicides containing heavy metals. In addition, heavy metals from point sources such as thermal power plants, coal or gold mining, textile industries, and others may also contaminate the soil. Improper discharge of waste material (sludge) or wastewater containing heavy metals may disrupt the soil environment and the food safety problem with respect to heavy metals is therefore one of the challenges to address. Reliable and effective sewage water treatment is critical for reducing heavy metal leaching to food crops from wastewater discharged from factories. Remote real-time sensing is required in order to track agricultural activities from any heavy metal contaminated soils and water irrigation system. In addition, stringent regulatory implementation should be enforced to prevent any irresponsible or illegal disposal of industrial discharges.

Food preservatives are substances used to protect food by the prevention or suppression or delay of changes induced by microorganisms and oxidation reactions, resulting in spoilage. *Tert*-butylhydroquinone (TBHQ) is a strong phenolic antioxidant added to prevent oxidative deterioration. The addition of this compound to the food does not cause the color, taste, or odor to change. The optimal daily intake of TBHQ is 0–0.2 mg/kg of body weight, according to the Joint FAO/WHO (Balram et al. 2021). TBHQ is used in numerous food products such as unsaturated vegetable oils, animal fats, and meat products as well as cosmetic products. Overdose intake of TBHQ can result in vision disturbances, contact dermatitis, medullary paralysis, seizures, and potential immune system damage (Balram et al. 2021). Other common preservatives used in food packaging, cosmetics, biodiesel, and pharmaceutical preparation to prevent the oxidation process are butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). The reasonable daily intake of BHA via food is 0–0.5 mg/kg/kg, according to the Joint FAO/WHO (Manoranjitham and Narayanan 2020). While for BHT, the acceptable daily intake is 0.25 mg/kg according to the European Food Safety and Authority (EFSA) (Wang and Kannan

2019). Excessive intake of BHA may cause cellular damage and proliferation in the fore stomach and promote cancer formation (Williams et al. 1999). While for BHT, it might exert adverse effect on the lungs, kidneys, myocardial cells, lipid metabolism in the liver and others (Babich 1982). Other common preservatives used in drinks, foods, cosmetics, personal hygiene products, and pharmaceuticals are benzoic acid and parabens (4-hydroxybenzoic acid esters). Due to their carcinogenic nature, benzoic acids have attracted public attention (Balram et al. 2021).

The *Staphylococcus aureus* bacterium is commonly found in foods that have been improperly handled and subsequently stored at a high temperature, such as ham, meats, and dairy products, as *S. aureus* has high salt tolerance, high heat resistance and is not easily destroyed through cooking. Staphylococcal entertotoxins (SEs) secreted by *S. aureus* are the major cause of staphylococcal food poisoning (SFP) (Argudín et al. 2010; Denayer et al. 2017; Permyakov et al. 2017) (Locke et al. 2020). An effective and rapid detection technique should therefore be established in order to detect the presence of toxins in food before it reaches the end consumers.

The presence of pesticide residue in the food could be highly toxic to human health. Pesticides are widely used in agriculture to destroy or control pests. It has been estimated that less than 0.01% of pesticides reaches its purposes of pest control, the remainder would enter the environment and pollute it, and eventually enter the food chain and end up in the food we consume. Consequently, the pesticide residue may be absorbed through the human digestive system. Examples of pesticides are organophosphate pesticides, acetamiprid, carbamate pesticides, and others (Nagabooshanam et al. 2020; Xu et al. 2017).

Antibiotic contamination has become a worldwide epidemic as it is persistent and exists in many environmental samples, foods, dairy products, and beverages that require more attention to prevent any dire consequences. Antibiotics are drugs used to treat infections by inhibiting the growth of germs and bacteria. But over time, when germs or bacteria have established resistance to them, it may be less efficient. If they enter the food chain, it could cause adverse health effect by decreasing blood cells (red and white) causing weakness, headache, diarrhea, muscle pain, blurred vision, temporary vision loss, and hypertension. Tetracycline, penicillin, fluroquinolone, and sulfonamide are examples of common antibiotics. Manufacturing industries, hospitals, and veterinary facilities discharge these antibiotics into groundwater and river water, resulting in the spread of antibiotic resistance (Tarannum et al. 2020).

6.3 Optical Detection Toward Accurate Food Quality Assessment

6.3.1 Optical Detection of Food Carcinogens

Carcinogens are substances that may cause the development of cancers upon exposure. During the food heating and processing process, it will induce the formation of carcinogens such as heterocyclic aromatic amines (HAA), polycyclic aromatic

hydrocarbons (PAH), and acrylamide. It is difficult to avoid carcinogens, especially those that are produced during food processing operations. In this section, only acrylamide will be addressed since this compound has been extensively reported. Other food carcinogens such as 3-chloropropane-1,2-diol (3-MCPD) may also be detected by biosensing approaches, but not many similar studies have been reported (Wong et al. 2020).

Acrylamide (2-propanamide), an unsaturated amide formed when reducing sugars and protein containing asparagine are heated (such as frying and baking) at elevated temperatures (Pundir et al. 2019; Sani et al. 2018), to give food color and flavor through the Maillard reaction (Pan et al. 2020). The thermal processing methods, the temperature range at which food is heated will affect the acrylamide content in carbohydrate-rich food. The acrylamide content is directly proportional to the processing time and temperature (Pan et al. 2020). In addition, there is also a direct correlation between the production of acrylamide and food color development (Wang et al. 2013). Since the tolerable daily intake (TDI) reported for acrylamide is 40 and 2.6 μg/kg day, respectively, in terms of neurotoxicity and carcinogenicity (Tardiff et al. 2010), therefore, for food quality assessment, accurate, sensitive, and robust methods and techniques for the detection of acrylamide in food should be developed and adopted.

Optical instrumental analysis techniques such as high-performance ultraviolet liquid chromatography (HPLC-UV) are still the common and widely used methods of detecting the presence of acrylamide in foodstuffs to date (Norouzi et al. 2018; Saraji and Javadian 2019; Wang et al. 2013). Many studies have been conducted using these methods to detect the acrylamide content in food. High accuracy, sensitivity, good reproducibility, and stability are shown by these analytical methods. The drawbacks are expensive instrumentation and high costs of detection (Wei et al. 2020). Other than that, a meticulous and tedious process for sample preparation and purification (clean-up process) is required to increase the sensitivity and accuracy of acrylamide detection as the food matrix is quite complex (Pan et al. 2020; Rashidi Nodeh et al. 2018).

One research was conducted to detect acrylamide in food using dummy molecularly imprinted silica nanoparticles (DMISNPs) as a dispersant to extract acrylamide in food samples by matrix solid phase dispersion (MSPD). Molecularly imprinted polymers (MIPs) are porous materials that are man-made and have unique binding sites for certain molecules. DMISNPs have high acrylamide affinity, mechanical and chemical robustness, simplicity in synthesis procedure, low preparation costs, and low consumption of toxic organic solvent during the synthesis process. Acrylamide can easily recognize DMISNPs and enter the cavities and form hydrogen bonds with their functional groups. The content of acrylamide can be quantified by integrating high-performance liquid chromatography with UV detection (HPLC-UV). For this method, the detection limit (LOD) and quantification limit (LOQ) are 15.3 ng/g and 40.3 ng/g, respectively, with a linear range between 0.05 and 5.0 μg/g (Arabi et al. 2016; Pan et al. 2020).

In another paper, the presence of acrylamide extracted from snack, seasoning, and refreshment food samples was detected using an iOS gadget-based digital imaging

calorimeter (iOS gadgets-based DIC). The acrylamide is converted to vinyl amine through Hofmann reaction prior analysis. The vinyl amine reacts with fluorescein to give fluorescence emission at 590 nm with the excited wavelength at 470 nm. It enables the acrylamide content in the food sample to be determined simultaneously and synchronously by simply exposing the sample that has been undergone Hofmann reaction along with the fluorescein to emit fluorescence light. Using an iOS gadget, the emitted fluorescence light is detected and captured. The captured digital images can be used for estimation of the acrylamide concentration of the sample solutions by processing the color values of the digital images. Besides, the color value of the standard acrylamide solutions can be plotted as the calibration graph and thus the unknown concentration of the acrylamide can be derived from the calibration plot. The method has 0.53 and 1.78 mg/L LOD and LOQ, respectively, with a linearity range between 1.00 and 10.0 mg/L (Wongthanyakram et al. 2020).

An instrument-free approach to determine the concentration of acrylamide in food samples is through a filtration-assisted approach. Acrylamide extract was mixed and interacted with the silver nanoparticles (AgNPs)-EDT system. EDT will react with AgNPs before the addition of acrylamide, resulting in the formation of the aggregate of AgNPs due to reduced electrostatic repulsion and cross-linkage. Owing to the presence of an aggregate of AgNPs, the color of the aggregate changes from yellow to gray. Using ImageJ software, the gray color intensity can be quantified and analyzed. It is possible to use the filter membrane to isolate aggregate AgNPs from unaggregated AgNPs. The aggregates are vacuum-filtered and retained on the filter membrane. Acrylamide will form complex with EDT upon introduction of acrylamide into the AgNPs-EDT framework and thus reduce the content of EDT. Consequently, there are less aggregate AgNPs. With greater acrylamide concentration, the color of the aggregate is more yellowish. Or in other words, the acrylamide-containing sample appears to have a lower gray intensity. This technique enables optical detection by naked eyes through the intensity of the gray color or can be subjected to ImageJ software analysis. It is possible to use UV-Vis spectrophotometers to validate the results obtained. Using this filtration-assisted method, the LOD and LOQ are 3.7 ng/mL and 11.1 ng/mL, respectively (Lin et al. 2021).

Other than that, electrochemiluminescence (ECL) can be used to detect acrylamide in food and this method is believed to be simple, convenient and has high stability and reproducibility. For this detection technique, $Ru(bpy)_3^{2+}$ was used as luminophore. Oxidized $Ru(bpy)_3^{2+}$ and oxidized acrylamide (at scanning potential close to 1.1 V) react with each other to obtain an excited state of $Ru(bpy)_3^{2+*}$. This excited state of $Ru(bpy)_3^{2+*}$ is unstable and tends to return to the ground state with release of energy and give the ECL signal. The ECL signals can be monitored and captured by cyclic voltammetry (CV). An increasing in ECL intensity is accompanied by an increased acrylamide concentration. The digital images of ECL emission are collected using a remote wireless camera at which Red, Green, Blue (RGB) model is converted to Hue, Saturation, Value (HSV) using MATLAB software. The V shows a linear relationship with the acrylamide concentration. This method offers a LOD of 1.2 μM with a linear range of 5–10 μM (Yang 2019).

Following the digital era, the future trend for the identification of carcinogens will rely more on digital optical images, where the concentration of targeted analytes is directly or even inversely proportional to parameters such as the intensity of color derived from digital images. The concentration of the targeted carcinogenic molecules can be measured using tools such as ImageJ or the RGB (Red, Green, Blue) of digital images can be transformed to HSV (Hue, Saturation and Value) using MATLAB and others for quantification by simply taking a real-time and on-site digital image of the optical emission from the contaminated food sample solution using a smartphone camera. The above optical sensing approaches of the food carcinogen acrylamide are summarized in Table 6.1.

6.3.2 Optical Detection Methods of Microbes

Bacteria are one of the causes of cases of food poisoning that have haunted us for decades, typically due to inappropriate techniques of food handling. *E. coli*, *S. aureus,* and *Salmonella* sp. are examples of common bacteria commonly found in food. There might be no distinction in terms of appearance, taste or smell of the microbe-contaminated food from the non-microbe-contaminated-food. Therefore, in order to detect and distinguish microbe-contaminated foods from non-microbe-contaminated foods, cost-effective methods that could be carried out in the shortest time possible should be developed.

For the detection of *E. coli* bacteria, mesoporous silicon (immunosensor) biosensors can be used. Nanostructured porous silicon (Psi) as an optical transducer of the biosensor functionalized with specific antibodies against *E. coli* has been used to capture and real-time detection of *E. coli* in food samples. *E. coli* bacteria detection is based on a shift in optical data when target analytes are captured or bound to the surface of the biosensor based on an antibody-antigen interaction. In other words, the white light is directed to the biosensor, and the film's average refractive index is recorded throughout the experiment and the wavelength change in the reflectivity spectrum is recorded. The reflectivity spectrum is then transformed to a single peak (Intensity versus Effective Optical Thickness (EOT)) by applying a fast Fourier transform (FFT). Biosensors capture of bacteria will reduce the intensity of the single peak. In this case, pre-treatment of the sample leading to prior lysis of the bacteria cell to extract the targeted protein and DNA fragments is not required for the direct capture of the target bacteria to the biosensor. This method of optical detection enables E. coli to be detected and quantified rapidly. However, because antibodies are used as a capture element, the sensor is confined to targeted analytes containing antibodies. In addition, the chemical stability of this sensor in corrosive environments should also be considered, as it is possible to observe a baseline drift in non-neutral environments. The LOD is 103 cells/mL for this method, with a linear range of 103–105 cells/mL (Massad-Ivanir et al. 2016).

A modified lectin-coupled porous-silicon-based biosensor was used in other studies to detect two types of commonly found food bacteria, *E. coli* and *S. aureus*, by reflectometric Fourier transform spectroscopy interference (RIFTS).

Table 6.1 Optical methods for the detection of food carcinogens

Food carcinogen	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
Acrylamide	HPLC-UV (DMISNPs-based dispersant)	~15.3 ng/g	~40.3 ng/g	0.05–5.0 μg/g	5–15 min	~10–20 USD	DMISNPs are mechanical and chemical robustness, and due to their unique binding cavities for molecular recognition, they have strong selectivity against acrylamide. It consumes less toxic organic solvents, using just 100 mL of ethanol and 3.2 mL of ammonia solution during DMISNPs synthesis	It does not allow for on-site detection at which samples are required to be brought back to the laboratory for analysis	Only one type of targets can be recognized per analysis. It does not allow simultaneous detection of various contaminants	Arabi et al. (2016), Pan et al. (2020)

Acrylamide	Fluorescence (using iOS gadgets-DIC)	~0.53 mg/L	~1.78 mg/L	1.00–10.0 mg/L	<5 min	~200–500 USD	Simple experimental setup that only includes a photography lightbox and iOS gadget. It facilitates acrylamide detection simultaneously and instantaneously	It is not a label-free detection method as fluorescein is needed to manifest the fluorescence emission	The result is affected by the fluorescein concentration. Increasing the fluorescein concentration will increase the color value up to 100 mg/L. Above this concentration, it induces reductions in fluorescence intensities	Wongthanyakram et al. (2020)
Acrylamide	ImageJ software (UV-Vis for confirmation)	3.7 ng/mL	11.1 ng/mL	–	~5 min	~10 USD	It does not require sophisticated instrumentation, trained personal as this method just uses naked eyes to observe the color changes of the AgNPs aggregate upon acrylamide addition. This method is suitable for the developing countries for compact, automated, and on-site detection	The use of AgNPs or AuNPs for the manifestation and development of color is required by this method. For this procedure, the cytotoxicity of those two nanoparticles should be considered	The target analytes chosen for this approach must be able to form aggregate with EDT in the AgNPs-EDT system and give color changes so that the results can be analyzed using ImageJ software	Lin et al. (2021)

(continued)

Table 6.1 (continued)

Food carcinogen	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
Acrylamide	ECL measurement and optical imaging analyzed by MATLAB	~1.2 µM	–	5 µM–10 mM	~10 min	~100 USD	A simple and promising method as the concentration of acrylamide is determined from the digital images of ECL emission. RGB has been converted to HSV. V is directly proportional to the acrylamide concentration. This enables on-site detection	It is not a label-free detection method as Ru $(bpy)_3^{2+}$ is needed as a luminophore	ECL intensity is affected by the scan rate and pH. According to the studies performed, ECL intensity is optimum at pH 7 and the scan rate is between 0.02–0.1 V/s	Yang (2019)

Owing to its unique carbohydrate-binding (glycan moieties of glycoproteins or glycolipids) properties and relatively inexpensive compared to other antibodies, lectin is selected rather than an antibody. First, the fresh PSi is oxidized to form oxidized PSi, followed by dipping to form APTES modified PSi in ethanolic (3-aminopropyl)triethoxysilane solution (APTES). APTES modified PSi is converted to glutaraldehyde modified PSi, which is then ready for lectin immobilization to form lectin modified PSi. A reflection spectrum is obtained for penetration of analytes into the pores of PSi. Reflection spectrum data is transformed to the Fourier transform (FFT) intensity. After the addition of target analytes, the amplitude of the peak decreases. The result showed that ConA (Concanavalin A) and WGA (Wheat Germ Agglutinin) lectins have greater binding affinity to *E. coli* and *S. aureus*. Lectin, as compared to antibodies, is inexpensive and more stable, but less specific than antibodies. But still, because lectin has more than one (polyvalent) binding sites, less specificity can be improved and compensated (Yaghoubi et al. 2020).

In addition, a fiber optic surface plasmon resonance (FOSPR) sensor based on antimicrobial peptides (AMP), Magainin I, and silver nanoparticles-reduced graphene oxide (AgNPs-rGO) has been developed. AgNPs-rGO is secured to the optic fiber surface followed by surface covering with AuNPs. Next, the Magainin I is immobilized onto the fiber optic probe. The advantages of such sensor are improved performance of SPR response and protection of AgNPs from oxidation. Magainin I acts as the recognition element that could specifically capture E. coli and results in the change of the refractive on the optical fiber surface and wavelength shift of the SPR absorption peak. While AgNPs-rGO acts as signal amplification and allows for low limits of detections of 5.0×10^2 cfu/mL (Zhou et al. 2018a, b).

Based on poly(carboxybetaine acrylamide) (pCBAA) brushes, biotinylated secondary antibodies and streptavidin-coated gold nanoparticles, another SPR biosensor was developed to specifically detect low levels of *E. coli* and *Salmonella* sp. in complex food samples such as cucumbers and hamburgers. The biotinylated secondary antibodies are immobilized on the pCBAA coating mounted on the SPR chip. The antibodies capture and bind to the bacteria (target analyte). The captured bacteria are then bound by secondary (2°) biotinylated antibodies. The binding of streptavidin-coated gold nanoparticles to the 2° antibodies is then followed to enhance the detection/sensor response signals (Vaisocherová-Lísalová et al. 2016). Table 6.2 summarizes the optical sensing approaches described above for potential microbes present in food.

6.3.3 Optical Detection Methods for Heavy Metals

Heavy metals, due to irrigation with contaminated water, mining or industrial emissions, are commonly found in agricultural food crops such as fruits and vegetables, as a result of the introduction of heavy metals to the soil matrix. Heavy metals are also found in the food during cooking as a result of leaching from the cookware.

Table 6.2 Optical methods for the detection of food microbes

Food microbes	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
E. coli	Antibody-mesoporous silicon biosensor (Immunosensor)	10^3 cells/mL	–	10^3–10^5 cells/mL	60 min	~100–500 USD	No sample pre-treatment is needed because the target bacteria can be directly captured on the surface of the biosensor. It is a method of label-free detection in which no fluorophore is required. The detection is based on reflection from the thin film biosensor's top and bottom interfaces	Less chemical stability in the corrosive environment of the PSi transducer	Limited targets (only those with antibodies can be detected)	Massad-Ivanir et al. (2016)

E. coli & *S. aureus*	Lectin-porous silicon biosensor	10^3 cells/mL	–	10^3–10^5 cells/mL	~30 min	~100–300 USD	Accurate and rapid detection, label-free detection of bacteria as detection is by looking at the intensity of FFT spectra. Lectin is used to replace antibodies as lectin is less expensive than antibodies	Lectin is less specific than antibodies	Due to the structural complexity of the lectin, they are limited to traditional methods of detection such as chromatography and spectroscopy	Yaghoubi et al. (2020)
E. coli	FOSPR	10^2 cfu/mL	–	10^3–10^7 cfu/mL	60 min	~500–1000 USD	For this detection method, AuNPs-rGO was used as it was verified that this composite could improve sensitivity about five times as it could change the conjugate and surrounding refractive mass of FOSPR significantly	This technique may be motion sensitive	For liquid samples only	Zhou et al. (2018a, b)

(continued)

Table 6.2 (continued)

Food microbes	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
E. coli	SPR	~10–60 cfu/mL	–	–	230 min	~500–1000 USD	For multi-step detection, the pCBAA coating offers high functional and surface-resistance capabilities. This sensor is capable of detecting two different microbes in a sample simultaneously	Multi-step detection assay involving incubation time between samples and sensor, capture of bacteria by sensor antibodies, binding of 2° biotinylated antibody to captured bacteria and binding to biotinylated antibodies of streptavidin-coated AuNPs to enhance response. The system could be motion sensitive	Likely change in antibody configuration during immobilization to the pCBAA surface	Vaisocherová-Lísalová et al. (2016)
Salmonella sp.		~10^3 cfu/mL								

Atomic Absorption Spectroscopy (AAS) has been widely used to detect heavy metals in food samples. Co, Ni, Cu, Zn, Cd, Mn, Mg, Fe, and Ca in Sage Tea have been determined by Flame Atomic Absorption Spectroscopy (FAAS). The sample is subjected to acid dissolution prior to analysis by FAAS.

By using FAAS coupled with MnO_2/3MgO nanocomposite, a sorbent for solid phase extraction for preconcentration, trace copper and lead in food can be detected. The analytes were desorbed from the nanocomposites after extraction using ethylenediaminetetraacetic acid. The extract is then analyzed using FAAS for copper and lead concentrations (Khayatian et al. 2018).

A novel method of in-syringe solvent dispersive solid phase extraction (ISSADSPE) method followed by FAAS to detect the nickel in the water and food samples has been developed. The sample solution was placed in the syringe barrel, followed by the addition of sorbent material to the sample solution. The analytes are deposited on the sorbent and, through the syringe membrane, the sorbent is separated from the sample solution. Next, ethanol was then used to extract the deposited targeted analytes on the sorbent prior to analysis using FAAS (Nakhaei et al. 2019).

Heavy metals can be detected using laser-induced breakdown spectroscopy (LIBS). LIBS is an in situ detector that enables the detection of solid, liquid, or gas samples with minimal sample preparation on different food matrices. In addition, it allows rapid and multiple elements detection. The high-power pulsed laser source is focused on the sample, which subsequently causes the sample molecules to break down into atoms. The laser energy allows a small number of samples to turn into a vapor and form a plasma at high temperatures. The atoms are excited by this high-temperature settings, and the unstable atoms relax to the ground state by emitting light radiation, which is in turn detected by the spectrometer. However, further studies need to be performed on its interaction with the food matrices, plasma formation, radiation emission, and signal analysis (Sezer et al. 2017). Studies on fresh vegetables contaminated with heavy metals by LIBS have been reported (Yao et al. 2017). Another LIBS study was carried out on a pork sample to detect the heavy metal chromium (Huang et al. 2016). In order to improve stability and sensitivity, it is necessary to eliminate the water content and some organics while using these techniques, as these compounds would affect the LIBS spectrum, such as higher noise and background signals (Huang et al. 2016; Yao et al. 2017). Since this approach is very new, further studies are needed to understand its interaction with different food matrices, plasma formation, emission of radiation and signal analysis. Table 6.3 provides a summary of the discussed optical detection methods for heavy metals present in food.

6.3.4 Optical Detection Methods for Food Preservatives

Food preservatives have been added to food for decades to prevent deterioration and spoilage and to lengthen the shelf life of the food. Excessive use has, however, been documented to promote cancer and affect metabolism (Prapainop et al. 2019). Therefore, quality control should also be in place to ensure food safety and quality.

Table 6.3 Optical methods for detection of heavy metals in food

Heavy metal	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitation	References
Co, Ni, Cu, Zn, Cd, Mn, Mg, Fe and Ca	FAAS (acid dissolution)	4.0–5.0 ppm	–	–	~15 min per sample	~10 USD per sample	FAAS has excellent accuracy and precision. The high-temperature flame is used to minimize interference by atomizing target analytes. Specific wavelengths are produced by hollow cathode light specific to targeted heavy metals to excite heavy metal atoms	Consume chemical solvents that are not environmentally friendly for digesting samples	Need experienced personnel to perform the instrumentation and analysis	

Cu^{2+}	FAAS (MnO_2/3MgO)	4 μg/L	–	10–900 μg/L	~15–60 min per sample	~10 USD per sample	In order to minimize matrix interference, the MnO_2/3MgO nanocomposite is used to isolate the target analytes prior to analysis. Nanosized MnO_2 has superior adsorptive performance while MgO has high ionic character, simple stoichiometry and crystal structure that can be prepared with different sizes and shapes	This nanocomposite has a short shelf life due to possible aggregation. Without any significant loss in its absorption performance, the nanocomposite can only be reused up to four times		Khayatian et al. (2018)
Pb^{2+}		11 μg/L	–	30–900 μg/L	~15–60 min per sample	~10 USD per sample				
Ni	FAAS (ISSADSPE)	0.7 μg/L	2.0 μg/L	2–150 μg/L	~15 min per sample	~10 USD per sample	Separation and preconcentration of targeted analytes by ISSADSPE to minimize matrix interference. A simple instrumental setup in which a syringe is used for the rapid separation and preconcentration process	As the separation process is performed by pushing the syringe plunger, this procedure is not automated, and it is not ideal for large-scale analysis	Chelating agent extraction is based on the pH of the sample solution. Therefore, the pH of the sample solution influences the stability of the metal-ligand complex	Nakhaei et al. (2019)

(continued)

Table 6.3 (continued)

Heavy metal	Optical method	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitation	References
Cd, Cr	LIBS	–	–	–	~15–30 min per sample	~50–100 USD per sample	In situ detection enables detection with minimal sample preparation in different food matrices (solid, liquid, gas). It facilitates multi-elemental detection. LIBS can analyze and characterize chemical composition in almost all substances	Performance depends on certain parameters such as wavelength, energy, pulse duration, etc. it has reproducibility issue due to small size of focused beam and small vaporized sample mass	A careful sample preparation step is required where water should be eliminated for stability and sensitivity and to minimize noise and background signals	Huang et al. (2016), Sezer et al. (2017), Yao et al. (2017)

Benzoic acid and paraben derivatives are common food-added preservatives. They can be detected using mercaptosuccinic acid capped cadmium telluride quantum dots (MSA capped CdTe). For the parabens, hydrolysis is performed to transform them to *p*-hydroxybenzoic acid (PHBA) as parabens are unable to interact directly with the quantum dots. Addition of MSA capped CdTe QDs to the target analytes solution in 1:1 ratio, the mixture is subject to fluorescent analysis. Benzoic acid and PHBA will result in fluorescent quenching of the MSA-CdTe QDs. In addition, upon addition of benzoic acid, there is a color change of MSA-CdTe QDs, therefore UV-Vis spectrophotometer can also be used for benzoic acid and parabens determination, where the increasing trend of the absorbance peak at approximately 456.50 nm has been perfectly shown by increasing from 0 mg/L to 100 mg/L benzoic acid. This approach gives a detection limit for benzoic acid and PHBA of 0.3 mg/L and 0.1 mg/L, respectively, with a linearity range from 1.0 mg/L to 500.0 mg/L (Prapainop et al. 2019).

In recent years, another *tert*-butylhydroquinone (TBHQ) food preservative has gained a lot of attention because it causes potential liver damage. In food manufacturing, TBHQ is popular as it can prevent putrefaction and deterioration of edible oils and lipids. Based on the competitive reaction between the photo-induced electron transfer (PET) effect and the complexation reaction between phenolic hydroxyl groups with the Fe(III) ions in TBHQ, a 'on-off-on' fluorescent sensor has been developed. For the fluorescence intensity measurement of the sample solutions, an excited wavelength at 360 nm was set. The "on-off-on" mechanism process is as follows (Yue et al. 2016):

1. On: The synthesized quantum dots (CDs) act as fluorophores, giving a certain fluorescence intensity at 360 nm when the excited electrons return to the ground state due to instability.
2. Off: In the presence of Fe(III) ions, the fluorescence intensity of CDs is quenched due to the photo-induced electron transfer effect between Fe(III) and CDs. The introduction of Fe(III) ions would lead to the entry of excited CD electrons into the unfilled Fe(III) ion orbital. This process deactivates the excited electrons and subsequently decrease fluorescence intensity and is referred to as fluorescence "quenching".
3. On: Next, with the introduction of TBHQ, fluorescence intensity gradually increases due to the strong complexation of TBHQ with Fe(III) ions. TBHQ will compete Fe(III) with CDs.

This "on-off-on" fluorescence sensor gives a linearity range from 0.5 to 80 μg/mL with a low detection limit of 0.01 μg/mL (Yue et al. 2016).

Other commonly used preservatives in food are formaldehyde, hydrogen peroxide, and sodium carbonate. For the detection of the above-mentioned preservatives, a fiber optic sensor is used based on the change in the refractive index of the outer region of the fiber cladding or on the concentration of the medium surrounding the sensing area. This technique can be used for liquid foods such as milk, juice, etc. and

can detect changes in the refractive index of less than 0.4% (Saracoglu and Hayber 2016).

A compact, selective, and on-site detection method should be developed for food preservatives in the future. A bent fiber optic sensor may be an option because it is compact, but not all target analytes are subject to change in the refractive index and one targeted analyte is not clearly distinguished from another by this method. Due to its simple instrumental setup in which an iOS gadget such as a smartphone equipped with a camera can be used to capture digital images of the sample optical emission, a digital image based on the parameters of the images captured to determine the preservative concentration can also be developed in the near future. In addition, it is also a rapid detection in which the digital image can be acquired in 1 s and then analyzed using software or applications such as MATLAB. Table 6.4 summarizes the above optical sensing methods for food preservatives.

6.3.5 Optical Detection Methods for Toxins

Some bacteria and fungi in food could secrete substances that are toxic to humans and these toxin-containing foods should be immediately detected and removed instantly from the consumer food supply chain to ensure food safety and quality.

Two types of toxins are available: bacteriotoxin and mycotoxin (secreted by fungi). One of the mycotoxins commonly found in maize, nuts, and spices is aflatoxin. Aflatoxin can be found in many forms, but aflatoxin B1 is the most toxic. In one study, almonds were used as almond matrices, showing a significant intrinsic fluorescence emission in the observed spectral range. High-performance fluorescence detection liquid chromatography (HPLC/FLD) coupled with machine learning algorithms—a binary classification model based on Support Vector Machine (SVM) was used for the total aflatoxin (B1 and B2) detection produced by the *Aspergillus flavus* bacteria in the slurry almond. Prior to HPLC-FLD analysis, the slurry almond was then extracted and filtered. The excitation wavelength used for the detection of fluorescence is 365 nm, while 435 nm is for emission. This technique's LOD is 0.2 ng/g. The accuracy value (ACC) and False Negative Rate (FNR) were calculated for the binary classification using SVM. In contaminant analysis, FNR is an important parameter which provides an indication of the misclassification of the contaminated food sample as a safe food sample. In developing countries, this technique is suitable because it is a simple setup with minimal sample preparation (Bertani et al. 2020).

Shiga toxin (Stx) is one of the potential *E. coli* toxin-producing bacteriotoxins produced by Shiga (STEC). The toxin affects the intestinal tract, causing diseases that range from hemorrhagic colitis to hemolytic-uremic syndrome (HUS). For the detection of this toxin, a portable and real-time optical sensing system has been developed. The sensing device consists of optical components: light sources, a Stx sample loading platform and a highly sensitive light detector, a photomultiplier tube (PMT) that detects and measures fluorescence from fluorescently tagged Stx, a control and data acquisition platform consisting of an amplifier-equipped

Table 6.4 Optical methods for detection of preservatives

Preservatives	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
Benzoic acid	Fluorescence (MSA-CdTe QDs)	0.3 mg/L	–	1.0 mg/L–500.0 mg/L	1–5 min	~50 USD per sample	The formation of hydrogen bonds with the preservatives between MSA-CdTe QDs enables detection. This approach reduces the use of organic solvents and only uses organic solvents during target analyte solid phase extraction (SPE)	On-site detection is not supported by this method and it is a non-label-free method. CdTe QDs demonstrate elevated cytotoxicity.	The experiment has only been performed on liquid samples such as fish sauce, coconut milk and some other beverages	Prapainop et al. (2019)
Parabens	Fluorescence (MSA-CdTe QDs)	0.1 mg/L	–	1.0 mg/L–500.0 mg/L	1–5 min	~50 USD per sample		To obtain PHBA prior to analysis, sample hydrolysis is required under alkaline conditions. CdTe QDs demonstrate elevated cytotoxicity		

(continued)

Table 6.4 (continued)

Preservatives	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
TBHQ	"On-off-on" fluorescence probe (CDs/Fe(III) system)	0.01 μg/mL	–	0.5–80 μg/mL	1–5 min	~50 USD per sample	The designed probe has high selectivity toward TBHQ as the introduction of BHA and BHT has an insignificant impact on the recovery of the fluorescence intensity	On-site detection is not supported by this technique and it is not a label-free method	Suitable in edible oil samples, but there is still uncertain validity in other food samples	Yue et al. (2016)
Formaldehyde, hydrogen peroxide, sodium carbonate	Bent fiber optic sensor	–	–	–	1–2 min	~5 USD per sample	The detection is based on the change in the refractive index (concentration of medium change) of the outer region of the fiber cladding. It offers simple,	The refractive index of the sample is significantly affected by the temperature of the medium. This method does not provide good selectivity toward	The detection method is only suitable for any target analytes which are subject to refractive changes only. The	Saracoglu and Hayber (2016)

							sensitive detection (able to detect less than 0.4% in refractive index change) and allows remote sensing. In addition, it is also a label-free detection method	different types of preservatives	bending angle should be precise as over-bending may cause power loss	

microcontroller unit (MCU) and a display component board. The advantage of this system is that it is battery-powered and thus compact, weighing around 770 g excluding battery, with a total size of 17 × 13 × 9 cm^3. Moreover, it does not require any peripheral computer or external display equipment. The light source is directed to the samples and the light emitted from the samples is directed to the PMT, where the light for the LCD display is converted to current and voltage. This sensing device provides a low limit of detection of 110 pM (D'Auria et al. 2020).

Another label-free detection technique for mycotoxins is using absolute internal reflection ellipsometry (TIRE), which is a combination of spectroscopic ellipsometry (SE) and surface plasmon resonance (SPR). Apparently, this aptamer assay is more sensitive than SPR alone and can classify certain analytes of low molecular weight such as ochratoxin A (OTA), aflatoxin B1, alkyl-phenols, and microcystin. In this study, OTA with a low molecular weight of 403.8 Da was detected. For the preparation of aptamers, gold and chromium layers have been evaporated and immobilized into the standard glass slide followed by binding to the DNA-based aptamers specific to OTA on the gold surface. Then, the TIRE method was used for the detection and measurement. The increasing introduction of OTA will trigger a progressive blue shift (shift to shorter wavelength of the TIRE spectra). This is explained by the decrease in the molecular layer thickness or refractive index upon OTA binding. This label-free model is capable of detecting OTA concentrations down to 0.01 ppb (Al Rubaye et al. 2018).

Among these optical methods, portable fluorescence device with PMT and LCD is worth further investigating for other toxins found in food. The portability of this device could provide on-site detection and could instantly separate those toxin-contaminated from others. Table 6.5 summarizes the optical sensing methods discussed in this section.

6.3.6 Optical Detection Methods for Pesticides

Pesticide residues in agricultural products are detrimental to human health. In order to ensure food safety and quality, detecting the level of pesticides in food is critical and enables regulation and monitoring of the use of pesticides in agriculture at the same time.

One of the useful direct pesticide detection techniques that can be used to ensure food safety and quality is surface-enhanced Raman spectroscopy (SERS). The unique and characteristic vibrational fingerprints provided by the molecules are the basis of this non-destructive detection. Prior to SERS analysis, extraction and clean-up of the sample is required. Density Functional Theory (DFT) is used to predict molecular conformation and spectral data (Xu et al. 2017). An in situ SERS detection for pesticides (thiram and thiabendazole) in fruits and vegetables has been developed in one study. For detection, jelly-like and slightly sticky Ag nanoparticles deposited on nanocellulose (Ag/NC substrate) were used. As it is abundant, environmentally friendly and has a nano-scale radius, nanocellulose (made from woods) is chosen. Stirring of AgNPs and NC produces the jelly-like appearance of the Ag/NC

Table 6.5 Optical methods for detection of toxins

Toxins	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
Aflatoxins	HPLC/FLD with SVM algorithms	0.2 ng/g	–	–	10–60 min	~10 USD per sample	A rapid and low-cost detection method suitable for developing countries with simple setup and minimal sample preparation. The algorithm can provide FNR value that could classify the contaminated food that could be labeled as a safe sample of food	The spectral reproducibility is moderate. When it is performed at different locations, the model offers different accuracy (the discrepancy is attributable to the differences in the geometrical arrangement of the setup as explained in the article)	The current reported technique cannot provide a detailed insight into the existence of contaminants and the estimation of shelf life for fresh food	Bertani et al. (2020)

(continued)

Table 6.5 (continued)

Toxins	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
Shiga toxin	Portable fluorescence device using PMT and LCD	110 pM	–	0–10 pg/μL	Not reported. Estimated less than 10 min	Not reported. Estimated 500–700 USD	Without any peripheral computer or additional unit, this device enables stand-alone and real-time detection of Shiga toxin as it is battery-powered based (portable). A highly sensitive PMT is used, which facilitates sample volume reduction and experimental procedure simplification	It is not a label-free detection where a fluorescent named Alexa Fluor 488 must be labeled for the detection of the toxin	This device is suitable for detecting small amounts of fluorescently labeled Shiga toxin. Suitability for other toxin types has not been documented	D'Auria et al. (2020)

Ochratoxin A	Aptamer assay with TIRE	0.01 ppb	–	–	Not reported. Estimated 10–20 min	Not reported. Estimated around 200–500 USD	Label-free detection of low molecular weight analytes. It provides a synthetic alternative to more expensive antibodies-based biosensing, taking advantage of the immobilization aspect over antibodies-based biosensing. Immobilization allows the DNA to be present at a specific location rather than randomly distributed over a region	The change in the refractive index could be affected by the mass transport of sample solution containing the target analytes	The developed aptamer assay is suitable only for OTA detection. Other types of specific aptamers are required for other mycotoxins, such as aflatoxin and zearalenone	Al Rubaye et al. (2018)

substrate. By only smearing the jelly-like Ag/NC substrate on the pesticide-containing fruit peels or vegetable surface, SERS measurement can achieve in situ and non-invasive detection. Besides, by observing the clear, sharp, and specific "fingerprint-like" Raman peaks, SERS allows multiple detection of different pesticides in the sample. The lowest reported detection limit for thiram is 0.5 ng/cm^2 and for thiabendazole is 5 ng/cm^2 (Chen et al. 2019).

One of the organophosphorus (OP) pesticides extensively used in agriculture to protect crops against pests and insects is *O*,*O*-Diethyl *O*-[4-methyl-6-(propan-2-yl) pyrimidin-2-yl] phosphorothioate or also known as diazinon. In order to detect trace concentrations of OPs in the food sample based on the fluorescence quenching effect of copper ions (Cu^{2+}) on lanthanide-doped conversion nanoparticles (UCNPs), a sensitive fluorescence biosensor was developed and reported. UCNPs own some distinctive properties and advantages such as having large anti-Stokes shifts, high quantum yields, long lifetimes, no photobleaching and non-blinking emissions, high chemical stability, and low cytotoxicity that enable them to be selected as the fluorophores over those conventional down-conversion organic luminescence materials. A fluorescence of high intensity would be given by UCNPs capped with branched polyethylenimine (PEI) itself. Upon addition of Cu^{2+} ions, the fluorescence is quenched due to the coordination of Cu^{2+} ions with the amino group of PEI of UCNPs, which is termed as "off" or known as fluorescence quenching. It is followed by the addition of acetylcholinesterase (AChE) and acetylthiocholine (ATCh) into the UCNPs-Cu^{2+} system. AChE is catalytically hydrolyzed by ATCh to form thiocholine (TCh). This TCh has a high affinity to bind with Cu^{2+} ions from the UCNPs-Cu^{2+} system, resulting in fluorescence intensity restoration and this phenomenon is referred to as "on." It was then followed by the addition of OPs pesticides that serve as an enzyme inhibitor and thus suppress the formation of TCh, resulting in fluorescence quenching again, which is "off." This "off-on-off" method gives a linear detection range from 0.1 to 50 ng/mL with LOD of 0.05 ng/mL (Wang et al. 2019).

A rapid detection of pesticides residues has also been developed by using flexible, transparent, and adhesive commercial tapes with SERS. The procedure is relatively simple, following the "paste, peel off, and paste again" steps. The pesticides analytes can be easily extracted from surfaces such as fruits and vegetables by simply pasting the adhesive tape onto the sample. After peeling off, the adhesive tape loaded with analytes was then pasted onto the Al_2O_3-coated silver nanorod (AgNR@Al_2O_3) which serves as SERS substrate where SERS signal could be read and obtained from there. In this study, tetramethylthiuram disulfide (TMTD) was identified as analytes. The LOD of this method is 28.8 ng/cm^3 or ~0.1 μg/g with a linear range from 10^{-5} to 10^{-6} M (Jiang et al. 2018).

SERS is a promising optical method among these, as it could provide rapid on-site and multiplexed detection of analytes. Other extraction methods for other pesticides or herbicides present on the surface of fruits and vegetables, such as acetamiprid, may be developed for future research. Table 6.6 summarizes optical detection methods for pesticides in foodstuffs.

Table 6.6 Optical methods for detection of pesticides

Pesticides	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
Thiram	SERS (Ag/NC substrate)	0.5 ng/cm^2	–	–	~5 min	~2000 USD	It allows in situ and non-invasive detection of multiple pesticides via "fingerprint" identification. A jelly-like and transformable Ag/NC substrate allows for identification by simply smearing the surfaces of the fruits and vegetables	There are uncontrollable aggregations in the Ag/NC substrate, which decreases the sensitivity and shelf life of the SERS substrate	Suitable only for those compounds that have fingerprints in the database of Raman spectra	Chen et al. (2019)
Thiabendazole		5 ng/cm^2	–	–						

(continued)

Table 6.6 (continued)

Pesticides	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
OPs (diazinon)	"off-on-off" strategy fluorescence biosensor (AChE modulated UCNPs-Cu^{2+})	0.05 ng/mL	–	0.1–50 ng/mL	~15–30 min	~10 USD per sample	This shows a great potential to monitor OPs in real samples. Due to the ability of the OPs (diazinon) to retard the enzymatic reaction of ATCh and AChE, this sensor has high sensitivity and selectivity toward OPs	It is not a method of label-free detection where UCNPs are needed for luminescence as a fluorophore. It is not an on-site detection in which samples need to be sent for detection to the laboratory	This approach is only acceptable for OP pesticides, which serve as an inhibitor of the enzyme. Other target analytes cannot be ideal candidates for inhibition of ATCh and AChE enzyme reactions	Wang et al. (2019)

TMTD	SERS with transparent adhesive tape	28.8 ng/cm^3 or 0.1 μg/g	–	10^{-5}–10^{-6} M	~5 min	~2000 USD	A simple and rapid extraction method with "paste, peel off, and paste again" using transparent adhesive tape. AgNR@Al_2O_3 (SERS substrate) is thermally stable in the air	The transparent adhesive tape pasted on the SERS substrate might weaken the intensity of SERS signals due to adsorption and reflection	Reasonable only for samples with a rigid surface that can withstand the pressure from pasting and peeling off. It is not ideal for sampling liquids	Jiang et al. (2018)

6.3.7 Optical Detection Methods for Antibiotics

Antibiotics such as penicillin, streptomycin, and kanamycin (KANA) have been commonly used in livestock breeding. Excessive use could establish antibiotic resistance, changing the response of bacteria to these antibiotics.

A SERS-based aptasensor for KANA has been proposed and developed. It is based on the principle of embedded and attached DNAs to form Au NPs-ssDNA on the surface of Au nanoparticles. Thiol groups form covalent bonds between these two compounds. The encapsulation of Au NPs-ssDNA with Ag shells was followed to form Au@Ag NPs-ssDNA. DNA aptamer was then added to form Au@Ag NPs-dsDNA. Au@Ag NPs-dsDNA is ready to be mixed with milk samples containing different concentrations of KANA and scanned for Raman spectra. The intensity of the Raman spectrum decreases with increasing KANA concentration. The lowest detection limit for this method is 0.90 pg/mL (Jiang et al. 2019).

Tetracycline (TC) is commonly used in food-producing animal as a growth promoter. It can be found in foods such as milk, eggs, and poultry. A fluorescent nanosensor has been developed for detection of TC antibiotics based on molecularly imprinted polymers (MIP) coated on graphene quantum dots (GQD). The GQD-MIPs solution is prepared using the sol-gel method. The addition of GQD-MIPs with carbonyl groups to different concentrations of TC was then followed, and subsequently summited for fluorescence measurement. Quenching of fluorescence intensity is observed upon the addition of TC. The authors have also demonstrated the effect of the GQDs-MIPs compared to the non-imprinted particles (GQD-NIPs) acting as reference. Both GQD-MIPs and NIPs have been reported to show fluorescence quenching, with the impact of GQD-MIPs on fluorescence response reduction being more significant than GQD-NIPs. Moreover, since the molecular imprinting technique was used to create the binding sites consistent with the targeted analytes in terms of shape, size, and functional groups, the selective recognition of the GQD-MIPs against TC is very satisfactory and effective. The LOD of this detection method is 1 μg/L with a linear range of 1–104 μg/L (Zhou et al. 2018a).

In another study, kanamycin (KANA) and neomycin (NEO) (classified as aminoglycoside group antibiotics) were detected using an ellipsometric aptamer-based sensor using spectroscopic ellipsometry (SE) and SPR-enhanced (SPRe) total internal reflection ellipsometry (TIRE) techniques. Thio-functionalized anti-kanamycin/ anti-neomycin aptamers were immobilized on cleaned sensor chip surfaces made of 50 nm Au film-coated glass slides, while amine-functionalized anti-kanamycin/ anti-neomycin aptamers were immobilized on a surface-modified silicon (Si) wafer. For those aptamers immobilized on Si surfaces, the detection of antibiotics KANA and NEO is through immersion of the aptamers in a solution containing specific antibiotics, followed by spectroscopic ellipsometer analysis (SE). The presence of antibiotics causes surface thickness to build up and the refractive index to change. While for those aptamers immobilized onto Au surfaces, KANA and NEO solutions were brought into contact with those aptamers, a total internal reflection device (SPRe-TIRE) and a flow system were required. A flow cell

(to which the target analyte solutions are injected to) consists of a glass prism coupled with a refractive-index-matching-oil. The antibiotics amount captured on the aptasensors is determined by the change in the angle of light reflected through the prism. The LOD of these two sensor platforms is between 0.1 and 1 nmol/L with a linear range between 0.1 and 1000 nmol/L (Caglayan 2020).

Aptamer is one of the advanced technologies that could specifically bind to the targeted molecules. Most of the aptamer is DNA or RNA based, which is relatively expensive. In the case of rapid and on-site detection, SERS is often a better option, as it is portable. Future research on the advancement of cost-effective extraction of target analytes for detection, such as using adhesive tape or filter syringe, could be developed. However, since they are not automated, these two extraction methods are inappropriate for large-scale detection. The aforementioned optical sensing techniques for antibiotics that are likely to be present in food are summarized in Table 6.7.

6.4 Comparison Between Different Optical Detection Techniques for Food Safety and Quality Assessment

Various optical detection techniques are available for food safety and quality assessment. The selection of one optical approach over the other mainly depends on the properties and characteristics of the target analytes. For example, if the target analyte has a high fluorescence activity or a high binding ability with the readily available fluorescein, the fluorescence sensing method may be appropriate for this analyte. While for other target analytes containing certain bio-recognizing elements, SPR, biosensor, and aptamer may be a considerable option for detection.

In terms of analysis time or detection time, excluding the sample preparation, the fluorometer can provide output data for each sample in less than 5 min by scanning through a certain wavelength range. Therefore, it offers a relatively rapid analysis. The capital cost of the fluorometer, HPLC-UV instrument and FAAS instrument may be a challenge for scientists, but the sample can be collected and sent to the testing laboratory where a sample which cost only around USD 10–50. It costs around USD 2000–3000 for the portable SERS detector, which is rather cost-effective as the detector can be used repeatedly to detect multiple samples and is ideal for routine screening of contaminated food samples. Biosensors, on the other hand, are a promising tool for real-time and on-site analysis, since biosensors can be made portable for field sensing. Relatively high accuracy, sensitivity, and selectivity could be given by biosensors. The novel LIBS technique has the ability for multiplexed target analytes (element) analysis in which the target analytes are break downed into atoms by high powered lasers and the analytes are determined and quantified from the LIBS spectra. This technique has recently been miniaturized into a portable LIBS for on-site and real-time analysis. It is worth to mention that SERS also allows multiplexed analytes detection based on the unique and characteristic vibrational fingerprints of the target analytes.

Table 6.7 Optical methods for detection of antibiotics

Antibiotics	Optical methods	LOD	LOQ	Linear range	Analysis time (excluding sample preparation)	Cost of analysis (not including sample preparation)	Advantages	Disadvantages	Limitations	References
KANA	SERS aptasensor (Au@Ag NPs-dsDNA)	0.90 pg/mL	–	10 µg/mL–100 ng/mL	~5 min	Estimated 2000–3000 USD	This approach demonstrates a strong selectivity against KANA antibiotics compared to any other antibiotics showing a decrease in Raman intensity during the presence of KANA, whereas other antibiotics have no effect on Raman intensity	For this detection, a DNA probe that is specific to certain antibodies to be tested is required. In addition, the DNA probe, estimated at about 200 USD for 1 g, is very costly	It does not allow the detection of other antibodies simultaneously, because of its relatively high selectivity. Suitable for liquid samples only	Jiang et al. (2019)

TC	Fluorescent nanosensor (GQD-MIPs)	1 μg/L	–	1.0–10^4 μg/L	~15–30 min	~10 USD per sample	This method demonstrates a strong selectivity toward TC due to the molecular imprinting technique based on the targets' shape, size, and functional groups	This methodology does not allow on-site detection of which samples are required for analysis to be taken to the laboratory	It does not allow the detection of other antibodies simultaneously, because of its relatively high selectivity	Zhou et al. (2018a, b)
Kanamycin & neomycin	Aptamer-based ellipsometric sensor	0.1–1 nmol/L	–	0.1–1000 nmol/L	~5 min	Estimated 3000–5000 USD	Good selectivity for target analytes with a particular RNA sequence	The expensive instrumental setup	Suitable for liquid samples only	Caglayan (2020)

Few commercially portable devices, such as handheld fluorometers or portable biosensors, are available on the market. Keeping pace with the digitalized era, our smartphone, the iOS gadget, can also be used as an optical detection device in which the applications or apps such as Color Analysis or Colorimeter for color measurement that can be installed and utilized for detection and measurement. The accuracy of analysis using these portable devices is considered to be high, but nevertheless it is still unacceptable for multiplexed target analysis. Comparisons are summarized and outlined in Table 6.8 between the various optical detection methods for food quality assessment.

6.5 Conclusion and Future Perspective

The presence of food contaminants is associated to food safety and quality, while food safety and quality are correlated to our health in turn. The issue of food contaminants should, therefore, not be treated indifferently. There is a need to develop portable devices that rapidly detect targeted contaminants in food and are cost-effective at the same time. Fluorescence, ECL sensor, SPR, SERS, biosensor, and aptamers, among the various optical methods discussed, have the potential to be miniaturized and become portable devices or systems that could provide on-site monitoring and detection convenience. In food quality assessment, on-site sensing is crucial as it allows the contaminated foodstuffs to be instantly detected and separated. While optical detection, due to its non-destructive and non-cell damaging properties, will be a promising option over other techniques, it allows rapid and sensitive detection at the same time. Future research could be conducted to integrate artificial intelligence into optical sensors, such as machine learning algorithms and deep learning or chemometrics. The Internet of Things (IoT) makes it possible to capture real-time sensor data and has the ability to store historical data massively in a database. Therefore, it is an encouraging alternative to quick, on-site and real-time routine screening of foodstuffs for food safety assessment.

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Table 6.8 Comparison between different optical detection methods for food safety and quality assessment

Optical methods	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
HPLC-UV	5–15 min	~10–20 USD	Simple, cost-effective instrumental practice. It gives a quantitative analysis that is rather precise, high resolution, and highly reproducible	It does not allow for on-site detection where samples are needed for analysis to be taken back to the laboratory, not portable	For routine and repeated testing, it is tedious. Standards, samples, and mobile phases need to be prepared, the instrument calibrated, and the column setup	Norouzi et al. (2018), Pan et al. (2020), Rashidi Nodeh et al. (2018), Saraji and Javadian (2019), Wang et al. (2013), Wei et al. (2020)
FAAS	~15–60 min per sample	~10 USD per sample	Quantitative analysis of heavy metals in food products is relatively inexpensive. FAAS has good accuracy and precision	It does not allow on-site detection where samples are needed for analysis to be taken back to the laboratory, not portable	It is only suitable for heavy metal analyte detection in food. For the detection of a specific heavy metal analyte, a specific hollow cathode light (HCL) is required, meaning only for single elemental analysis in short and therefore low throughput	Khayatian et al. (2018), Nakhaei et al. (2019)

(continued)

Table 6.8 (continued)

Optical methods	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
Laser-induced breakdown spectroscopy (LIBS)	~15–30 min per sample	~50–100 USD per sample	It allows in situ detection with minimal sample preparation in various food matrices and multiple-elemental detection	This method has a reproducibility problem due to the small size of the focused beam and the small mass of the sample that has been vaporized	Careful sample preparation by removing water from the sample is required for stability and sensitivity in order to minimize noise and background signals	Huang et al. (2016), Sezer et al. (2017), Yao et al. (2017)
Fluorescence	<5 min	~20–700 USD	Fluorescence sensitivity is 1000 times better than UV-Vis, and thus smaller sample sizes are needed for detection. This method shows a high selectivity as only certain molecules or molecules-fluorescein combination can give light emission within a certain	Scientists might find the capital cost of the fluorescence system a challenge. The existence of bubbles during the preparation of samples could result in data fluctuations. In some cases, a fluorescein is required to bind/	It is only suitable for fluorescence-possible target analytes or combinations of target analytes with fluorescein (with strong binding ability). This approach is influenced by the sample solution's pH	D'Auria et al. (2020), Prapainop et al. (2019), Villena Gonzales et al. (2019), Wang et al. (2019), Wongthanyakram et al. (2020), Yue et al. (2016)

			range of wavelength. The development and structure of a detection protocol using a portable fluorescence detector is promising	label the analytes to give emission		
Electrochemiluminescence (ECL) sensor	~10 min	~100 USD	There is no bulky detector needed and it is therefore portable. The chemical compound is used as luminophore. ECL emissions is captured by a camera and is interpreted and analyzed using MATLAB software for the determination of analyte concentration	$Ru(bpy)_3^{2+}$ is usually used as a luminophore. This is not a strategy for label-free detection	The pH of the sample solution and the scan rate affect this method	Yang (2019)
Surface plasmon resonance (SPR)	~60–230 min	~500–1000 USD	This method enables monitoring with high sensitivity in real time. In	Mass transport may have an effect in the refractive index change that	The sample to be detected must be made into a solution as the sample solution is	Nguyen et al. (2015), Vaisocherová-Lísalová et al. (2016), Villena Gonzales et al. (2019), Zhou et al. (2018a, b)

(continued)

Table 6.8 (continued)

Optical methods	Analysis time (excluding sample preparation)	Cost of analysis (excluding sample preparation)	Advantages	Disadvantages	Limitations	References
			addition, it is a compact and label-free detection in which the interaction of the target analyte without fluorescein with the ligands can be measured The other advantage of this approach over the others is that it does not always require the step of sample purification, it is possible to directly use crude sample for analysis	could give a false-positive signal	required to flow across the SPR surface for detection	
Surface-enhanced Raman spectroscopy (SERS)	~5 min	~2000–3000 USD	It is a portable technique with a miniature device that can offer spontaneous	It has limited sensitivity and is not suitable for measuring target analytes' trace	As metallic substrate is necessary for SERS detection, it poses a challenge	Bruzas et al. (2018), Chen et al. (2019), Jiang et al. (2018), Jiang et al. (2019),

			results through its distinctive Raman fingerprint. It is also a strategy for label-free detection. It facilitates multiplexed analysis of targets	concentrations that are less than 1% of their concentration. Time for detection is slower than fluorescence	to prepare SERS substrate	Villena Gonzales et al. (2019)
Biosensor	~30–60 min	~100–500 USD	This is a portable device with high sensitivity and suitable for trace concentration detection. It offers real-time and label-free detection (do not rely on fluorescein)	Normally, as a recognizing element for target analytes, costly antibodies or DNA would be involved	It is affected by the number and type of interferents present in complex food matrices. Not only that, but its sensitivity is also affected by pH and temperature	Amin et al. (2020), Massad-Ivanir et al. (2016), Yaghoubi et al. (2020)
Aptamers	~10–20 min	~200–500 USD	Highly selective and efficient as short chains of nucleic acid or amino acid (100 times smaller than the antibody) that complement the target analytes are used. Such a device is portable	Highly expensive short chain nucleic acid or amino acid	The chain of nucleic acid and amino acid degrades easily, and it is highly affected by pH and temperature	Al Rubaye et al. (2018), Ali et al. (2019), Caglayan (2020)

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7 Conventional Technologies and Opto-electronic Devices for Detection of Food Biomarkers

Nafiseh Kazemifard, Behzad Rezaei, and Zeinab Saberi

Abstract

Since the products of the food industry are directly related to human health, quality control is crucial in this industry. Therefore, it is vital to comply with quality requirements. Providing fast, accurate, and inexpensive methods for measuring various analytes including pathogens, pesticides, carbohydrates, and other analytes, in the quality control of the food industry is so important that dozens of articles are published every day, and thousands of researchers around the world finding the flaws of common methods and finding new methods. The integration of nanotechnology and chemical analysis can be a promising way to achieve new measurement methods. In this chapter, the application of nanotechnology in food analysis is briefly and usefully reviewed.

Keywords

Nanomaterials · Nanotechnology · Synthesis techniques · Food-technology · Detection methods

7.1 Introduction

Food analysis is an interdisciplinary research field that has a noteworthy impact on health, society, and the economy. Analysis of food is necessary for determining product quality, investigating compliance with national and international food standards, enforcing regulatory rules, and requirements of nutrient labeling. Therefore, there are two key aspects of food analysis: food quality and food safety. Studies

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in food analysis are focused on the characterization of food products in terms of nutritional value, quality, supplementary materials added, microbiological quality, and toxic components spontaneously occurring in the product or during the food processing. Approaches of food analysis are used by industry, government/control agencies, and academia. Recently, food problems and diseases have influenced millions of people's lives around the world. According to the Centers for Disease Control and Prevention (CDC), 48 million Americans have annually been affected by Foodborne diseases, 128,000 are hospitalized and 3000 died (Finger et al. 2019). Approximately, 600 million cases of foodborne diseases are reported worldwide each year (World Health Organization 2015). Therefore, food safety has been becoming a major global issue.

Analysis of food needs to develop highly sensitive, robust, cost-effective, and efficient techniques to vouch for the quality, traceability, and safety of foods in accordance with the regulations and demands of consumers. Analytical techniques have a significant role in food analysis, both in the control of quality as in the safety. various methods can be applied to food analysis including electrochemical and optical techniques, polymerase chain reaction (PCR), methods of chromatography, capillary electrophoresis (CE), flow injection analysis (FIA), enzyme-linked immunosorbent assay (ELISA), mass and Raman spectroscopies (Mustafa and Andreescu 2018).

With the advent of nanoscience, the capacity of the sensing systems is being improved using nanotechnology. Nanomaterials with sizes below 100 nm have made attracting attention owing to unique structural, physical, and electrical properties such as high specific surface area, reactive capability, physiochemical stability, and other special characteristics that can only be observed in the nanoscale, not in the bulk materials. There are various nanostructured materials that can be classified based on dimensions: 0D (all the dimensions are within nanoscale) that are nanoparticles like carbon and quantum dots; 1D (one dimension is outside the nanoscale) includes nanotubes, nanowires, and nanowires such as carbon nanotubes (CNTs); 2D (two dimensions are larger the nanoscale) includes nanosheets and nanocoatings like graphene and 3D (any dimension is not in nanoscale) contains dispersions of nanoparticles, nanoprisms, and nanoflowers (Tiwari et al. 2012). In recent years, nanotechnology has played a growing role in the sensing design in various fields including food analysis. The benefits of nanosensing can direct their application in various processes of the food industry: from the preparation of raw materials, control of quality, surveillance of storage conditions and to guarantee food safety. There are two foremost approaches, top-down and down-up to prepare nanomaterials (Tiwari et al. 2012). These two methods include a variety of techniques shown in Fig. 7.1.

In this chapter, a brief overview of the most important sensing systems based on nanomaterial using numerous detection technologies for food analysis is described. For this purpose, analytical techniques are classified as electrochemical techniques, optical methods, ion mobility spectrometry, surface acoustic wave sensor, enzyme-linked immunosorbent assay, and lateral flow tests. To date, there are several analytes of interest for food analysis including *food pollutants, components with*

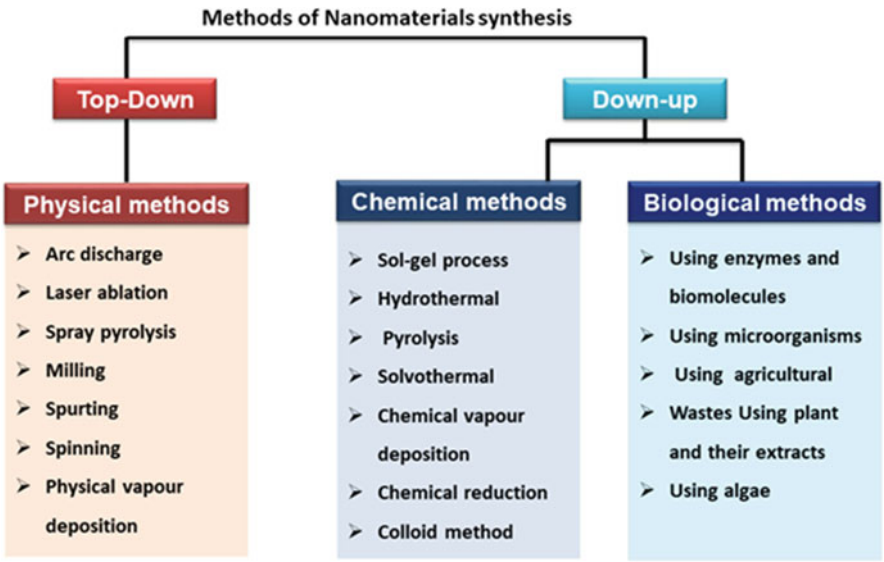

Fig. 7.1 Different methods of nanomaterials synthesis

nutritional values, and *food spoilage compounds.* Food pollutants indicate the presence of microorganisms and harmful chemicals that can get into foods via a variety of conditions including polluted soils, air and water, agricultural treatments, cross-contamination, and food processing like pesticides and heavy metals. Nutritional values denote food quality of contents that have an effect on the body. They related to proteins, sugars, minerals, vitamins, fats, minerals, and antioxidants (Mustafa and Andreescu 2020). For each part, a limited number of nanomaterials-based sensors are presented. Since so far several review articles have been published, it is recommended to read the published review articles to read more examples.

Pathogens: Viruses, parasites, and bacteria are biological sources of foodborne pathogens that lead to intoxication and debilitating infection such as acute diarrhea and meningitis. Foodborne pathogens have important effects on human health and the economy (Bintsis 2017). Some pathogens have been identified by CDC that is as the major factors of foodborne illness, hospitalization, and death in the USA. They include *Salmonella*, *Campylobacter*, *Staphylococcus aureus*, *Escherichia coli*, *Norovirus*, and *Listeria monocytogenes*.

Salmonella: It is a kind of Enterobacteria that can cause gastrointestinal disease and salmonellosis (*Salmonella* infection). *Salmonella* can be transmitted with the consumption of raw or inadequate heated food from an animal source (meat, eggs, poultry, and milk).

Campylobacter: It is a group of campylobacteriaceae that is recognized as one of the most popular origins of human gastroenteritis. The main sources of

campylobacter are unpasteurized milk and raw or insufficiently heated poultry, pork, and beef (Silva et al. 2011).

Escherichia coli (*E. coli*)*:* It includes a big and variant category of bacteria that present in the intestines of humans and warm-blooded animals. The majority of them are harmless but certain types can cause gastrointestinal diseases. Types of raw or half-cooked meat, raw milk, and polluted vegetables can transmit *E. coli* to humans.

Norovirus: It is known as the winter vomiting bug that is a very contagious infectious virus. It leads to vomiting and diarrhea in the majority of adults and children. Risk factors for contracting the disease include straight contact with infected people and consuming polluted foods (Iturriza-Gomara and O'Brien 2016).

Listeria monocytogenes: It is a kind of anaerobic bacterium that can grow in cells of the host. It can be found in environments like water, soil, animals, and rot vegetable and can spread by these sources. The listeriotic severity differs and can be lead to death in some cases, particularly in the elderly, newborns, pregnant women, and immuno-compromised people (Buchanan et al. 2017).

Staphylococcus aureus: It is a skin-associated bacterium that causes clinical infections such as bacteremia, infective endocarditis, and infections of the skin, soft tissues. Food products and meats contaminated with this pathogen contain harmful toxins that resistant to heat and not annihilated by cooking (Tong et al. 2015).

Pesticides are chemical substances that include herbicides, insecticides, rodenticides, and fungicides that can be categorized into organophosphates, organophosphorus, neonicotinoids, organochlorines, carbamates, and pyrethroids. They are applied to protects crops via controlling pests like rodents, insects, fungi, and weeds. By their nature, they are unsafe and toxic to humans and other organisms. Studies have shown that human exposure to pesticides is linked to serious health problems such as hypersensitivity, cancer, birth defects, and Parkinson's disease (Nicolopoulou-Stamati et al. 2016).

Carbohydrates are as main energy sources and for imparting vital textural properties. They include sugars, starches, and fibers. Sugar is a general name for sweet and soluble carbohydrates, used in foods. Sugars are classified as monosaccharides (like glucose, fructose, and galactose) and disaccharides (like lactose, sucrose, and maltose) (Cummings and Stephen 2007).

7.2 Electrochemical Techniques

Electrochemical methods are based on chemical reactions and electricity. In these techniques, chemical reactions are monitored by the following current (voltammetry), potential and charge (potentiometry and coulometry), or a significant change in the conductivity (conductometry). An electrochemical sensing system applied commonly two or three chemically stable electrodes. In recent years, sensors

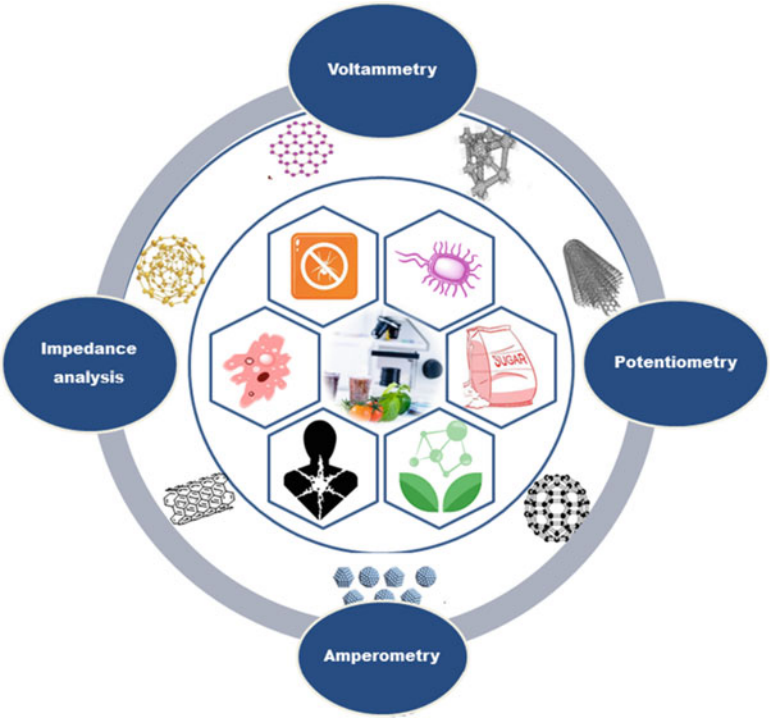

Fig. 7.2 Nanomaterial-based electrochemical methods used in food analysis

based on electrochemical assay have been attracted tremendous attention in food analysis due to their low detection limit, great accuracy, and high sensitivity. Numerous electrochemical approaches have been used to characterize and quantify the signal including differential pulse voltammetry (DPV), amperometry, cyclic voltammetry (CV), chronoamperometry, square wave voltammetry (SWV), linear sweep voltammetry (LSV), and electrochemical impedance spectroscopy (EIS) (Rezaei and Irannejad 2019)

The introduction of nanomaterials in electrochemical sensing systems offers new opportunities (such as the potential for miniaturized platforms, improved sensitivity) owing to their properties. Sensors/electrodes based on carbon materials are widely used in electrochemical applications because of their low cost, low background current, and large potential window. Therefore, CNTs and graphene are promising materials in electrochemical sensors. Moreover, metallic nanoparticles including Au NPs, Ag NPs, and plutonium nanoparticles (Pt NPs), metal oxide nanosheets, and incorporation of carbon-based materials with metallic nanoparticles or nanosheets have been applied for electroanalytical sensing (Maduraiveeran and Jin 2017; Shrivas et al. 2020). Figure 7.2 shows the schematic depiction of a variety of electrochemical methods using nanomaterials employed for analysis of chemical analytes in food analysis.

In the following, some applications of electrochemical assays for the detection of pathogens, pesticides, carbohydrates, and other analytes are mentioned. Because it was not possible to summarize and review all papers in this field, some of them are listed in Table 7.1.

7.2.1 Pathogens

The electrochemical techniques used to recognize and determine pathogens can be mostly distinguished as DNA-based assays or immunoassays using nanomaterials (Cesewski and Johnson 2020). Integration of DNA sequences, enzymes, aptamers, and antibodies offer new hybrid systems for food pathogens. For example, Eissa and Zourob (2020) reported a biosensor for parallel detection of two pathogens: *Listeria monocytogenes* and *Staphylococcus aureus*. They applied AuNPs modified SPCEs with specific peptide/MNPs. The determination was achieved by measuring the increase in SWV peaks. Detection limit were obtained 9 CFU mL^{-1} and 3 CFU mL^{-1} for *Listeria monocytogenes* and *Staphylococcus aureus*, respectively. Electrochemical sensors based on microfluidics are found as outstanding candidates for point of care testing. Chand et al. developed a polydimethylsiloxane microfluidic platform combined with a screen-printed carbon electrode modified by graphene-AuNPs composite for norovirus analysis (Chand and Neethirajan 2017). A linear range from 100 pM to 3.5 nM with 100 pM as detection limit for norovirus was got. The voltammetric assay displays a linear response ranging from 10^1 to 10^7 CFU mL^{-1} with 0.376 CFU mL^{-1} as a detection limit. In an additional study, Bu et al. offered a portable platform for the detection of pathogenic bacteria, *E. coli* O157:H7 (Bu et al. 2019). The sensor was based on hybrid nanocomposite including PtNPs peptide–$Cu_3(PO_4)_2$ and hand-held hydrogen detector for detection of the produced hydrogen based on an electrochemical method. A detection limit was 10 CFU mL^{-1}.

7.2.2 Pesticides

To decrease the toxic effects and bioaccumulation of pesticides in the ecosystems, determining trace level and dose adjustment are necessary. Therefore, the improvement of current approaches and the development of novel procedures is essential for pesticide measurement at trace concentrations (Wang et al. 2020b). At present, electrode modification is applied as the most common method to enhance the performance of electrochemical sensors for pesticide analysis. For this purpose, the modifying electrode with nanomaterials has been considered. Some examples are described in the following.

Jiang et al. presented an electrochemical biosensor for measuring pesticides using AgNPs stabilized on nitrogen-coated graphene. The selectivity of this sensor has been significantly improved by attaching the aptamer to AgNPs. A wide linear range (1×10^{-13}–5×10^{-9} M) and a low detection limit (3.3×10^{-14} M) were obtained for measuring acetamiprid (Jiang et al. 2015). Huang et al. prepared a methyl

Table 7.1 Summary of the application of nanotechnology in food analysis

Nanomaterials	Analyte	Method	Linear range	Detection limit	Food sample	Ref
QDs	*Salmonella*	Fluorescence	10^4–10^7 CFU mL^{-1}	10^4 CFU mL^{-1}	—	Yang and Li (2006)
	E. coli		10^4–10^7 CFU mL^{-1}	10^4 CFU mL^{-1}		
AuNPs/MNPs	Norovirus	SPR	10^2–10^7 copies mL^{-1}	84 copies mL^{-1}	—	Takemura et al. (2019)
CDs	Indoxacarb	Fluorescence	4–102 nM	1 nM	Apple, tomato	Shirani et al. (2020)
Au/Ag NPs	Norovirus	Colorimetry	10^2–10^6 copies mL^{-1}	13.2 copies mL^{-1}	—	Khoris et al. (2019)
TiO_2	Catechin	Reflectance	5×10^{-5}–2.5×10^{-4} M	3.72×10^{-7} M	Tea	Apak et al. (2012)
Gold nanorods	Campylobacter	SPR	NR	10^2 copies mL^{-1}	—	Shams et al. (2019)
AuNPs/MNPs	*Listeria monocytogenes*	Colorimetry	10^2–10^4 CFU mL^{-1}	1.0×10^2 CFU mL^{-1}	Lettuce	Chen et al. (2018)
CdTe/QDs	Glucose	Fluorescence	0.5–16 mM	0.5 mM	Serum	Li et al. (2009)
GO/AuNPs	Sucrose	LSPR	NR	NR	—	Nayak et al. (2015)
AuNPs	Parathion	Colorimetry	15–65 and 140–1000 ppb	0.7 ppb	Water	Wu et al. (2017b)
AgNPs	Methomyl	SERS	1.0×10^{-3}–1.0×10^3 μg mL^{-1}	5.58×10^{-4} μg mL^{-1}	Tea	Hassan et al. (2020)
	Acetamiprid		1.0×10^{-3}–1.0×10^3 μg mL^{-1}	1.88×10^{-4} μg mL^{-1}		
	2,4-Dichlorophenoxyacetic acid		1.0×10^{-2}–1.0×10^3 μg mL^{-1}	4.72×10^{-3} μg mL^{-1}		

(continued)

Table 7.1 (continued)

Nanomaterials	Analyte	Method	Linear range	Detection limit	Food sample	Ref
CDs/CoOOH	Lysozyme	Fluorescence	3.1–110 nM	0.3 nM	Serum	Saberi et al. (2020)
MnO_2 nanosheets	Antioxidant (ascorbic acid)	Colorimetry	0.25–30 μM	62.81 nM	Juice, fruit	He et al. (2018)
CeO_2 NPs	OTA	Colorimetry	0.2×10^{-9}–3.75×10^{-9} M	0.15×10^{-9} M	Milk	Bülbül et al. (2016)
CeO_2 NPs	Antioxidants	Colorimetry	0.2–9 mM	20–400 μM	Tea and mushroom	Sharpe et al. (2013)
MWCNTs	*E. coli*	Amperometry	—	10 CFU mL^{-1}	—	Cheng et al. (2008)
MNPs	Campylobacter	EIS	1.0×10^3–1.0×10^7 CFU mL^{-1}	1.0×10^3 CFU mL^{-1}	—	Huang et al. (2010a)
MWCNTs	Paraoxon	Amperometry	0.01–150 nM	0.004 nM	Cabbage, spinach	Mahmoudi et al. (2019)
Graphene/AuNPs	Aflatoxin B1	CV	3.2 fM–0.32 pM	1 fM	Milk, rice, peanut, flour	Linting et al. (2012)
CDs/ZrO_2	Methyl parathion	CV	0.2 ng mL^{-1}–48 ng mL^{-1}	0.056 ng mL^{-1}	Rice	ReddyPrasad et al. (2019)
NGQDs@NCNFs	Nitrite	CV and EIS	5–300 μM	3 μM	Sausage, pickle	Li et al. (2017)
Pd-AuCSNs/QDs/GNRs/GO	Sudan I	ECL	0.001–500 ng mL^{-1}	0.3 pg mL^{-1}	Tomato and chili sauces	Wang et al. (2018)
AgNPs	Pendimethalin	SWASV	70–2000 nM	36 nM	Lettuce, honey	de Lima et al. (2016)
	Ethyl parathion		40–8000 nM	40 nM		
GO/CuNPs	Profenofos	DPV	0.01–100 nM	0.003 nM	Spinach, rape	Fu et al. (2019)
	Phorate		1–1000 nM	0.3 nM		
	Isocarbophos		0.1–1000 nM	0.03 nM		
	Omethoate		1–500 nM	0.3 nM		

MnO_2 nanoflowers	Dichlorvos	DPV	10^{-6}–10^{-10} M	3×10^{-10} M	Cucumber and pear juice	Sun et al. (2020)
CuO-TiO_2	Methyl parathion	DPV	0–2000 ppb	1.21 ppb	Water	Tian et al. (2018)
PtNPs/MWCNTs	Sucrose	Amperometry	1×10^{-9}–1×10^{-4} mol L^{-1}	1×10^{-9} mol L^{-1}	Juice	Bagal-Kestwal and Chiang (2019)
TiO_2/MWCNTs	Glucose	DPV	1.6 nM–1 μM	0.82 nM	Sugar-substitutes/ biscuits	Kalaivani and Suja (2019)
SWCNTs	Sucrose	Amperometry	0–5 mM	2 μM	Juice	Antiochia et al. (2014)
Cu_2O/RGO	Glucose	DPV	10–150 μM	0.05 μM	Plasma	Karami et al. (2019)
rGO/MWCNTs/ CDs	Lysozyme	DPV	20 fmol L^{-1}–10 nmol L^{-1}	3.7 fmol L^{-1}	Egg	Rezaei et al. (2018)
		EIS	10 fmol L^{-1}–100 nmol L^{-1}	1.9 fmol L^{-1}		
Graphene nano ribbons	Antioxidant (ascorbic acid)	Amperometry	0.1–4 mg L^{-1}	0.05 mg L^{-1}	Juice	Yang et al. (2013)
AuNPs	Bisphenol A	EIS	0.5 fM–5 pM	80 aM	Milk	Ensafi et al. (2018)
AuNP/ Grnanosheets	Caffeic acid	DPV	0.5–50.0 μM	0.05 μM	Tablets	Zhang et al. (2013)
Fe_2O_3/NPs	Aflatoxin B2	LFA	NR	0.9 ng mL^{-1}	Peanuts, hazelnuts, pistacia and almonds	Tang et al. (2009)
Au NPs	Tulathromycin	LFA	NR	10 ng mL^{-1}	Milk and honey	Liu et al. (2018b)

(continued)

Table 7.1 (continued)

Nanomaterials	Analyte	Method	Linear range	Detection limit	Food sample	Ref
Au NPs	OTA	LFA	NR	1.5 μg kg^{-1}	Maize, wheat and durum wheat	Laura et al. (2011)
Au NPs	Zearalenone	LFA	NR	100 μg kg^{-1}	Grain samples	Kolosova et al. (2007)
Au NPs/Ag NPs	Aflatoxin B1	LFA	NR	0.1 ng mL^{-1}	Rice, wheat, sunflower, cotton, chilies, and almonds	Liao and Li (2010)
Au NPs/Ag NPs	Abrin-a	LFA	NR	0.1 ng mL^{-1}	Soybean milk	Yang et al. (2011)
Graphene oxide nanocomposite	2,4-Dichlorophenoxyacetic acid	IMS	0.3–200 μg L^{-1}	0.09 μg L^{-1}	Rice	Saraji et al. (2019)
Carbonaceous aerogel nanocomposites	Ethion	IMS	1–30 μg L^{-1}	0.09 μg L^{-1}	Vegetables	Mohammadi et al. (2020)
Carbonaceous aerogel nanocomposites	Chlorpyrifos	IMS	1–70 μg L^{-1}	0.21 μg L^{-1}	Vegetables	Mohammadi et al. (2020)
Polypyrrole nanowire	Bisphenol A	IMS	10–150 ng g^{-1}	1 ng g^{-1}	Peas, bean, and corn	Kamalabadi et al. (2016)
Magnetic nanobeads	*Salmonella* cell	Acoustic wave sensor	—	2 cells μL	Milk	Papadakis et al. (2018)
SiO_2 nanoparticles	*E. coli* O157: H7	Acoustic wave sensor	—	1.8×10^{-15} M	—	(Ten et al. (2017)

parathion sensor using a Pd/MWCNTs-modified electrode (Huang et al. 2010b). The linear range was reported from 0.10 to 14 μg mL^{-1}, and 0.05 μg mL^{-1} is a detection limit. Khosropour and his coworkers proposed an electrochemical assay based on a glassy carbon electrode (GCE) modified with VS_2QDs-graphene nanoplatelets/carboxylated MWCNTs nanocomposite and aptamer for diazinon analysis. The aptasensor showed wide dynamic ranges of 5.0×10^{-14}–1.0×10^{-8} M and 1.0×10^{-14}–1.0×10^{-8} M with 1.1×10^{-14} and 2.0×10^{-15} M for DPV and EIS methods, respectively (Khosropour et al. 2020). Bao et al. designed an electrochemical acetylcholinesterase (AchE) biosensor for analysis of organophosphate pesticides (Bao et al. 2019). Three-dimensional graphene and CuO nanoflowers were used to prepare the working electrodes that improved enzyme stability and enhanced-biosensor performance. Wide linearity to malathion was achieved ranging from 1 ppt to 15.555 ppb with 0.31 ppt as the detection limit.

7.2.3 Carbohydrates

Sugars are the main form of carbohydrates. Controlling the amount of sugar in foods is essential owing to health issues connected to sugar consumption (glucose, lactose, sucrose, fructose, etc.), such as diabetes and obesity. Until now, numerous studies have been reported which among them, electrochemical biosensors were mostly applied based on glucose oxidase (GOx) for analysis of glucose, mutarotase or Gox for sucrose, and GOx or b-galactosidase for lactose by following consumed oxygen or produced H_2O_2 (Cock et al. 2009; Vargas et al. 2013). However, non-enzymatic sensors have been considered that applied nanoparticle catalysts.

For example, Yang and coworkers presented a miniaturized electrochemical platform based on microfluidic paper and an SPE electrode modified with PtNPs and GOx enzyme for glucose detection. PtNPs are utilized as electrocatalysts for sensitive detection of H_2O_2. Due to the voltammetric behavior similarity of glucose and H_2O_2, the determination of H_2O_2 was performed. With increasing concentration of glucose in the range of 0.5–3.0 mM, oxidation current was enhanced. A detection limit was achieved as 9.3 μM (Yang et al. 2014). Antiochia et al. fabricated an amperometric biosensor using CNTs paste electrode for quantitation of fructose in honey samples (Antiochia et al. 2004). This electrode was modified by 3,4-dihydroxybenzaldehyde as an electropolymerized film and D-fructose dehydrogenase. Under optimized parameters, the biosensor was able to measure fructose in linear range 5×10^{-6}–2×10^{-3} mol L^{-1} with 1×10^{-6} mol L^{-1} as the limit of detection. In another study, a microfluidic paper-based electrochemical sensor was designed to measure glucose by modifying the working electrode with the zinc oxide nanowire (Li et al. 2015). Easy to build, low cost, and portability were the advantages of this method in POC testing. This method, in which glucose oxidase enzyme was used to increase sensitivity, had a limit of detection of 59.5 μM. García and Escarpa developed a carbon SPEs using nickel nanowires for electrochemical analysis of carbohydrates (García and Escarpa 2011). Analytical performance in

terms of high mechanical stability, good precision (RSDs $\leq 2\%$), fast response time, and good recovery rates (95–115%) were obtained.

7.2.4 Other Analytes

In addition to the above three categories, some analyzes were considered for the analysis of food such as toxins such as heavy metals, nutritional components such as antioxidants, polyphenols, proteins and vitamins, compounds of food spoilage, and poisoning such as melatonin.

In a study, a GCE modified with AuNPs were applied in the electrochemical device for the parallel detection of antioxidants in edible oil samples (Lin et al. 2013). Compared to the bare GCE, the modified electrode presented a noteworthy increase in the peak currents. The linear concentration ranges (detection limits) were achieved 0.10–1.50 (0.039) μg mL^{-1} for butylated hydroxyanisole, 0.20–2.20 (0.080) μg mL^{-1} for butylated hydroxytoluene, and 0.20–2.80 (0.079) μg mL^{-1} for butylated hydroquinone. Ochratoxin A (OTA) is one of the food-polluting mycotoxins in the world. An electrochemical aptasensor was presented by Taghdisi's group for OTA determination (Abnous et al. 2017). This method applied a gold electrode modified with SWCNTs as signal amplifiers, aptamers as sensing tools, complementary DNA, and methylene blue as the redox marker a limit of detection is as low as 52 pM. The biosensor was employed to determine OTA in grape juice samples. An electrochemical senor was proposed by Chen's group for evaluating antioxidants capacity in fruit juice (Yang et al. 2013). In this method, a glassy carbon electrode was modified using guanine immobilized on graphene nanoribbon. The sensor depends on damage of guanine which is induced by OH radicals produced by Fenton-type reaction. Ascorbic acid was applied as the standard antioxidant. A linear range and detection limit were obtained 0.1–4 mg L^{-1} and 4.16 mg L^{-1}, respectively.

7.3 Optical Techniques

Optical sensing methods are a category of chemical sensors based on optical phenomena, which composed of a chemical sensing element (recognition receptor) and a transduction element. The interaction of electromagnetic radiation with the sample is evaluated by changing a specific optical parameter that is associated to the analytical concentration (McDonagh et al. 2008). Optical sensing can be founded based on different optical principles including absorbance, luminescence, fluorescence, reflectance, and phosphorescence. Optical sensing methods allow rapid, portable, and easy-to-use detection. These techniques have been widely used in food applications.

Thanks to the advancement of nanotechnology, a combination of optical sensors and nanomaterials provide new tools with improved performance (sensitivity, the limit of detection, and linear range). Nanostructured materials used in optical sensors

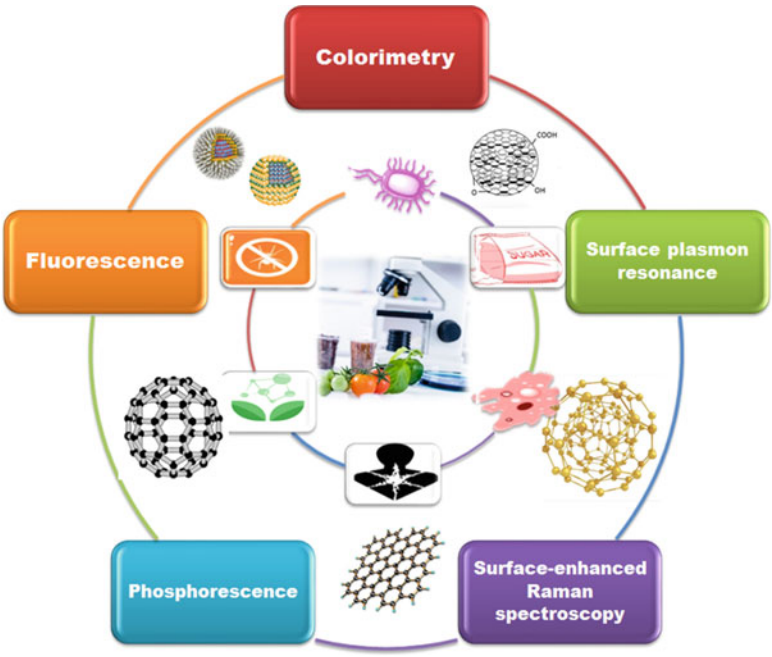

Fig. 7.3 Different types of nanomaterials-based optical techniques

include nanoparticles of noble metals (Au, Ag, Pt), Fe_2O_3, carbon-based nanomaterials (CDs, CNTs, and graphene), Metal oxide nanomaterials (ZnO, TiO_2), and Quantum dots (Pérez-López and Merkoçi 2011). Figure 7.3 demonstrates a schematic diagram of diverse kinds of optical techniques based on nanomaterials that are widely utilized for the analysis of food. In the following, an overview of the most used nanomaterials is presented for the development of food sensing.

Countless optical sensors based on nanomaterials have been made and used in the field of food analysis for determining foodborne pathogens, pesticides, sugars, and others, not all of which can be described in this text, and only some figures of merit of some of them are provided in Table 7.1.

7.3.1 Pathogens

Fluorescence, colorimetry, and surface plasmon resonance (SPR) are common optical (bio)sensing techniques that applied for pathogen detections.

Su and Li represented an optical sensor based on CdSe/ZnS QDs as fluorescence labels for *E. coli* O157:H7 detection (Su and Li 2004). Anti-*E. coli* O157 antibodies conjugated to magnetic beads were applied to capture and separate the target bacteria, selectively. The fluorescence signal increased in the range of 10^3–10^7 CFU mL^{-1}. The detection limit was 10^3 CFU mL^{-1}. Zhao et al. used a

molecularly imprinted technology and CdTe QDs as a fluorescence probe for sensing analysis of *Listeria monocytogenes*. In molecular imprinting, the synthesis of a polymer is performed in the presence of an analyte (as a template). After analyte extraction, the polymer will contain cavities that are matched to the analyte in size and shape. The sensor was applied to detect the target in milk and pork samples. The limit of detection was obtained as 10^3 CFU mL^{-1} (Zhao et al. 2019). An optical sensor was fabricated to measure norovirus based on the localized SPR of AuNPs and CdSe/TeS QDs (Nasrin et al. 2018). The fluorescence of QDs was quenched by forming QDs/AuNPs nanocomposite. After addition norovirus, steric hindrance-induced SPR signal from vicinal AuNPs caused the enhancement of the fluorescence QDs. This method detected norovirus in the range 10^2–10^5 copies mL^{-1} with 95.0 copies mL^{-1} as a detection limit. In a study by Weerathunge and coworkers, a colorimetric NanoZyme aptasensor approach was proposed for the detection of norovirus (Weerathunge et al. 2019). This biosensor employed the catalytic activity of AuNPs with the specific aptamer that blue color was produced in the presence of this norovirus. The limit of detection was achieved 30 viruses mL^{-1} of sample. In another study, SERS nanoprobes based on microfluidics dielectrophoresis and AuNPs were prepared to detect bacteria including *Salmonella enterica* serotype Choleraesuis and *Neisseria lactamica* (Lin et al. 2014). This device is developed by immobilizing specific antibodies onto the nanoaggregate-embedded beads (silica-coated) and dye-induced aggregates of AuNPs. The detection limit was estimated 70 CFU mL^{-1}.

7.3.2 Pesticides

Especial attention has been paid to the fabrication of optical sensors for pesticide analysis. Myriad optical sensing methods have been defined using recognition tools such as molecularly imprinted polymer (MIP) polymers (Ensafi et al. 2016; Kazemifard et al. 2020b) which a template is added during polymerization to create selectable cavities to increase probe selectivity, aptamer, antibody, and enzyme that applied to identify pesticides. Incorporation of recognition tools and nanomaterials improves the sensitivity and time of analysis (Yan et al. 2018). Here, some of these sensors are described and more are listed in Table 7.1.

Saberi et al. reported a label-free aptasensor based on cationic CDs as a fluorescence probe for acetamiprid detection. In the presence of acetamiprid, the fluorescence signal quenched by aptamers was recovered proportionally to the acetamiprid concentrations. The detection limit of the method was 0.3 nM with a linear range from 1.6 to 120 nM (Saberi et al. 2019). Another study used SERS optical fiber substrates for the analysis of permethrin pesticide. The laser-assisted photochemical technique was applied to grow and immobilize Ag nanodendrites on the multi-mode fiber end. The method displayed good concentration linearity from 0.1 to 20 ppm with 0.0035 ppm as a detection limit (Pham et al. 2019). In another study performed by Kazemifard and coworkers, detection of Thiabendazole was reported in juices based on a molecularly imparting technique and CDs. An MIP was prepared in the

presence of thiabendazole as template. Under optimal conditions, a linear range and a detection limit were achieved 0.03–1.73 μg mL^{-1} and 8 ng mL^{-1}, respectively (Kazemifard et al. 2020a). Compared to other techniques, paper-based assay is an effective way to the real-time analysis of various analytes, including pesticides, because it is cheap, simple, and reliable, which can be more selective using diffrent functional groups. Bagheri's group proposed a colorimetric paper-based assay for monitoring organophosphate and carbamate pesticides in apple juice and rice (Bordbar et al. 2020). Au and Ag NPs were dropped on the hydrophilic areas of a paper and modified L-arginine, quercetin, and polyglutamic acid. A digital camera was used to record color changes. Detection limits (mL^{-1}) were obtained 29.0 for carbaryl, 22.0 for paraoxon, 32.0 for parathion, 17.0 for malathion, 45.0 for diazinon, and 36.0 for chlorpyrifos.

7.3.3 Carbohydrates

As mentioned before, the sensing of sugars plays a significant role in food analysis and medical diagnosis. Electrochemical sensing methods used for this purpose have some problems in terms of ease to use, longevity, and time-consuming. The growing demand for inexpensive and user-friendly (bio)sensors has been prompted many researchers to develop sensors based on optical methods in this field (Jernelv et al. 2019). For example, a fluorometric and colorimetric assay was developed for glucose analysis using Au@AgNPs and CDs (Liu et al. 2018a). The Ag shell of Au@AgNPs quenched the fluorescence of CDs. The enzymatic-triggered oxidation of glucose on Ag shell produces H_2O_2 and gluconic acid by etching effect. As a result, changes in absorbance of the silver shell (decrease) and CDs fluorescence (increase) were related to the glucose concentration. The detection limits of colorimetric and fluorimetric biosensors were 0.20 and 0.67 μM at dynamic range 0.50–300 μM and 2.0–400 μM, respectively. A simple sensor was fabricated by Crista and coworkers for sensing fructose based on CDs (Crista et al. 2019). CDs were synthesized from by 3-hydroxyphenylboronic acid by hydrothermal method. The detection limit of the sensor was 2.04 mM and its linear range was from 0 to 150 mM. A maltose biosensor has been developed using electron transfer between protein-Ru(II) complex and CdSe/ZnS QDs (Sandros et al. 2006). Maltose detection was obtained based on the maltose-induced conformation variation to change the distance of the Ru-CdSe nanoparticle. The method displayed a linear response ranging maltose from 250 nM to 1.0 μM.

7.3.4 Other Analytes

There are numerous types of food analytes except for sugars, presides, and pathogens groups that are being analyzed using optical nanosensors. For example, melamine is added to milk as an adulterant to supply an obvious increase in the content of protein. Seo Yeong et al. reported an LSPR sensing chip for analysis of

melamine in milk products (Oh et al. 2019). AuNPs were deposited on a glass substrate with a chemical receptor, p-nitroaniline. The detection limit and the dynamic range were 0.01 ppb and 0.1–1000 ppb, respectively. Food azo dyes like Sudan I used for coloring foods have mutagenic and carcinogenic effects that these dyes classified as a third category carcinogen. In a study, a handy colorimetric immuno-dip strip was developed with Au nanocolloid for the determination of Sudan I in foods. The strip was arranged using a nitrocellulose membrane treated with Sudan I antigen. Immersing the strip in a mixture of nanocolloidal Au labeled with Sudan I monoclonal antibody and Sudan I, severe red color was formed that reflected the concentration of Sudan I. A visual detection limit was 10 ng g^{-1} for samples of tomato sauce and chili powder (Wang et al. 2013). A fluorescence method was reported by Wang and coworkers for the determination of vitamin B_{12} (VB_{12}) using CDs and based on FRET (Wang et al. 2015). t-CDs was obtained from citric acid by thermal reduction strategy through heating at 300 °C. VB_{12} was detected in the range 1–12 μg mL^{-1} with 0.1 μg mL^{-1} as a detection limit. An SPR sensor was fabricated using modifying optical fiber by Au@Ag core-shell NPs doped in SiO_2-TiO_2-ZrO_2 ternary matrix for detection of vitamin A (Prakashan et al. 2019). The sensing ability and selectivity of the NPs were investigated by absorption spectroscopy. The method has a wide range of 10–1000 μM with a low detection limit of 10 μM.

7.4 Enzyme-Linked Immunosorbent Assay

ELISA, which stands for Enzyme-Linked Immunosorbent Assay, is a technique that consists of four basic components, including the adsorbent substrate, the recognition element, the enzyme label, and chromogenic reagent (Cho and Irudayaraj 2013). The adsorbent substrate usually consists of an antigen or antibody to bind to the supporting material. In the next step, the labeled biomolecules can be complementarily integrated with the substrate, and eventually, this integration produces a signal that is usually the color change of a chromogenic agent. The main key of the ELISA method is the reaction of antibodies and antigens, which ensures the selectivity of the method (Wu et al. 2019). Complementary antibody (or antigen) labeled with the enzyme label is then incubated with the fixed antigen and the chromogenic reaction is catalyzed. Then chromogenic is added and a color change occurs which can be seen with the naked eye and is a quantitative signal. ELISA is widely used in clinical fields, food and beverage industry, and environment (Wang et al. 2016). This method has a good sensitivity that can be easily improved by modifying the enzyme labels. In addition, the selectivity of the method is very good. For all its conveniences, the traditional ELISA has some drawbacks such as a tedious process needed experienced and skilled person, a large sample size and its detection limit is hardly in the nano molar scale (Cho and Irudayaraj 2013). Upon closer inspection, it can be understood that the reason for these defects is the structure of ELISA, which includes four main parts as mentioned before. Therefore, with the help of innovative technologies, such as the use of nanotechnology, the structure of traditional ELISA

can be changed and its disadvantages can be eliminated or reduced (Wu et al. 2019). This method can be improved by modifying each of the four ELISA elements using nanomaterials. For example, nanofibers, MIP, and nanoparticles can be used to modify the adsorbent component. Nanobody and aptamer can be used to modify the recognizing elements. Copper sulfide nanoparticles, cerium oxide nanoparticles, composites consisting of silicon oxide and gold-platinum (Au-Pt@SiO_2 composites), and graphene oxide can be used to improve the labeled enzyme because these alternatives have a similar function to peroxidase. Finally, alternatives to chromogenic agents can be metal nanoparticles such as Ag NPs and Au NPs (Dutta et al. 2015; Wu et al. 2017a).

7.4.1 Pathogens

Hoon Cho et al. used an ELISA-based biosensor to identify pathogenic microorganisms including *Escherichia coli* O157:H7 and *Salmonella typhimurium* in food samples (Cho and Irudayaraj 2013). In this work, the sample was first concentrated using magnetic nanoparticles. Au NPs and magnetic nanoparticles have been used in the construction of this biosensor by attaching to the antibodies of the target bacteria, first, the magnetic nanoparticles caused the bacteria to accumulate in the food samples, in other words, they caused the bacteria to concentrate, and then the Au NPs coupled with secondary antibodies to detect the bacteria. The detection limit of the method was obtained for *Escherichia coli* O157:H7 and *Salmonella typhimurium* as 3 per mL. In another work, Guo et al. used the ELISA approach to use Au NPs to detect *E. coli* O157:H7 in milk samples. In this method, ELISA wells were modified with bacterial antibodies as well as DNA. The detection limit of the method was 1.08×10^2 CFU mL^{-1} that was 185 times better than traditional ELISA (Guo et al. 2016). Au NPs have also been used to detect Listeria spp in milk by ELISA. Wang et al. measured the pathogen after 8 h of enrichment with a detection limit of 1×10^9 CFU mL^{-1}. The basis of this method was the fixation of target antibodies to detect the P60 protein on *Listeria* spp. on Au NPs (Wang et al. 2016).

7.4.2 Pesticides

Wang et al. used SiO_2 nanoparticles to measure 2,4-dichlorophenoxyacetic acid by ELISA the basis of the method was the competitive combination method. This method used 2,4-dichlorophenoxyacetic acid antibody labeled with horseradish peroxidase to detect the analyte with a detection limit of 0.079 ng mL^{-1} (Wang et al. 2017a). In other works, AuNPs were used to detect kitazine pesticide (Malarkodi et al. 2017) and triazophos pesticide (Du et al. 2018) in fruits and vegetables by ELISA.

7.4.3 Other Analytes

Nano-ELISA has been used to measure the residues of veterinary drugs including amantadine (Yu et al. 2018), sulfadimethoxine (Peng et al. 2013), and maduramicin (Song et al. 2018) in poultry. The nanoparticles used in both amantadine, sulfadimethoxine were Au NPs, while nanomagnetic beads were used to measure maduramicin. Sulfadimethoxine with a detection limit of 0.2 μg kg^{-1} and amantadine with a detection limit of 0.51 nM, and maduramicin with a detection limit of 72 μg kg^{-1} were measured in food samples. Aflatoxin B_1 is another analyte measured by Xiong et al. by developed ELISA method modified with gold nanorods. Corn was the real sample of this study in which aflatoxin B1 was measured visually at a detection limit of 12.5 pg mL^{-1}, which was 32 times better than conventional ELISA (Xiong et al. 2018).

7.5 Surface Acoustic Wave Sensor

The signal of chemical sensors can be electrochemical, optical, or acoustic kind. In the meantime, acoustic wave sensors have interesting advantages, for example, they are sensitive to the mass of an *analyte*, so their signal is based on the change of mass (Länge 2019). In addition, this sensor can be provided in small and portable dimensions and can be easily placed in wireless systems. In addition to being simple, acoustic sensors are fast, sensitive, and inexpensive and can be used to detect gas and liquid samples. There are two types of acoustic sensors: surface acoustic sensor and bulk acoustic sensor. The common denominator of these devices is that they use the piezoelectric and reverse piezoelectric effect (Chang et al. 2007). The basis of these sensors is the conversion and detection of electrical energy and acoustic waves. The mass-dependent velocity of the acoustic wave is considered in these sensors. The electronic nose (e-nose) is an array of acoustic sensors that can detect different analytes in gas samples simultaneously. An electronic tongue (e-tongue) has the ability to detect different analytes in a liquid sample. Polymers and MIPs—used to improve selectivity—can be used to coat array sensors. Other coatings can be materials such as organic-metallic materials, carbon nanotubes, diamond nanoparticles, and cells and macrocycles, etc. (Gronewold 2007).

The number of reported works for measuring food analytes using nanoparticle-modified acoustic wave sensors is very small. In one case, an acoustic wave sensor was developed by Papadakis using micro/nanotechnology to measure *Salmonella* cell in milk. In this method, magnetic nanobeads and DNA are used for cell capture and amplification, respectively. The detection limit of the method was 2 cells μL^{-1}. According to the authors, using a pre-enrichment stage and multiple analysis have made this method successful. It can be an alternative method of electrochemical sensors in the food industry and food quality control (Papadakis et al. 2018). In other work, Ten et al. used a shear horizontal surface acoustic wave to detect *E. coli* O157: H7 using SiO_2 nanoparticles. The nanoparticles used in this sensor play the role of waveguide and can bind and stabilize biomolecules. A specific sequence of

nucleotides of this bacterium in the form of single-stranded DNA was fixed on the surface of the substrate, which was modified $LiNbO_3$ which acts as a probe. The basis of the sensor was coupling the probe to the complementary sequence of the sample bacteria. The detection limit of the sensor was reported as 1.8×10^{-15} M (Ten et al. 2017).

7.6 Ion Mobility Spectrometry

Ion mobility spectrometry (IMS), which is a method of rapid separation of the gas phase, is based on the mobility differentiation of various species to separate them on a millisecond timescale (Wang et al. 2020a). Items that affect the mobility of an ion include mass, charge, size, and shape of a species, all of which are important in this separation. In this method, the species are first converted to ions in the gas phase and floated in a drift tube to which an electric field is applied, and a stream of buffer gas flows in the opposite direction, thus the species are separated according to the ratio of mass to charge (*m/z*) (Borsdorf and Eiceman 2006). They reach the detector separately. This method may be coupled with a mass analyzer to form a hybrid system (Gabelica and Marklund 2018). The application of nanoparticles in the IMS method for the food industry is usually in the improvement of the method integrated with IMS. This means that, for example, extraction methods with nanomaterials have been improved and then IMS has been used as a detection method.

7.6.1 Pesticides

Saraji et al., preconcentrated 2,4-dichlorophenoxyacetic acid using nanocomposite as a sorbent consisted of an amino-functionalized zirconium-based metal-organic framework/graphene oxide, then used IMS to measure it. The linear range of this method was 0.3–200 μg L^{-1}, and its limit of detection was 0.09 μg L^{-1}. This method was used to measure 2,4-dichlorophenoxyacetic acid in rice (Saraji et al. 2019). Mohammadi et al. combined liquid-phase microextraction and IMS to determine ethion, and chlorpyrifos (Mohammadi et al. 2020). They used a nanostructure sorbent called a carbonaceous aerogel. Ethion and Chlorpyrifos were measured in the range of 1–30 μg L^{-1} and 1–70 μg L^{-1} with limit of detections as 0.09 μg L^{-1} and 0.21 μg L^{-1}, respectively. The mentioned method has been used to measure these pesticides in vegetables and water.

7.6.2 Other Analytes

In another integrated method, the solid-phase microextraction of polypyrrole nanowire was combined with IMS and used to measure bisphenol A in canned food samples such as peas, bean, and corn by Kamalabadi et al (2016). The linear range was reported as 10–150 ng g^{-1} and the detection limit was 1 ng g^{-1}.

7.7 Lateral Flow Tests

Lateral flow test (LFT) is a rapid method used to measure analytes in liquid samples such as blood, serum, milk, and beverages for medical diagnosis and to control the quality of food and soil (Tripathi et al. 2018). The results of this method can be observed by the naked eye. This technique in some cases is coupled to detectors to get more data. LFT is fast and does not require much skill to use, so it can be easily used in laboratories and at home. LFT can be based on the sandwich method (seeing color when the test is positive) or the competitive method (color disappearance when the test is negative) (Raeisossadati et al. 2016). As shown in Fig. 7.4, this system consists of important components, including a sample pad, conjugate pad, nitrocellulose membrane, test and control lines, and finally absorption pad. The sample pad controls the sample flow (Blazkova et al. 2009). Conjugated antibodies are located in the conjugate pad. The target molecule attaches to these antibodies and migrates with it to the next component. Target-bound conjugated antibodies move to the nitrocellulose membrane and bind to the reactants in the test line, resulting in a colored line. The intensity of the color depends on the concentration of the target molecule. In this way, in addition to performing a quality test, a quantitative test can also be performed. The final component of this system is the absorbent pad, which absorbs samples that come out of nitrocellulose (Tripathi et al. 2018).

Because commercially labeled and non-labeled Au NPs are readily available and their synthesis is not expensive and complicated, they are widely used in the LFT method. Their high stability and nonbleaching properties are other reasons that make AuNPs a good option for labeling antibodies. Other nanoparticles used in this method are Ag NPs, quantum dots, and magnetic nanoparticles (Raeisossadati et al. 2016). Quantum dots are zero-dimensional fluorescent nanoparticles that have attractive properties (Ensafi et al. 2015; Haghani et al. 2020).

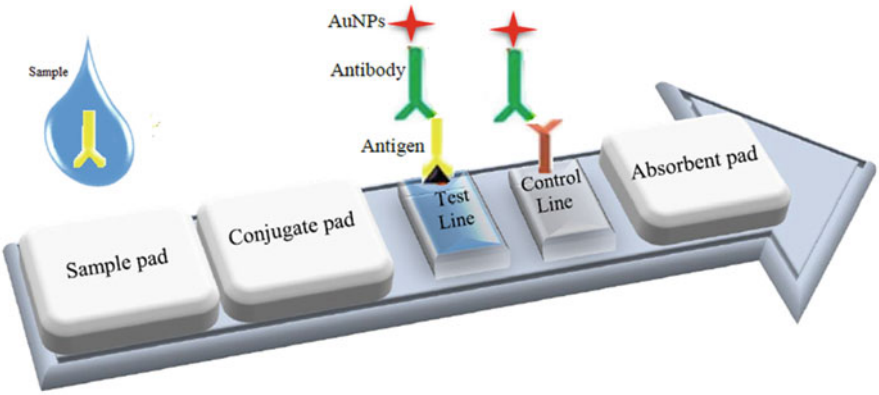

Fig. 7.4 Schematic of the LFT method and its various components

7.7.1 Pathogens

L. monocytogenes were measured in a lateral flow measurement system reported by Wang et al (2017b). In this method, a monoclonal antibody (1C1 mAb) of P60 protein was labeled with Au NPs. Antibodies have been used to capture the analytes as a biomolecular ligand. The detection limit of the method was reported to be 3.7×10^6 CFU mL^{-1}. Another method used DNA in LFT known as the NALFIA method, which stands for nucleic acid lateral flow immunoassay (Blazkova et al. 2009). This method, reported by Blažková et al., was used to measure *Listeria monocytogenes* in food samples. In this NALFIA method, polyclonal antibodies were fixed on the nitrocellulose membrane and carbon nanoparticles were immobilized on the surface with neutravidin. So double-labeled amplicons were sandwiched between antibodies and carbon particles. The superior features of this method, according to the author, were being faster than the usual electrophoresis method and not using dangerous chemicals. In order to further enhance the signal, silver and Au NPs can be used simultaneously, as Rong-Hwa reported a method using the LFA method to measure staphylococcal enterotoxin B in food samples (Rong-Hwa et al. 2010). In this method, gold colloidal nanoparticles with silver enhancement were used to meliorate the detection limit of the method by 10 pg mL^{-1}.

7.7.2 Other Analytes

Liu et al. reported a method for measuring tulathromycin in food samples such as milk and honey using the LFT-based method (Liu et al. 2018b). In this method which was described as an easy and selective method by the authors, the monoclonal antibodies were labeled with Au NPs and coated as a capturing agent on the nitrocellulose membrane. The detection limits of the method for measuring tulathromycin in milk and honey were reported to be 5 ng mL^{-1} and 10 ng mL^{-1}, respectively.

Analytes including OTA (Laura et al. 2011), deoxynivanelol (Kolosova et al. 2007), and zearalenone (Kolosova et al. 2007), which are food contaminants, were also measured by the LFT method modified with Au NPs. OTA was measured in maize, wheat, and durum wheat with a detection limit of 1.5 μg kg^{-1}. Deoxynivanelol and zearalenone also were measured in grain samples with cut-off levels of 1500 μg kg^{-1} and 100 μg kg^{-1}, respectively. Aflatoxin B_2 was also measured by Tang et al. using a combination of nanoparticles in food samples using the LFA method. In this work, magnetic nanogold microspheres were used in which Fe_2O_3 nanoparticles were used as the core and the shell was Au NPs. The detection limit of the method was 0.9 ng mL^{-1}, which was three times better than the method where only the nanoparticles used were Au NPs (Tang et al. 2009).

7.8 Conclusion and Perspective

Nanosensors technologies display promising potentials to user-friendly and in-field application devices. These are based on numerous sensing transduction modes (such as optical, electrochemical, etc.) and principles of assays. These sensors can be applied in food analysis including food contaminants, components with nutritional values, and food spoilage compounds. Despite the feasible advantages of these sensors as compact tools, most of them have been limited to library work. The industrial models of these nanosensors in food analysis and safety testing are proved convincing, by precise validation studies. There is a chance that the food industry could benefit from these sensors to observe the safety and the quality of foods. The advancement of smart sensors remains a novelty to be explored in the future. As for applications in food safety, the combination of nanosensors with generally used communication devices including smartphones can result in enhanced portability of these sensors.

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Applications of Intelligent Packaging for Meat Products

8

Afiqah Nabihah Ahmad and Syazana Abdullah Lim

Abstract

The growing concern of food wastage, quality issues and demand from consumers have led to the emergence of innovative intelligent food packaging. An attractive feature of intelligent packaging is to allow a real-time monitoring of food product along supply chain and provide up-to-date information on its status throughout transport and storage until it reaches consumers. This chapter aims to provide a forward-looking information on intelligent tools and other imperative attributes of intelligent packaging systems as reported in literature and those that have secured commercial practicality for applications in the food supply chain. Importantly, this chapter also highlights the initiated efforts with regard to developing diverse types of diagnostic tools for intelligent food packaging application that can determine the freshness of meat products. Such examples include the implementation of pH-sensitives dyes, time temperature indicators, data carriers such as radio frequency identification, and electrochemistry embedded into packaging as a stepping-stone to detect meat deterioration. A short section on the concerns surrounding to the extensive release of intelligent packaging will also be discussed.

Keywords

Intelligent packaging · Biosensors · RFID · Time-temperature indicators

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8.1 Introduction

Food wastage, particularly of perishable items, is a prevalent worldwide concern majorly influenced by food spoilage. This global food issue could arise at any point in a supply chain resulting in a broad spectrum of circumstances—not just in terms of financial loss and contamination, but also in terms of food quality and, most significantly, food safety. The phenomenon is a daunting prospect to tackle due to the complicated and unpredictable nature of the food supply chain. Thus, food needs to be adequately packaged and preserved to maintain its wholesomeness and quality by protecting them from physical, environmental, chemical, and microbial harms (Youssef and El-Sayed 2018; Hoseinnejad et al. 2018). Food packaging should also provide details regarding the contents of the food to ensure the food has been verified and is free of dangerous and unwanted substances when reaching consumers (Lim and Ahmed 2016b). Traditionally, a food packaging serves a dual purpose—it is both necessary and pervasive. It is necessary because food safety and quality would be jeopardized without it, and it is pervasive because practically all food is packaged in certain kind (Robertson 2010). Recent trend shows that packaging designs are ever-evolving where modern packaging is expected to perform roles beyond their typical functions such as shelf-life enhancement by means of innovative solutions (Dobrucka and Cierpiszewski 2014). Nowadays, as a food packaging is no longer taking only passive part in the food industry, technological advancements such as sensors, internet-based networking devices or internet of things (IoT), big data, cloud computing, and consumer-oriented technologies have allowed packaging to operate ahead of their rudimentary qualities (Chowdhury and Morey 2019).

The integration of biosensors with packaging has led to the emergence of innovative intelligent food packaging. Perumal and Hashim (2014) and Bunney et al. (2017) defined a biosensor as an analytical device that associates a biologically sensitive recognition element (such as an enzyme) immobilized on a physicochemical transducer, linked to a detector to recognize the existence of one or more specific analytes, concentrations, and kinetics in a sample. As of now, research focusing on biosensors comprises of mainly devices for medical diagnosis (Masson 2017; Lim and Ahmed 2016a; Andryukov et al. 2020), and there are limited applications available in the food sector. The potential applications of biosensors in the food industry are visualized in Fig. 8.1. The different types of biosensors will not be discussed in detail and past the scope of this chapter. A comprehensive review on biosensors can be found in Lawal and Adeloju (2012), Park et al. (2015), Kerry et al. (2006), Yasmin et al. (2016), Fang et al. (2017), Holman et al. (2018), Müller and Schmid (2019) and Sionek et al. (2020).

Intelligent food packaging is a unique concept aimed to address common issues faced by food industries such as food wastage, spoilage and safety. This next-generation packaging is able to sense, identify, and communicate with consumers on the status of a food product or/and its environment by presenting a "spoilage index" on food packaging for consumers' use (Dudnyk et al. 2018; Mustafa and Andreescu 2018). Intelligent packaging has a pivotal role in the food packaging industry ever since the implementation of more than one intelligent function, for

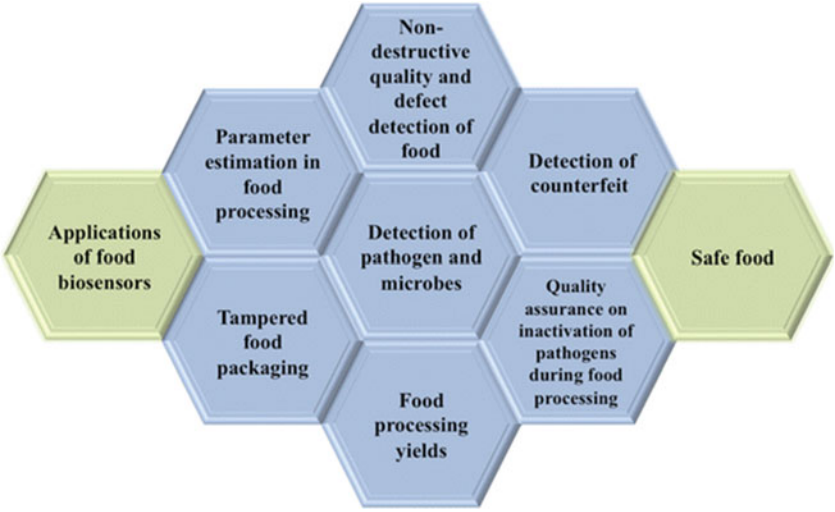

Fig. 8.1 Various applications of biosensors in food industries. (Copyright, Lim and Ahmed 2016b)

instance, in monitoring product quality/safety in its environment, movement through the supply chain, sensing and documenting relevant product information (Yam et al. 2005). While it is estimated that intelligent packaging accounts for roughly 5% of the overall value of the packaging industry, it is expected that demands will escalate rapidly in the coming years, and this is reflected through the number of patent applications and patents issued (Balbinot-Alfaro et al. 2019). The major challenges currently confronted by the industry are ensuring the quality and to protect its food items to prevent repeated occurrences of foodborne illnesses around the world. Intelligent packaging, which includes built-in sensors and indicators, has been dubbed as a reliable tool for the management of food freshness and ultimately, safety. To accomplish this, various potential components are embedded into devices to release or absorb substances from and into packaged food to prevent product degeneration (Arvanitoyannis and Stratakos 2012; Prasad and Kochhar 2014). Additionally, for the precise determination of certain analytes directly related to the spoilage process, various types of biosensing technologies have been used (Rotariu et al. 2016). According to Ghaly et al. (2010), biogenic amines and compounds resulting from the decomposition of nucleic acids, such as xanthine, hypoxanthine, and other metabolites, are the most common one being detected.

As meat products are the most studied food products in the industry, the rapid advancements in meat evaluation have inevitably enabled the utilization of biosensors. The motivation for this is that the spoilage products from meat are toxic, can cause intoxication, allergies, and even death if ingested in high concentrations (Lineback and Stadler 2009).

Therefore, the purpose of this chapter is to discuss the ongoing advances of diagnostic tools for intelligent food packaging application that can identify meat deterioration. Colorimetric and pH-based biosensors, data carriers such as radio

frequency identification (RFID) devices, and time-temperature indicators (TTI) are typical hardware components in intelligent packaging systems that will be discussed in reaction to consumers increasing concerns regarding issues related to food safety. These aforementioned devices and techniques are popular examples that can be used to determine meat freshness and at the same time, permitting control of the environment and product packaging. Lastly, conclusion and future challenges and perspectives of intelligent food packaging were explained in detail to give a strong basis for further research in this area.

8.2 Intelligent Packaging Technology for On-Site Detection of Meat Deterioration

8.2.1 Utilizing pH-Sensitive Dyes to Monitor Meat Quality

During storage, the freshness of meat tends to degrade due to microbial spoilage and biochemical reactions producing odour. These intrinsic microbiological and chemical changes allow a direct evaluation of the quality of meat products. Colorimetric sensor/biosensor is a form of intelligent packaging technology that is widely used as a non-destructive spoilage index assessment of meat products and a range of other foods. The most common principle of this approach is by utilizing the change in colour due to the presence of reaction between volatile components and chemical dyes caused by vapour detection and differentiation. This emerging technology also utilizes cameras or supplementary image-capturing appliances as opposed to naked eye detection to examine the quality of meat-based products attributable to spoilage (Ghaani et al. 2016; Kuswandi et al. 2011a, b). However, there is relatively a small body of literature that is concerned with colorimetric biosensors based on naked-eye detection.

Much on the current literature on pH-sensitive dyes pays particular attention to dyes synthetically originated such as bromothymol blue pH dyes as the most commonly employed in the meat packaging industry to scrutinize the development of carbon dioxide produced as a result of microbial growth. pH dyes react with the levels of carbon dioxide in order to induce a change the colour. Other metabolites, such as SO_2, NH_4, volatile amines, and organic acids, have also been used as target control molecules in addition to carbon dioxide (Smolander 2003). These compounds are produced due to biochemical and microbiological reactions on food protein due to spoilage, resulting in a pH transition. The core idea is that the developing target micro-organisms induce irreversible shifts such as variation in pH which incidentally result in a colour change, certifying a straightforward signal of the quality of the food product contained by the package (Brizio 2016).

As indicated previously, a change in pH can be displayed via colour change of biosensors. This can in turn, aid users to be notified on the quality of meat product. Figure 8.2 depicts an example of freshness sensors that employs various types of synthetic dyes for fish spoilage monitoring (Morsy et al. 2016). Meanwhile, Fig. 8.3 shows representations of pork and silver carp in relation to TVB-N contents during

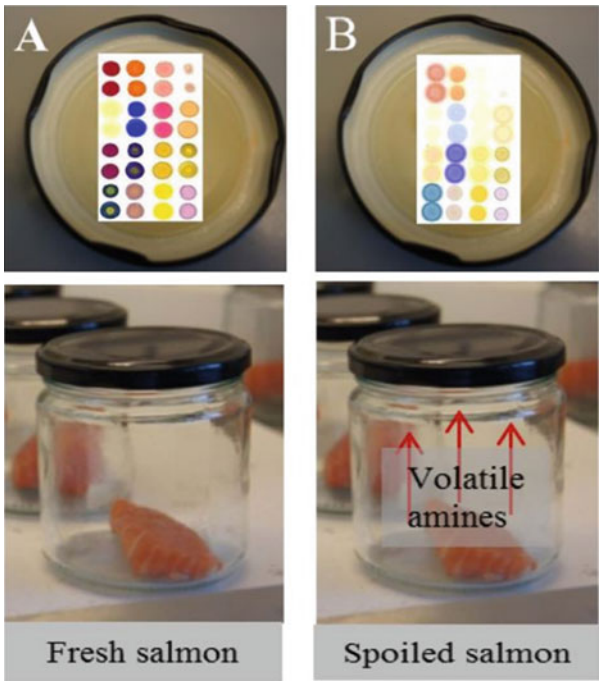

Fig. 8.2 Fresh Atlantic salmon (*salmo salar*) in closed jars for fish spoilage monitoring at room temperature using colorimetric sensor assay based on synthetic dyes. (**a**) 0 h and (**b**) 24 h. Changes in colour were related to compounds released during fish decomposition. (Morsy et al. 2016, Copyright belongs to Elsevier)

storage at 4 °C after being packaged by safe and cost-effective amine-responsive films incorporated with natural dried rose (Zhai et al. 2020). Other pH dyes that have been reported in the literature are xylenol blue, bromocresol purple, bromocresol green, cresol red, phenol red, methyl red, and alizarin. One recent example is a study by Lu et al. (2020), where bromothymol blue and methyl red were utilized as pH-responsive dyes in sugarcane bagasse nanocellulose hydrogel as a colorimetric freshness indicator for intelligent food packaging.

Current progresses in intelligent packaging to detect meat spoilage have focused on utilizing natural colour pigments in developing colorimetric biosensors to prevent the potentials of migrations of chemical dyes on packaged meats. Despite the increasing trends of employing natural colour pigments as pH-sensitive dyes, there are still only a handful of research carried out based on natural dyes as colorimetric biosensors. This provides extended opportunity for colorimetric biosensors to have applications in a variety of products including fresh foods, fruits, and seafood. Typically, visual pH sensors are composed into three main groups. The primary group comprises of dyes immobilized by physical adsorption on a compact support such as an ion exchanger; the following includes dyes covalently fixed to hydrophilic support, for example, cellulose or glass, and lastly, the third involves polymer matrices for the dyes to be physically entrapped in (Abolghasemi et al. 2016; Pourjavaher et al. 2017). As the use of bio-based polymer as matrices to entrap dyes is of significance recently, Table 8.1 summarized the pH-sensing approach on perishable meat products utilizing various types of natural anthocyanin (from

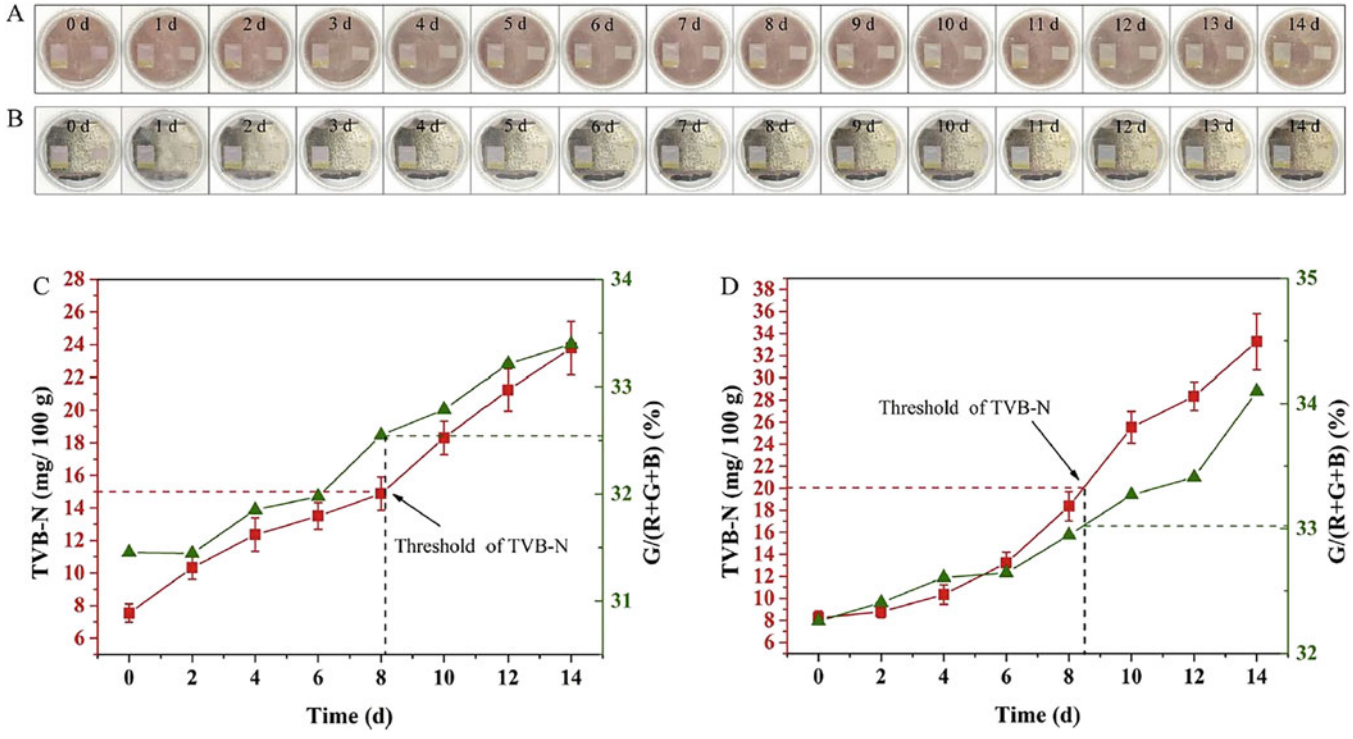

Fig. 8.3 The illustrations of (**a**) pork and (**b**) silver carp, and the relation between TVB-N contents and G/(R+G+B) (%) values of AG-AN/GG-2%TiO2 film in terms of (**c**) pork and (**d**) silver carp sample, during storage at 4 °C using amine-responsive bilayer films incorporated with dried rose anthocyanin. (Zhai et al. 2020, Copyright belongs to Elsevier)

Table 8.1 pH-sensing mechanisms utilizing various types of natural and safe to use anthocyanin to detect meat freshness

Main biopolymer	Anthocyanin	pH range/ visual feature	Colour changes	Experimented sample	Colour changes after spoilage point	Intrinsic characteristics	References
Starch + chitosan	Red cabbage	pH 2–13	Red to yellow	Fish	Yellow (72 h, 25 °C and 4–7 °C)	Sensitive biodegradable films able to visually detect fish spoilage	Silva-Pereira et al. (2015)
Agar/potato starch	Purple sweet potato	pH 2–10	Red to green	Pork	Green (48 h, pH 7.42)	Non-toxic, reliable responses to pH variations; simple and visual method to detect food quality	Choi et al. (2017)
EVOH[a]/ montmorillonite	Mulberry	pH 2–12	Rose red to yellow	Shrimp	Light blue (30 h, 25 °C) TVB-N: 24.89 mg/100 g	Ammonia and pH-sensitive films with enhanced barrier and mechanical properties	Kang et al. (2018)
Gelatin + gellan and gum	Red radish	pH 2–12	Red to yellow	Fish (black carp)	Yellow-green (7 days, 4 °C) TVB-N: 53.71 mg/ 100 g	Easy-to-use edible and pH-sensitive films with electrochemical writing	Zhai et al. (2018)
Cassava starch	Blueberry residue	pH 2–11	Red to grey	Chicken	Grey (10 days)	Visually perceptible pH-sensitive films	Luchese et al. (2018)
PVA/Chitosan nanoparticles	Mulberry	pH 1–13	Red to green	Fish	Green	Sensitive colour responsive films with enhanced physical properties	Ma et al. (2018)

(continued)

Table 8.1 (continued)

Main biopolymer	Anthocyanin	pH range/ visual feature	Colour changes	Experimented sample	Colour changes after spoilage point	Intrinsic characteristics	References
Cassava starch	*Lycium ruthenicum Murr.*/goji berry	pH 2–13	Red to yellow	Pork	Green/yellow (48 h, 25 °C, pH 7.45) TVB-N: 41.19 ± 1.74 mg/ 100 g	Remarkable pH-sensitive films with enhanced water vapour and UV-visible light barrier ability, tensile strength, and antioxidant potential	Qin et al. (2019)
Chitosan/PVA	Red cabbage	pH 1–13	Red to blue-green	Pork belly	Yellow (exposed to ambient air, 24 h)	pH indicative films with satisfactory mechanical properties and rapid colour change	Vo et al. (2019)
Chitosan	Purple rice and black rice	pH 3–11	Pink to purple	Pork	Green	pH-sensitive films with antioxidant ability	Yong et al. (2019)
k-carrageenan gum/hydroxypropyl methylcellulose	*Prunus maackii* (cherry)	pH 3–13	Red to blue	Pork	Blue (48 h)	Green film with pH-sensitivity, antioxidant activity, enhanced tensile strength, and barrier properties	Sun et al. (2019)
Bacterial nanocellulose film	Black carrot	pH 2–11	Red to grey	Fish (trout and carp)	Blue-khaki (15 days/ 4 °C, pH 7.09-7.22) TPC: 9.74 and 9.61 $\log_{10}$	Naked-eye detection, low-cost, easy-to-use, and eco-friendly	Moradi et al. (2019)

					CFU/g TVB-N: 45.03 and 43.13 mg N/100 g		
ι-carrageenan	Butterfly pea + *Brassica sp.* (mixed 1:1)	pH 1–13	Red to yellow	Shrimp	Blue-green	Safe, non-destructive, flexibly visual method for direct assessment of food freshness	Ahmad et al. (2019)
Starch/PVA[b]/ Chitosan	Roselle	pH 2–12	Red to yellow	Pork	Yellow (72 h, 25 °C) TVB-N: ~40 mg/100 g	Smart indicator film with high tensile strength with high antioxidant activity	Zhang et al. (2019)
Chitosan + oxidized chitin nanocrystal	Curcumin	pH 3–10	Yellow to orange-red	Hair tail and shrimp	Red	Smart films were sensitive to pH changes. Incorporation of nanocrystal improved the films mechanical strength and water vapour barrier	Wu et al. (2019)
Agar	*Arnebia euchroma* root	NA	Pink to violet	Fish	Bluish-violet (24 h, 25 °C)	Better colour response observed in lower dye content	Huang et al. (2019)
Chitosan + oxidized chitin nanocrystals	Black rice bran	pH 2–12	Red to greyish green	Shrimp and pomfret meat	Greyish green	pH-sensitive intelligent films with enhanced mechanical, UV-barrier, and antioxidant character	Wu et al. (2019)

(continued)

Table 8.1 (continued)

Main biopolymer	Anthocyanin	pH range/ visual feature	Colour changes	Experimented sample	Colour changes after spoilage point	Intrinsic characteristics	References
Sago starch	Butterfly pea	pH 2–14	Red to yellow	Poultry	Green (48 h, pH 10.30) TPC: 6.78 ± 0.74 CFU/g	Real-time monitoring, safe to use, and non-toxic colorimetric indicators	Ahmad et al. (2020)
Bacterial cellulose film	*Echium amoenum*	pH 2–12	Violet to yellow	Shrimp	Yellow (4 days, 4 °C, pH 7.23) TPC: 7.24 $\log_{10}$ CFU/g, TVB-N: 41.18 mg/100 g	High colour stability and unaffected morphological characteristics	Mohammadalinejhad et al. (2020)
Carboxymethyl-cellulose/starch	*Iponea batatas* (L.) lam, purple sweet potato	pH 2–12	Red to yellow	Fish	Bluish-violet (48 h, 25 °C, pH 8) TVB-N: 21.55 mg/100 g	NH_3 and pH-sensitive films with good tensile strength	Jiang et al. (2020)
Carboxymethyl-cellulose + cellulose nanofiber	Shikonin (*Lithospermum erythrorhizon* roots)	pH 2–12	Reddish pink to light blue	Fish	Blue violet (36 h, pH 6.9)	Hydrophobic films and antioxidant properties observed	Ezati et al. (2021)
Starch + carbon nano dots	Butterfly pea (*Clitoria ternatea*)	pH 2–12	Reddish pink to green	Pork	Green	Good mechanical strength, water barrier, and antioxidant activity	Koshy et al. (2021)
Chitosan + oxidized chitin nanocrystals	Red cabbage	pH 3–10	Red to yellow	Hairtail and shrimp	Yellow	Non-toxic, sensitive, and biodegradable smart films with	Chen et al. (2021)

						UV-blocking, water vapour, and oxygen barrier properties	
Cellulose acetate composite	Black carrot	pH 1–12	Red to yellow	Chicken	Purple	Short response time (~2 min), great colour stability and interactive "Janus" principle	Franco et al. (2021)
Methylcellulose/ chitosan nanofiber composite	Barberry	pH 1–14	Red/ crimson to yellow	Lamb	Pale peach (72 h, pH 7.5)	Distinct colour change. Improved physical, mechanical, moisture resistance, and water vapour properties of films with considerable antioxidant activity	Alizadeh-Sani et al. (2021)

[a]*EVOH* ethylene-vinyl alcohol copolymer
[b]*PVA* poly(vinyl) alcohol

flowers, colour-rich vegetables, and herbs) and bio-based material as polymer matrices. It is important to note that most of the intelligent pH-sensitive films developed in a form of colorimetric biosensors were predicated on total viable counts and biogenic amines.

8.2.2 Incorporation of Data Carriers into Intelligent Packaging

Barcodes and RFID tags are mainly data carrier devices that can be incorporated into intelligent packaging technology. In multi-scale departmental stores, barcodes are commonly used to speed up record keeping, goods reordering, and price testing (Manthou and Vlachopoulou 2001). A barcode is a collection of sequential side-by-side lines that contain hidden encoded data. The message received is decoded and interpreted by an optical barcode scanner, which then sends it to a system for further processing. RFID tags, on the other hand, are made up of three parts: a microchip tag connected to a small aerial, a reader responsible for sending radio signals and receiving responses from the tag in response to those signals, and a network device or web server that links the company and the RFID equipment (Kumar et al. 2009). The most advanced RFID systems can accept data from up to 100 m away and store up to 1 MB of data. The presence of a battery in active tags distinguishes them from passive tags, in which no battery is installed. RFID technology has emerged in recent years as a novel method for storing and communicating real-time information concerning agricultural products for automated identification and traceability utilizing RF electromagnetic fields without the need for human interference (Bibi et al. 2017; Meng and Li 2016). Furthermore, several lines of evidence suggest that the traceability systems in earlier method were performed manually with poor precision and accuracy in measurements. Often, packages contain valuable or perishable goods. The use of RFID tag in this situation is extremely critical as this technology do not need monitoring. Additionally, research is currently underway to find ways to integrate RFID systems in intelligent packaging that can monitor meat-based products during the storage period.

A number of studies have begun to examine the incorporation of RFID into intelligent packaging application for monitoring the quality of meat freshness. Such example can be seen in Eom et al. (2014) work, whereby, they have successfully developed a cost-efficient meat freshness monitoring system using the smart RFID tag by using MICS-5914, a commercial gas sensor as the main detection method. In order to give an accurate value, Eom et al. (2014) utilized the interface circuit of this sensor, to get a precise data and it is constructed from three parts: a noise filter, an amplifier, and a low pass filter. The system also uses temperature sensor and humidity sensor which serve as an additional auxiliary sensor to determine the food poisoning mark. Interestingly, the developed monitoring system can show the meat freshness of pork at four distinct grades: High, Medium, Low, and Spoilage. The findings in the experiment showed that the system was able to perform quickly and accurately, and the results obtained were comparable to existing methods that employed electronic noses to measure freshness (Eom et al. 2014).

Another similar study that employs RFID technology to monitor meat freshness is by Chung et al. (2017). A novel proximal fish freshness monitoring using battery-less smart sensor tag was developed. The sensor tag transmits data and harvests RF energy using HF RFID technology that follows the ISO15963 protocol. The harvester had the ability to collect sufficient radio frequency (RF) energy from the reader by using RF energy coupling within a maximum distance of 30 cm and a single energy chip was used to store the received power for sensing circuit. By monitoring both the temperature and the concentration of H_2S or NH_3 gas in the fish in the range of −40 °C−105 °C, 0–200 ppm, and 0–100 ppm, respectively, the device acquired the capability to accurately track the quality of packaged fish as well as analyse the process of spoilage until it reached a toxic level (Chung et al. 2017). In addition, the designed sensing module consumed less than ~10 mW due to the utilization of an ultra-low-power sensors. This facilitated an effective RF energy coupling and sensing data transmission due to the expansion of distance between the RF reader and the smart sensor tag (Chung et al. 2017).

RFID sensor techniques will continue to attract interest in a variety of fields in both industry and academia as RFID tags are well known to serve more potential advantages, as this system offers numerous benefits such as traceability, minimized counterfeit, labour-saving costs, inventory management, security, minimized food loss, and most importantly, improvement of safety and quality of meat products. A more complex data, such as nutritional information, cooking instructions, relative humidity, and temperature, can also be stored on RFID tags. So far, extraordinarily little attention has been paid to the role of RFID in intelligent packaging and the futuristic promising applications. It is no doubt the use of RFID tags in conjunction with intelligent packaging resulted in a more accurate monitoring of food safety and efficiency, making it more convenient for both consumers and manufacturers and more means to improve the performance of RFID sensor techniques should be explored such as the potential of chip-less RFID for food safety monitoring or RFID sensor based IoT applications. As a matter of course, some commercially available packaged food integrity indicators include Novas® (Insignia Technologies Ltd.) colour-changing label tag that is incorporated into film lid to detect freshness of meat or other food products that is flushed with CO_2 (Ahmed et al. 2018). Another example is an in-package monitor for immediate detection of O_2, known as Ageless Eye (Mitsubishi Gas Chemical Inc. n.d.). Its main applications include packaging control, verifying sealing, and breathability (Ahmed et al. 2018).

8.2.3 Packaging Featuring Time-Temperature Indicators

Time-temperature indicators (TTI) are simple and react to temperature fluctuations, rather than the nature of the food or the concentration of chemical substances. This detection strategy is the most commonly used systems in packaging today (Poyatos-Racionero et al. 2018). Owing to TTI's astonishing characteristics, which are simple, effective, and easy to use devices, TTI is a popular choice to monitor, record, and indicate the effect of temperature on the quality of product from manufacturing until

it reaches the consumers (Giannakourou et al. 2005). A key aspect of TTIs is that these devices are user friendly, allowing consumers to check food quality through a colour response that correlates to the quality of food product at a certain temperature when it is integrated as part of the food package (Kim et al. 2012). Food packages featuring TTIs are examples of intelligent packaging, due to their use of a system that monitors the conditions of the food in real time, allowing an on-site detection of food freshness in addition to informing consumers about the conditions of transport and storage of these products. TTIs can establish the actual parameters of food quality and safety before consumption, an invaluable feature of TTIs. There is a growing body of literature that recognizes the importance of food safety, and the integration of TTIs in intelligent packaging have further promoted the development of its commercial forms that exists in the market such as 3M Monitor Mark™ (3M company), Keep-it® (Keep-it Technologies) and Tempix® (Temptix AB), Cook-Chex (Pymah Corp.) (Poyatos-Racionero et al. 2018).

Focusing on TTIs that are designed to monitor meat freshness, the trend is quite promising. Recently, Brizio and Prentice (2015) developed a new smart TTI, whose principle of operation is centred on the reaction between starch and iodine, followed by the action of an amylase on this complex, triggering a discoloration at a rate that is dependent on the medium's time and temperature. The smart TTI successfully indicated the time history and temperature of poultry products easily and accurately. Furthermore, it could also be stored frozen for an extended period of time without affecting its performance. Other than providing convenience, the use of this new TTIs in chicken-based products offered an interactive and true shelf-life status of products to the consumers and manufacturers and at the same time, allowed the identification of potential inefficiencies in the food supply chain (Brizio and Prentice 2015.

Meng et al. (2018) fabricated a solid-state enzymatic TTI to monitor chilled fresh pork. The developed TTI was comprised of two separate parts, a cover as a moisturizing body and a coating as a reaction body. The shelf life of chilled fresh pork was evaluated through the colour evolution of TTI from mazarine (safe to eat) to colourless, indicating spoilage. Meng et al. (2018) selected thiobarbituric acid (TBA) as quality indicators in their TTI and by investigating the kinetic properties of TBA, the pork deterioration was determined, and the principle was met. Interested readers can read an excellent application of TTs devices in quality monitoring and shelf life of food products during storage by Pandian et al. (2020) as well as Gao et al. (2020).

8.2.4 Assessing Meat Freshness Employing Electrochemistry

With a plethora of existing biosensors, electrochemical-based biosensor has demonstrated to be a popular choice for the detection meat deterioration (Johnson et al. 2019) and pathogens in food products as reported in literature. This section will present a short overview with specific attention on xanthine, a specific biomarker produced by spoilage microorganisms, detection in meat for illustration purposes.

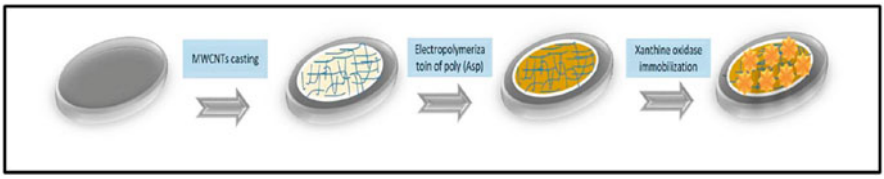

Fig. 8.4 The schematic illustration of the fabrication process of the electrochemical biosensor based on enzyme using poly(L-aspartic acid)/multi-walled carbon nanotube bio-nanocomposite for xanthine detection in fish meat. (Yazdanparast et al. 2019, Copyright, Elsevier)

Yazdanparast et al. (2019) developed a simple-to-prepare electrochemical biosensor based on enzyme using poly(L-aspartic acid)/multi-walled carbon nanotube (MWCNT) bio-nanocomposite for xanthine detection in fish meat at different storage times (Fig. 8.4) on differential pulse voltammetry method. The immobilization of xanthine oxidase was done on glassy carbon electrode and the synthesis of Poly(L-Asp) film was performed by the straightforward electrochemical deposition of the L-Asp using cyclic voltammetry. Consistent with the findings made by Yazdanparast et al. (2019), MWCNT association with poly(amino acid) for the modification of electrode exemplified a suitable platform for immobilization of xanthine oxidase enzyme biomolecules. The fabricated biosensors showed a linear range of 0.001–0.004 and 0.005–50.0 μM with high selectivity and low detection limit.

The fabrication of novel amperometric xanthine biosensor was also designed and developed by Dalkiran et al. (2014) for the detection of xanthine in fish samples. The biosensors were based on cobalt oxide nanoparticles, chitosan, and MWCNT modified on glassy carbon electrode and the immobilization of xanthine oxidase and co-immobilization of bienzyme xanthine oxidase/horseradish peroxidase. Similarly, Sadeghi et al. (2014) developed a low-cost and stable amperometric xanthine biosensor based on covalently immobilized crude xanthine oxidase on a hybrid nanocomposite film via glutaraldehyde used for determining xanthine based on amperometric detection of hydrogen peroxide reduction at −0.35 V. The biosensor had a rapid onset of action to xanthine by 8 s and a linear working concentration range from 0.2 to 36.0 μM ($R^2 = 0.997$) with a detection limit of 0.1 μM (signal/noise [S/N] = 3). With a sensitivity value of 13.58 μA μM^{-1} cm^{-2}, the sensor was successfully used to assess the freshness of chicken and fish (Sadeghi et al. 2014). Other excellent examples based on electrochemical-based biosensors can be referred to Ghasemi-Varnamkhasti et al. (2018)'s review on the potential use of electronic noses, electronic tongues, and biosensors as multisensory systems for spoilage examination in foods. Interested readers can also refer to additional literatures written by Johnson et al. (2019), Azam et al. (2018), Baratella et al. (2018) and last but not least, Rotariu et al. (2016).

8.3 Challenges to the Extensive Release of Intelligent Packaging

The technologies required to fabricate food spoilage indicators have existed for a while although they are still hardly ever found in major commercial markets. This could be due to the consumers as well as the retailers' hesitance towards the safety of the packaging itself. Although the benefits of such intelligent packaging technologies are clear, they are still not free from any emerging obstacles. Intelligent packaging that uses synthetic dyes for instance, may include chemicals that could, under exceptional events, percolate into the insides of the package exposing unwanted danger to the consumer. Other than that, intelligent packages every so often require the foods to be packed in different approaches in order enable easy detection of the chemicals discharged from the food due to spoilage. Furthermore, according to Ahmed et al. (2018) and Parisi et al. (2015), countless traditional and other sensing devices developed based on unsafe sensing materials such as carbon nanomaterials and metal nanoparticles have disqualified this important criterion. One of the greatest challenges is the waste generated from intelligent packaging is unmanageable and unsustainable for recycling. This drawback poses a major challenge to industry. The guidelines and strategies for the recycling and treatment of conventional packaging waste have been in effect for quite some time, however, the real-world experience of recycling this category of packaging waste proofs strenuous. In order to solve this issue, it is essential to conduct an advanced research on the treatment and recycling of complicated packaging waste. In particular, by finding a fitting raw materials and taking into account of its biodegradability as well as the overall composition to allow for the advancement of intelligent packaging. Recent evidence suggests that, organic biocompatible materials are comprehensively applied in the development of innovative and novel packaging systems that have the capability to address safety concerns while also providing an effective sensing mechanism (Ahmed et al. 2018).

8.4 Conclusion and Future/Emerging Prospects

Intelligent packaging systems are designed to meet the needs of the food supply chain and consumers by alerting retailers and end users to possible issues that may arise during transportation and storage. This includes details on the perishable muscle foods' freshness, microbiological quality, security, temperature status, and shelf life. The most advanced packaging systems are those that combine intelligent packaging with biosensing technologies that aims in providing fast, effective, and factual information about the safety and quality of meat products, and at the same time attempting to counter any negative changes that have occurred in food products. RFID tags, for example, have nearly transformed conventional barcodes due to their ability to monitor several objects in real time and store a vast amount of data. Moreover, intelligent packaging can be combined with other innovative technologies such as active packaging, nanomaterial packaging, and biodegradable

packaging. Further research should be done to develop a functional, user-friendly, and easy-to-use sensing device with several functions although consumers still need to play a significant role for these ground-breaking innovations to be commercially feasible. To conclude, intelligent packaging system with on-site diagnostic tools such as pH-sensitive dyes in colorimetric biosensors, smart sensors utilizing RFID technology, TTIs, and electrochemistry association have assisted in the improvement of safety, quality, shelf-life, authenticity, traceability, protection, and convenience of meat products. In spite of its limitations commercially, it has undoubtedly ushered a breakthrough in the packaging industry, with new methods and advances in meat packaging expected to emerge in the coming days.

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RFID Near-field Communication (NFC)-Based Sensing Technology in Food Quality Control

9

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Abstract

The demand for wireless, passive, low-cost, and portable detection systems is on the rise for environment monitoring, food safety, and medical diagnosis. The use of Radio Frequency Identification (RFID) in the food industry sector as a smart label can improve the monitoring of food products, prevent spoilage, and ensure food safety. In particular, the use of RFID technology makes it possible to develop battery-free sensor systems and their use in sensing tags for smart food packaging is attractive. Near-Field Communication (NFC) RFID-enabled sensing has the advantage of using wirelessly powered sensors communication through inductive coupling. Such tags or smart labels could help reduce food spoilage by alerting the consumer or food provider when a product is likely to be or has been compromised and hence help to address the hunger-related global challenges. This chapter presents the application of the RFID technology in the food industry with a discussion of several works developed to test the ability of RFID technologies in the NFC to perform food traceability. The purpose is to show that the wireless, passive, low-cost, and flexible NFC tag sensors could unfold new dimensions for different food sector applications.

Keywords

Food monitoring · NFC · RFID sensor · Near-field communication

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9.1 Introduction

The need to ensure food availability for consumers is a major concern nowadays due to the continued growth in the world's population as well as to maintain the stability of markets and economy (Burchi and De Muro 2016; ScienceDirect 2013). While the food production has increased due to the great advances in agriculture science and technology (FAO 2021; ScienceDirect 2008), there also a significant amount of food wastage either during the food production process or during the distribution process to the consumers. For example, United Nations Food and Agriculture Organization (FAO) estimates show roughly one-third of all food produced for human consumption is lost or wasted worldwide (FAO 2020). This corresponds to 1.3 billion tonnes of food per year. Much of this wasted food is still safe to eat, but consumers throw it away because it is close to or beyond its printed expiration date (Vermeir et al. 2020). Smart labels could provide better estimates of food quality than the printed expiration date (Escobedo et al. 2021c). Besides food wastage, health risks associated with food safety play a major role in the food consumption economy (Zwietering et al. 2021; Jin et al. 2020; Membré et al. 2021). In this context, an efficient and reliable monitoring system of food products can be implemented to reduce food wastage and to ensure food quality. This can ensure appropriate matching between food supplies and demands, as well as proper handling during storage and transit traceability (Escrig et al. 2020).

Recently, packaging technologies have allowed several smart packaging labels that can be used to trace the food products and to improve food safety and quality (Zhang et al. 2016; foodnavigator.com 2020; Skinner 2015). This trend could add value for both the consumers and the brands. Radio Frequency Identification (RFID) technology (He and Das 2017) has been widely used in Track and Trace applications (Abugabah et al. 2020; Rajasekar 2021; Baumbauer et al. 2020; Preradovic and Karmakar 2010; Maskey et al. 2020). It allows updating the status of data items while they are moving along a supply chain. Also, by adding sensing capability it can sense and report ambient conditions such as temperature, humidity, and pressure using either on-board or connected sensors (Lazaro et al. 2018; Okba et al. 2019; Matbouly et al. 2017; Zannas et al. 2020, 2018; Meng and Li 2016). RFIDs are able to update stored information such as the status of the traceable (Abugabah et al. 2020). This updating capability allows the information about the characteristics of every sensing node passed by the item to be recorded in enough detail for traceability robustness as well as easily detecting contamination by continual measurement and reporting of ambient conditions. In this way, they could help to extend the shelf life of products, reduction of food waste. On top of that, they make it possible to pass information to the end consumers and increasing consumer engagement. One main disadvantage of RFID technology is its relatively high cost compared to other traceability systems, which makes its use limited to sections of the production chain in which the goods are relatively expensive such as meats, cheeses, and beverages (Bibi et al. 2017).

Contrary to visual traceability techniques such as bar codes (Tiwari 2016), RFIDs offer data possessing as well as the capability to store and update information locally

(Sung 2015). Moreover, bar codes that are widely applied in the food sector do not have the capability to sense and report ambient conditions or to hold two-way communication with a reader (Ghaani et al. 2016). Therefore, when the entire set of costs and benefits are together considered, the cost-based distinction between bar code and RFID tag disappears or becomes insignificant. Indeed, RFID technology is gradually surpassing bar code technology in the field of food traceability, and more industrial food sectors are adopting RFID solutions (Rajo-Iglesias et al. 2014)

This chapter presents a state of the art of RFID technology in the food industry. The chapter discusses several works developed to test the ability of RFID technologies to perform food traceability in food industry with a specific focus on RFID applications in detecting food spoilage. A basic overview of RFID technology to help understand its general characteristics along with the main features and differences between RFID systems is provided. This chapter is divided into the following sections, first, the need for RFID technology in the food industry is discussed with different industrial examples and implementations. Then RFID principle of operation is presented, the classification of RFID labels and their power consumption is also discussed. Finally, few examples of the implementations of RFID in NFC are presented for food packages monitoring.

9.2 The Need for RFID Technology in Food Industry

To guarantee the safety and quality of food products, traceability has been utilized to ensure food product quality, which depends on specific characteristics of the food and its production process. Different conditions can affect the food characteristics such as the weather conditions, biological variations, seasonality, storage, transportation, and cooling facilities (Kumar et al. 2009). Based on these characteristics, the risks such as cross-contamination of batches may occur when different batches are mixed or when the same resource is used for the production of different intermediate food products. In addition, a quality check will be a challenge when raw materials are provided from different suppliers (Davis et al. 2021).

Based on FAO (Food and Agriculture Administration) standards of Food Hygiene (2009), "food safety is the assurance that food will not cause harm to the consumer when it is prepared and/or eaten according to its intended use." Numerous opportunities exist for food safety violations during the processes, procedures, or stages that any given food product passes through on its way from farm to fork (Nukala et al. 2016).

Considering that the quality and safety of food is a major concern in global food supply chains (Kruse 1999), efficient traceability systems should be implemented to ensure the following: (a) Effective and efficient management of raw-material production by the identification of potential deviations or errors in processes, (b) better food quality and safety by the detection of defects in food production equipment before or as soon as they take place, (c) prevention of the contamination by appropriate quality and safety measures throughout the food supply chain, (d) the ability to extend food product's shelf life by proper management of their ambient

conditions (e.g., gas, temperature, humidity) throughout the food supply chain, and (e) manage the food inventory by reducing the overall wastage of food products so that less raw materials are consumed (Haleem et al. 2019).

Based on the currently available technologies, the identification and sensing functionalities of RFID technology can help with the management of information flow within the supply chain. The development of RFID sensors labels has already improved monitoring of the cold chain of perishable food products, environmental monitoring, as well as the presence of microbial organisms. In the following paragraphs, the main applications of applying RFID systems in the food industry and their effects on overall food quality and safety are detailed.

Application in management of the food supply chain and inventory: RFID labels are used to track food products during distribution and storage in supply chain management, it replaces the barcode because of its advantages of not requiring line of sight to read the label (Angeles 2005). Moreover, RFID system's range of operation is larger as compared to that of a barcode where RFID readers can simultaneously communicate with multiple RFID labels which have the ability to store more data compared to a barcode (Duroc and Tedjini 2018; Chetouane 2015). By implementing an RFID system in a store, it can be used to maintain an accurate database of its inventory that automatically alerts a warehouse management system once the inventories are low (Valente and Neto 2017). This improves the speed and efficiency in stock management and operations as well as improving inventory tracking throughout the supply chain (Lee et al. 2009; Fan et al. 2015; Hellström and Wiberg 2010). Many major distribution companies have implemented RFID technology for their business, for instance, British Telecommunications which is a major communication company has implemented RFID technology by launching a new online real-time RFID food tracking system BT foodnet (Connolly 2007). This online network provides access to synchronized real-time data for the status of all stock items as they pass throughout the supply chain for suppliers and retailers. BT food net combines barcodes and RFID read/write labels with a secure Internet platform for data exchange which speeds up and reduces the cost of recalling products (BT Auto-ID Services 2021). Moreover, Wal-Mart stores were the first major company to push for RFID implementation in supply chain management (Hardgrave et al. 2008; MH&L 2005). The implementation has taken place in 2005 where products are tracked as they enter Wal-Mart's distribution centers and then in turn are shipped to individual stores through Electronic Product Code (EPC). Other examples of the application of RFID in food supply and inventory are the development of smart food containers enhanced with UHF RFID labels which record historic information about a food product and helped to achieve better inventory control, improve events management such as cold-storage room replenishment, or reduce products close to expiration date (Athauda and Karmakar 2019). Many food sectors have implemented RFID for food tracking and quality monitoring such as tracking the ambient condition in the wine industry (Rahman 2015), the control of raw materials and in weighing (Ionescu and Ionescu 2013), mixing, and baking processes involved in the preparation of biscuits and cakes in biscuit industry (Biscuit—RFcamp Ltd 2021) and in cheese manufacturing to trace cheese along the

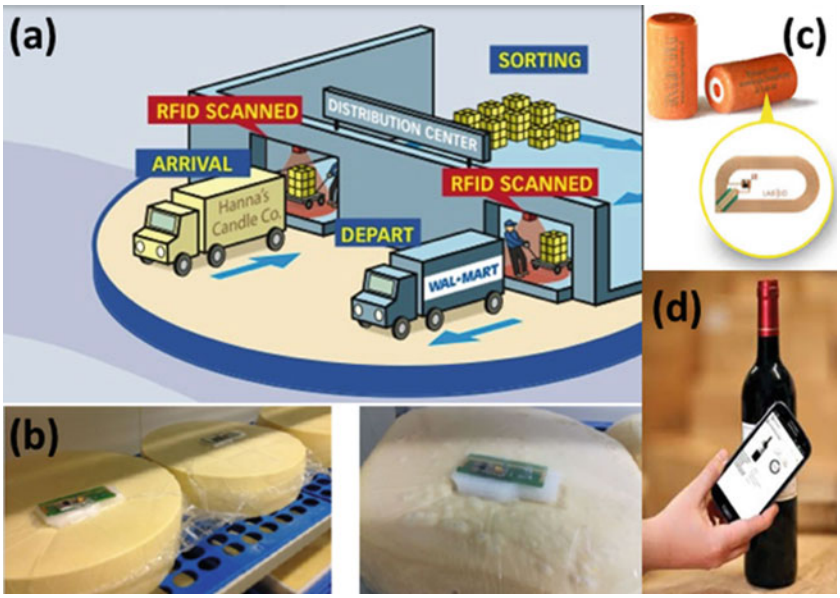

Fig. 9.1 Using RFID in different food chains supply and inventory. (**a**) In storage and distribution. (**b**) In cheese manufacturing for monitoring cheese maturity. (**c**, **d**) In wine industry for ambient conditions and items tracking

supply chain with great precision and providing the costumer of the cheese history after purchase (Fosso Wamba and Wicks 2010; Perez-Aloe Valverde et al. 2010; Abdelnour et al. 2018). Figure 9.1 presents some examples of using RFID technology in chain and inventory applications.

Application in preservation and condition monitoring: RFID chips with advanced electronics have the ability to include sensing capabilities (Cui et al. 2019). These RFID chips can be used to monitor environmental conditions, storing the product's data, and transmit the collected information upon request. For instance, Infratab Inc (2021). developed RFID tags in both HF and UHF bands which can monitor the shelf life of foods to which they are attached. Other works (Gomes et al. 2015) proposed a low-power system for food monitoring that is compliant with the standard ISO15693 for identification purposes and used proprietary commands for temperature logging.

An integrated smart label for tracing food information and monitoring its preservation conditions has been reported with humidity, temperature, and light intensity sensors (Cartasegna et al. 2009, 2011). Another system based on a combination of RFID technology and variable sensor types shows the integration of different sensors is possible depending on the requirements (Schumacher et al. 2012). Few examples of RFID application in food preservation and monitoring are shown in Fig. 9.2.

Applications in food safety: One of the main demands of the food market is the ability to send the food spoilage information for a long distance without any physical

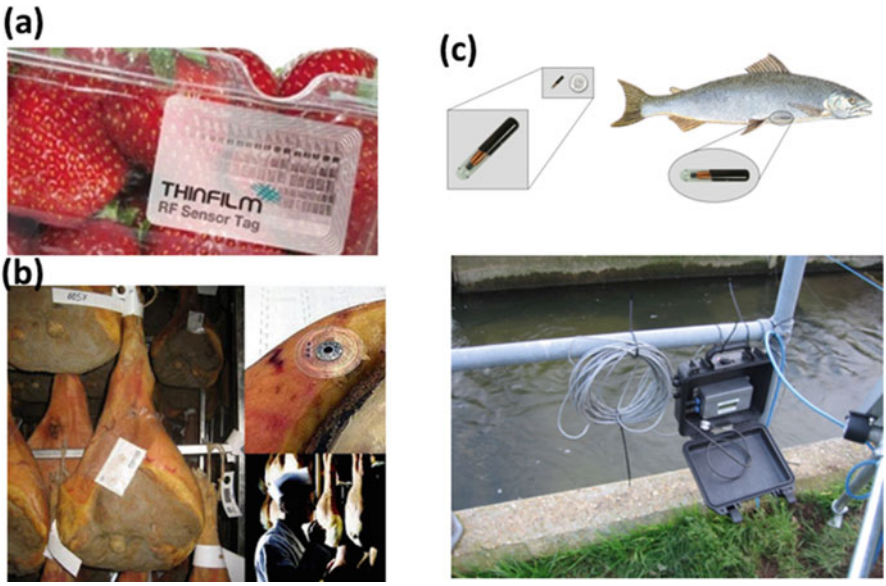

Fig. 9.2 Application of RFID in food preservation condition and quality monitoring (**a**) Quality and preservation of fruits and vegetables in supermarkets. (**b**) Meat quality tracking in storage (**c**) in fish industry for monitoring fish growth in farms

intervention. RFID systems offer a smart solution that can be used to ensure that food products such as meat, fruits, and dairy products remain within a safe range of surrounding conditions such as temperature, humidity, and pressure during transportation and storage (Kumari et al. 2015) Fig. 9.3 shows the implementation of RFID in safety food monitoring.

In addition to improving food safety, RFID technology can help to reduce operating costs, meet compliance requirements, and improve efficiency in the food industry (Ruiz-Garcia and Lunadei 2011). For example, a traceable safety information coding for beef cattle based on RFID and improved EPC has been proposed which solves the coding problems of key information in the procedures of tracing the quality and safety of beef cattle. This resulted in an operating cost reduction and strong scalability. Moreover, pathogen detection in the liquid food supply chain can be detected using a wireless RFID sensor tag using gold nanoparticles. Detection is based on resonance frequency shift of RFID tag response which is correlated with the concentration of bacteria in the milk.

9.3 RFID Classification and Principles of Operation

An RFID system consists of a radio frequency tag and a reader, as shown in Fig. 9.4. The reader is responsible for generating and transmitting the interrogation signal to the tag and then decodes the tag's backscatter signal. Due to the development of the

Fig. 9.3 Safety of consumables can be monitored using RFID technology. With sensor integration the safety of the food product can be determined by analyzing the gas content of the package which determines the safety of the product

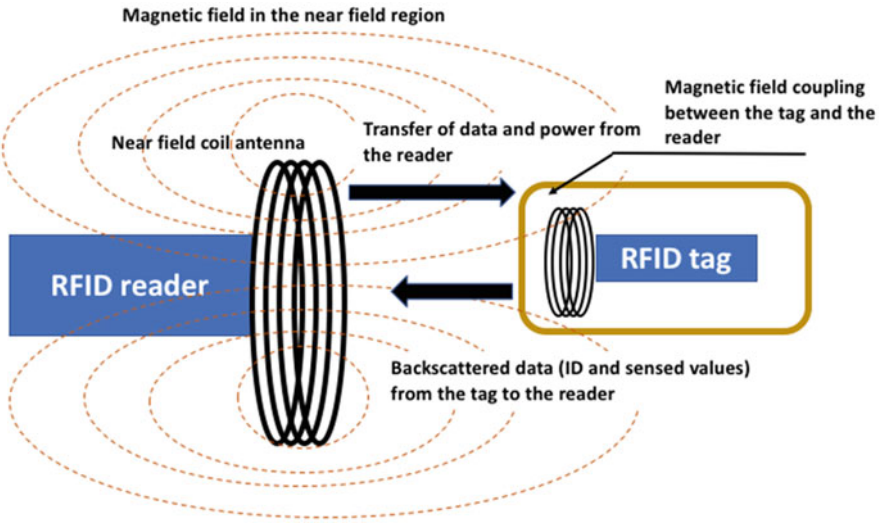

Fig. 9.4 Near-field communication and power transfer mechanisms for RFID tags operating at HF frequency

field of RFID different types of RFID systems have emerged (Landt 2005; Roberti 2005). Each system has its features where the main differences between one system and another are based on operation frequency, communication protocol, power regulations, and reading distance (EPCglobal Inc. 2015). RFID systems can be

categorized in terms of the tag as "near-field" RFID (low frequency and high frequency) based mainly on inductive coupling and "far-field" RFID (ultrahigh frequency) based on signal propagation and backscattering.

9.3.1 RFID Near-field Coupling (NFC) Communication

This category of RFID systems includes both LF and HF systems where the communication between the RFID tag and the reader is achieved by magnetic coupling (Hossein Motlagh 2012). A near-field tag consists of an antenna which is an inductive coil L, an electronic chip that performs the communication operations as well as contains the tag identifier, and finally a capacitance C which is used to adjust the resonance frequency of the tag LC circuit (Finkenzeller 2011).

In the near-field configuration, the communication is done when a reader passes a large alternating current through a reading coil, thus, resulting in an alternating magnetic field in its locality. When the near-field tag is placed in the vicinity of the generated magnetic field of the reader as shown in Fig. 9.4, an alternating voltage will appear across the inductive loop antenna of the tag (Rahul et al. 2015). This voltage is first rectified in the energy harvester unit of the tag in order to power the electronics of the tag chip. Also, the demodulation of the interrogation signal is achieved to get the interrogation information. RFID Tags based on near-field coupling send data back to the reader using load modulation (Al-Ofeishat and Al Rababah 2012). The load modulation generates a current variation proportional to the load applied to the tag's coil give rise to its own small magnetic field which will oppose the reader's field and therefore the reader coil can detect data as a small variation in current. This signal which is encoded as tiny variations in the magnetic field strength represents the tag's identification (ID) (Martins et al. 2018).

The reader can then recover this signal by monitoring the change in current through the reader coil. A variety of modulation encodings are possible depending on the number of ID bits required, the data transfer rate, and additional redundancy bits placed in the code to remove errors that results from communication channel noise. Near-field coupling is the most straightforward approach for implementing a passive RFID system. This is why it was the first adopted approach and has resulted in many subsequent standards, such as ISO 15693 and 14443, and a variety of proprietary solutions (Chen et al. 2019a).

Near-field communication has some limitations, first, the energy available for data transfer decreases significantly with the distance since the magnetic field drops off at a factor of $1/r^3$, where r is the separation of the tag and reader (Jain and Dahiya 2015). Also, as the popularity of the NFC tags increases, applications require more ID bits as well as higher data rates which can be achieved by using higher operation frequencies. This led to new passive RFID designs which are based on far-field communication in order to overcome these constraints (Allah 2011).

9.3.2 Power Consumption Classification of RFID System

One way to classify the RFID labels is based on the way of activating the tags. In this case, one can divide the RFID systems into "active" and "passive," where in the case of the active tag the chip is powered by a battery and transmits signal to the reader, whereas a passive tag is activated by harvesting power from the reader interrogating signals. In addition to the aforementioned two categories, there is also a semi-passive configuration where a passive tag can be enhanced with a battery allowing to power additional sensors or to increase the tag read range (Roh et al. 2009).

For passive RFID systems, the RFID tag has no on-board power source, however, it is activated by using the power emitted from the reader. The passive RFID tags modulate the backscattered signal to transmit the stored information back to the reader. Passive RFID tags have the advantage of being simpler in structure, lighter in weight, and less expensive while offering a virtually unlimited operational lifetime. Passive tags have the disadvantage of having short read rage compared to the active tags, also they have limited storage capacity for information and poor performance in a noisy environment (Moraru et al. 2017; Dastoori et al. 2009).

For active RFID systems, tags have their on-power source as well as internal electronic circuitry for performing various operations (Cicioni et al. 2008; Chen et al. 2019b). In this category, the on-board power source supplies the microchip operation and transmits data to the reader. The on-board electronics incorporate microprocessors, sensors, and input/output ports, etc. In an active RFID system, the tag always communicates first, followed by the reader. As the presence of a reader is unnecessary for the data transmission, an active tag can broadcast its information to surroundings even in the absence of a reader. This type of active tag, which continuously transmits data with or without the presence of a reader, is also called a transmitter. Another type of active tag enters into a sleep or low-power state in the absence of interrogation by the reader. The reader wakes up the tag from its sleep state by issuing an appropriate command. The ability to enter into a sleep state conserves battery power, and consequently, this type of tag generally has a longer battery life than an active transmitter tag. This type of active tag is called a transmitter/receiver (Yoon et al. 2009).

In between passive and active tags, there is the category of semi-passive tags. They have their own power sources; however, they do not have a radiofrequency transmitter; instead, they are based on the principle of backscattering modulation to transmit their information to readers. The advantage of semi-passive tags is that they are cost-effective compared to active tags (Feldhofer et al. 2012; Che et al. 2010).

9.4 Current Implementations of RFID Technology in Food Industry

In most food packages, the presence of undesired gases could indicate the loss of quality and shelf life of the food, as they originate from the oxidation of the content or the microbial growth (Araque et al. 2018). Microbiological contamination can

spoil the food causing swollen food packages. The package swelling is generally caused by carbon dioxide or ethanol formation, which are colorless gas. The inflation in a food package can be detected using a flexible and conformable strain sensor integrated with it. Flexibility is an important feature of smart labels. Temperature variation is another critical aspect in determining the shelf life of food products. It can provoke the growth or survival of food spoilage microorganisms and bacteria (Stannard et al. 1985). There are several other parameters, depending on the type of packaged food, that need to be evaluated, mostly electrochemical sensors serve this purpose. The colorimetric sensor, pH sensors, and variant gas sensors are some of these sensors (Park et al. 2020; Zhang et al. 2017).

The data acquisition from sensors in most of the labels is achieved using wireless technologies such as RFID, NFC, or Bluetooth. Lightweight, flexibility, security, and low-power consumption are desired properties for these wireless sensor systems. Considering that currently, the most smartphones are NFC enabled, using proximity-based technology can help the consumer to check the quality of the purchased foods easily with their phones. Developing customized applications is growing fast to respond to the need of the consumer. However, for food packaging, the accurate readings of the sensor (for instance temperature sensor) are not always required and a simple indicator such as a LED connected to the NFC tag can help the consumers to identify whether the food is still suitable for use (Escobedo et al. 2021c) The turn-on energy for the LED could be harvested through the NFC reader.

The temperature and stain are the two critical physical parameters that can indirectly help assess the food quality. For this reason, the following two sections present recent implementations of NFC sensor tags for food package monitoring with detailed demonstrations.

9.4.1 Flexible Strain Sensor with NFC Tag for Food Packaging

The strain sensor is a device used to measure the strain or mechanical deformation producing an electrical response. Various transduction mechanisms such as triboelectric, piezoelectric, optical, capacitive, and resistive have been utilized to sense strain (Nikbakhtnasrabadi et al. 2021; Escobedo et al. 2021a; Bhattacharjee et al. 2020a; Dubey et al. 2020), however, the resistive mechanism is widely used to measure the surface strain accruing at the surface of an object.

Conventional strain sensors are rigid and thus not suitable to detect small deformations in food packages (Hughes and Iida 2018). This could be addressed by exploiting flexible strain sensors. These sensors can be fabricated using techniques, for instance, printing methods (Rosati et al. 2019; Manjakkal et al. 2018; Khan et al. 2015a, b), conductive fabrics (Kim et al. 2017; Pullanchiyodan et al. 2020; Manjakkal et al. 2020a), polymer-based materials (Park et al. 2016; Soni et al. 2020; Manjakkal et al. 2020b), and even biodegradable materials (Hosseini et al. 2020a, b; Yogeswaran et al. 2020). Plastic films such as polyamide (PI), polyethylene terephthalate (PET), polyethylene naphtholate (PEN), etc. that are conformable and flexible are common materials used as substrates in these sensors.

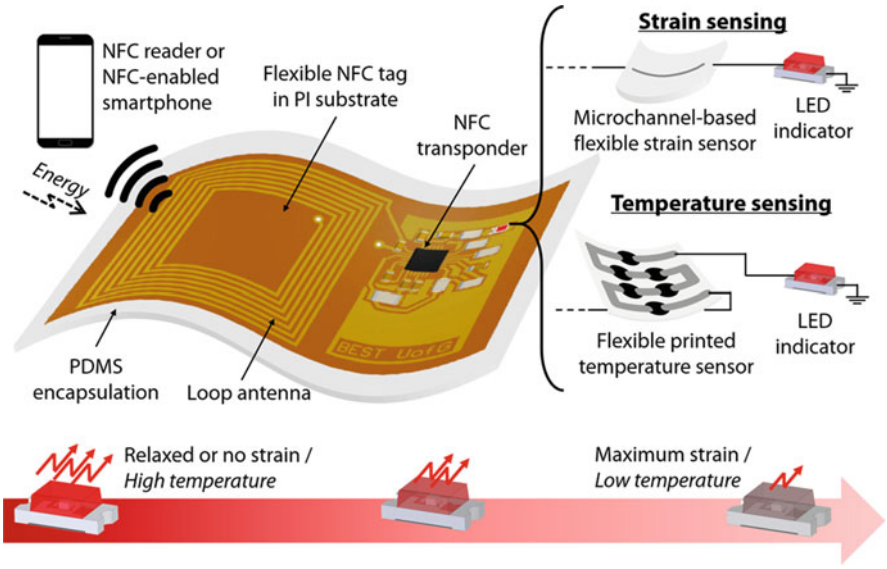

Fig. 9.5 Smart flexible NFC tag for sensing and monitoring (Escobedo et al. 2021c)

The choice of flexible substrate depends on the requirements of the application (Escobedo et al. 2021a, b; Hosseini et al. 2020b; Dahiya et al. 2020, 2019; Manjakkal et al. 2021a, b).

Figure 9.5 shows an example of smart tag with strain and temperature sensors for food package monitoring. The tag uses a microfluidic channel-based flexible strain sensor as shown in Fig. 9.6. It was developed using a thin layer of Polydimethylsiloxane (PDMS) and creating a microchannel while the PDMS film is still uncured (Bhattacharjee et al. 2020a; Escobedo et al. 2020). The channel was filled with conductive poly (3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) polymer. The sensors were characterized using a digital multimeter (Agilent 34461A) along with a customized LabVIEW program. A home-made setup was used to apply uniaxial strain to the sensors and resistance changes corresponding to the applied strain were collected using the LabVIEW program. The details of setup are explained elsewhere (Dang et al. 2018). These resistive sensors showed an average three-fold ($\Delta R/R_0$ ~1250) increase in the resistance for an applied strain of 10%. The gauge factor (defined as GF = $(\Delta R/R_0)/(\Delta L/L)$) was found to be 12,500. Since the sensor is developed to monitor any damages to food packages, the flexibility along with stability and robustness are desired features.

The custom antenna used in the smart tag uses a squared inductor layout and dedicated layout for the integrated circuit (IC) and external capacitor. The designed circuit was developed using an ultraviolet (UV) lithography technique to directly pattern copper on a polyimide (PI) sheet. The PI film had a thickness of 50 μm, a relative permittivity of $\varepsilon_r = 4.7$, and a loss tangent of tan $\delta = 0.02$. The copper film had a thickness of 35 μm and conductivity of $\sigma = 4.6 \times 10^7$ S/m. Advanced Design

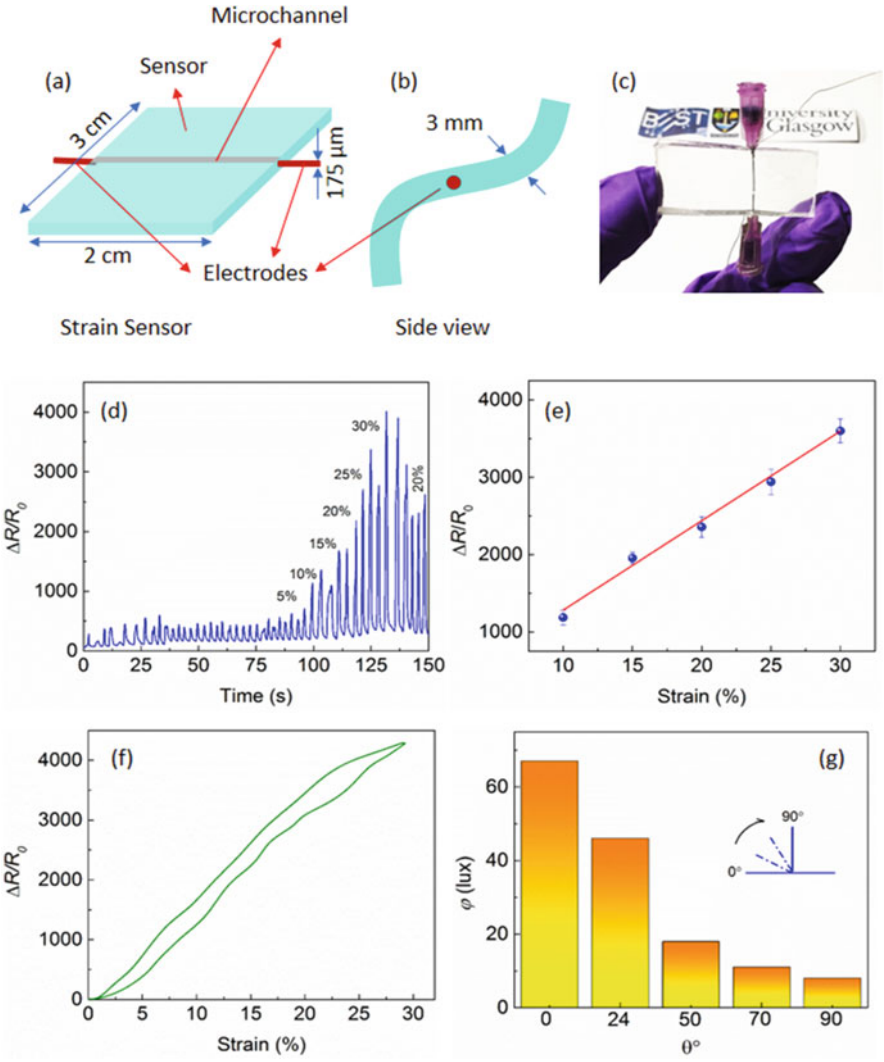

Fig. 9.6 (**a**, **b**) Schematic diagram of the fabricated strain sensor; (**c**) Optical image of the fabricated strain sensor; (**d**) Temporal response of the sensor for different amount of applied strain; (**e**) Strain sensor response with applied strain; (**f**) Hysteresis of the fabricated sensor for 30% applied strain; (**g**) The intensity of the LED (φ) with strain on the sensor due to different angle of bending (θ) (Escobedo et al. 2021c)

Simulator (ADS, Keysight Technologies, Santa Clara, CA, USA) was used to simulate and study the effect of substrate properties. The tag was finally embedded in Polydimethylsiloxane (PDMS) as protective encapsulation. PDMS (Sylgard 184-Dow Corning, U.S.) was supplied as a two-part component kit comprising of a base (part A) and a curing agent (part B). Both parts were mixed in a 10:1 ratio (A:

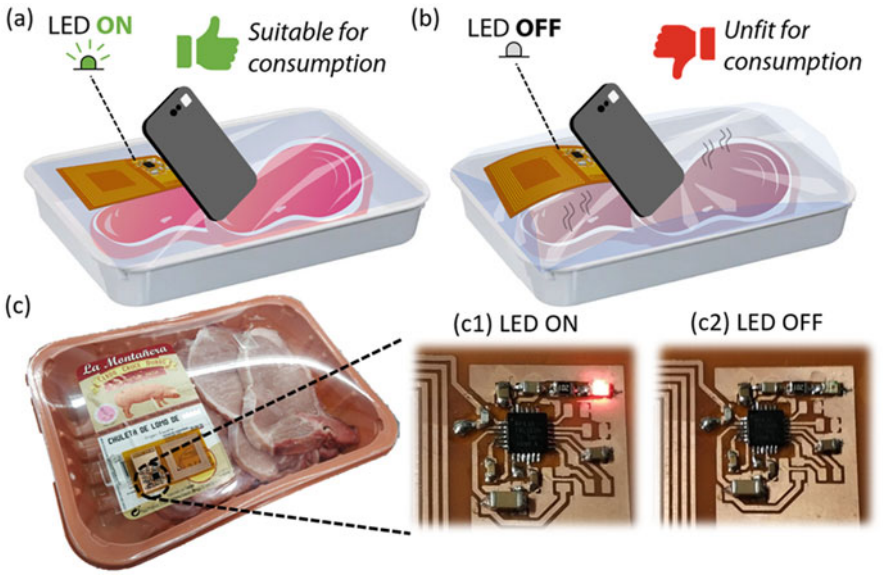

Fig. 9.7 Application showing the NFC strain sensor tag attached to a food package for meat spoilage detection. The LED will be (**a**, c1) ON if the product is suitable for consumption, or (**b**, c2) OFF if the food is unfit for consumption (Escobedo et al. 2020)

B). The mixture was then degassed in a vacuum desiccator for 15 min to have a bubble-free mixture. Following this, the mixture was poured into a rectangular mold (7×5 cm^2), forming a thin layer of PDMS. The tag was placed on the film allowing the tag to embed into the mixture. Afterward, the filled mold was cured for 2 h at a relatively low temperature of 60 °C to prevent any damage to the electronic components.

The implementation of tag, shown in Fig. 9.7, includes the LED which is used as a simple way to spot the strain variations. A light-meter smart phone application was also used to measure the illuminance of LED in terms of light intensity, which is corelated with the variation in the strain. The power to turn on the LED was supplied through the NFC reader. The tag with NFC-based strain sensor was attached to a meat package for the detection of food spoilage as illustrated in Fig. 9.7. After bringing the NFC reader close to the tag, the LED is ON with maximum brightness when the product is suitable for consumption; whereas, the LED will be OFF or in the lowest intensity if the package swells due to the growth of bacteria leading to gases in the food package. Likewise, when the LED is not fully bright this can indicate the spoilage is undergoing inside the package due to bacterial activities.

9.4.2 Flexible Temperature Sensing NFC Tag for Smart Food Packaging Applications

The second example is focused on the use of NFCs to monitor the temperature in a semi-quantitively method. Semiconductor materials-based temperature sensors are the most common type of temperature sensors (Niu and Lorenz 2017; Dahiya et al. 2014). Conductive polymers also have been studied significantly recently for temperature sensing, due to their relatively high conductivity (Escobedo et al. 2021a; Soni et al. 2020; Lu et al. 2019; Kumaresan et al. 2021; Bhattacharjee et al. 2021). Although they suffer from some limitations, for instance, low stability at high temperatures. PEDOT:PSS is a well-known organic conductive polymer which is suitable for realizing the temperature sensors on flexible substrates because it is highly flexible and has high current sensitivity over a wide range of temperatures (Vuorinen et al. 2016). An example of PEDOT:PSS based temperature sensor is shown in Fig. 9.8. The sensor was fabricated on a flexible Polyvinyl Chloride (PVC) substrate containing a PEDOT:PSS based sensing element. The flexible temperature sensor was fabricated using conductive silver paint (RS 186-3600) on a commercial PVC substrate. The PVC was cut into 2 × 2 cm pieces and two electrodes were formed using the Ag ink on the flexible PVC substrate using silver paste. The samples were then dried in a conventional oven at 50 °C for 30 min. The gap between the two electrodes was ~2 mm. Furthermore, a 10 μL of PEDOT:PSS was dispensed in the 2 mm gap using a micro-pipette. The samples were further dried at 50 °C for 1 h in the oven. Then, the samples were characterized using a controlled hot plate (Stuart CD162) to monitor change of resistance corresponding to the temperature variation. Figure 9.8 also shows the scheme of the experimental setup. The sensor was placed on the hotplate and the electrodes were connected to a digital multimeter (Agilent 34461A) connected to a custom LabVIEW application. The real-time temperature was monitored using a high-precision IR thermometer (FLUKE 62 MAX). The experiments were carried out in ambient conditions. The temperature of the hotplate was increased to the desired value and the sensor response (i.e., change in the resistance) was observed. The resistance was found to decrease with the increasing temperature. This temperature sensor showed a ~60% decrease in resistance for a temperature change from 25 to 85 °C and the sensitivity of ~1% for each 1 °C.

The PEDOT:PSS based temperature sensor can be merged with antenna so as to develop multifunctional device, i.e. antenna used as for sensing as well as data transmission. Figure 9.8 shows this scheme with custom antenna consisting of a planar squared inductor and PEDOT:PSS forming part of the antenna. Taking into account its inductance, internal capacitor value (C_{int}) of the RF430FRL152H IC and an external capacitor of $C_{\text{ext}} = 39$ pF, which was placed in parallel to C_{int} to complete the resonant circuit, the circuit resonance occurs at 13.56 MHz. Considering that resonance is obtained at $f_0 = 1/2\pi\sqrt{LC}$ and $C_{\text{int}} = 35$ pF at the frequency of interest, the inductance value required for the resonance of the tag is about 3.9 μH. However, for smaller antenna dimensions, the squared planar inductor in Fig. 9.8 has

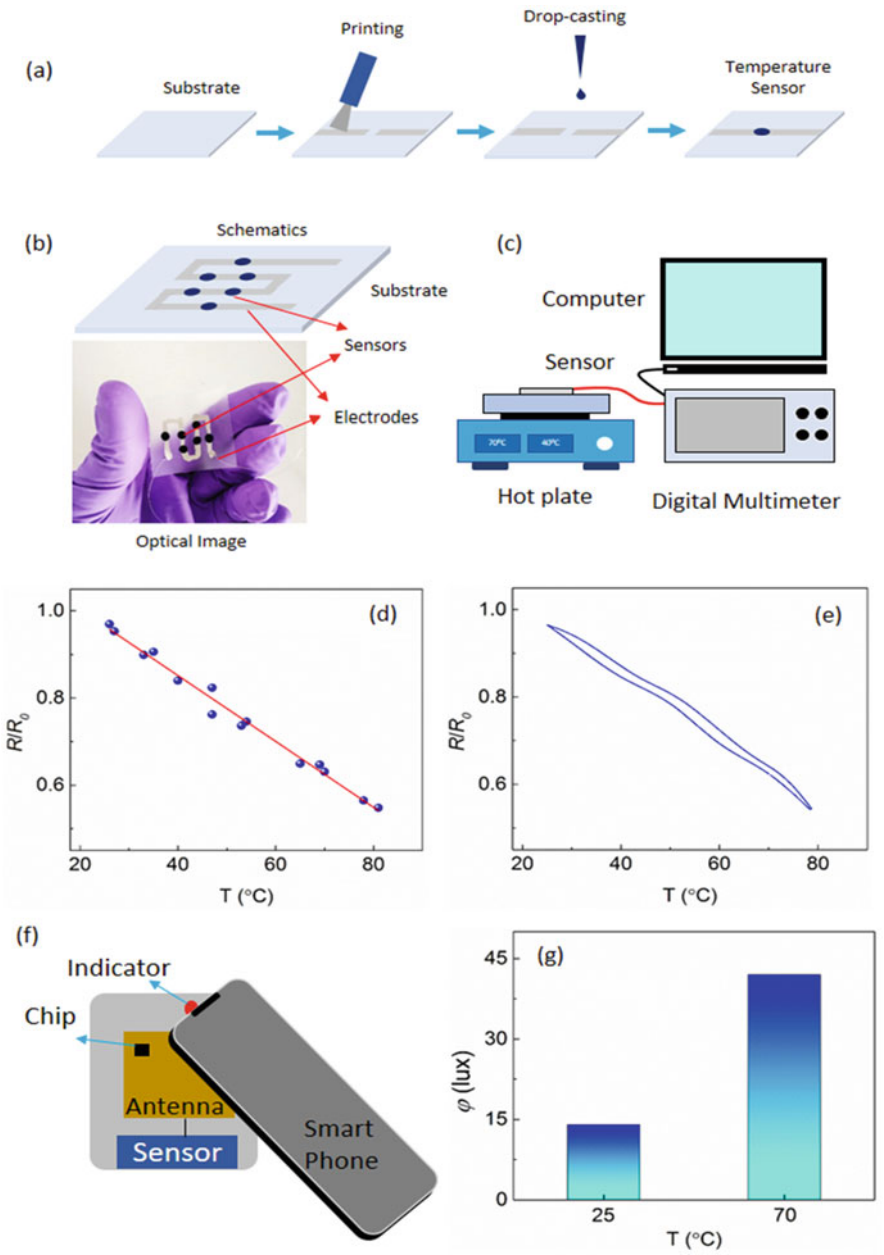

Fig. 9.8 (**a**) Schematic illustration of the fabrication steps of the flexible temperature sensor, (**b**) the change in the sensor response (R/R_0) with time (t); (**c**) the response (R/R_0) of the sensor for a temperature increase of ~5 °C, from 40 to 45 °C; (**d**) the response of sensor at different temperature values (T), (**e**) change in normalized conductance (σ/σ_0) with temperature (Bhattacharjee et al. 2020b). (Copyright 2021 IEEE)

$L_{ant} = 1.85$ μH, with an external capacitor of $C_{ext} = 39$ pF placed in parallel to C_{int} to complete the resonant circuit. A custom battery-less flexible NFC tag that can be powered from an NFC reader was also fabricated on the tag along with a visual LED indicator connected in series with the sensor.

Several aspects can affect the performance of the sensor, such as the technology within the NFC chip, the tag antenna size and design, and the reader antenna itself. In a flat position and with the Xiaomi Mi6 smartphone used in this work, a maximum vertical reading distance of 43 mm was achieved. Several curvatures were tested to study their impact on the tag´s reading distance. For that purpose, the tag was bent by fitting it to the convex surfaces of hollow cardboard cylinders with different radii (R). Selected cylinder radii were $R = 100$ mm, 50, 20, and 10 mm. As an example, Fig. 9.8e shows the case of $R = 20$ mm. The bending angle (θ) in radians can be calculated as the component´s length in the curvature direction (L) divided by the cylinder radius (R). The length was considered to be $L = 26$ mm, which is the size of the designed squared antenna. Therefore, for the selected radii the bending angles were in the range from ~15° up to ~150°. Those values are equivalent to the bending required for fitting to human limbs, with $R = 100$ mm equivalent to the approximate curvature of a thigh and $R = 20$ mm equivalent to a finger. The reading distance was reduced with the bending radius, being 40 mm for the case $R = 100$ mm down to 23 mm for $R = 10$ mm. In the intermediate cases of $R = 50$ mm and 20 mm, the measured reading distances were 35 mm and 32 mm, respectively.

Like the strain sensing arrangement explained in the previous section, the temperature sensor was also connected in series to a LED. The resistance of the fabricated temperature sensor decreased with the increasing temperature. Hence, for a higher temperature, the optical intensity of the connected LED increases. In the presence of an NFC reader, the intensity of the LED varies depending on the temperature. This sensor in the tag also semi-quantitatively shows the temperature of any package. Figure 9.8f schematically shows the sensing tag with a lux-meter mobile application, while Fig. 9.8g illustrates the intensity of the indicator at different temperatures. The intensity at 70 °C was measured to be ~42 lux whereas the intensity was ~14 lux at room temperature (~25 °C).

9.5 Conclusion

Products safety is a major concern in the food sector, especially the traceability of food products which is obligated by the law. RFID is an emerging technology solution which have the potential to improve the management of monitored information in the supply chain and security in the food sector. In the recent years, implementations for RFIDs have been explored in various sectors such as in animal identification and tracking as well as in the food chain for traceability control, etc. These implementations give confidence about the reliability of RFID based approach. By integrating various sensors with the RFID tag, more improvements can be achieved, for example, monitoring product's conditions combined with identification. In this chapter, the expansion of the use of RFID technology for the

traceability of food products has been presented. Examples of recent implementations of the RFID which takes place within the different stages of the supply chain from production have been demonstrated. The recent implementations of NFC-RFID show that an NFC-based sensor system can allow a smartphone user to detect food spoilage at an early stage. A distinct advantage of NFC over generic RFID lies in the peer-to-peer communication that can be achieved between an NFC-based system and any NFC-enabled smartphone acting as the remote reader, making this technology within the reach of any individual user. In the future, such systems could lead to automated decision-making, where the best course of action is automatically implemented with smart labels triggering an internet-connected device; for example, a robot in a supermarket.

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Advances in Biosensing Technology in the Pharmaceutical Industry

10

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Abstract

Advances in biosensing technology have led to the increasing application of these devices in drug discovery, high-throughput screening, target identification, and drug analysis. This chapter reviews recent developments in the design, fabrication, and applications of biosensing technology with optical, electrochemical, thermometric, piezoelectric, magnetic, and micromechanical detection in the pharmaceutical industry. Examples of practical biosensors for measuring neurotransmitters, antibiotics, disease biomarkers, and physiological components are provided, as well as recent trends with multiplexed detection, high-throughput screening, and drug discovery applications.

Keywords

Biosensors · Drug screening · Bioanalysis · Instrumentation · Pharmaceuticals

10.1 Introduction

The development of practical biosensors that can provide a simple cost effective modality is of great interest in pharmaceutical industry for monitoring active ingredients, high throughput screening, drug discovery and analysis. Enhanced sensing technologies are also needed to support the need for personalized monitoring of pharmaceutical doses and compounds. Biosensor devices that incorporate a biological, biologically derived, or a biomimetic material that is intimately associated with or integrated within a physicochemical transducer or transducing

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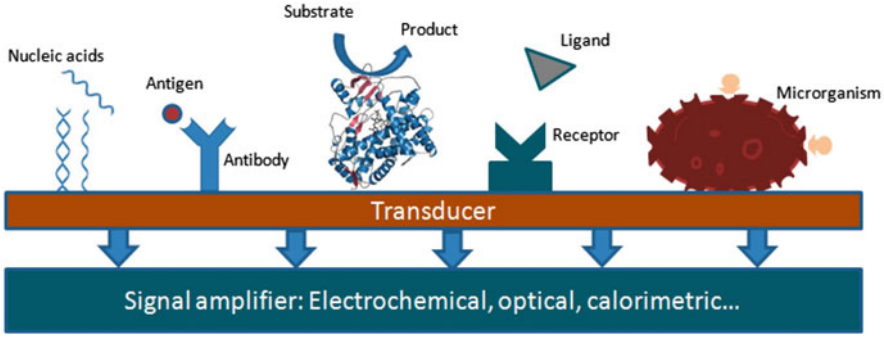

Fig. 10.1 Illustration of common types of biosensors based on their biorecognition elements (Khan and Andreescu 2020)

microsystem (Fig. 10.1) represent a fast growing emerging technology in the pharma industry (El Harrad et al. 2018). The biological element, or receptor molecules, senses the presence of target analytes and can provide users with information on the type, nature, activity, or concentration of the compounds of interest. The design of a practical biosensor typically involves attachment of the bioreceptor onto a physical transduced that is capable of quantifying the binding interaction and generating a measurable signal. Compared with traditional methods, biosensors have several distinct advantages such as high specificity, low cost, and possibilities for large-scale manufacturing of miniaturized high-throughput platforms. Biosensors such as the glucometer are well known and established in bioanalysis. Many other devices are in the development stage and can provide alternatives to commonly used laboratory-based measurement technologies in pharmaceutical industry, which are largely dominated by chromatographic methods. They can be used for real-time and online pharmaceutical process control, to monitor chemical or biochemical production processes, or for checking the quality of pharmaceutical formulations.

The past years have registered an increasing number of commercial biosensing devices and the field continues to be an active area of research in both academia and industry (Meadows 1996). Early biosensors were created to analyze critical physiological parameters such as urea, glucose, and lactate. Of these, enzyme-based biosensors are the most common, providing a rapid and convenient way to determine physiological analytes. The conversion of these biomolecules into readily detectable species, by using a biocomponent such as an enzyme, attached or in close proximity to a physical transducer, allowed the determination of compounds in complex matrices such as blood, urine, sweat, or saliva that are difficult to analyze at a low cost using traditional analytical methodologies (Thevenot et al. 2001).

Research has been done on using these biosensors in the pharmaceutical industry for example for monitoring chemical parameters in pharmaceutical processes and products. Recent work focuses on immobilized proteins, tissues, or living cells within microfabricated sensors for high- throughput drug screening and discovery. These devices contain sensing components that are sensitive to various physical or

chemical parameters, enabling multiparametric monitoring. Additionally, they can be used for point-of-care testing of biomarkers or physiological components or processes and for drug screening applications. This chapter summarizes some recent trends concerning the research, development, and application of biosensors in the pharmaceutical area. Recent innovative concepts in the development of nanosensors and microfluidics devices are discussed with examples of specific applications in bioanalysis and pharmacology.

10.2 Biosensing Design: Materials, Bio-immobilization and Integration of Sensing Components

A wide variety of biosensing devices for clinical and pharmaceutical applications have been developed that utilize a variety of biological recognition elements and physical transducers. Key design challenges necessary to be overcome in developing a practical biosensor with appropriate functionality in real environments and matrices are to (1) immobilize the biomolecule and maintain it in an active state, (2) develop sensitive platforms and transduction systems to measure molecular level responses, and (3) remove interferences to provide the required selectivity and sensitivity for practical applications. In this complex structure, the type and nature of the material used at the interface and the assembly of the individual components play a critical role in ensuring an efficient transduction of the biorecognition signal (Othman et al. 2016). The recent exponential growth in the development of nanoscale materials, 2D, 3D, mesoporous, layered or multidimensional structures enable hierarchical assembly of the sensing components for enhanced recognition providing significant improvements in the performance of biosensing devices (Khan and Andreescu 2020). Examples include structures like nanoparticles, biomimetic nanomaterials, MXenes, metal organic frameworks, and nanostructured films and materials such as graphene, e.g., graphdiyne (GDY) (Gao et al. 2019) transition metal oxides and dichalcogenides, and MXenes (Khan and Andreescu 2020) that provide a large density of surface functionalities enabling optimum configurations for biological sensing.

Modern biosensing devices integrate nanoscale or layered materials with biological components that have a molecular recognition functions toward compounds and processes. Their fabrication requires an appropriate biointerface, bio-immobilization, evaluation of biological activity, generation of response and sensing function. A summary illustrating the complexity of the sensing structure and the varying types of materials that can be used is provided in Fig. 10.2.

The activity of immobilized bioreceptors is dictated by the accessible surface area, surface functional groups, hydrophilicity, and the bio-immobilization procedure. While there is no generally applicable material or universally applicable strategy for the immobilization of all bioreceptors, a set of requirements should be considered: (1) biocompatibility, (2) surface functionality, (3) stability, (4) diffusion of target compounds to the active sites, (5) selectivity and sensitivity, (6) manufacturability and low cost. Various strategies are available to immobilize

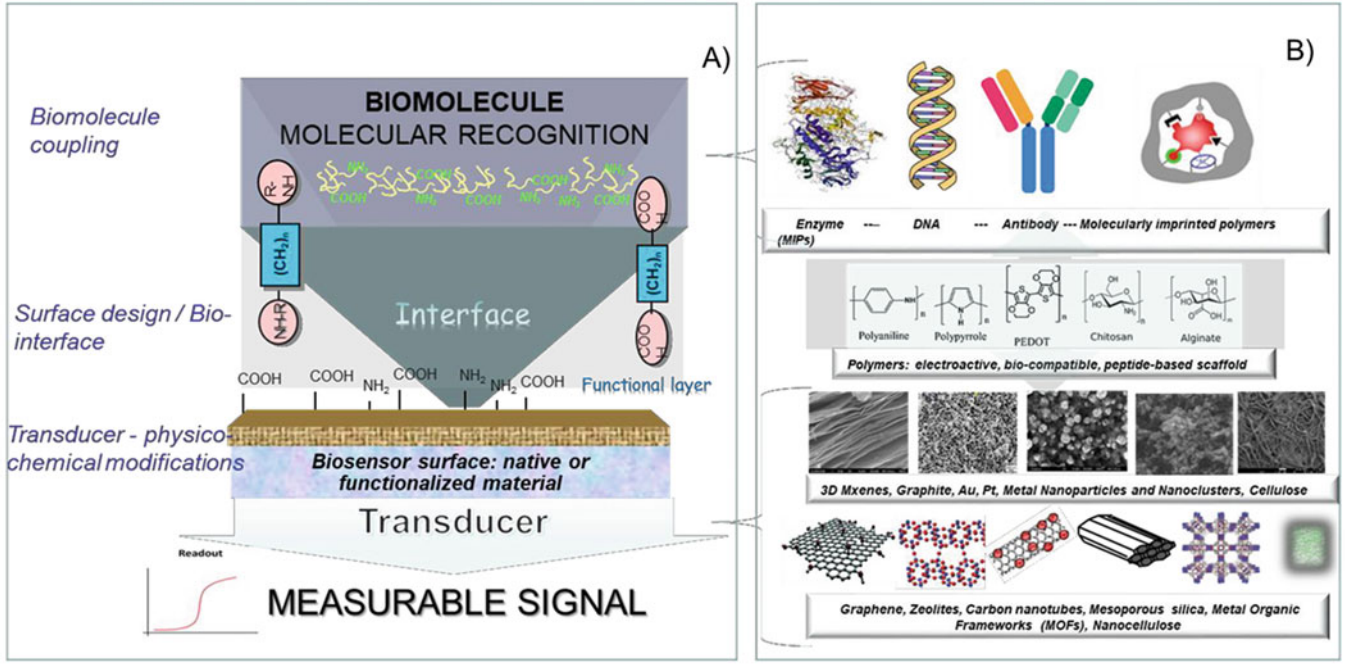

Fig. 10.2 Biosensing interface showing integration of biomolecular recognition with physical transduction (**a**) and examples of transduction materials (**b**) including a variety of polymers and inorganic structures

biomolecules onto the surface of physical transductors including physical adsorption, covalent binding, entrapment, self-assembly, and affinity methods. The selection of the method is dictated by the detection method and the material used to construct the biosensor. In a typical design, the sensing platform is a planar, possibly microfabricated surface with anchoring sites for biorecognition and a transduction system containing an easy to use readout with integrated calibration and data analytics. Some of these can be adapted as wearable or implantable configurations to allow for real-time detection and continuous drug monitoring. Examples include sensors on paper, thread, or plastic (Martinez et al. 2007; Metters et al. 2013; Ornatska et al. 2011) integrated with colorimetric (Martinez et al. 2007; Dungchai et al. 2010) or electrochemical (Reches et al. 2010; Nie et al. 2010; Dungchai et al. 2009) transduction. Essential to the development of practical biosensors is the possibilities to fabricate these platforms in large quantities and at low cost.

Recent advances in manufacturing and 3D printing methods (Finny et al. 2020) makes it possible to rapidly fabricate sensors in large quantity and produce identical devices in a short time and at a low cost. In particular paper-based analytical devices or PADs represent a powerful class of biosensing devices that provide unique opportunities for low cost detection in the pharmaceutical industry. In this format, reagents can be stored or added on hydrophobic channels and allowed to migrate to the reaction site (Martinez et al. 2007, 2008; Pelton 2009; Cate et al. 2013) while quantification can be obtained using portable technology such as digital cameras or cell phones (Zhao et al. 2008).

10.3 Biosensors in the Pharmaceutical Industry: Needs and Opportunities

Several areas in the pharmaceutical industry can benefit from the availability of low cost biosensing technologies such as: drug development, real-time testing, and bedside patients monitoring. Biosensing devices can be used for process monitoring in bioreactors, high-throughput screening and drug discovery as well as for testing and decentralized detection of drug residues (Yu et al. 2005). These can include low cost microelectronic sensors for pH, temperature, dissolved oxygen and multiparameter testing, as well as DNA, immuno and enzyme-based sensors for pharmaceutical biomarkers, drug–target measurement, and identification of active ingredients in pharmaceutical formulations.

Drugs such as anti-inflammatory and analgesics (e.g., salicylates, acetaminophen), neurotransmitters like dopamine and serotonin, and neuronal drugs like catecholamines, benzodiazepines, neuroleptics, and antidepressants, as well as cytotoxic agents, tetracycline and quinolones can be determined with low cost biosensors (Gil and de Melo 2010).

Additionally, the exponential demand for pharmacokinetic studies and analysis in the early stages of drug development have created opportunities for developing biosensors that can provide a pharmacokinetic profile under physiological conditions (Meadows 1996). Protein-based biosensors with electrochemical, optical, or surface

plasmon resonance (SPR) detection provide unique opportunities for routine analysis and diagnostics (Goncalves et al. 2014). Noninvasive sensors can be valuable tools to study the permeability and delivery of drugs and for measuring metabolites. Integrating instrumentation with remote sensing functions and wireless connectivity provides additional capabilities for home-based testing.

The sections below summarize the status of the different classes of biosensors, with optical, electrochemical, SPR, thermometric, micromechanical and detection and their applications in the pharmaceutical industry.

10.4 Examples of Biosensing Systems for the Pharmaceutical Industry

10.4.1 Optical Biosensors

Optical biosensors mainly use surface plasmon resonance (SPR) (Fig. 10.3), waveguides, and resonant mirrors to analyze biomolecular interactions (Cooper 2002). These devices take advantage of the evanescent wave phenomenon to characterize interactions between the bioreceptor that is bound to the SPR surface and the analyte. Binding of the analyte to the immobilized receptors alters the refractive index of the medium near the surface and this change is monitored in real time to quantify the affinity of the analyte toward its receptor and measure the association/dissociation kinetics. The earliest commercial optical biosensors were developed in the late 1980s, and since then their use in research and development has seen a tremendous rise in the pharmaceutical and diagnostic industries (Cooper 2002). While optical methods like absorbance and fluorescence are well-established, surface methods like SPR and surface-enhanced Raman spectroscopy (SERS) have contributed significantly to the use of biosensors in the pharmaceutical industry (Olaru et al. 2015). Optical biosensors developed for drug determination usually take

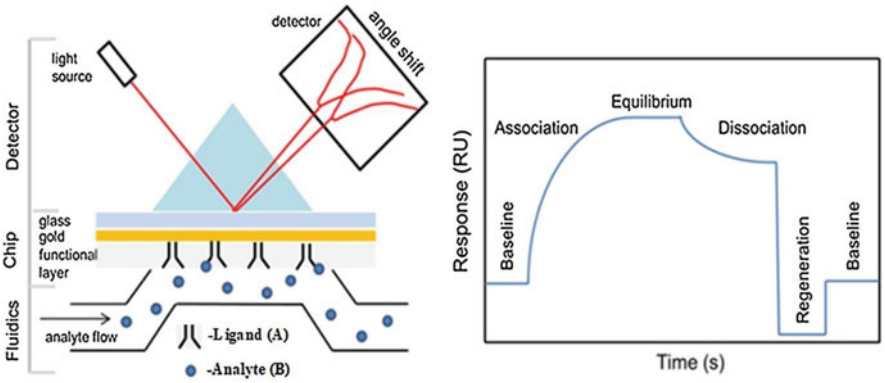

Fig. 10.3 Typical setup for an SPR biosensor (left) and a typical binding cycle (right) (with permission from (Cooper 2002))

advantage of the selectivity of the antigen–antibody and drug protein interactions. Immunosensors that use affinity-based ligand interactions are a good example of this technology that has demonstrated utility for the measurement of physiological parameters in clinical chemistry, drug complex assays and for the analysis of complex samples, as demonstrated by measurements of phenytoin in blood and cocaine metabolites in urine (Astles and Miller 1994; Nath et al. 1999). These sensors combine the high analyte selectivity with the proximity of the physical transducer enabling measurements of the local changes at the solution-transducer interfaces.

Recent designs that integrate nanomaterials have more recently enabled the fabrication of complex nanostructures that can be used to guide light thereby allowing researchers to investigate optical properties at the nm range (McDonagh et al. 2008). A few of these advances have been applied to detect pharmaceuticals (Kantiani et al. 2009; Gonzalez-Martinez et al. 2007). One such application is the study of a natural estrogen, 17β-estradiol by SPR which enabled kinetic analysis and quantitative monitoring of estrogen/ligand interactions providing opportunities to understand the mechanism of complex formation to aid in the optimization of drug candidates (Rich et al. 2002). Estrogen receptors are transcription factors that regulate genes that are involved in the development and physiological functions of the reproductive system (Cheskis et al. 1997). The SPR system was robust, involved no labels and was able to measure reaction rates and affinity binding information, detecting conditions that provide increased selectivity for screening and selection of more powerful therapeutic agents. Similar studies to understand ligand-binding effects and conformational changes can be done with DNA complexes using combined SPR and Quartz crystal microbalance (QCM). Such methodology has been applied to investigate the effect of 17β-estradiol and its binding to a specific DNA with formation of estradiol–DNA complexes (Peh et al. 2007).

10.4.2 Electrochemical Biosensors

Electrochemical biosensors have made significant progress in the detection of pharmaceutical compounds. Electrochemical detection occurs at the interface between the analyte of interest and a working electrode to which a potential is applied with respect to a reference electrode and the corresponding change in current associated with the reduction or oxidation of the target analyte is measured (Qian et al. 2021). Electrochemical sensors have advantages such as high sensitivity, selectivity, ease of use, miniaturization and portability, enabling low cost detection. Redox active compounds such as catecholamine neurotransmitters like dopamine and serotonin can be easily determined by electrochemistry. These devices enable real time *in vivo* and *in vitro* detection with high spatial resolution due to their cost effectiveness and relatively simple design (Ozel et al. 2015, 2011; Njagi et al. 2010). Non-electroactive species such as glucose, lactate or glutamate can be determined using enzyme-based electrodes that incorporate specific enzymes, i.e., glucose oxidase, lactate oxidase, or glutamate oxalises; and detection is accomplished by

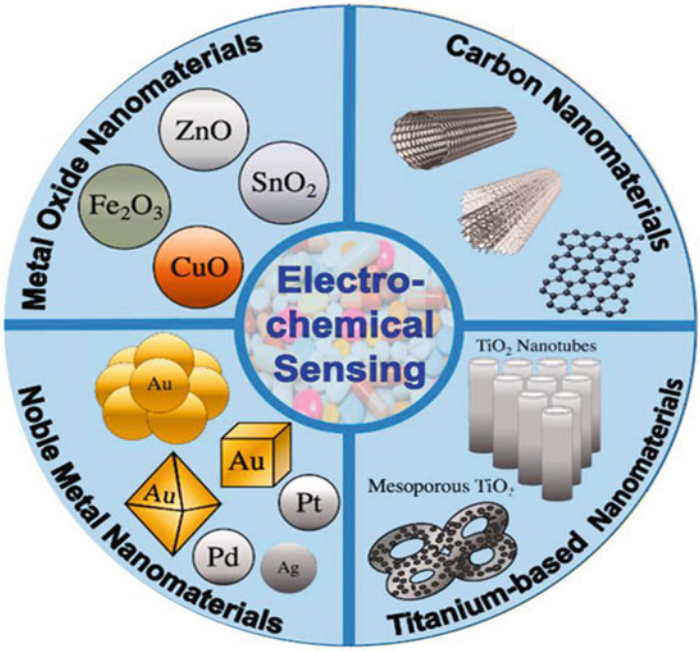

Fig. 10.4 Nanomaterials used as electrochemical catalysts and electrode materials in electrochemical biosensors for the detection of various pharmaceutical compounds (with permission from (Qian et al. 2021))

measuring the product of the enzymatic reaction, i.e., H2O2 at an electrode surface (Sardesai et al. 2015; Ozel et al. 2014). Various electrode configurations have been reported and some electrochemical sensors for the detection of glutamate and lactate are available commercially.

Recent advancements have been made with the use of nanoscale materials, which provide improved detection due to their enhanced electrical conductivity and a large surface area, resulting in improved signal, speed, selectivity, and detection capabilities. Nanomaterials such as metal nanoparticles, 2D and 3D materials have also shown the capability to enhance stability and loading of biomolecules. Figure 10.4 illustrates various nanomaterials which have been incorporated in the design of electrochemical sensors and biosensors for the detection different classes of pharmaceutical compounds (Qian et al. 2021).

An example of such a system uses carbon nanotubes (CNTs), to promote electron-transfer reactions and to increase the active surface. Taking advantage of these characteristics and using an array of CNT field-effect transistors (CNT-FETs) it was possible to detect pharmaceutical anabolic steroids such as stanozolol and methylbodenone (Martinez et al. 2010). In this study, specific antibodies for stanozolol and methylbodenone were immobilized onto CNTs and the recognition of the steroids was achieved by detecting changes in the voltage and the current.

Another class of nanoscale materials, metal nanoparticles have been extensively used as signal amplifiers and bio-immobilization matrices to provide a microenvironment for biomolecule immobilization thereby enhancing or retaining their biological activity. Gold nanoparticles also facilitate electron transfer between the immobilized molecule and the electrode surface and as a result they are widely used in electrochemical biosensors (Pingarron et al. 2008).

An electrochemical biosensor for screening estrogenic substances using bilayer-lipid membranes modified with gold nanoparticles as the matrix to immobilize estrogen receptors was developed (Xia et al. 2010). In this study, the specific binding of the estrogenic substances with the receptors caused conformational changes in the lipidic membrane and the changes caused by the binding of estrogens were monitored by impedance measurements. Since gold nanoparticles facilitated absorption of a large amount of protein receptors onto the membrane, this biosensor had sensitive limit of detection of 1 ng/L of the pharmaceutical estrogen 17β-estradiol. The sensor enabled assessment of the estrogenic activity in agreement with a cell proliferation assay. Other studies utilize self-assembled monolayers on gold electrodes to detect the antibiotic penicillin G with detection limit of 3×10^{-15} M (Thavarungkul et al. 2007). Gold nanoparticles were also used to create composites with a polymer, poly (3-methylthiophene), which was deposited on a glassy-carbon-electrode surface for the determination of dopamine, uric acid, and ascorbic acid. The detection limits in this study were 2.4×10^{-7} mol L^{-1} for dopamine and 1.7×10^{-7} mol L^{-1} for uric acid (Huang et al. 2008).

Other biosensors have been designed using aptamers or antibodies immobilized on metal nanoparticles or carbon based structures as detection platforms for pharmaceuticals. Using a supramolecular nanostructure with two anti-cocaine aptamer subunits where one was assembled on an Au support, and the second labeled with Pt, CdS, or Au nanoparticles, cocaine was detected with an LOD of 1×10^{-5} M (Golub et al. 2009) without interfering signals. Carbon nanotubes decorated with gold nanoparticles and a conductive polymer poly-[2,5-di-(2-thienyl)-1H-pyrrole-1-(p-benzoic acid)] (pDPB) have also been used as an amplifier in an electrochemical immunosensor to detect the pharmaceutical antibiotic neomycin with an LOD of 6.76 ± 0.17 ng/m (Zhu et al. 2010). An amperometric immunosensor based on cadmium sulfide nanoparticles-modified dendrimer-bonded to a gold nanoparticle conducting polymer was developed to detect chloramphenicol based on the immuno-interaction between the free and labeled chloramphenicol with the antibody (Kim et al. 2010). This biosensor had a limit of detection of 45 pg/mL with good specificity as the presence of other antibiotics did not cause any interference.

Another antibiotic, oxytetracycline, which is difficult to detect because of its similarity with other tetracycline compounds such as doxycycline or tetracycline was determined with an ssDNA aptamer immobilized on to an interdigitated array electrode chip incorporating thiol-modified surfaces. The changes in current were monitored using cyclic voltammetry and single wave voltammetry provided a quantification range of 1–100 nM oxytetracycline concentration with high specificity and the ability to differentiate from other tetracyclines (Kim et al. 2009). Similarly,

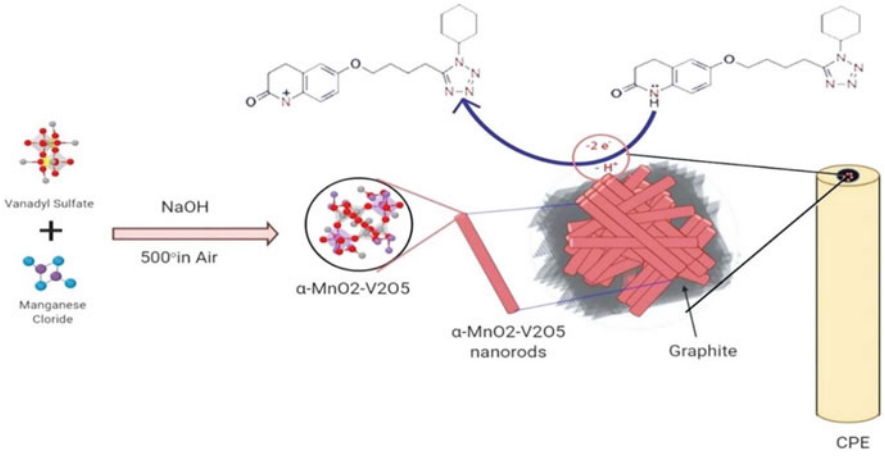

Fig. 10.5 Graphic of the preparation of the nanocomposite for constructing an electrochemical sensor for the detection of Cilostazol, and the oxidation mechanism (with permission from (Saleh et al. 2021))

aminoglycoside antibiotics in low micromolar ranges were detected in blood serum using an RNA-aptamer-based biosensor (Rowe et al. 2010). In this study it was found that the use of ultrafiltration through a low-molecular-weight-column removes the relevant nucleases from serum, enhancing detection of this aminoglycoside at relevant concentrations using the biosensor. Label-free detection of the antibiotic ciprofloxacin in pharmaceutical processes at very low concentrations of 3 pmol/L was achieved using an impedimetric biosensor based on electrogenerated poly (pyrrole-N-hydroxysuccinimide) with a layer of anticiprofloxacin antibody for immunoreaction (Giroud et al. 2009). A label-free impedimetric flow-injection immunosensor was developed to measure penicillin G in milk with a wide linear range between 1.0×10^{-13} and 1.0×10^{-8} M with a detection limit of 3.0×10^{-15} M by monitoring impedance at a single frequency (Thavarungkul et al. 2007).

Carbon paste electrodes modified with nanomaterials have also been used as detection platforms for pharmaceutical compounds. Using lanthanum-hydroxide nanowires in a carbon powder, the pharmaceutical non-steroidal anti-inflammatory drug mefenamic acid was determined by linear sweep voltammetry based on the electrocatalytic response registered toward the oxidation of mefenamic acid via one-electrode and one-proton transfer with a detection limit of 6.0×10^{-12} M (Liu and Song 2006). The low detection limit was attributed to the increased surface area of the electrode caused by the doping of the carbon powder with nanowires. An electrochemical biosensor based on MnO2-V2O5 nanorods was developed for the detection of the antiplatelet prodrug Cilostazol in pharmaceutical formulations (Fig. 10.5). This sensor showed a linear range of 0.11–100.00 μM at pH 7.0 and a limit of detection of 2.48×10^{-8} M (Saleh et al. 2021).

10.4.3 Thermometric Biosensors

Thermometric biosensors, also called calorimetric biosensors measure the absorption or evolution of heat in biological reactions (Ramanathan and Danielsson 2001). Thermometric biosensors are most popular for enzymes which are combined with temperature sensors that measure the heat of the reaction released when the enzyme interacts with its substrate, calibrated against the concentration of the substrate. The use of calorimetry as a transduction mechanism in enzymatic biosensors have been reported for the quantification of various analytes such as to detect binding of retinoic acid to a HRP conjugate, a mechanism that was used for thermometric detection of retinol (Ramanathan et al. 2000). A label-free, high-throughput microplate calorimetric biosensor has been reported for the quantification of ascorbic acid in food and pharmaceutical products (Vermeir et al. 2007). In this biosensor the heat generated from the exothermic reaction between ascorbic acid and ascorbate oxidase was differentially monitored between two neighboring wells of a custom made wafer equipped with a sample and reference well (Fig. 10.6). The biosensor had an operational concentration range from 2.4 to 350 mM of ascorbic acid with a limit of detection of 0.8 mM. Validation experiments performed on fruit juice samples, food supplements, and a pharmaceutical pain reliever supplemented revealed that the method correlated well with HPLC reference measurements. One of the main advantages of the calorimetric biosensor is the low cost of analysis due to the low amounts of enzyme and reagents needed. It is also possible to integrate such a biosensor in fully automated laboratory analysis systems for high-throughput screening and analysis (Vermeir et al. 2007).

Other works report a calorimetric biosensor for label-free detection of cancer cells using a microcalorimeter based on MEMS (Micro Electro Mechanical Systems)-technology by monitoring the heat generated in the biochemical reaction between antibody and the HER2/neu receptor in cancerous cells (Park et al. 2007). Other calorimetric biosensors show potential for point-of-care metabolic disease management (Kazura et al. 2017). In this device, the sample is drawn to a nanocalorimeter through a capillary channel, making this system suitable for monitoring blood through a finger prick. The device performance was demonstrated in a model assay for hydrogen peroxide quantification using catalase. The device was able to determine 50 μM H2O2 using less than 1 μL of sample. This biosensor can be multiplexed and adapted to many metabolic diseases utilizing different immobilized

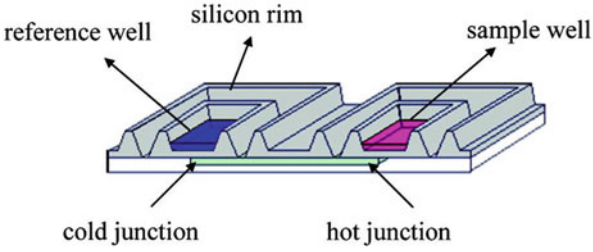

Fig. 10.6 Schematic of the microplate differential calorimeter. A complete microplate consists of 48 such combinations of reference wells and sample wells (reproduced with permission from (Vermeir et al. 2007))

enzymes. A calorimetric biosensing system with high-throughput sample analysis that can enable remote calorimetric detection of urea via a flow-injection analysis technique has been reported. The system was constructed from a thin micromachined quartz crystal resonator (QCR) as a temperature sensor placed in the proximity to a fluidic chamber containing an immobilized enzyme. The detection performance of the system was concentration dependent in the 1–50 mM range with a resolution of 1 mM urea (Gaddes et al. 2015). Such miniaturized systems can be used to detect other biomarkers such as glucose, creatinine, cholesterol, urea, and lactate, continuously over extended periods through a reaction column packed with immobilized enzymes.

10.4.4 Piezoelectric Biosensors

Piezoelectric biosensors are devices that use the principle of affinity interaction on a piezoelectric platform or piezoelectric crystal that senses oscillational change due to a mass bound on the its surface (Pohanka 2018). Piezoelectric sensors are attractive for the detection of a wide range of pharmaceutical compounds using immunosensing approaches. One such sensor was developed for the detection of bisphenol A (BPA) using an immunosensing surface consisting of nanoparticles having a diameter of 200 nm coupled to anti-BPA antibodies, to increase the mass change on the surface upon BPA binding and therefore increase the frequency shift detected (Park et al. 2006). In this competitive immunoassay BPA competes with a BPA-horseradish peroxidase conjugate for binding to anti-BPA antibodies, coupled to a piezoelectric (PZ) immunosensor. A limit of detection of 0.1 ng mL^{-1} was achieved; however, when nanoparticles coated with anti-BPA antibodies were used, the sensitivity of the assay was improved by almost eight times reaching BPA concentrations below 10 ng mL^{-1} (Park et al. 2006). Another biosensor for sensing estrogenic substances using a quartz crystal microbalance has also been developed which uses a genetically engineered construct of the hormone-binding domain of the α-estrogen receptor (Fig. 10.7) (Carmon et al. 2005). Here the receptor was immobilized onto a piezoelectric quartz crystal through a single exposed cysteine thereby enabling formation of a uniform orientation on the surface of the crystal. Similar designs have been reported for the measurement of glucose using an electrochemical gold-based sensor (Andreescu and Luck 2008). Similar label-free biosensors can be designed for measuring a wide range of ligands that can bind to the estrogen receptor and other pharmaceutical markers.

Other piezoelectric sensors for the determination of pharmaceuticals make use of molecularly imprinted polymers (MIP) deposited onto a piezoelectric crystal with engineered cages matching the shape and size for the target compounds. A MIP-based biomimetic acoustic wave piezoelectric sensor for the determination of paracetamol, with high selectivity and sensitivity was fabricated (Tan et al. 2001a). The sensor demonstrated a detection limit of 5.0×10^{-3} μM and was able to determine paracetamol in samples like urine and serum. Similar systems for the determination of phenacetin were reported with a detection limit was 5.0×10^{-9} M

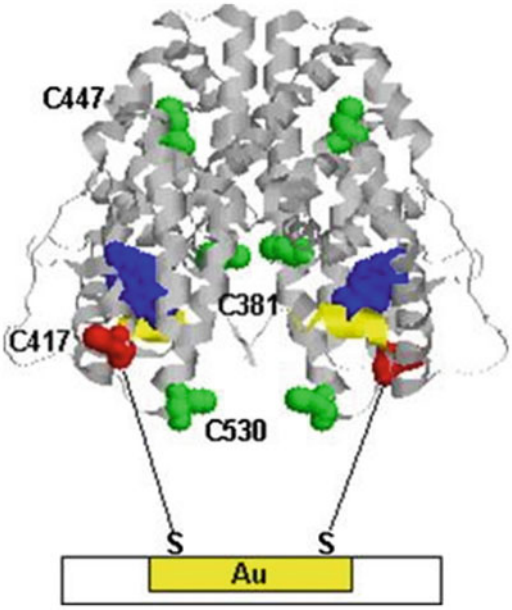

Fig. 10.7 Illustration of human beta defensin (HBD) on the gold surface of the piezoelectric crystal. The cysteine residues, estradiol in blue, helix 12 in yellow, and the placement of the gold sulfur bonds to each of the dimer lobes are shown in space-filling forms (reproduced with permission from (Carmon et al. 2005))

(Tan et al. 2001b) and methamphetamine with a detection limit of 1 μg mL^{-1} (Guerra et al. 2009). Piezoelectric affinity sensors for cocaine and cholinesterase inhibitors have also been reported, based on the formation of affinity complexes between a cocaine derivative and an anti-cocaine antibody, or a cholinesterase enzyme. A limit of detection below 100 pmol l^{-1} for cocaine and a total analysis time of 15 min were reported (Halamek et al. 2005).

10.4.5 Magnetic-Based Biosensing Detection

Biosensing devices that incorporate magnetic particles to improve washing and separation steps have shown enhanced performance by minimizing matrix effect (Sanvicens et al. 2011; Khan et al. 2019). The use of magnetic particles enables analysis of samples without involving extensive pretreatment steps such enrichment or purification. These include particles with sizes ranging from 10 to 100 nm consisting of magnetic elements such as iron, cobalt, manganese, chromium, gadolinium, nickel, and their alloys (Khan et al. 2019). The functionalization of their surface with bioreceptors for separation, purification, and detection is known to enhance the analytical applications for detection of a broad range of analytes in food and pharmaceutical industry. Most common magnetic biosensors combine magnetic bead separation, immunological assays, and electrochemical transducers. An example is presented in Fig. 10.8 illustrating the detection of sulfonamide antibiotics (Zacco et al. 2007).

The immunological reaction to detect the sulfonamide-based antibiotics was performed using a direct competitive assay that uses a horseradish peroxidase tracer, which acts as the enzymatic label. Successful detection was achieved for the detection of sulfamethazine directly in a diluted, raw, full-cream sample with detectability values below the maximum legal residue limits established by the European Union for those types of samples (limit of detection of 0.36 μg/L). Another similar study using an electrochemical magneto sensor to detect folic acid in milk was reported with a detection limit of μg l^{-1} (13.1 nmol l^{-1}, 5.8 μg l^{-1}) in skimmed milk (Lermo et al. 2009).

Electrochemical detection with magnetic particle with immobilized enzymes has also been reported. An amperometric biosensor that uses horseradish peroxidase enabled the study of clozapine, dibenzodiazepine drug in the micromolar concentration (5–25 μM) range (Yu et al. 2006). Detection was achieved by the use of a magnetized solid paraffin carbon paste electrode that attracts magnetic microparticle. An electrochemical method based on modified magnetic particles for the determination of ethinylestradiol in water was developed where the particles were used to enable the separation and preconcentration via antigen–antibody binding (Martinez et al. 2012). Detection was accomplished by using anti-ethinylestradiol antibodies immobilized onto magnetic microspheres. A limit of detection of 0.09 ng/L was reported (Martinez et al. 2012). A method for the determination of c-reactive protein (CRP), a protein that is routinely monitored in blood as a marker for inflammatory processes was described and tested in human blood, serum, saliva, and urine. Detection is based on two different anti-CRP antibodies (monoclonal, IgG) for trapping CRP; a linear detection range of from 25 ng/ml to 2.5 μg/ml with a detection limit between 10.0 and 25.0 ng CRP/ml was reported, comparable to typical hsCRP-ELISA-assays (Meyer et al. 2007).

10.4.6 Micromechanical Sensing

Electromechanical sensors using sensitive cantilevers enable label-free detection of biological entities and measurements of drug–target interactions inexpensively. Quantification and characterization of protein–protein interactions are important in the pharmaceutical industry to identify potential drugs and being able to measure the affinity of drug candidates to target. These devices can be used in a broad range of applications in the pharmaceutical industry in genomics, proteomics, and drug discovery (Xu and Mutharasan 2009; Johnson and Mutharasan 2012). A general design of a resonant-mode cantilever for label-free detection of biologics containing a 1 × 3 mm and a piezoelectric layer for actuation and sensing resonance is shown in Fig. 10.9 (Johnson and Mutharasan 2012). Cantilever-on-chip containing hundreds of cantilevers are relatively easy to fabricate and can be modified with oligonucleotides, proteins, biomimetic materials or MIPs for selective binding and study of drug candidates. A MIP-based micromechanical cantilever sensor system capable of detecting ciprofloxacin, a quinolone antibiotic, was reported with high specificity and fast response with a limit of detection of 0.8 μM (Okan et al. 2017).

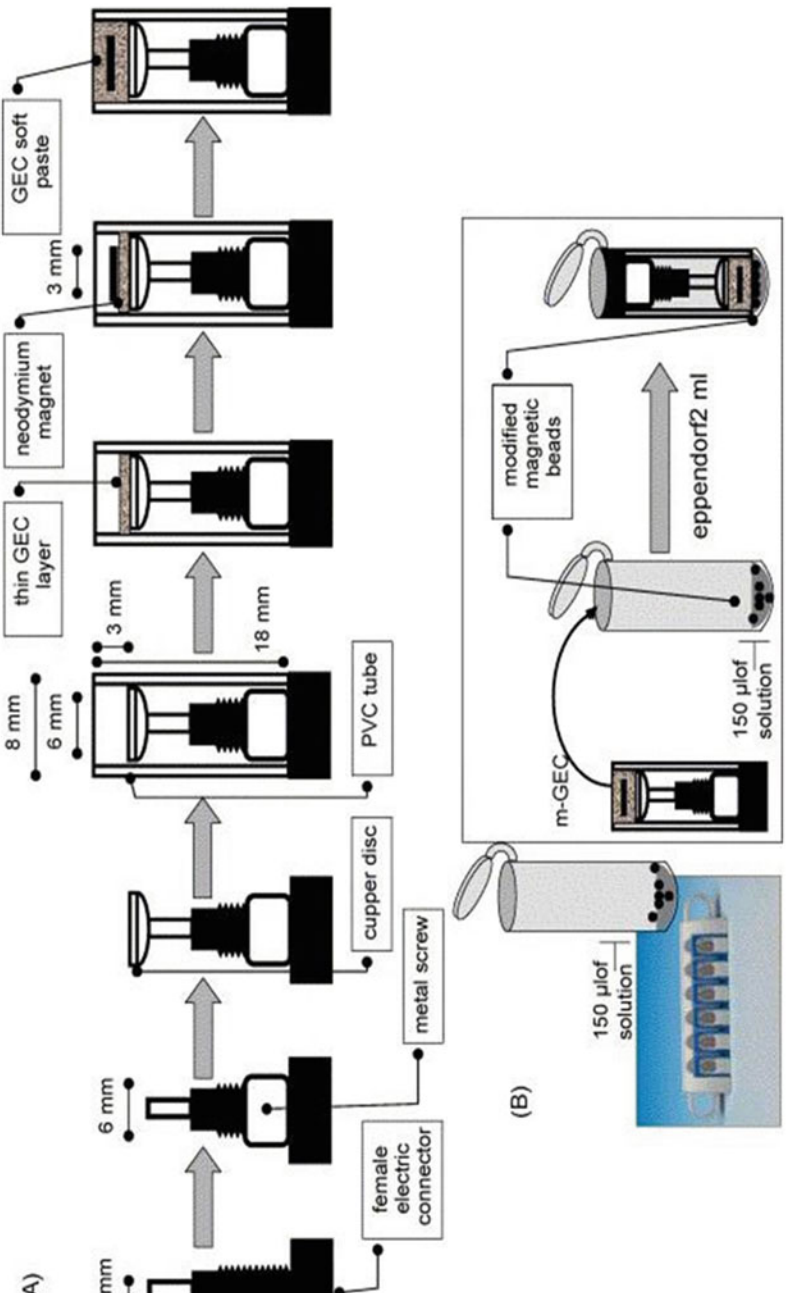

Fig. 10.8 (**a**) Illustration of the magnetic sensor (magneto graphite–epoxy composite) construction. (**b**) Representation of magnetic sensor (m-GEC) attracting the previously modified magnetic beads (with permission from (Zacco et al. 2007))

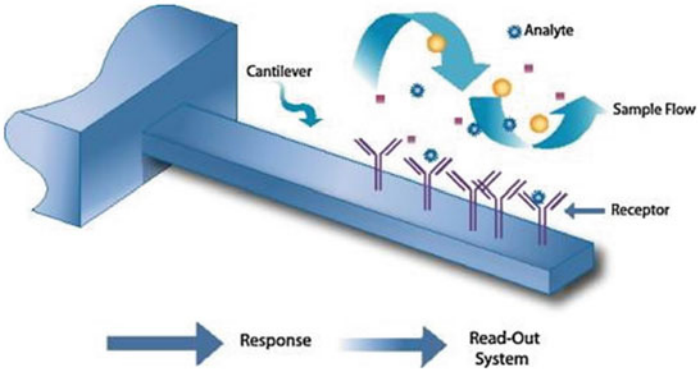

Fig. 10.9 Working principle of a dynamic-mode cantilever sensor (reproduced with permission from (Johnson and Mutharasan 2012)

Cantilever biosensors have the capability to measure DNA–DNA hybridization as well as identify single base mismatch of short oligonucleotides at femtomolar to nanomolar levels (Su et al. 2003; Mertens et al. 2008). A microcantilever resonance-based sensor with nanoparticle probes was able to detect target DNA detection limit of 0.05 nM (Su et al. 2003). A piezoelectric-excited millimeter-sized cantilever (PEMC) sensor enabled detection of DNA hybridization at 1 fM in a human serum and in the presence of noncomplementary strands (Rijal and Mutharasan 2007). These results suggest that ssDNA can be detected at 2 amol without involving a sample preparation step or labeled reagents. Binding forces and adhesion between proteins that have traditionally been investigated using atomic force microscopy (AFM) can also be measured by cantilever biosensors. Such example includes the study of binding interactions such as biotin–streptavidin (Shu et al. 2007; Shekhawat et al. 2006). Similar interactions such as liposome-protein, antibody-antigen reactions or quantification of proteins or liposomes were also successfully characterized using cantilever biosensors (Campbell and Mutharasan 2005; Kooser et al. 2003; Hyun et al. 2006). A label-free protein assay based on a nanomechanical array with antibody-immobilized cantilever was developed for the detection of myoglobin and creatine kinase with sensitivity limits below 20 μg ml^{-1} myoglobin (Arntz et al. 2003). Such sensors can be used for simultaneous detection of a range of biomarkers in a single step at a significantly reduced analysis time.

Cantilever biosensors have successfully demonstrated their potential for measuring DNA hybridization, protein–protein interaction, and antibody–antigen interaction in complex matrices. Their ability to measure biomolecular interactions and monitor conformation changes allows it to be used for affinity-based measurements that are common in the pharmaceutical industry especially in drug discovery. Further, cantilever arrays enable rapid detection of multiple analytes on the same platform. Scalability of these devices further makes them attractive candidates in high-throughput pharmaceutical analysis.

10.5 Conclusions

Traditional analytical methods for the analysis of pharmaceuticals involve time-consuming sample processing and preparatory steps, such as pretreatment, optimization steps or extraction prior to analysis. Owning to their low cost, high sensitivity, and selectivity and possibilities for miniaturization, biosensors have the potential to overcome these challenges and be used as cost-effective devices that can provide complementary data or be used as a screening tool as an alternative to more traditional analytical instrumentation. Their development, which has seen tremendous growth in recent years, opens up new and exciting opportunities for improved analysis in the pharmaceutical industry. This chapter summarized recent efforts dedicated to the development of biosensors of potential use in the pharmaceutical industry, with focus on optical, electrochemical, piezoelectric and micromechanical sensors. It was shown that biosensing devices provide unique opportunities for the analysis of pharmaceutical compounds such as antibiotics or estrogenic molecules, for studying protein–protein, to identify potential drugs and quantify the affinity of drug candidates to their target. In light of recent developments, fabrication of nanoscale and microfabricated devices will be of further interest for the detection of therapeutic drugs and for the investigation of physiological processes with high spatial and temporal resolution. In the future, it is expected that the integration of biosensing technologies in the pharmaceutical industry will improve analysis and process control and provide enhanced opportunities for personalized monitoring and bed-site testing.

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Sensor Systems for Drug Analysis Their Interferences

11

Behzad Rezaei and Sudabe Mandani

Abstract

This chapter introduces sensors that can determine the drug amount in complex environments, including biological fluids such as sweat, tears, urine, plasma, etc. Determining the drug amount in the body is essential to understanding the function of the drug and its proper use. Today, analytical determination systems for a variety of drugs have undergone significant advances that improve sensitivity and selectivity. Among the analytical sensors, there are optical and electrochemical biosensors that have been used to measure clinically preferred drug molecules such as anticonvulsants, anticancer drugs, antibiotics, heart failure, cocaine, heroin, and (meth) amphetamine, etc. The development of digital healthcare devices and wearable electronic sensors over the past few years has revolutionized drug determination systems. Due to the importance of drug measurement, in the following, various sensors and the developments that have taken place in this field are mentioned.

Keywords

Drug determination · Sensors · Biosensors · Wearable drug sensors · False-positive and false-negative interferences

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11.1 Introduction

The detection of tiny amounts of drugs and metabolites in live organs has been verified of immense value due to ensure safer and more efficient therapy. According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), the use of prescription drugs in biological fluids has recently increased, chiefly due to sanitation and health system-related problems to the patients and medical staff (Spengler 2018). Specific adviser reports for drug studying due to drug determination clinical matter have included by FAO and WHO, which is offered as individualizing a drug's dose by keeping a drug's amount in the biological fluids within a drug level to operate as an instruction for personnel healthcare. Drug studying has been introduced since the beginning of the 1970s for the determination of pharmacological behavior and keeping a drug's plasma amount in the stated therapeutic field (W.H. Organization 1972). A certain action of a drug and the effects of organisms on uptake, access, toxicology, release, metabolism, pharmacodynamics, and pharmacokinetics and the effect of drugs on organisms can be estimated by studying their binding to receptors and chemical interactions (pharmacodynamics). Drug determination is an essential tool for studying drugs with high toxicity and a narrow therapeutic window. For this, various conditions have been created that limit the drug to this type of substance. Figure 11.1

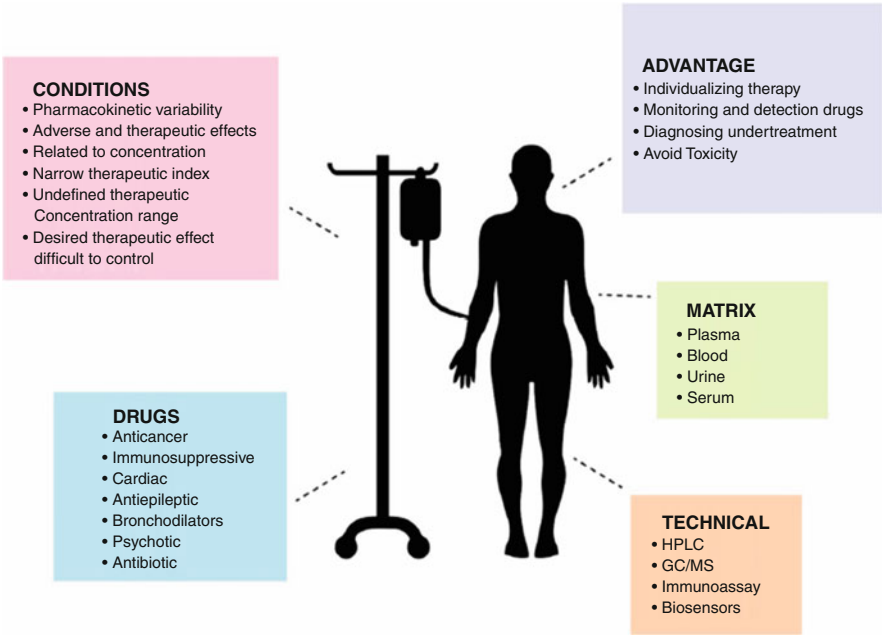

Fig. 11.1 The function of the drug in the body, proper use, and reporting methods for determining the amount of drug. These materials are measured in a variety of ways, including HPLC, GC/MS, immunoassays, and biosensors by various biological matrixes (Garzón et al. 2019)

demonstrates the function of the drug in the body and its proper use and determination methods (Garzón et al. 2019).

The drug monitoring process is based on several disciplines, including pharmacokinetics, pharmacodynamics, and chemical analysis (Jolley et al. 1981; Jolley 1981). Drug determination is a basic procedure when administering drugs with a limited dosage and high toxicity, which dangerous for the patient's life. This monitoring, carry out in various biological fluids, including sweat, blood, serum, tear, plasma, urine, etc. (Mercolini et al. 2007). The function of specialized methodologies for drug determination will permit the pharmacodynamics and pharmacokinetic analysis of drugs and help to set the drug concentration before or after their administration period.

The discovery, synthesis, trafficking, and use of illicit drugs are constantly growing, with serious consequences for the ecosystem, society, and human health. In general, drug abuse is a global challenge that requires and it has an interdisciplinary process. Thus, an urgent demand for the fast, sensitive, portable, and simple operation has increased for a wide range of drugs in a variety of matrices, from police and criminal samples, clinical fluids, and hair to wastewater. Analytical sensors are offered as a proper alternative to complex methods including chromatography and spectroscopy. Today, analytical determination systems for a variety of drugs have undergone significant advances that help improve sensitivity and selectivity through the advanced transducer and signal amplifiers. Among the analytical sensors, there are optical and electrochemical biosensors that have been used to measure clinically preferred drug molecules such as anticonvulsants, anticancer drugs, antibiotics, heart failure, cocaine, heroin, and (meth) amphetamine, etc. (Garzón et al. 2019; Gil and Melo 2010).

11.2 Sensor Principles

A chemical sensor is a system that converts chemical data from the amount of the desired analyte to total mixture analysis to a useful analytical response. As mentioned above, chemical data may be derived from a sample chemical reaction or the physical properties of the system under investigation (Mercolini et al. 2007). Sensor systems include some main components: (1) the transducer with an electronic readout, (2) the data processing agent, (3) the sample compartment, (4) the layer on the transducer that is responsible for selectivity (Fig. 11.2). Sensors are complementary to the classical analytical tools. They are mostly used in process control or in the monitoring of operations where the target value changes relatively quickly. The quality and specifications of the sensor depend directly on the detection system, the selected layer, and the fluids. Today, a wide range of electronic, electrochemical, and optical detection principles have been developed and fully discussed (Gil and Melo 2010).

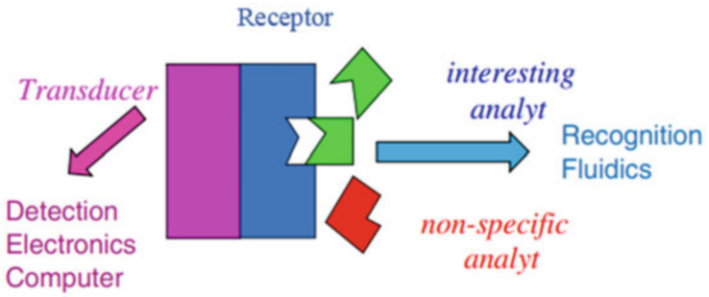

Fig. 11.2 Sensor principle: the sensor system originally includes three main components: a recognition factor, transducer, and control and processing system (Gauglitz 2018)

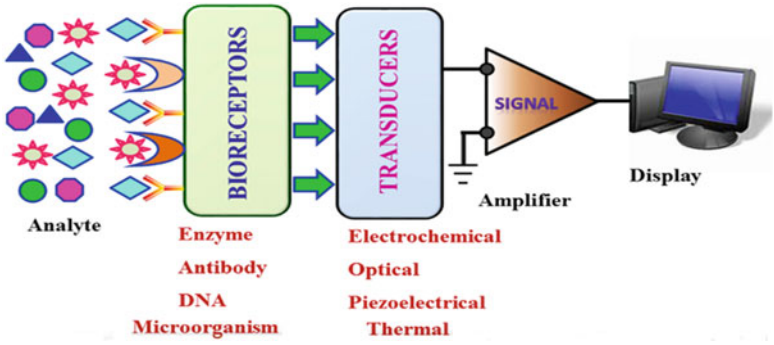

Fig. 11.3 The functioning principle of the biosensor

11.2.1 Biosensors

A biosensor is an analytical instrument that interacts selectively with a target species in a suitable sample and converts its value as a measurable electrical response, through the appropriate combination of biological identification agents (enzymes, antibodies, cells, DNA, microorganisms, etc.) (Fig. 11.3) (Gil and Melo 2010) with an adequate transducer. As a result of recent technological and scientific advances, such instruments are likely to play an increasingly essential role in generating analytical signals in all fields of human effort, inclusive environment, food industry, medicine, and military. Particularly, biosensors will offer the basis of cheap and simple instruments to obtain chemical results, bringing the sophisticated analytical ability to the non-expert and general public alike. The market possibilities for the rapid operation of modern progress in this section are notable. Biosensor research is also likely to have a significant effect on the development of novel electronic devices (Gauglitz 2018). The most commonly used biosensors are optical (comprise fiber optic and surface-plasmon resonance systems) and electrochemical (comprise amperometric, conductimetric, impedance, and potentiometric biosensors). One of the most successful applications of biosensors in medical examinations is the

electrochemical measurement of glucose in the blood by capturing GOx within polyethylene on the metal electrode surface and determines the quantity of oxygen reacted with the enzyme. These biosensors are now commercialized in various forms accessible mainly in single-use configurations for self-determining of glucose in the blood (Girardin et al. 2009). However, there is a growing tendency to develop new biosensors not many have achieved the degree of diagnosis of the glucose sensor. Biosensors focused on their usage in the medical field and expressed that the slow, restricted technology transfer could be related to cost considerations and several key technical limitations (i.e., stability and validity). The weak biocompatibility between the attainable materials and the complex nature of the medical samples could lead to unfavorable events, which could affect the validity, sensitivity, and stability of the sensor. Notable upfront investment in research and development is a prerequisite for the successful commercialization of biosensors (Baldini 2005). A biochemical sensor is a completely interdisciplinary device, and the generation of a novel sensor requires a group of researchers from diverse fields (e.g., physics, chemistry, engineering, optoelectronics, medicine, and biochemistry).

11.3 Drug Determination

This chapter focused on the monitoring methods and possible interferences of drug determination in the biological fluids, which is corresponded to increased effect and/or toxicity in the alive organs, pharmacological effects of the desired drug are not determined simply, and drug amount relevant harmful effects (Schwickart et al. 2014). Drug amount at the active site cannot be determined exactly, but harmful effects can be better related to plasma analyzed than dosing schedules (De Vries et al. 1994). Various methods have been necessarily used in drug determination due to the property of the investigated drugs to be determined in sweat, human blood, plasma, tear, saliva, serum, and urine. Different of the most commonly used methods have been gas chromatography-mass spectrometry (GC-MS/LC-MS-MS), high-performance liquid chromatography (HPLC), and diverse immunoassays (Say 2006; Hughes et al. 2016). The chromatographic methods are characterized by being the most complex, expensive, and specific standard techniques; however, these devices require expert personnel, involve long sample pre-processing step, need costly reagents any time the sample is analyzed in the device, and require a specialized laboratory for processing them, meaning that monitoring cannot be done in situ for patients (Taylor 2004). Recently, due to the importance of simple, rapid, and on-time monitoring of drugs in biological fluids, various analytical sensors and biosensors have replaced the mentioned complex methods for measuring drugs. Hence In this section, the most widely used sensors in drug measurement will be briefly discussed.

11.3.1 Sensor for Drug

By increasing the demand for feasible and low-cost determination procedures, analytical sensors have attracted regard for use in the qualitative reviews of drug molecules, medicines, and other desired analytes in pharmaceutical experiments. Analytical sensors allow quantification not only of the active element in medicinal structures but also of the investigation of metabolites and degradation of products in biological matrices (Gil and Melo 2010; de Souza Gil and de Melo 2010). Analytical sensors have become a suitable alternative to most time-consuming and expensive pharmacological monitoring techniques. To this end, much investigation has been done to the optimization of stabilization methods and in the obtention of the response. Today, modern biological and biomimetic determination methods have been developed (de Souza Gil and de Melo 2010). A few uses of biological recognizing factors for coupling with transducers consist of the use of pedophilia oxidase coupled with the ferrocyanate (as electron mediator) to the quantification of theophylline, the use of enzyme aryl-acyl-amidase to determine aminophenol via acetaminophen for the quantification of paracetamol indirectly; quantification of salicylate in the existence of NADH and oxygen by salicylate hydroxylase; and use of tyrosinase for the determination of peroxides, catecholamines, and phenolic derivatives (Luz et al. 2005). The analytical techniques exploited in the development of the sensors from the quantification of a response generated directly, via interaction between the analyte and the recognizing factor, or indirectly, containing coupling reactions and mediators. The basis of the operation of analytical sensors is relying on enzymatic interactions, whereby corresponding to the nature of the products in the biochemical reaction, and the molecular characteristics of the analyte, the best type of transducer can be chosen (Luz et al. 2005). For example, amperometric transducers are the best selection for oxidizable drugs and the enzymes: tyrosinase, laccases, dismutase, peroxidases, superoxide between other oxidases that could be applied as the biological composite in molecular recognizing factor (Erdem et al. 2000; Shipovskov et al. 2012; Gurgel and Gil 2009). As well, optical sensors are so interesting for various samples because they presented many advantages involved the possibility of miniaturization and integration, capability for long-distance application, vast monitoring area, limited background signal, self-reference and low cost, and so on (Chen et al. 2016; Han et al. 2019). Hence, the typical biomarker monitoring technologies include radio-immunoassay, enzyme-linked immunosorbent assay (ELISA), or blotting methods are generally very expensive, slow, not suitable for in situ determination, have restricted sensitivity and selectivity, and need the collection, labeling, and analysis of the analytes by a proficient staff (Chen et al. 2016; Han et al. 2019). Moreover, the main production of natural receptors are expensive and require sophisticated methods, such as the use of alive creature for antibody synthesis, which has limited the operation life and durability under harsh conditions (Ertürk Bergdahl et al. 2019). So the demand to develop a highly sensitive, good selective, quick, cost-effective, label-free, stable, and reusable manner for in situ determination of drugs in environmental samples and biological analytes is still exists. To suppress these limitations of natural receptors, artificial

antibodies, molecularly imprinted polymers (MIPs) maybe a good replacement for biosensor applications. MIPs are artificial receptors appropriate to the target species and they are able of identifying and binding their targets with specificities and affinities in comparison to those of natural receptors (Karoyo and Wilson 2015). This is because MIPs possess diagnosis pores that are complementary to their template molecules in size, shape, structure, and surface chemistry. So, MIPs have become more interesting replacement diagnosis agents for analytical sensors due to their many characteristics such as excellent thermal, physical and chemical stability, reusability, low cost, and easy construction, long life (Huang et al. 2021).

11.3.2 Electrochemical Sensor for Drug Determination

Recently, the progress in electrochemical methods has made these techniques applied to pharmaceutical researches due to their superb sensitivity, high response speed, low cost with and elimination of boring preparation methods relative to other complex analytical procedures (Muthuraman and Moon 2012). Electrochemical methods have been confirmed to be useful for developing highly sensitive and selective procedures for the quantification of pharmaceuticals, organic molecules, metal ions, and so on, in biological matrixes (Kang et al. 2012). As well, electrochemical methods have the lucrative properties to quantify the biomolecular interactions and electrode transfer mechanism of pharmaceutical analytes which supply an overview into the metabolic method of drugs (Zima et al. 2009). Some electrochemical techniques, including stripping analysis and square wave voltammetry (SWV), differential pulse voltammetry (DPV), cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), linear sweep voltammetry (LSV) due to their high sensitivity, are suitable to determine the trace amount of drugs to picogram level in a fast manner as compared to the time-consuming quantification methods (Fig. 11.4). The characteristics that confirm the superiority of DPV over other electroanalytical methods have the short analysis time of examinations, low need for electroactive species, and fewer problems with modification on the electrode surface (Umar et al. 2017).

Drug determination targeting epidermally recoverable biological samples (i.e., sweat, tear, urine, etc.) have different usages, such as drug compliance/abuse determination and individual administration drug amount. Therefore, electrochemical-based techniques are proper because they uniquely use the electroactive property of target molecules for the determination process, eliminating the dependence on the accessibility of recognition agents. However, to adapt these techniques for different usage, three primary problems should be stated: (1) developed a sensitive electrochemical determination device by a great signal to noise ratio (S/N), (2) decoupling the confounding effect of possible interfering materials that naturally exist in complex biological samples, and (3) developing portable electrochemical excitation and response acquisition/transmission systems. For this purpose, first, the instruction for the measurement of electroactive drugs is introduced, which focuses on the assessment and determination of proper monitoring electrodes and

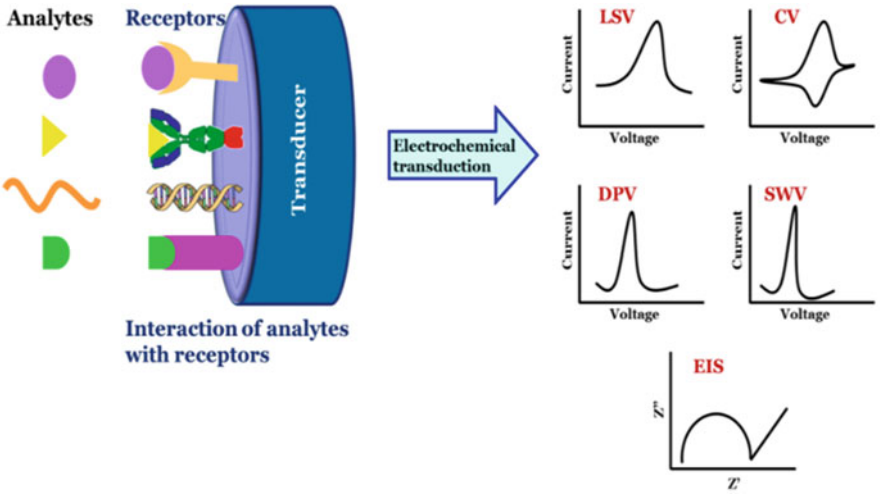

Fig. 11.4 Schematic image of electrochemical sensor for drug monitoring (various electrochemical methods, such as stripping method and square wave voltammetry (SWV), differential pulse voltammetry (DPV), cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), linear sweep voltammetry (LSV)) ()

characterization of the interference from a framework of physiologically relative electroactive molecules. This instruction was employed to instate the design space and performance settings for the management of a coupled monitoring system and analytical instruction to display analytes to reply drug readouts in the composite.

The novel introduced sensing systems can exploit as a base for novel wearable sensor development endeavors aiming to determine electroactive analytes include pharmacological samples (Lin et al. 2020). The development of biochemical monitoring devices, microfluidic systems, and wireless electronic systems has enabled the (semi) continual determining of clinically endogenous and exogenous components in epidermally resumed biological samples (i.e., sweat, tear, urine, etc.). Given the low-molecular-weight exogenous characteristic of the drugs, in general, biological recognition factors (i.e., antibody, enzyme, DNA) are not generally accessible to develop the determination interface and drug molecules typically reveal at trace amounts biological matrix, rendering their determination in the complex biological medium (involving highly potential interfering materials) difficult. As mentioned in the text, various voltammetry techniques can be exploited to manufacture drug-determination interfaces, because they specially leverage the electroactive property of the desired drug for determination, eliminating the reliance on the availability of recognition agents. Specifically, pulse voltammetry (containing differential pulse voltammetry (DPV) and square wave voltammetry (SWV)) is vastly utilized for the determination of electroactive molecules, due to high sensitivity and its capability to minimize non-faradaic background signal. The principle of determination in these methods is relied on applied potential (between the working and reference electrodes) and recording the related current intensity at the characteristic redox

potential of the desired analyte, the measured peak signal intensity is related to the target amount.

All the electroactive materials in the biological fluid can contribute to the voltammetric signal, where their activities are effectively superimposed, potentially leading to the covered of the desired drug's fingerprint peak in the recorded voltammetric signal. Hence, the interfering effect of electroactive materials must be intently estimated and separate from the recorded signal. In the system, to obtain sample-to-answer amount, portable voltammetric excitation and signal acquisition and transmission ability should be realized within a small footprint, in this regard the miniaturization of great lab devices is necessary. A framework is introduced in which the assessment and determination of suitable probing electrodes for electrochemical examinations and the properties of internal interferences are performed. Three drugs are considered, dipyridamole (DP), acetaminophen (APAP), and caffeine (CAFF) and which can be electrochemically oxidized at low potentials (1.0 V). These drugs were selected especially because of their importance in the treatment of the disease and their proven use in determining outcomes for the recovery of patients. For instance, DP is useful in treating cardiovascular disease due to its vasodilator and antiplatelet characteristics, and monitoring of antiplatelet therapy is critical for stroke patients. APAP is also a pain reliever and antipyretic that is used with significant changes in metabolism, and therapeutic checking can help control patients' experience of toxic metabolites. CAFF is one of the beneficial drugs for the treatment of airway blockage and prematurity apnea, as well, monitoring the therapeutic process has shown to be effective in individualizing dosage and alleviate drug toxicity. In the examination of the voltammetric performance on the carbon-based electrode candidates (which can define the oxidation of drugs), the diamond electrode that doped by boron, due to its wide potential window and high durability, can be the proper sensing electrode. With an intentional surface modification of the BDDE, nano- to sub/low micromolar range determination ability was realized for all the drug tested. Also, the interference of a panel of physiologically related electroactive molecules (e.g., uric acid (UA), amino acids) was characterized corresponded to the surveyed of the desired targets.

11.3.3 Optical Sensors for Drug Determination

Optical biosensors are devices which function is basically on the change in the optical properties of desired targets, such as absorption, refractive index, fluorescence, or light scattering, as a result of the interaction between the analyte and receptor agent (Fig. 11.5) (Singh et al. 2020). This recorded signal corresponded to the amounts of analytes, measured by the use of biological recognition agents (i.e., enzymes, DNA, antigens, cells, complete tissue, so forth) as biorecognition agents. Optical biosensors have numerous benefits as one group of the best probes, which have higher sensitivity and versatility, these thus enable faster and online estimations, and possible to adjust for multichannel and multiparameter determination systems (Long et al. 2013). These sensing systems have been used for

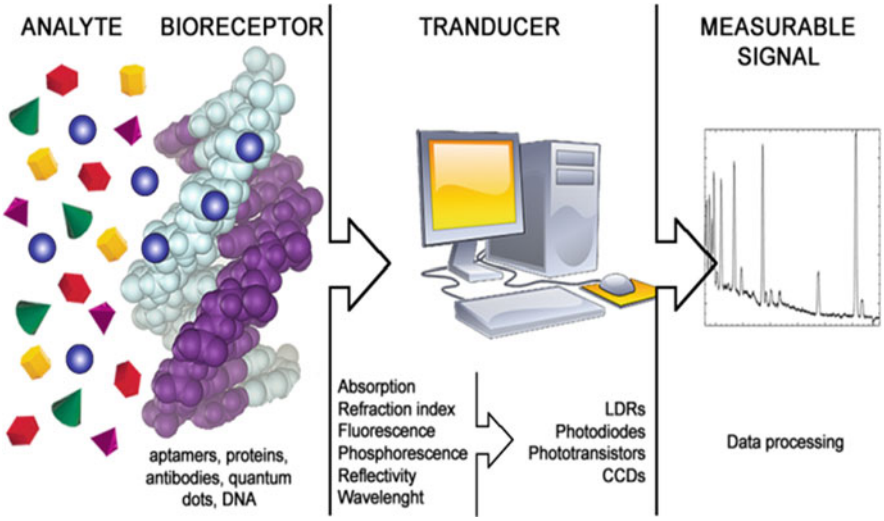

Fig. 11.5 Schematic diagram of the optical sensor for drug monitoring (Martins et al. 2013)

monitoring a wide range of drugs, include various antibiotics of recent resort involving hazards of toxicity with various side effects in patients. Optical biosensors are one of the most widely used biosensors and are used to measure various species, including a variety of drugs. It has also become a viable option in clinical diagnosis due to its high molecular detection capacity and ability to be used for real-time measurements.

Amikacin, for example, is one of the drugs that has been quantified by optical biosensors. It is an antibiotic for the last resort that is mainly used against infections of gram-negative microorganisms resistant to gentamicin and tobramycin and causes very serious side effects such as ototoxicity, nephrotoxicity, and kidney damage. The optical biosensor enables fast and sensitive quantification in the blood (Dey and Goswami 2011). Optical biosensors are also used to quantify antineoplastic drugs that cause serious side effects such as toxicity in patients. However, these drugs are not constantly monitored due to the lack of online solutions and the low cost of using them for the patient. Mitoxantrone and methotrexate are currently being determined because they are widely used to treat some cancers, including leukemia, lymphoma, lung and breast cancer (despite high toxicity), and are determined in the blood (Fan et al. 2008).

Optical biosensors can be classified into two general groups: bio-optrodes and the evanescent field-based type. Bio-optrodes are based on the interaction between the desired sample and a recognition factor that causes a quantifiable change in optical properties. This alteration is evident by active groups such as fluorescent molecules, dyes, and chemo or biol luminescent (Garzón et al. 2019; Ndukaife 2012). Evanescent field-based biosensors are based on electromagnetic waveguides that transmit light after several internal reflections with total reflection conditions, thus a peak field capable of penetrating internal reflections at a certain interval from the waveguide surface, which is improved by the receiver (Mapar 2018; Lu 2018). Optical

evanescent wave biosensors are the most numerous and are identified using an electromagnetic field and the ideal source of evanescent field detection to measure any biochemical reaction occurring in it, so they are essential devices for analysis and identification of chemical or biological substances with a high level of sensitivity and selectivity (Taitt et al. 2005; Lim 2003).

11.3.4 Wearable Drug Sensors

The development of digital healthcare devices, wearable electronic sensors have evolved rapidly over the past few years and are expected to expand even further in the early decade (Fig. 11.6). The next development of wearable systems is the move

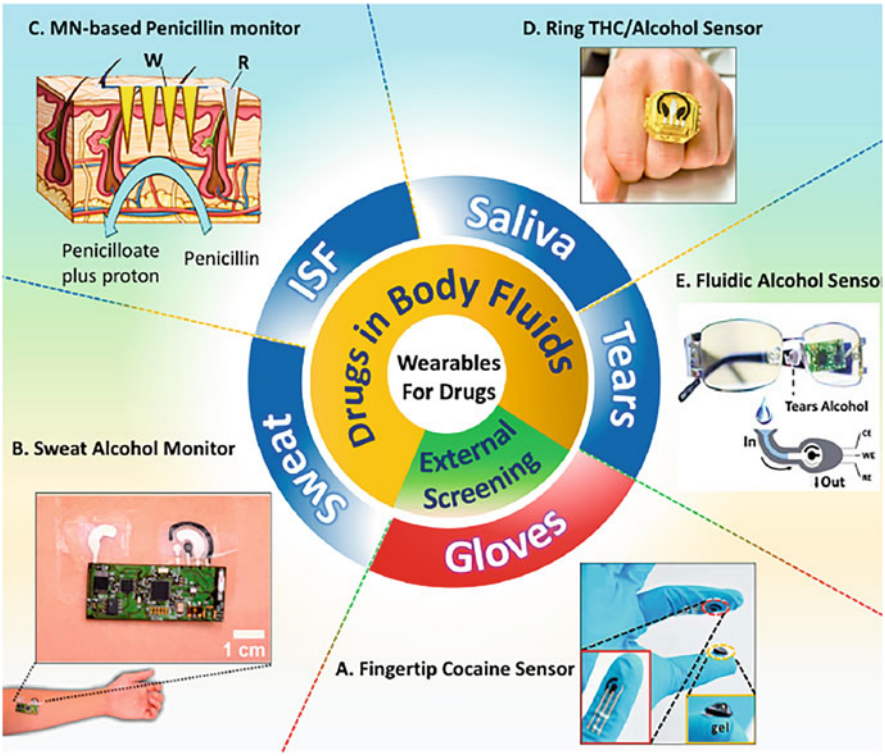

Fig. 11.6 Some electrochemical wearable sensing systems for drug determination. (**a**) External drug estimation: Wearable glove sensing system for determination of dubious analytes, displaying a screen-printed electrode onto the flexible finger surface, and a conductive gel stabilized on the thumb. (**b**–**e**) Drugs determination in biological matrixes. (**b**) Sweat examination: image of a skin-worn alcohol iontophoretic-sensing tattoo instrument with the integrated flexible electronic panel. (**c**) ISF monitoring: microneedle sensing system for in situ drug determination of phenoxymethylpenicillin. (**d**) Saliva examination. (**e**) Tear's examination: Fluidic alcohol prob; photograph and diagrams of the fluidic Instrument and portable electronics integrated into the eyeglass basis (Teymourian et al. 2020)

toward integrated wearables, nanomaterials, and nanocomposites are the focus of research into modern concepts for integration. In addition, the conversion of current devices and wearables based on integrated technology may be significant while maintaining their functional capabilities. Nanomaterial-based wearable sensors have already marked their attendance with considerable differentiation, while nanomaterial-based wearable sensors are yet in their infancy (Jayathilaka et al. 2019).

Briefly, the operational and design configurations provided by the proposed framework pave the way for the development of a mobile sensing system and the analytical framework for providing reading electroactive materials readout in sample-to-response method. It is also permissible to describe the effect of electrically active species in epidermally recyclable biological fluids (consisting of amino acids and urea) on the sensor response to describe/identify distorted potential window (s). Further work on suppressing the effect of possible electrical interference, by designing surface change methods and a suitable analytical form to allow the use of developed methods to quantify a wider range of analytes (such as those in which oxidation peaks reside). Also, an iontophoresis connection must be integrated to comply with the procedures proposed for wearable-based systems. Also, an iontophoresis connection must be integrated to comply with the procedures proposed for wearable-based systems (Lin et al. 2020; Emaminejad et al. 2017). In addition, the inclusion of auxiliary probing interfaces for on line calibrations of the determination systems (i.e., pH) and characterization of sweat permeation plot (i.e., rate, volume, etc.) may help normalize the readings versus inter/intrasubject physiological alterations and variability of the gland activation. Moreover, surface remediation methods may need to be designed (Kiran et al. 2012) to reduce the effects of sediment and contamination on the sensor surface in the long run. To this end, along with engineering efforts and information about the clinical utility, it is critical to conduct extensive clinical research to determine the relationship of target electronegative drug molecules (e.g., DP) in the blood and sweat to biological confounders, (i.e., inter-/intraindividual changes). Overall, the proposed design framework and wireless voltammetry determination system could serve as a basis for future efforts to develop a wearable sensor for utilizations, including pharmaceutical/drug abuse for personal treatment operations. Wearable sensors are designed to measure alcohol, cocaine, and penicillin, and efforts are underway to design wearable sensors for other therapeutic and addictive drugs.

11.3.5 Surface Functionalization in Drug Determination

One of the most important aspects when determining a drug via biosensors is the selection of a solid surface and developing a suitable chemical surface (Olaru et al. 2015; Cooper 2002). As drug determination is estimated in the blood (serum or plasma environment), where numerous proteins exist, it is crucial to maintain a healthy, degradation-free sample. On the other hand, drug determination should be used for ligands in which proteins, integrity, natural composition, and functionality

are usually significant (Savino et al. 2012). The chemical selectivity of functional groups of proteins that are immobilized directly to the analyte must be identified by surface density, homogeneity, and the absence of artifacts on the sensor surface. To select the exact function of the sensor surface, three important aspects must be considered, as follows: (a) the kind of analyte, (b) the kind of ligand, and (c) the kind of surface. For the former, there are several sensing surfaces or chips based on printing methods, such as thermal jet inkjet printers (with and without modification) (Emaminejad et al. 2017), precipitation of some inert metals include gold, platinum, etc., which is applied by a chemical film such as protein A, carboxymethyl dextran, streptavidin, and lipophilic modification, and so forth. After selecting the appropriate sensor surface, some of these surfaces should function as golden levels to improve the sensitivity and selection of biosensors. According to case b, the nature and construction of the ligand define the best approach to improve surface quality (such as UV radiation, wet chemicals, organosilanization, and ionized gas treatment) (Coperet et al. 2016; Nel et al. 2009)). Various physical and chemical techniques have been exploited to functionalized the surfaces. Physical methods improve the surface in terms of hardness, removal of contamination and grease, and the size of the surface pores. The above facilitates the further uptake of biomolecules or immobilization through the stability of the chemical method for analytical quantification. Likewise, chemical techniques must create a long, intense interaction between the structure of the sensor and its surface. The functionality of the surface must, in some respects, provide the spatial orientation of the molecules (for example antibodies). For the above, coupling covalent, disulfide-based, affinity capture, amine coupling, nickel-nitrilotriacetic acid (Ni-NTA) based, biotin-avidin based, antibody-based, and protein G or A based and other materials are applicable. Finally, for case c (the kind of the desired sample), multiple examinations for drug determination contain small components of synthetic nature, such as antineoplastics, antibiotics, and anticoagulants that vary from macromolecules include biopharmaceuticals. Based on the past prospect, including various elements, surface functionality has been applied in drug determination. Estimation of vancomycin amounts by a microneedle-optofluidic biosensor that activates streptavidin-biotin due to its high affinity, binding, stability, and compatibility with various chemical procedures. Biotin binds to assembled monolayers (SAM) of methoxy polyethylene glycol-thiol (mPEG-SH) and produces a sensitive sensor surface for gold. This determination system makes it possible to estimate vancomycin level with proper sensitivity (0.41 AU/decade) and low LOD (84 nM) in medical range concentrations (0.3–40 nM) for very small amounts (0.6 nL), as well as carrying fast measurements (completely less than 5 min) (Ranamukhaarachchi et al. 2016). Other proper functionalized surfaces have been applied to measure testosterone, methotrexate, and antibiotics levels by use of the optical technique in biological fluids (Masson et al. 2015). Most of the experiments for drug determination by biosensors are suitable for small molecules. However, in recent years the development of new optical biosensors to determine the level of biopharmaceuticals in plasma has increased, such as the determination of the levels of antibodies and anti-drug antibodies for infliximab (IFX) and anti-TNF-alpha in the plasma. (Beeg et al.

2019). For the quantification of these analytes, sensor surfaces were functionalized by amino coupling sulfo-N-hydroxysuccinimide/1-ethyl-3(3-dimethyl aminopropyl)-carbodiimide (NHS/EDC).

11.4 Interferences

11.4.1 Common Interferences in Drug Determination

In the sensing biosensors, antibodies are used as receptors to detect intended targets (antigens). Although the complementary antibody interacts with the analyte via a specific noncovalent bond, various interferences including false-negative and false-positive interferences are possible (Ismail 2009; Diaz-Amigo 2010). Some interferences are alike in chemical analyses and immunoassays, and some are unique for this system. In cases such as obtaining unacceptable results, observing a nonlinear relationship in dilute samples, the inconsistency with other test results, or the clinical result if various immunoassays in the quantification of the similar sample provide significantly various results (Fig. 11.7). This section briefly mentioned these possible interferences:

1. Cross-interaction with endogenous and exogenous non-antibody-structured materials
2. Hook effect
3. Matrix effect

By being aware of the types of possible interferences in sensing systems, it is possible to eliminate undesirable results, diagnostic error, treatment error, and error in test results, and to avoid further and unnecessary experiments (Favresse et al. 2018). Interferences with drug testing divide into two groups: those that lead to false-negative outcomes and those that lead to false-positive outcomes. The terms false negative and false positive in the text refers to the experimental result as compared with the true outcome; A false-positive result is a result that is positive for a particular type of drug if the donor has not taken any of these substances (Smith and Bluth 2016). In return, a false-negative outcome when the analyte screens negative for a group of drugs when in fact, the donor has consumed one of the examined materials. False-positive screen results are not a major concern for most toxicology laboratories, as confirmatory exams will remove the screening differences (Johnson-Davis et al. 2016). Compared with the initial screening examination, verification testing is always more sensitive and specific. False-negative outcomes are a severe concern, hence, a sample with a negative display will not be sent for confirmation testing. Therefore, if the donor intentionally did not take medication, this is a cause for concern (Manchikanti et al. 2011).

Most materials do not show any drug interference, even at overdoses that may be seen in cases of suicide. In the following stated a list of possible drug interferences: acid phosphatase in serum by ibuprofen and theophylline; non-prostatic acid

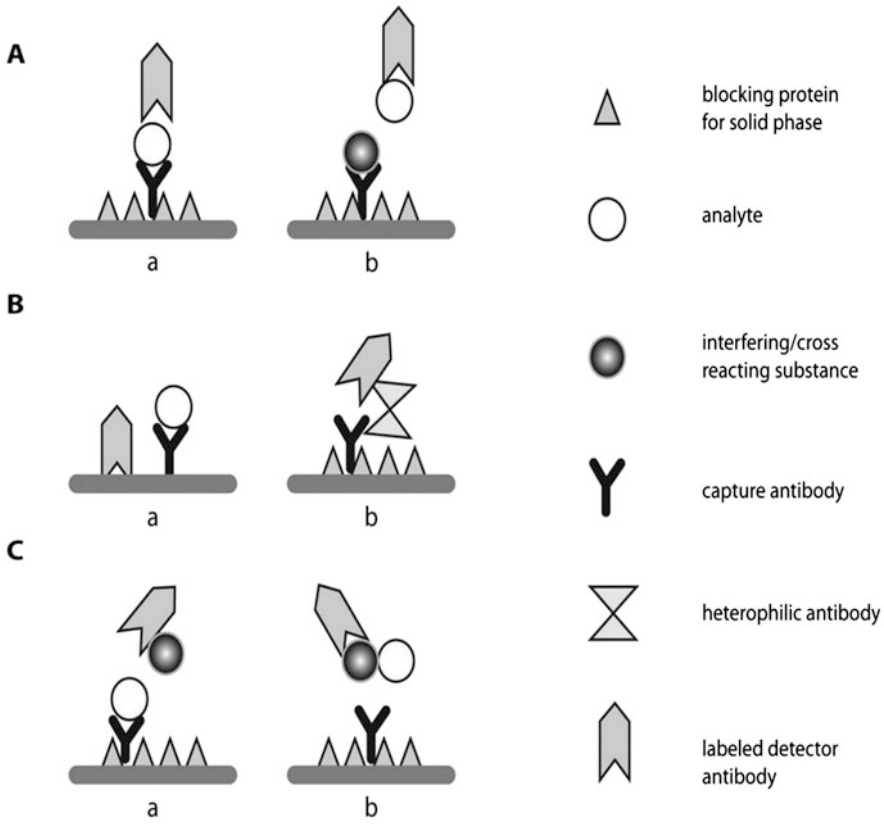

Fig. 11.7 Various possible interferences in immune sensing systems: (**A**) (a) determination with no interference; (b) cross-interaction of an interfering material with the capture antibody, resulting in the false-negative outcome; (**B**) positive interference: (a): unspecific interaction of the labeled probe antibody with unblocked solid phase; (b): bridge interaction by heterophilic antibodies; (**C**) negative interference: (a): change in the sterical structure of binding of interfering protein to Fc part of detector antibody (b): covering of the epitope on the sample surface by a protein (Dodig 2009)

phosphatase in serum by cefoxitin and doxycycline; creatine kinase MB in serum by doxycycline; total bilirubin in serum (Jendrassik ± Grof method) by rifampicin and intralipid; total bilirubin in serum (DPD method) by intralipid; creatinine in serum (Jaffe method) by cefoxitin; fructosamine in serum by levodopa and methyldopa; carbamazepine in serum by doxycycline, levodopa, methyldopa, and metronidazole; methyldopa and tetracycline; uric acid in serum by levodopa, digitoxin in serum by rifampcin; phenytoin in serum by doxycycline, ibuprofen, metronidazole, and theophylline; C3 in serum by intrepid; C4 in serum by doxycycline; theophylline in serum by acetaminophen, cefoxitin, levodopa, doxycycline, phenylbutazone, and tobramycin; rifampicin in serum by cefoxitin, levodopa, doxycycline, rifampicin, and valproic; acid phenylbutazone in serum by phenylbutazone; rheumatoid factor in serum by ibuprofen and metronidazole; pancreatic amylase and amylase in urine by

acetylcysteine, cefoxitin, ascorbic acid, gentamicin, levodopa, methyldopa, and oxacin; magnesium in urine by acetylcysteine, gentamicin, and methyldopa; b2-microglobulin in urine by ascorbic acid; total protein in urine by ascorbic acid, Ca-besylate, and phenylbutazone. Interference in acid phosphatase, creatine kinase MB and bilirubin methods was evident at the low amounts of analytes, and so it may be ignored at high concentrations. Laboratory tests can not exactly have the in vivo various interference effect of drug interactions and metabolites in the body. In this text, only a group of drug interferences are mentioned, the effect of which has been investigated under in vivo analysis, but cannot state a comprehensive. Rapid developments in analytical chemistry and the introduction of new drug preparation make it very crucial that the clinical researcher remains vigilant of the possibility of drug interference. This study aims to provide a model for further interference studies for diagnostic kit manufacturers or pharmacological chemists evaluating new approaches. In this study, the mechanism of interference is not discussed (Sonntag and Scholer 2001).

11.4.2 False Positive

False-positive interferences usually belong to a class of drugs or substances that are often structurally similar to the type of drugs being monitored. Antibodies have been developed in monitoring reagents to determine common epitopes, especially in drug categories with many compounds (sympathomimetic amines, benzodiazepines, narcotics). This scheme allows the researcher to be able to control different types of drugs in specific groups. However, it is possible that the materials are structurally similar to the target group and, therefore, the probe may inadvertently make a mistake. Often there is no intention of the sample donor to produce a false-positive result (Smith and Bluth 2016). Table 11.1 reported the generally known drug interferences (Moeller et al. 2008; Brahm et al. 2010). Different compounds can cause false-positive immunoassay outcomes. Common structural motifs show some of these events, but false-positive results can also be caused by different structures. It should be noted that antibodies attach to a three-dimensional structure. But some similarities are observed between the two-dimensional chemical structures of the interaction compounds, the absence of the same chemical form does not eliminate the possibility of the interaction of the safety assay. It is also important to recognize that drug metabolites can also produce false-positive results (Saitman et al. 2014).

11.4.3 False Negative

False-negative interferences may or may not be deliberately swallowed to obscure the ingestion of drugs that do not want to be monitored. False-negative tests are more troubling because, based on the test scenarios of most toxicology laboratories, negative screening samples are no longer tested. Some immunoassay examinations are subject to the “hook effect,” a phenomenon that can result in a false-negative test

Table 11.1 Drug that causes false-positive immunoassay determinations

Desired drug	Interfering substance
Amphetamines	Amantadine benzphetamine bupropion chlorpromazine clobenzorex I-deprenyl desipramine dextroamphetamine ephedrine fenproporex isometheptene labetalol methamphetamine L-methamphetamine methylphenidate phentermine phenylephrine phenylpropanolamine promethazine pseudoephedrine ranitidine Ritodrine Selegiline thioridazine trazodone, trimethobenzamide, trimipramine etc.
Benzodiazepines	Oxaprozin Sertraline
Cocaine	Coca leaf tea Topical anesthetics containing cocaine etc.
Opioids	Dextromethorphan, heroin Poppy seeds Quinine Quinolones Rifampin Verapamil etc.
Phencyclidine	Dextromethorphan diphenhydramine doxylamine ibuprofen Meperidine mesoridazine thioridazine etc.

outcome. Immunoassays are based on the binding of an antibody and antigen. When a drug is present in such high amounts that there are no binding sites left on the antibody, the analyte may exist with falsely low amounts. If the amount of the sample is below the test cutoff, the outcome will be negative. However this is uncommon, it cannot be ruled out, nor can it be predicted. Fortunately, the novel developed immunoassay testing kits have made design improvements over the years and the occurrence of such a phenomenon has been greatly detracted (Reisfield et al. 2007).

In terms of delivering the right result, false-positive monitoring testing is not a concern for clinical laboratories that regularly perform screen tests to confirm results. Usually, in the laboratory, only the requested test is performed by the client, whether a physician or a non-health institution (hiring agency, human resources department, etc.). If the ordering entity does not approve the request for testing to save the cost, the technician should be aware of the false-positive rate for all drug compounds in which they are screened. These false-positive results cause confusion, which has been corrected by appropriate validation studies and a better understanding of toxicology testing in general. Test request centers should also be aware of the extent to which screening tests respond to the order or use. Point-of-care test units include all-in-one cup tests and other dipstick-type testing devices have been shown significantly higher cross-reactivity and, consequently, a higher false-positive rate compared with laboratory-run immunoassay tests.

In addition, the same precautions should be considered if the facility in question has not requested confirmatory testing. Briefly, it is the ordering centers that

determine how they want to use the benefits and limitations of the drug trial they order (Schwarz et al. 2016). The clinical pharmacology laboratory can be a valuable property in understanding and teaching comfort in assisting the physician in the field of laboratory testing and thus achieving this endpoint. This chapter summarized some of the main applications of these analytical sensors for clinical analysis and their interferences. Despite the limitations of the reproducibility of these methods (sensitivity, selection) and the compatibility of enzymes and other biological identification agents, the biosensor is still a focus of research. Thus, many studies on the development of new material converters, as well as methods of stabilizing identifiers can be found in the literature. However, the integration of these devices for use in pharmaceutical analysis and the introduction of formal methods require more research.

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Biosensors for the Detection of Spoilage Levels and Excess Preservatives in Seafood

12

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Abstract

Elevated levels of biogenic amines formed as a result of microbial metabolism, as well as the excessive use of preservatives, can affect the quality of seafood. Therefore, a highly selective and sensitive analytical tool capable of analysing ultralow levels of pathogen contaminants and preservatives is required to ensure food quality and safety. However, monitoring the freshness of seafood using a miniaturized biosensing system that reveals product quality during real-time analysis remains a difficult task for food industries around the world. The incorporation of engineered nanomaterials and bioreceptors into the design of sensing element, as well as their potential application in aquatic settings, could

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allow for continuous monitoring of food status, thereby extending shelf-life and reducing food waste. Nevertheless, most biosensors developed are still in their infancy and will require significant work before being deployed in aquatic settings. Therefore, issues regarding the reliability, selectivity and sensitivity of the biosensor must be addressed when applied to a complex food matrix. This book chapter summarizes the state-of-the-art of chemical and biological sensors for assessing seafood quality by estimating spoilage levels and excess preservatives in foodstuffs. Furthermore, the biorecognition principle behind various sensors employed for preservative and biogenic amines is also discussed in this book chapter. The techniques explored have great potential for use in quality control, ultimately facilitating real-time monitoring of preservatives and microbial contaminants in seafood products.

Keywords

Seafood · Biomarkers · Preservatives · Biosensors · Detection · Spoilage levels

12.1 Introduction

Seafood, especially diverse species of echinoderms, molluscs, crustaceans, and fish, are is rich in minerals, vitamins, fat and protein. These seafood are widespread owing to their high nutritional value and high flavour (Carelli et al. 2007). Nevertheless, the shelf-life of seafood is influenced by the change in pH value, levels of various nutrients, and variation in moisture content. Besides, the instant death of seafood after harvest in the sea causes rapid biochemical and microbial reactions in seafood, which make a substantial difference in nutritional and sensory properties and subsequently shorten shelf-life (Zhou et al. 2019). Typically, most types of seafood are rich in polyunsaturated fatty acids, making them very vulnerable to lipid oxidation. The effects of oxidation of lipid molecules in seafood include colour change, nutrient depletion, toxic molecule formation, and the development of unpleasant flavour and odour (Fu et al. 2019).

The physicochemical and morphological variations influence the complexity of seafood deterioration. On the other hand, the total deterioration of fish quality is the result of microbial metabolic processes, while the early loss of fish freshness is due to biochemical processes and indigenous enzyme activities (Zhang et al. 2017). Therefore, the process parameters, storage conditions, and distance between seafood processing facilities and harvesting sites should be taken into account while estimating the degradation and quality of seafood (Caglayan and Üstündağ 2020). Moreover, the inherent and extrinsic factors and processing techniques can directly or indirectly affect the shelf-life and quality of seafood. During the collection, storage, handling, distribution, and transport of seafood, standard operating procedures, good sanitary practices, and analysis of toxic elements in food products are essential to improve the quality of seafood and control the deterioration of food products (Bertani and Lu 2021). There has been immense interest in improving the

shelf-life of packaged food through the use of various non-thermal and preservation methods due to the shortage of fresh frozen foods, particularly high-quality seafood products (Marques et al. 2020).

Nutrient deficiencies and deterioration induced by biochemical, enzymatic, and microbiological changes in seafood are generally prevented through the use of natural and synthetic preservatives, including sulphur dioxide, sodium nitrite, and sodium benzoates (Marques et al. 2019, 2020; Kampeera et al. 2019). However, the accretion of these chemical preservatives in tissues can be harmful to human health. Salt treatment is one of the most popular and widespread natural preservative techniques employed to extend the shelf-life of seafood due to its efficacy and inexpensive synthesis process (Liu et al. 2020; Campàs et al. 2007; Kumar et al. 2020). The efficacy of salt in preventing seafood against deterioration is primarily due to its ability to decrease water activity in the edible tissues of seafood, thereby preventing enzymatic activity and bacterial growth. On the other hand, research findings on halophilic and halotolerant bacteria suggest that these microorganisms can thrive in salt-preserved seafood by utilizing energy to remove salt from their cells, thus preventing protein accumulation in the cytoplasm (Bavisetty et al. 2018; Ma et al. 2021). In certain cases, the rapid increase in the density of these microorganisms can also lead to the deterioration of seafood as a result of fermentation. Many natural preservatives have also been shown to substantially replace chemical preservatives, including bioactive peptides, chitosan, bacteriocins, essential oils, and plant extracts, due to their antioxidant and antimicrobial capabilities, particularly to prevent the degradation of seafood by lipid oxidation and microorganisms (Nurlely et al. 2021; Wang et al. 2021a). Therefore, it is essential to establish efficient processing treatments to increase the shelf-life of fresh seafood products. Moreover, the demand from customers for good quality and modestly processed seafood products has recently attracted a great deal of attention. Nevertheless, year-to-year fluctuations in outbreaks of foodborne diseases are associated with increased demand from consumers for minimally processed seafood products. These trends highlight the significance of developing chemical and biological sensors to detect spoilage levels and excess preservatives in seafood products (Gupta et al. 2021; Hash et al. 2019).

Typically, sensors consist of biological or chemical recognition elements explicitly engineered to detect the analyte of interest and a physical transducer that transforms this recognition event or biochemical process into a detectable signal, providing qualitative or quantitative output. Biosensors or Biological sensors use bioreceptors, including antibodies, aptamers and enzymes, which are associated with the physical transducer to provide enhanced selectivity for a target biomolecule (Hashem et al. 2021; Vinoth et al. 2021). Conventionally, mass-based detection, optical, electrochemical, and colorimetric techniques are extensively used to monitor the binding process between bioreceptors and target biomolecules. Although nanobiosensors have had a significant impact in the field of clinical diagnostics, their application in certain areas, including the food industry, is still in its early stages. So far, sensors have been developed to recognize chemical or pathogenic contaminants, allergens, and genetically engineered materials, assess authenticity and evaluate raw

materials (Hashem et al. 2021; Vinoth et al. 2021). The integration of chemical and biosensors in packaging technologies is growing and has been very successful in recognizing a wide range of biomarkers for the evaluation of the freshness of seafood. Here, we have briefly summarized the state-of-the-art of chemical and biological sensors for assessing seafood quality by estimating spoilage levels and excess preservatives in foodstuffs (Hashem et al. 2021; Vinoth et al. 2021). Furthermore, the biorecognition principle behind various sensors employed for preservative and biogenic amines is also discussed in this book chapter.

12.2 Classification of Biosensor

Biosensors are classified according to the type of transducer and biorecognition element and are shown below.

1. Biorecognition element: biomimetic, cell, DNA, antibody and enzyme
2. Transducers:
   a. Optical—Raman, FTIR, fibre optic and other
   b. Electrochemical—voltammetric, conductometric, potentiometric, amperometric and impedimetric
   c. Mass-based—magnetoelastic and piezoelectric

In addition to the appropriate analytical technique employed, the biosensor should meet the following criteria: good repeatability and reproducibility, high stability, enhanced sensitivity, elevated selectivity, rapid response time, wide detection range, and low limit of detection. New kinds of biosensors composed of different transducers are being constructed. For instance, electrochemical and optical transducers are integrated to form photoelectrochemical transducer in which the interaction of illuminated light with electrochemical systems is studied (Ghasemi-Varnamkhasti et al. 2018; Velusamy et al. 2010).

Over the past decade, there have been tremendous technological developments in the field of electrochemical sensors. Biomolecules such as urea and glucose are the analytes initially recognized with the use of electrochemical sensors, and later macromolecules such as bacteria, viruses, whole cells, proteins, and other pathogens are detected (Ghasemi-Varnamkhasti et al. 2018; Velusamy et al. 2010). The electrochemical sensing platform is currently capable of monitoring DNA materials, detecting tumour biomarkers, studying specific interactions between antibodies and antigens, etc. (Ghasemi-Varnamkhasti et al. 2018; Velusamy et al. 2010).

12.2.1 Electrochemical Detection

Electrochemical sensor is a widely explored analytical tool that includes an electrochemical transducer. Using the biorecognition element, the electrochemical sensor provides both quantitative and semiquantitative analytical information on analyte

concentrations in real-time (Carelli et al. 2007). The analyte undergoing oxidation or reduction reactions induces changes in the electrical response that can be assessed in various ways. In electrochemical sensors, the measured attributes are either potential or current. The consumption or generation of electrons at the electrode-electrolyte interface of the electrochemical system occurs as a result of dynamic changes in the properties of the solution and is recorded against the reference electrode that serves as the basis for analysis (Alonso-Lomillo et al. 2010). Since the electrochemical process takes place near the interface between the working electrode and the electrolyte, it depends on the activity of the species rather than the concentration of the solution (Castilho et al. 2005). There are also electroanalytical methods that do not rely solely on redox reactions and do not employ direct electron flow. For instance, changes in the electrode surface resulting from biomolecular interactions such as ligand-receptor and antibody-antigen and surface biofunctionalization are investigated. Electrochemical biosensors designed to study these types of biomolecular interactions estimate parameters including impedance, capacitance or resistance (Draisci et al. 1998). The simple way to convert a biomolecular interaction into a proportional electrical signal makes it attractive for effective and sensitive detection. A multitude of electrochemical characteristics can be measured and assessed using electrochemical techniques such as electrochemical impedance spectroscopy, conductometry, voltammetry, amperometry and potentiometry (Wimmerová and Macholán 1999). In addition, there are a variety of electrode materials that can be utilized as biorecognition elements, as well as efficient matrixes for electrocatalyst immobilization.

12.2.1.1 Electrochemical Cell

The traditional electrochemical setup used for biosensor studies consists of three electrodes, namely, the reference electrode, the counter electrode, and the working electrode. Platinum, gold, and glass carbon are the most popular working electrode materials used for the electrochemical detection of analytes because they have high electrical conductivity and chemical stability (Tombelli and Mascini 1998). Polarized working electrodes can elicit a redox reaction on the electrode surface depending on the electrochemical reaction being analysed. Electrode materials have a significant impact on the biosensor response, as all electrode materials used in biosensor studies possess unique chemical and electrochemical properties. Besides that, working electrodes should also offer a low signal-to-noise ratio and excellent reproducibility characteristics (Omanovic-Miklicanin and Valzacchi 2017). The cost and biocompatibility are also extremely important. On the other hand, the flow of electrons between the counter electrode and the working electrode is provided by the auxiliary electrode, which forms a closed circuit in the electrochemical cell. The surface area of the working electrode must be greater than the auxiliary electrode to evade the kinetic limit of the electrochemical process. Typically, platinum and carbon wire are employed as auxiliary electrodes. On the other hand, the potential of the working electrode can only be quantified if the reference electrode maintains a stable potential, thus balancing the reaction at the working electrode/electrolyte interface (Gumpu et al. 2014). The silver wire covered with a thin layer of silver

chloride immersed in saturated potassium chloride solution, the standard hydrogen electrode, and the calomel electrode are the three reference electrodes widely used in the design of electrochemical biosensors.

In addition to the traditional three-electrode configuration, there are variants and scaled up versions. The microfluidic cell framework allows for extremely easy analysis by consuming a relatively small volume of sample and offers elevated sensitivity by limiting the effects of potentially interfering species. As the microfluidic-assisted electrochemical sensing platform consumes fewer reagents, less waste is produced. For instance, lab-on-a-chip-based devices include a three-electrode configuration that scales to a size of a few square centimetres with many laboratory functions built into a single chip (Wimmerová and Macholán 1999). In recent times, advanced lab-on-a-chip devices capable of handling a tiny volume of sample at the picolitre scale have been fabricated. In particular, electrodes in a small area with micrometric width and spacing are typically printed or deposited on the top surface of flexible polymer substrates to form screen-printed electrodes that are used to measure ultralow levels of analytes in real samples. Besides that, these electrode materials are available at a low cost, which allows them to produce large quantities of screen-printed electrodes in a single run.

12.2.1.2 Electrochemical Techniques

As the designed potentiostat consists of low-noise operational amplifiers, voltammetry has become one of the most popular electroanalytical techniques. The current is typically measured in voltammetry experiments by applying a potential between the working electrode and the counter electrode (Nurlely et al. 2021). In particular, electrochemical sensors based on the voltammetry technique produce current signals with an intensity directly proportional to the amount of target chemical species. Furthermore, the voltammetry technique is also suitable for all kinds of biorecognition elements. Differential pulse voltammetry, square wave voltammetry, and cyclic voltammetry are the popular electroanalytical techniques commonly used for the detection of biomolecules (Vinoth et al. 2021). Among these electroanalytical techniques, cyclic voltammetry is extensively employed to study the process of electrochemical coupling on electrode surfaces. Square wave voltammetry, as a reliable detection technique, is efficient, highly sensitive and capable of detecting analytes at ultralow concentrations, paving the way for the quantitative analysis of biomolecules in real samples. In addition, the shape of the peak is simple and easy to analyse for the target analytes (Caglayan and Üstündağ 2020; Kampeera et al. 2019). On the other hand, differential pulse voltammetry, a standard electroanalytical technique, has the advantage of low capacitive background current and high sensitivity, which play an important role in the qualitative and quantitative analysis of microbial pathogens in seafood (Bavisetty et al. 2018). Electrochemical impedance spectroscopy is another widely used electroanalytical technique for the detection and quantification of biomolecules. In this electroanalytical technique, the impedance measurements are strongly influenced by the variations in the electrical field resulting from the association between biorecognition element and analyte. This powerful electroanalytical tool allows researchers to study the

response of an electroanalytical system by applying an oscillating potential at different frequencies, typically in the range of 10 Hz to 50 MHz, which provides more information on kinetics and interfacial phenomena than traditional electroanalytical techniques used in sensing applications.

12.2.2 Optical Techniques

Optical biosensors are effective analytical tools that can detect processes resulting from interactions between analytes and biorecognition elements and translate the detected optical signal into the amount of target analytes based on the number of photons detected rather than electrons (He et al. 2020). To date, Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), fluorescence spectroscopy, and surface plasmon resonance (SPR) spectroscopy are the optical transducers widely used for sensing applications. SPR, a highly sensitive analytical technique, is extensively utilized in the recognition of microbial pathogens (Tan et al. 2019). Typically, SPR sensor uses a thin conductive metal oxide film, which is held between two transparent media of different refractive indices. The detection mechanism of SPR sensors is based on the fact that light is reflected and refracted at the interface of two transparent media when p-polarized light is illuminated at the interface (Tian et al. 2021). The SPR sensing system upon illumination with p-polarized light leads to attenuation of light intensity at a particular angle and promotes the adsorption of photons by a conductive metal oxide film. The binding interaction between the biorecognition element and the target species causes a change in the refractive index that can be monitored by SPR, which forms the basis for detection and quantification (Silva and Hellberg 2021). The potential benefits of SPR-based biosensors encompass low sample volume requirements, detailed kinetic information of affinity partners, swift response to concentration spikes, enhanced selectivity and sensitivity through the use of nanosized particles, and feasibility for complex sample detection. Although SPR-based biosensors offer high sensitivity and label-free detection of microbial pathogens, their applicability in clinical and industrial settings is limited (López-López et al. 2018).

Among many of the optical characteristics, fluorescence has been the most commonly used transducer by various researchers, primarily based on several parameters, including luminescence energy transfer, non-radiative, quenching efficiency, anisotropy, lifetime, and intensity. Organic fluorophores are an attractive option for the development of fluorescent probes in most fluorescent biosensors because they are bright and very stable. Furthermore, the fluorescent characteristics of many of these organic fluorophores are sensitive to changes in the environment, which are essential for biosensing applications (He et al. 2020; Tian et al. 2021; López-López et al. 2018). To detect biomolecules at ultralow levels, the biorecognition elements, like antibodies, are immobilized on the surface of the sensing element through the use of crosslinking agents or covalent modifications. Subsequently, the fluorescent substance tagged with target molecules is introduced to the surface of the sensing element, resulting in the binding of the target molecules

to the biorecognition elements. This is the basic principle of the detection mechanism behind the fluorescent-based biosensors (Omanovic-Miklicanin and Valzacchi 2017). The limitation of this approach is that certain fluorescent substances are bleached rapidly after exposure to light and are highly susceptible to matrix constituents and external conditions, including the pH value of the solution. In addition, both indirect and direct labelling approaches have their own drawbacks. The indirect labelling approach is much more complex and time-intensive, whereas the direct labelling approach based on certain fluorophores is less reliable and more harmful to the labelled target biomolecules compared to the tiny biomolecules labelled in the indirect labelling approach (Silva and Hellberg 2021).

Raman spectroscopy has been one of the most powerful spectroscopic techniques owing to its high molecular specificity and provides a fingerprint for the recognition of target biomolecules (Xue 1997; Virtanen et al. 2017). Raman spectroscopy utilizes cost-effective instrumentation that requires less sample preparation, as the immobilized recognition element is highly selective towards the target chemical species. Raman spectroscopy has not been widely applied to biological material owing to its extremely low signal yield. Nevertheless, two analytical techniques have been utilized to improve the sensitivity of biosensors, including surface-enhanced Raman spectroscopy and resonance Raman effects, which provide 10^8- and 10^6-fold enhancement in Raman signal intensity, respectively (Xue 1997; Virtanen et al. 2017). In general, the enhancement in Raman signal strength is known to be directly attributable to the interaction between highly concentrated electromagnetic fields and target chemical species. The downside of employing this analytical technique is that, even now, it is a modern technique and has been widely utilized by physicists instead of bioengineers until now, but still needs approval from the molecular biology and diagnostic communities in the implementation of advanced technology for use in many research areas (Xue 1997; Virtanen et al. 2017).

12.2.3 Mass-Based Techniques

Over the past decade, magnetoelastic and piezoelectric techniques have been widely employed for the detection and quantification of chemical species. Ferromagnetic alloys, which are amorphous in nature and have a ribbon-like structure, are generally used for the fabrication of magnetoelastic sensors (Tombelli 2012; Hong et al. 2010; Zou et al. 2020; Lu et al. 2012; Fazial and Tan 2021). Typically, magnetoelastic sensors are designed and developed with a size of 0.04 m $\times$ 0.006 m $\times$ 25 $\times$ 10^{-6} m. In magnetoelastic sensors, elastic waves are generated due to the production of longitudinal vibrations in the sensor when exposed to time varying pulsed magnetic fields. Subsequently, magnetic flux is generated as soon as the formation of elastic waves occurs within the sensing material (Tombelli 2012; Hong et al. 2010; Zou et al. 2020; Lu et al. 2012; Fazial and Tan 2021). In addition, magnetoelastic sensors associated with biorecognition elements have also been extensively utilized for the detection of biomolecules, where the difference in the amount of biomolecule that interacts with the immobilized biorecognition element causes a change in the

resonance characteristics that forms the basis for the quantification of target biomolecules in real-time samples. Another technique that has been extensively used for the construction of biosensor is piezoelectric based (Tombelli 2012; Hong et al. 2010; Zou et al. 2020; Lu et al. 2012; Fazial and Tan 2021). In piezoelectric-based biosensors, an alternating voltage is applied to the surface of the sensor using two electrodes. When the quartz crystal is connected to the oscillator circuit, the alternating voltage applied between the electrodes induces mechanical oscillations in the quartz crystal, thereby determining the corresponding oscillation frequency. The difference in the mass of the piezoelectric sensor when exposed to a real-time sample can be determined by the change in the oscillation frequency. This type of sensing mechanism behind piezoelectric sensors provides quantitative information about the physical characteristics of an analyte of interest (Tombelli 2012; Hong et al. 2010; Zou et al. 2020; Lu et al. 2012; Fazial and Tan 2021).

12.3 Biosensors for Pathogen Detection

The need for efficient food security has grown considerably in recent times. As reported in the literature, illnesses induced by bacterial contamination account for 40% of all infectious diseases. These infectious illnesses caused by foodborne pathogens have a major impact on the lives of people and the health of the environment (Bridle and Desmulliez 2021). The major predominant pathogens that cause foodborne illnesses are parasites, viruses, and bacteria; however, fungal foodborne illnesses are also reported. Among the various foodborne pathogens, bacteria are the most prevalent and are responsible for the highest number of foodborne disease outbreaks worldwide, including the number of hospitalizations (63.9%) and fatalities (63.7%) recorded. Excessive consumption of bacteria-contaminated food induces sensory impairment, acute joint inflammation, mental disorder, kidney failure, and repetitive intestinal irritation. Furthermore, foodborne illness can exist due to contaminants formed by fungi or bacteria, which can persist even after food processing (Di Nardo and Anfossi 2020). Pathogenic microorganisms and their toxins can easily affect fresh foods such as chicken and beef or eggs, fruits, vegetables, dairy products, and also processed seafood.

An effective microbiological environmental monitoring system can provide information on potential microbiological vulnerabilities in food products, identify issues and thus facilitate robust microbiological safety. Surveillance of microbial food safety leads to better welfare, higher production, increased income, and sustainable growth (Huang et al. 2018). That is why national authorities have been recommended to adopt adequate food safety measures to improve food security and nutrition. Therefore, scientists are making significant efforts to develop simple and efficient approaches to meet the need for regular testing and monitoring of microbial pathogens in food products (Kaya et al. 2021). The need to detect microbial contaminants in processed foods encompasses many analytical techniques, most of which are very advanced and expensive.

In the traditional approach, the recognition of pathogens is mostly based on the detection of specific biochemical and microbiological components. The polymerase chain reaction method, the microbial colony-counting method, the microbial-culture method, and the immunology-based method are the four types of traditional approaches used for the recognition of pathogens. The culture technique produces reliable estimates owing to its increased sensitivity and selectivity. Based on the growth of different species of microbes that thrive on seafood products, particular pathogenic microorganisms are recognized. The process involves targeted plating, selective growth of microbes, uninhibited growth of indigenous microbes and recognition, which takes a couple of days to yield results (Vu et al. 2021).

Polymerase chain reaction (PCR) is a widely known technique for the recognition of pathogens. Based on their nucleic acid sequence, viruses, bacteria, and protozoa are recognized using PCR. Diverse PCR techniques are used for the recognition of pathogenic microbes, including multiplex PCR, real-time PCR, and reverse transcript PCR. Nevertheless, the technique uses expensive tools, and the quantification, separation, and amplification of DNA technology make it a difficult and complicated process to complete the test. Furthermore, PCR needs qualified professionals to carry out the overall process (Nguyen and Il Kim 2020). Another popular method widely used for the recognition of pathogens is the immunological detection technique, which relies on the binding interaction between antibody and antigen. This technique has been effectively employed to recognize *E. coli* and *Salmonella*. Other techniques commonly used for immunological recognition include flow injection immunoassay, enzyme-linked immunosorbent assay, enzyme-linked fluorescent assay, and enzyme immunoassay. The advantage of these methods is that they require less time to recognize the presence of pathogens in seafood than the culture technique. Nevertheless, these methods do not allow real-time detection of pathogens (Cesewski and Johnson 2020).

On the other hand, the principle of recognizing microbial pathogens using a bioreceptor modified electrode describes an attractive and simple electrochemical biosensing approach that does not necessitate the use of technically skilled professionals and sophisticated instruments. This approach usually employs voltammetry techniques to explicitly detect microbial by-products and metabolites (Chen et al. 2020). In addition, microarray devices can also be used to detect pathogens by recognizing redox biomolecules naturally produced by microbial cells. The microelectrodes commonly used in these microarray devices could detect low levels of pathogens in seafood by delivering a large current density with low capacitive current. Despite this, the current measured at the microelectrode is in the nanoampere to picoampere range, which is relatively low. The disadvantage can be overcome by employing a series of hundreds of individual microelectrodes in which the intensity of the current signals increases significantly with the number of electrodes in the microarray sensor device (Di Nardo and Anfossi 2020; Huang et al. 2018; Nguyen and Il Kim 2020). In comparison to the electrochemical detection of pathogen-specific biomolecules, electroactive species, and cellularly derived materials, certain pathogens necessitate the fabrication of multi-layered nanostructures on the electrode surface for pathogen detection. Rapid advancements

and innovations in emerging 2D nanomaterial synthesis, detection approaches and electrode design, including screen-printed electrodes, paper-based electrodes and quantum dots modified electrodes, have dramatically improved the limit of detection and sensitivity of pathogen sensors (Bridle and Desmulliez 2021; Kaya et al. 2021; Nguyen and Il Kim 2020). Aside from achieving low detection limits, yet another obstacle in the field of electrochemical biosensing is the simultaneous detection of numerous different pathogenic species (Kaya et al. 2021; Vu et al. 2021; Nguyen and Il Kim 2020). The amalgamation of microfluidic and electrochemical devices is an intriguing technique that has been widely used for these complex detection schemes. Microfluidic devices use the control of fluid movement to perform sample processing, isolation, and recognition within the chips that are often compact and small in size. Furthermore, microfluidic chips can be designed with a variety of functions for the rapid detection of different pathogen species, enabling high-throughput screening of target pathogens (Nguyen and Il Kim 2020; Cesewski and Johnson 2020; Chen et al. 2020).

In mariculture, reliance on fishing for the production of various marine fish is growing globally owing to stringent legal laws, rising costs, and the decline of conventional fishing industries (Thandavan et al. 2013). Therefore, recognition of changes in the quality of marine fish after capture is of paramount importance. During fish storage, a significant number of fish are always kept on melting ice to maximize their shelf-life (Leonardo et al. 2017). Nevertheless, the presence of spoiled sea fish in a large quantity of sea fish during storage can deteriorate other freshly caught fish. For this reason, diagnostic tests on frozen fish are important to assess the quality of the fish on a daily basis and to identify infections and diseases at an early stage (Yazdanparast et al. 2019). Thus, there is a strong demand to construct a monitoring system for swift and accurate assessment of fish quality.

Scientific research has shown that blood glucose levels in marine fish differ depending on the degree of stress; their levels can be correlated with nutrient intake and respiratory abnormalities, which can be considered as indicators of fish health (Serrano et al. 2020). Furthermore, the substantial reduction in blood cholesterol levels can also be correlated with the ability of the fish to combat infectious diseases (Kobun 2021). On the other hand, fluctuations in lactic acid and cortisol levels act as significant indicators for the diagnosis of stress levels in marine fish. These assessments are traditionally performed utilizing diagnostic test kits developed for human use and involve complex processes, including sampling, processing, blood collection, and fish capture by absorption spectrometry (Riu and Giussani 2020).

12.3.1 Biogenic Amine Sensors

Biogenic amines produced from the pathogenic decarboxylation of their respective amino acid precursors are tiny organic polycations with heterocyclic (histamine and tryptamine), aromatic (phenylethylamine and tyramine) and aliphatic structures (cadaverine, putrescine, spermidine and spermine), typically found in marine fish, which are associated with several biological processes (Henao-Escobar et al. 2016).

Based on the number of amino groups, the biogenic amines are classified into polyamines, diamines, and monoamines. At low levels, these biogenic amines are not considered to be a significant threat to humans. Nevertheless, seafood that contains high levels of biogenic amines can have numerous pharmacological and toxicological effects on human health. In particular, most are either vasoactive or psychoactive amines, which affect both the vascular and nervous system (Frébort et al. 2000).

Histamine poisoning, which induces a reaction called scombroid fish poisoning, is the most prevalent intoxication ever recorded. This leads to numerous neurological, hemodynamic, cutaneous, and gastrointestinal disorders. On the other hand, phenylethylamine, tryptamine, and tyramine cause hypertension and migraines, while cadaverine and putrescine inhibit enzymes such as histamine methyltransferase, diamine oxidase, and monoamine oxidase. The high levels of these biogenic amines in seafood and their products serve as indicators to detect the degree of microbial spoilage (Lavagna et al. 2021). In addition, the formation of this type of biogenic amine is strongly affected by the composition of microbes, seafood, and various other factors associated with microbial growth through food processing and storage. The production of biogenic amines can also be accelerated by different circumstances, including increased temperature, lack of refrigeration, and loss of power over an extended period of time, leading to increased production of biogenic amines and microbial proliferation (Zhang et al. 2019).

Once fish are caught at sea, microbial pathogens cause muscle protein deterioration, which ultimately results in the aggregation of a variety of volatile nitrogen containing compounds, especially ammonia, through the bacterial action on nitrogenous compounds and amino acids. The amount of accumulated volatile nitrogen containing compounds offers quantitative analytical information on the deterioration of dead fish and is suitable for the assessment of sensory data (Mustafa et al. 2021). Trimethylamine oxide is commonly distributed in a wide range of sea fish and is decomposed to trimethylamine by the enzymatic (trimethylamine oxide reductase) action of bacteria. The existence of a substantial level of trimethylamine can often be correlated with the loss of freshness of sea fish products because trimethylamine is not present in frozen marine fish during the first 5 days of refrigerated storage (Mohammed et al. 2016). The formation of trimethylamine in various species of marine fish is also characterized by an elevated amount of hypoxanthine. Volatile sulphur compounds like dimethyl sulphide, methanethiol, and hydrogen sulphide are also common components of spoiled sea fish products formed by the action of bacteria on sulphur containing methionine, cysteine, and amino acids.

Marine fish and products made from fish are highly edible owing to their unique features, as already described. Marine fish must be effectively frozen instantly after harvest to delay microbial and autolytic spoilage (Mustafa et al. 2021). Depending on the species of fish, the typical shelf-life of marine fishery products that are instantly frozen after capture varies from 1 to 2 weeks. Recent research findings on the effect of refrigeration on the shelf-life of frozen fish has shown that microbial contamination doubles as the storage temperature increases from 273 K to 276 K, whereas the frozen fish deteriorates by a factor of five or six when the storage

temperature is 283 K, which dramatically shortens the shelf-life of frozen fish. On the other hand, exposure to gamma radiation, dehydration, storage conditions, and freezing are the commonly used processing methods to increase the shelf-life of frozen fish products (Frébort et al. 2000). One of the significant issues in the assessment of biogenic amines is their trace amounts in a complex matrix. Therefore, developing advanced fish health diagnostic tools for rapid and selective recognition of biogenic amines is of utmost importance.

Most biogenic amine sensors based on an optical platform use the traditional sensor design in which a probe for detecting the target biogenic amine is attached to the solid surface of the sensing system or immobilized in a microporous membrane. Conventionally, simple soaking, spin coating, and knife coating are employed to deposit the biorecognition layer (Quan et al. 2021; Saravanakumar et al. 2020; Shojaeifard et al. 2021; Nedeljko et al. 2017; Wang et al. 2021b). The probe is often embedded as a thin film in the polymer layer, or may eventually reside on another film, such as nanofibres, hydrogel, polymer particles, silicon or gold. Following the probe immobilization procedure, various optical techniques are used to detect biogenic amines. The analytical signal produced by this type of optical biosensing system is proportional to the amount of biogenic amines that bind to the bioreceptor (Quan et al. 2021; Saravanakumar et al. 2020; Shojaeifard et al. 2021; Nedeljko et al. 2017; Wang et al. 2021b). However, since most biogenic amines lack structural characteristics that facilitate optical recognition, they must be converted to corresponding derivatives with the desired recognition features. There are several types of derivatization reagents, including redox reagents, fluorogenic molecules, fluorophores, and chromophores (Quan et al. 2021; Saravanakumar et al. 2020; Shojaeifard et al. 2021; Nedeljko et al. 2017; Wang et al. 2021b). This type of regent has been extensively employed for the derivatization of polyamines, secondary amines, and primary amines to produce coloured products, which are then chromatographically determined using a fluorescence or absorbance detector. Nevertheless, many of these techniques necessitate the use of complex and sophisticated instrumentation that cannot be deployed in resource-limited settings, and the associated reagents cannot be employed in the fabrication of optical biosensors for biogenic amines due to their lack of storage and operational stability within the sensor membrane. On the other hand, biosensors based on electrochemical transducers provide a low-cost and easy-to-use point-of-care platform for the selective, swift, reliable, and sensitive recognition and quantification of biogenic amines (Quan et al. 2021; Saravanakumar et al. 2020; Shojaeifard et al. 2021; Nedeljko et al. 2017; Wang et al. 2021b).

12.3.1.1 Role of Nanoparticles in Biogenic Amines Detection

Advances in nanotechnology have reached several critical milestones in the detection and quantification of biogenic amines. The analytical response characteristics of nano-biosensors can be enhanced by the unique and interesting physicochemical attributes of nanoparticles, including rapid response times and excellent catalytic efficiency. They also increase the electron transfer rate, offer ultrahigh surface area-to-volume ratio and superior sensitivity for effective adsorption of enzymes,

including polyamine oxidase, diamine oxidase and monoamine oxidase (Yazdanparast et al. 2019). Furthermore, they can also mimic the catalytic behaviour of the enzyme by coupling with biomolecules for selective biorecognition of biogenic amines. Nanozymes are nanoparticles-based intrinsic enzymes, which serve as potential substitutes for bioactive enzymes, thus overcoming the inherent disadvantages of enzymes (Gumpu et al. 2014, 2016). In specific, a large number of carbon nanomaterials and metal nanoparticles have been utilized to fabricate efficient biosensors. In addition, zeolites and gold nanoparticles are extensively employed to construct amperometric biosensors. Since their excellent electrical conductivity offers adequate electrical wiring between the electrode and the active sites of the immobilized enzymes, limited diffusion limitations are imposed. The development of core-shell nanoparticles with the gold core and conductive polymer shell is also emerging rapidly in recent years due to their diverse structure and composition which can be used for specific purposes (Henao-Escobar et al. 2016).

12.3.1.2 Sensing Mechanism Involved in the Detection of Biogenic Amines

The biosensors developed for the detection of biogenic amines are based on the inclusion of an enzyme in the immediate vicinity of the working electrode. During enzyme catalysis, the immobilized enzyme either generates electroactive species or engulfs an electroactive reactant so that the target biomolecule can be explicitly quantified by consumption or generation of reactants (Gumpu et al. 2014). A group of natural enzymes that play the main role in the evaluation of biogenic amines are amine oxidases (AOx). Until now, polyamine oxidase, diamine oxidase, and monoamine oxidase were the enzymes commonly used for the development of modified electrodes to catalyse the oxidation of biogenic amines in the presence of water and molecular oxygen with the release of hydrogen peroxide and ammonia (Gumpu et al. 2016).

$$\text{Biogenic amine} + O_2 + H_2O \overset{\text{AOx}}{\rightarrow} \text{Ammonia} + \text{Aldehyde} + H_2O_2$$

$$H_2O_2 \overset{\text{Electric potential}}{\rightarrow} 2H^+ + O_2 + \text{electrons}$$

For instance, Gumpu et al. (2014) modified glassy carbon electrode with core-shell nanoparticles of polyaniline and ceria for the recognition and quantification of histamine in fish samples using amperometry as an electroanalytical technique (see Fig. 12.1). They utilized diamine oxidase enzyme as a biorecognition element to specifically recognize histamine in tiger prawns, and the detection mechanism was based on the interaction between histamine and diamine oxidase. Besides, the same group developed ceria nanospheres modified glassy carbon electrode as an efficient platform for the immobilization of diamine oxidase and applied it to the electrochemical detection of putrescine in tiger prawns (Gumpu et al. 2016). The developed biosensor is suitable for use in aquatic settings because of the specific interaction

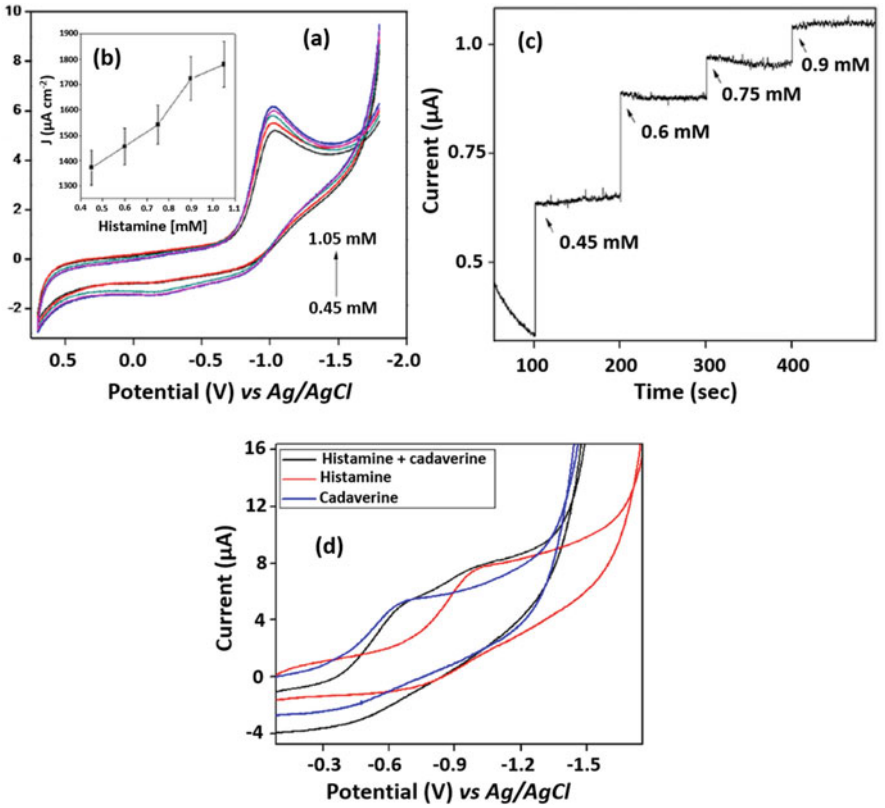

Fig. 12.1 (**a**) Cyclic voltammograms and (**b**) calibration plot for varying concentration studies of histamine on modified GCE/CeO_2 at 524 K-PANI/DAO in 0.1 M PBS (pH 7.4), (**c**) amperometric response for varying concentration studies of histamine on modified GCE/CeO_2 at 524 K–PANI/DAO in 0.1 M PBS (pH 7.4) at –0.1 V and (**d**) comparative study of specificity studies of histamine, cadaverine and combination of histamine, cadaverine (reproduced with permission from Gumpu et al. (2014))

between diamine oxidase and putrescine, as well as the enhanced electron transfer mediated by ceria nanospheres (see Fig. 12.2).

12.3.2 Biosensors for the Detection of Formaldehyde

The International Agency for Research on Cancer has listed formaldehyde as a Group I carcinogen because it is considered toxic to animals and humans. Formaldehyde accrues in the human placenta and dramatically shortens the lifespan (Aini et al. 2016). Formaldehyde is widely utilized as a bath treatment in mariculture and the preservation of seafood products. These days, sellers of marine fish have started using formaldehyde, widely regarded as formalin, to prevent spoilage of marine fish,

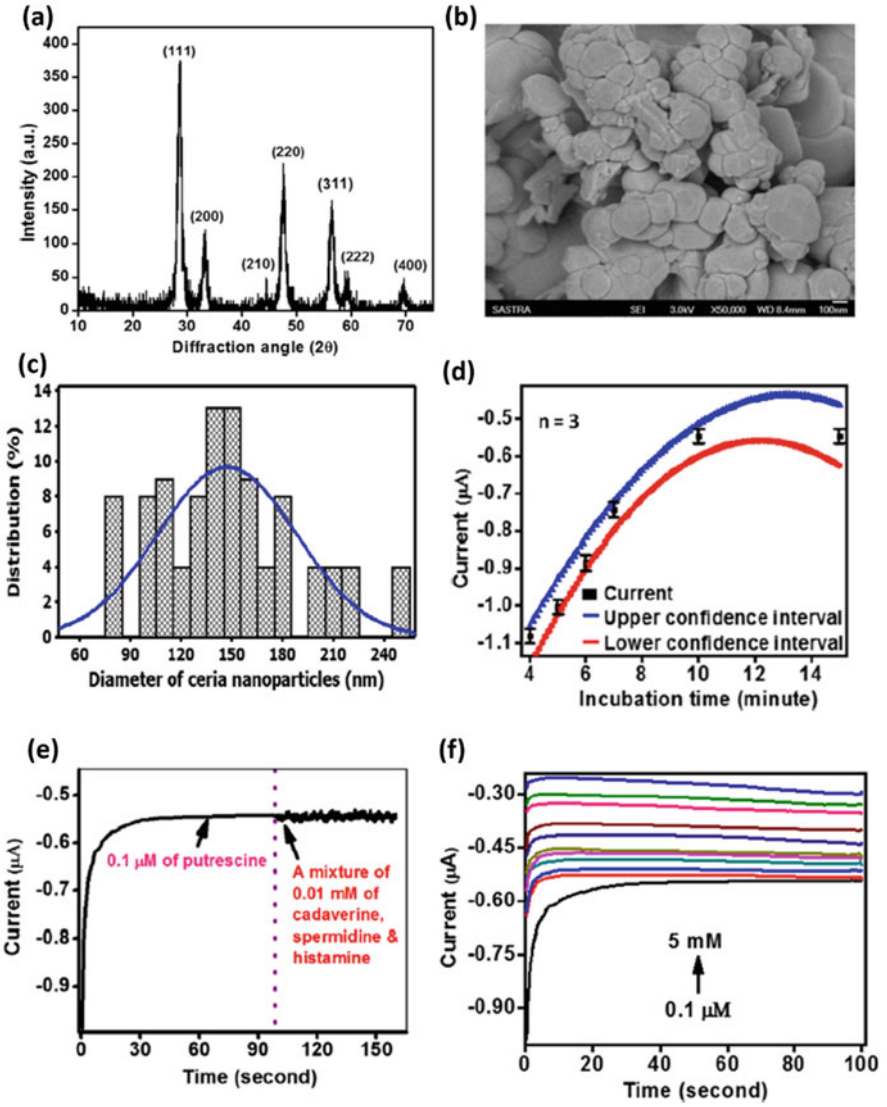

Fig. 12.2 (**a**) X-ray diffraction pattern, (**b**) FE-SEM image and (**c**) particle size distribution of the as-prepared CeO_2 nanoparticles. (**d**) Effect of incubation time of putrescine and (**e**) interferents (mixture of 0.01 mM of cadaverine, spermidine, and histamine) on the amperometric response using GCE/CeO_2/DAO/Chitosan in PBS (0.1 M, pH 7.4) containing 0.1 μM putrescine performed at an applied potential of 0.729 V and (**f**) amperograms of GCE/CeO_2/DAO/Chitosan for increasing putrescine in 0.1 M PBS (pH 7.4) at an applied potential of 0.729 V (reproduced with permission from Gumpu et al. (2016))

as the compound is a recognized food preservative. Recent reports and studies have shown that the use of formalin in the bodies of marine fish to prevent decomposition is very common, especially in Asian countries. Ineffective cold storage facilities and the transportation of seafood over a long period of time make seafood vendors succumb to this kind of malpractice.

Although formaldehyde is used as an antimicrobial agent, it is a harmful chemical that induces little corrosion of the gastrointestinal lining, causing vomiting (Aini et al. 2016). Seafood producers often apply formaldehyde to freshly caught seafood, including echinoderms, molluscs, crustaceans, fish, etc., at a harmless level to increase their shelf-life. On the other hand, marine fish typically produce low quantities of formaldehyde owing to the deterioration of bodily substances with post-mortem chemical compounds (Ozoner et al. 2013). In addition, formaldehyde can be produced during the ageing of fresh fish. Furthermore, enzymatic activities and certain biochemical reactions, including bacterial metabolism and lipid oxidation, are also responsible for the formation of formaldehyde in marine fish. This may potentially induce physical harm to fish meat or the development of biochemical toxins, including biogenic amines or other undesirable substances.

Electrochemical sensors are regarded as a viable alternative for formaldehyde recognition and quantification because they offer rapid response, high sensitivity, elevated selectivity and real-time measurements. Herschkovitz et al. (2000) modified screen-printed electrodes with $Os(byy)_2$-poly(vinylpyridine) and formaldehyde dehydrogenase to specifically recognize ultralow levels of formaldehyde through the chemical interaction between the immobilized formaldehyde dehydrogenase enzyme and formaldehyde (see Fig. 12.3). The electrochemical reactions that occur in the vicinity of the chemically modified screen-printed electrodes are as follows:

$$\mathrm{HCHO} + \mathrm{NAD}^+ + \mathrm{H_2O} \rightarrow \mathrm{HCOOH} + \mathrm{NADH} + \mathrm{H}^+$$

$$\mathrm{NADH} + \mathrm{OS_{ox}} \rightarrow \mathrm{NAD}^+ + \mathrm{OS_{red}} + \mathrm{H}^+$$

$$\mathrm{OS_{red}} \rightarrow \mathrm{OS_{ox}} + 2\mathrm{e}^-$$

The effectiveness of electron transfer from nicotinamide adenine dinucleotide hydride (NADH) to the screen-printed electrode via the $Os(byy)_2$-poly (vinylpyridine) mediator determines the rapidity of the electrochemical sensing process. The detection limit of the developed sensor was 30 ng mL^{-1}. Besides, Aini et al. (2016) synthesized nanocomposites consisting of chitosan and gold nanoparticles embedded in an ionic liquid and deposited on the surface of glassy carbon electrode to quantify the wide range of formaldehyde in fish samples, including *Thunnus tonggol* and *Lutjanus malabaricus*. They utilized methylene blue as a redox mediator to enhance the rate of electron transfer, thereby increasing the sensitivity of the developed electrochemical against formaldehyde and enabling rapid detection within 5 s. Similarly, an electrochemical sensor based on

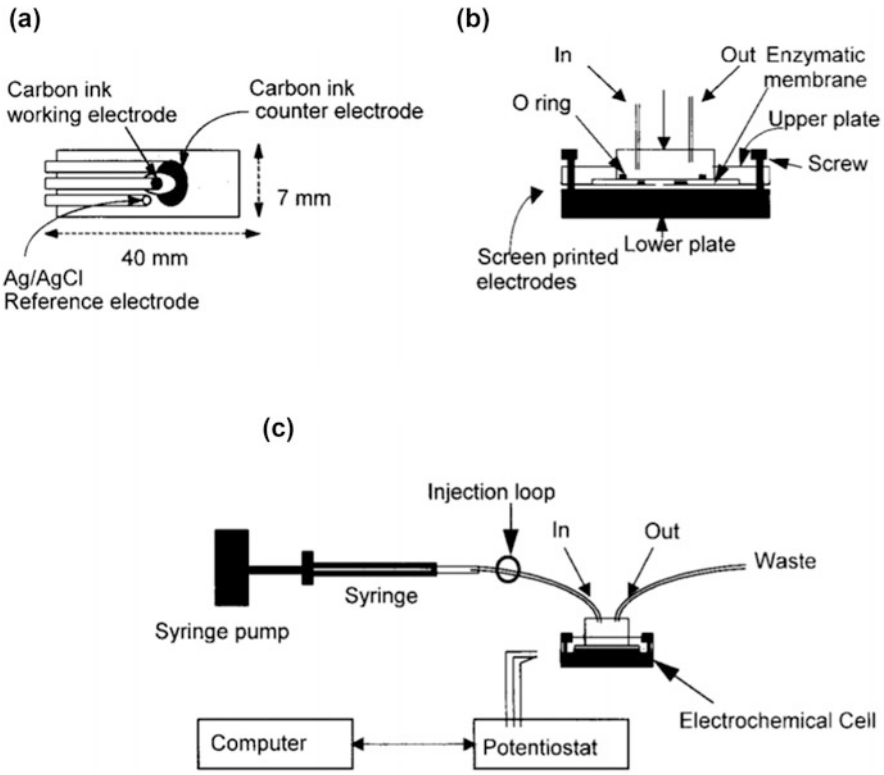

Fig. 12.3 The electrochemical cell setup. (**a**) Screen-printed electrodes. (**b**) The electrochemical flow cell. (**c**) The whole measuring system (reproduced with permission from Herschkovitz et al. (2000))

nanocomposites of polypyrrole, formaldehyde dehydrogenase and poly(glycidyl methacrylate-co-3-methyl thienyl methacrylate) was also reported for the determination of formaldehyde (Ozoner et al. 2013). Other commonly used approaches include fluorometry and spectrophotometry, both of which are based on the Hantzsch reaction. Recently, Veríssimo et al. (2020) coated the tip of optical fibre with polyoxometalate salt, which causes the interaction between formaldehyde and polyoxometalate to take place, resulting in a change in the intensity of the bands observed at 261 and 329 nm. The proposed optical sensor based on polyoxometalate modified optical fibre exhibited detection and quantification limits of 0.2 and 0.6 mg L^{-1} for formaldehyde, respectively.

12.3.3 Biosensors for the Detection of sulphur Dioxide

Sulphur dioxide, a colourless gas, is commonly used as a food preservative and a refrigerant in food processing industries. Under the jurisdiction of the Food and

Drug Administration (FDA), sulphur dioxide is utilized as a food additive in the United States of America for fish, meat, syrups, fruit juices, vegetables, wine, and beer (Hodgson et al. 1999). In particular, it serves as a food preservative in seafood and related products due to its inherent antimicrobial properties. Furthermore, sulphur dioxide acts as an inhibitor of several enzymes that eventually lead to the discolouration process (Tyagi et al. 2014). Additionally, sulphur dioxide can prevent enzymatic browning reactions facilitated by polyphenol oxidase and inhibit the proliferation of certain yeast. Numerous seafood products have been shown to contain substantial levels of sulphur dioxide. This is the outcome of a preservative or processing approach in which seafood is distributed on screens underneath where heated sulphur is present. When heated, the cloud of fine suspended sulphur particles in gaseous form gently passes through the seafood and leaves certain traces. Excessive consumption of seafood contaminated with sulphur dioxide has irreversible adverse effects on human health (Tyagi et al. 2014).

Hodgson et al. (1999) developed an efficient electrochemical sensor to recognize and quantify various levels of sulphur dioxide in the range of 1–100 ppb. The electrochemical sensor was fabricated with a porous gold-solid polymer electrolyte so that the sulphur oxide diffused from the sample comes into direct contact with the electrode surface, allowing for the detection of trace amounts of sulphur oxide as low as 1 ppb. Besides, Tyagi et al. (2014) also reported on the use of metal nanoparticles (V_2O_5, MgO, NiO, CuO, and PdO) integrated tin oxide nanocomposites to design an e-Nose for the detection of sulphur dioxide. Among the various developed sensors, the e-Nose based on nanocomposites made of NiO and SnO_2 showed the highest sensing response with a swift response time of 80 s when operated at 453 K.

12.3.4 Biosensors for the Detection of Sodium Benzoate and Sodium Lactate

Chemical preservatives, like sodium benzoate and potassium sorbate, are often employed to preserve the nutritional quality and improve the shelf-life of seafood in certain Asian countries (Alizadeh et al. 2012). Nevertheless, the use of such artificial ingredients could induce allergy outbreaks or adverse effects in customers if they ingest more sodium benzoate than the recommended daily allowance for an extended period of time in their diet. Nowadays, customers prefer to eat nutrient-dense foods that are relatively low in sodium and fat and provide additional nutritional value. These seafoods will require a significant decrease in the utilization of synthetic ingredients and a substantial use of natural organic additives in seafood preservation (Akter et al. 2017).

Alizadeh et al. (2012) developed a solid-state sensor to selectively recognize benzoate using benzoate-doped polypyrrole as an efficient platform in which pulsed galvanostatic technique was employed to electropolymerize polypyrrole on the platinum electrode surface in the presence of benzoate ion to form benzoate-doped polypyrrole film. The potentiometric sensor was calibrated against benzoate solutions at concentrations ranging from 90 μM to 20 mM, yielding a linear response

for benzoate up to 20 mM and a detection limit of 50 μM. Although the proposed sensor does not require an ion exchanger, plasticizer or internal filling solution, sample pre-treatment is necessary to separate the benzoate from potentially interfering species. On the other hand, a small sample size is sufficient for performing high performance liquid chromatography analysis, and testing can be tailored to the level of quantification required. For instance, Akter et al. (2017) employed HPLC to detect benzoate using an isocratic solvent system consisting of acetic acid buffer and sodium acetate buffer of pH 4.0 prepared in a ratio of 20:80. The chromatograms were acquired at 254 nm for different concentrations of benzoate, exhibiting detection and quantification limits as low as 2.31×10^{-3} and 7.6×10^{-4} mg mL^{-1}, respectively. Despite the fact that the HPLC-based approach yielded promising results, optimizing experimental conditions such as mobile phase pH, composition, flow rate, and column type is necessary to achieve enhanced response for a given concentration of benzoate. Recently, Dinç Zor et al. (2016) used HPLC to detect benzoate at concentrations ranging from 5 to 30 μg mL^{-1} under optimized experimental conditions in which Box–Behnken design was employed to find the optimal flow rate, mobile phase pH, and composition of acetic acid and sodium acetate buffer, thereby enabling highly sensitive benzoate detection.

Sodium lactate, a major constituent of muscle tissue, is produced as a result of bacterial fermentation. Sodium lactate has been utilized to limit the spread of some microbes during storage, as well as to improve the quality and shelf-life of seafood and seafood products (Liu and Tan 1999). Furthermore, sodium lactate has been shown to have antimicrobial activity against certain microorganisms, including *Listeria monocytogenes* and *Clostridium botulinum*, which have caused serious issues in seafood and seafood products. The research results also show that the addition of sodium lactate can inhibit the growth of *Clostridium botulinum* on seafood products to a level below 3.5% (Hibi et al. 2012).

Hibi et al. (2012) developed a wireless monitoring system to detect the levels of lactic acid in fish products in real time. They utilized platinum-iridium wire as a working electrode, on which lactate oxidase was immobilized by crosslinking with glutaraldehyde. The developed biosensor system could detect concentrations of lactate in the range of 0.04–6 mg dL^{-1}. Finally, Hibi et al. combined a biosensing device with a wireless radio wave-based monitoring system to effectively monitor lactate concentrations for 60 h. Although the proposed wireless monitoring system continuously detects lactate levels in fish products, its accuracy in detecting ultralow lactate concentrations has not been fully established. On the other hand, optical biosensors have emerged as a viable option for lactate detection as they can provide adequate accuracy compared to other detection platforms. Liu and Tan (1999) developed an optical fibre lactate sensor capable of rapidly measuring lactate levels in less than 5 min. The surface of the optical fibre probe was modified with lactate dehydrogenase, which serves as a biorecognition element in the fabrication of lactate biosensor. Furthermore, successive engineering of the surface of the optical fibre probe with amine and aldehyde functional groups facilitated specific adsorption of lactate, enabling lactate recognition down to the micromolar concentration level. Recently, researchers have been interested in developing a range of multifunctional

flexible sensors, as they can facilitate continuous, real-time monitoring of sodium lactate contaminants in seafood products. For instance, Han et al. (2017) employed a piezoelectric biosensing unit composed of zinc oxide arrays and lactate oxidase enzyme in which the generation of a piezoelectric signal due to the chemical interaction between lactate and lactate dehydrogenase enzyme does not require an external power supply or battery, thereby forming a self-powered biosensing system.

12.3.5 Biosensors for the Detection of Borax

Borax has long been utilized as a preservative in a number of seafood products. Since borax is extremely effective against pathogenic yeasts and less effective against certain bacteria, it is widely used to preserve seafood (Simple Qualitative Detection Method of Borax in Food 2014). Furthermore, borax can also be employed to improve the crispness and elasticity of seafood and to help avoid discolouration of marine fish. At trace levels, borax can be transformed into boric acid in human blood. In humans, the adverse effects caused by a significant decrease in the daily intake of boric acid contaminated seafood are considered highly unlikely (Yunianto et al. 2021). Nevertheless, consuming too much boric acid contaminated seafood for a few days can sometimes directly affect the brain, kidney, liver, intestine, and stomach and can even lead to death. Animal studies have shown that high consumption of seafood contaminated with boric acid over an extended period of time can often induce reproductive and adverse cognitive development effects. Impeded fertility and testicular lesions have also been found in laboratory animals when boric acid is administered daily. Besides that, there has been no scientific evidence that boric acid is harmful to genes or carcinogenic. Due to the risk of developing toxicity in humans, the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations have declared that it is dangerous to use boric acid as a preservative for seafood (Fast Detecting Test Paper for Borax and Boric Acid in Foodstuff 2006).

Yunianto et al. (2021) utilized a fibre optic sensor to detect a wide range of borax in food products. The absorbance value measured at 419 nm during the first stage of evaluation in food products confirmed the increase in the boracic content. In the second stage of assessment, the transmittance intensity values decreased linearly with increasing borax concentration in food products, demonstrating the ability of the developed fibre optic sensor to recognize borax with enhanced accuracy. Besides, paper-based sensors incorporating promoters, stabilizers, acid agents and curcumin have also been used to detect borax in food products (Fast Detecting Test Paper for Borax and Boric Acid in Foodstuff 2006). The proposed paper-based sensor offered high rapidity and portability and could provide better performance results in terms of sensitivity and selectivity than other analytical methods. The advantages of the paper-based sensor that make it popular for the detection of borax in food products are its simplicity, ease of use, accurate detection, and visual evaluation with the naked eye. Furthermore, to rapidly determine the prevalence of borax in food products, a simple qualitative approach was employed in which the

chemical interaction between borax and phenolic lipids causes a colour change from red to yellow, which has been used as a visual indicator to specifically assess the presence of borax in food products (Simple Qualitative Detection Method of Borax in Food 2014).

12.3.6 Biosensors for the Detection of Chitosan

Food preservatives can also be derived from natural sources that do not have significant adverse effects on human health. Over the past decade, technological advances have also been attempted in the production of natural food preservatives (Muzzarelli 1988). One of the natural food preservatives is the use of chitosan. Every day, a large quantity of shrimp waste is discarded due to the increased consumption of seafood, whose head and shell parts contain a significant amount of chitin, which is isolated and transformed into chitosan by removing sufficient acetyl groups in chitin utilizing strong bases or diluted acids (Abou-Shoer 2010). Chitosan is extensively employed in the food industry as a potential natural preservative potential substitute for borax and formaldehyde and has the ability to reduce microbial activity, thus decelerating the decomposition process. In addition, the polycationic nature of chitosan helps to reduce the proliferation of mould and bacteria on seafood products. Once the marine fish is caught at sea, it is immediately immersed in water containing 1.5% of chitosan to preserve the fish without refrigeration and to keep it fresh for a specified period of time. Another way to preserve marine fish is by spraying 2.5% of chitosan (Eikenes et al. 2005).

Muzzarelli (1988) proposed a colorimetric sensor to detect and quantify chitosan in which Cibacron brilliant red 3B-A was employed to provide quantitative data on the binding interactions between chitosan and Cibacron brilliant red 3B-A using Lambert-Beer law. Although the developed optical method can detect unknown levels of chitosan, it has not been applied to modified chitosan like glutamate glucan and N-carboxymethyl chitosan. In another work, Eikenes et al. (2005) described a fluorescent-coupled liquid chromatographic system to selectively detect chitosan based on acidic hydrolysis with acetic acid (see Fig. 12.4). The proposed sensor recognized chitosan with an enhanced fluorescence response over a wide linear range up to 45 mg g^{-1} with a satisfactory recovery of 86%. Besides, Abou-Shoer (2010) reported a simple and effective strategy to quantify chitosan using colorimetry as an analytical technique. The response of the proposed biosensor depends on the specific binding between the acid dye bromocresol purple and chitosan, and this binding process forms the basis for quantification of chitosan.

12.4 Conclusion

Elevated levels of biogenic amines formed as a result of microbial metabolism, as well as the excessive use of preservatives, can affect the quality of seafood. Therefore, a highly selective and sensitive analytical tool capable of analysing the

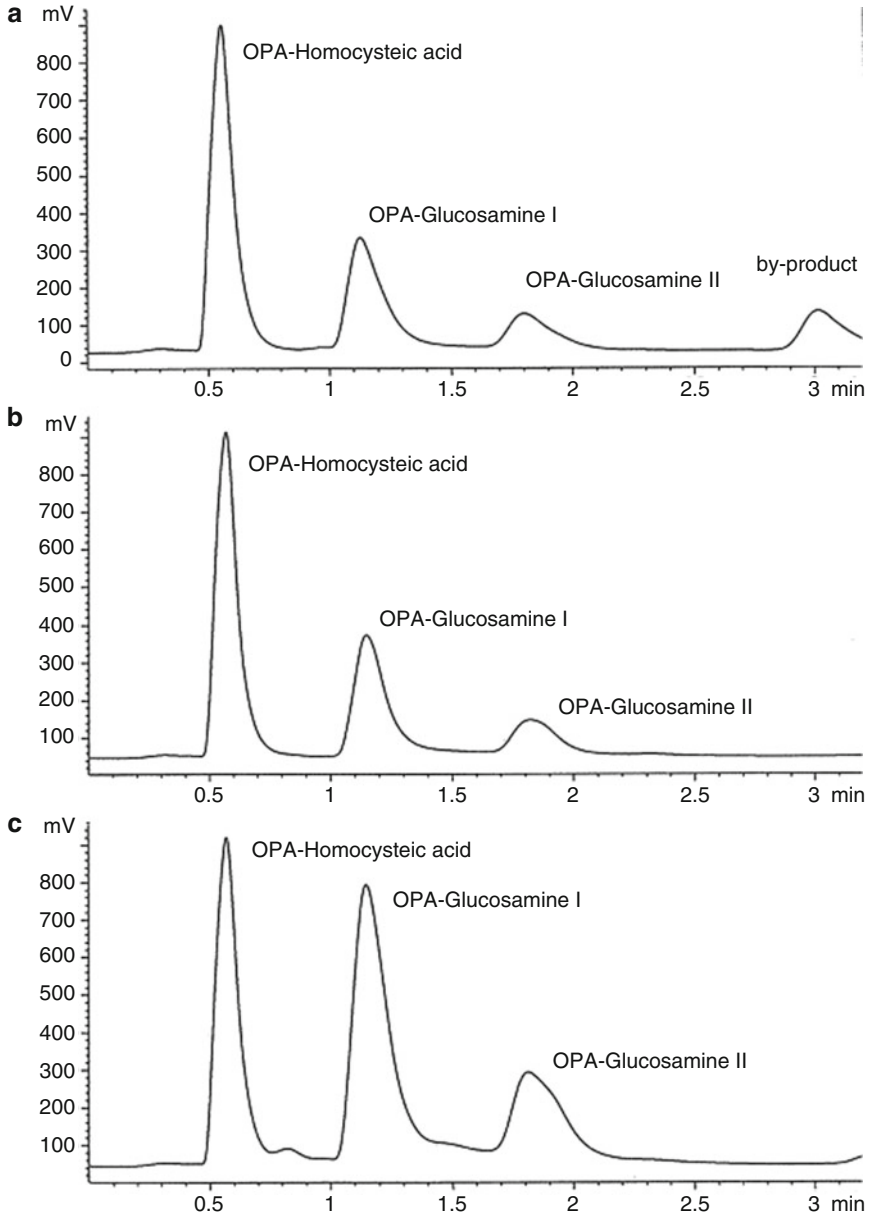

Fig. 12.4 Typical chromatograms for the HPLC analysis of glucosamine. The figure shows a chromatogram of a standard glucosamine solution derivatized with an OPA reagent that had been stored for 1 day at 4 °C (**a**), a freshly made OPA reagent (**b**) and a typical run of a hydrolysed sample with a freshly made OPA reagent (**c**). The first peak represents homocysteic acid and the second peak represents glucosamine (reproduced with permission from (Eikenes et al. 2005))

presence of ultralow levels of pathogen contaminants and preservatives is required to ensure food quality and safety. However, monitoring the freshness of seafood using a miniaturized biosensing system that reveals product quality during real-time analysis remains a difficult task for food industries around the world. The incorporation of engineered nanomaterials and bioreceptors into the design of sensing element, as well as their potential application in aquatic settings, could allow for continuous monitoring of food status, thereby extending shelf-life and reducing food waste. Nevertheless, most biosensors developed are still in their infancy and will require significant work before being deployed in aquatic settings. Therefore, issues regarding the reliability, selectivity, and sensitivity of the biosensor must be addressed when applied to a complex food matrix. The application of biosensors and chemical sensors for the quantification of biomarkers, as well as the implementation of analytical techniques for determining the freshness of seafood products, is a growing area of research. Despite considerable advances, there is still a need to validate the use of biosensing tools in aquatic settings for assessing the quality of seafood products. One of the most challenging tasks in this research area is the complexity of food samples, as well as the difficulty of rapidly quantifying spoilage biomarkers in closed packaged food without extensive sample processing. Therefore, monitoring for the presence of foodborne pathogens and excess preservatives in seafood products is of the utmost importance to ensure food quality and safety. Considering food quality and safety, an accurate, cost-effective, swift, sensitive, selective, and easily accessible method that can monitor even minor changes in the level of fish spoilage biomarkers is needed. The techniques explored have great potential for use in quality control, ultimately facilitating real-time monitoring of preservatives and microbial contaminants in seafood products. Electrochemical and optical sensors are preferred over other analytical techniques because of their applicability for effective and rapid on-site assessment of spoilage levels and excess preservatives in seafood products. Mediators are often employed to enhance the transfer of electrons between the surface of working electrode and the active sites of immobilized bioreceptors. Numerous intriguing biosensor prospects, including the use of nanofilms, nanoelectrodes, and multifunctional nanocomposites, are currently being investigated. The development of efficient biosensors would greatly aid researchers in detecting ultralow levels of biogenic amines and revealing the effects of excess preservatives in seafood products. An intriguing future prospect is how to control the excess of preservatives present in seafood samples while ensuring that the seafood meets high quality and safety standards.

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Utilizing Big Data as Analytical Tool for Food Safety Applications

13

Hasnanizan Taib and Syazana Abdullah Lim

Abstract

All food is at risk of contamination, and their consumption has caused an estimated 600 million people to fall ill every year. This chapter will provide a contextualized overview of big data technologies along with their roles, success applications, and various approaches in the food safety domain. The roles of Convolutional Neural Network (CNN), a deep learning algorithm for big data analytics, of food safety related data of various formats will also be discussed. It aims to recommend CNN as a potential algorithm for data analytics in parallel to rising developments of smartphone-based biosensors for applications in the food safety domain.

Keywords

Big data technologies · Convolutional neural network · Smartphone-based biosensor data · Food safety

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13.1 Introduction

Globally, contaminated food consumption has caused an estimated 600 million, or almost 1 in 10 people, to fall ill every year, leading to 420,000 deaths and a loss of 33 million healthy life years. Moreover, more than 200 different diseases, ranging from diarrhea to cancers, can be caused by some harmful bacteria, viruses, parasites, or chemical substances present in that unsafe food (World Health Organization 2021). To prevent or at least minimize foodborne illness, the essential emphasis in every procedural practice of food preparation, handling, and storage for global supply chain food safety should always be the prime concern. From farm to factory to fork, scientific assessment, management, and communication of contaminant risk should be done at every food production stage to prevent and control foodborne diseases.

Big data is transforming the society for the better, and it can hugely benefit the society in countless areas, including public health. Big data roots from the fast and overwhelming flow of data obtained from smartphones, the Internet of Things (IoT), and social media, leading to the invention of systems capable of processing data efficiently. It is associated with three concepts, i.e., volume, variety, and velocity; thus, generated big data are too large and complex for traditional database systems, technologies, and processes. The food industry also adopts big data technologies such as artificial intelligence, machine learning, natural language processing, predictive analytics, text analytics, data visualization, and data mining. Big data analytics can provide predictive insights, assist in making real-time decisions, and design monitoring systems and sampling strategies in all stages of the food supply chain. In the food safety domain, typical big data analytics such as data mining, predictive analytics, and machine learning, in particular, deep learning, have opened up immense opportunities to turn the big data into significant valuable insights or discoveries.

Smartphones nowadays have built-in capabilities with added accessories that enable them to sense different types of information for various deployments such as point-of-care testing (POCT), point-of-need detection, or point-of-use analysis applications. They are advanced with some detection abilities that can function like microscopes, ultrasound probes, stethoscopes, and label-free biosensors. POCT has been embraced in numerous industries (Roda et al. 2016), ranging from medical diagnostics, water quality monitoring, food safety, food processing quality control, and food pathogen detection. Thus, smartphone-based biosensing integrated with low-cost biosensors has the advantage of obtaining more detection tests that are readily available to unlimited users, in contrast to traditional biosensing performed in laboratories with limited access, resulting in an insufficiently amount of biosensor data for advanced analytical purposes and decision-making. In the food industry, this significantly means swift communication in case of a foodborne illness outbreak initiated by the general researchers or public.

Advanced technologies such as next-generation sequencing (NGS) and nanotechnology play their role in food safety too. NGS techniques can provide rapid routine testing for food pathogens, reducing the incidence of foodborne illnesses (Milicchio

and Prosperi 2017; Milicchio et al. 2018; Jagadeesan et al. 2019). Simultaneously, nanotechnology can also enhance food safety (Kumar et al. 2020; Hua et al. 2021; Ramezani et al. 2020; Kannan and Guo 2020); in alerting consumers and food distributors on food safety issues. Moreover, nanosensors are effective and precise in detecting the presence of any food pathogens. For examples, in Zhang et al. (2019), the authors developed a capillary biosensor for rapid detection of Salmonella using Fe-nanocluster amplification and smartphone imaging; Calabretta et al. (2020) have proposed a nano-lantern on paper for smartphone-based ATP detection; Guo et al. (2019) proposed magnetic nanoparticle immunoseparation, nanocluster signal amplification and smartphone image analysis for rapid detection of *Salmonella typhimurium*. Furthermore, Zeinhom et al. (2018a, b) presented smartphone-based immunosensor coupled with nanoflower signal amplification for rapid detection of *Salmonella enteritidis* in milk, cheese, and water; Fahimi-Kashani and Hormozi-Nezhad (2020) suggested a smartphone-based ratiometric nanoprobe for label-free detection of methyl parathion; in Zhang et al. (2018), the authors have developed a grating-coupled surface plasmon resonance smartphone biosensor for lipopolysaccharides detection; and lastly in Wang et al. (2019), the researchers have proposed microfluidic biosensor for online and sensitive detection of Salmonella typhimurium *via* fluorescence labeling and smartphone video processing.

The next few sections in this chapter will provide an overview of recent advancements in big data technology offered by state-of-the-art smartphones and explore their excellent potential to assist in decision-making by food industries. Although the usage of big data technology is still at its infancy stage, we will demonstrate how developments in this area will lead to near future implementations in the food safety domain.

13.2 Big Data and Its Enablers in Food Safety

Big data is an enormous data sets collection that grows exponentially with time. Its computational analysis can reveal valuable information such as patterns, trends, and associations with its applications is revolutionizing across all sectors of the economy globally as well as within and beyond science. Big Data generated from smartphones, social media, and the IoT has grown in an unprecedented pace in either structured or unstructured format, with no exception to the food industry. It is reported that big data in food safety remains in its infancy; however, it is embraced well by the entire food supply chain (Jin et al. 2020; Strawn et al. 2015; Pollard et al. 2018; Wang et al. 2015a, b).

Knowledge and insights discovery from big data has created massive value for food science and technology, including food safety. Familiarizing the sources of big data related to food safety as well as the ways they are stored and visualize reliably can provide a path for big data analytics to pave the way.

13.2.1 Sources of Big Data in the Food Safety Domain

In relation to food safety issues, the primary sources of big data include online databases, a database of a distributed network of public health and universities' laboratories such as the GenomeTrakr, internet of things (IoT) based portable sensors and smartphones, and social media (Jin et al. 2020).

13.2.1.1 Online Database

Some of the available online databases that contain information related to food safety are JECFA evaluations (**http://apps.who.int/food-additives-contaminants-jecfadatabase/search.aspx**) containing biological/chemical monitoring data; Foodborne Diseases Active Surveillance Network (FoodNet) for outbreak surveillance (**http://www.cdc.gov/foodnet/index.html**), containing tracking trends for infections transmitted commonly through food; and Pulsenet that contains genome sequence for foodborne bacterial disease surveillance (**http://www.cdc.gov/pulsenet/about/index.html**). Marvin et al. gave a broad overview of the online food safety database containing information about food safety, such as related information on a hazard, exposure, and surveillance reports (Marvin et al. 2016).

13.2.1.2 IoT Devices

Internet/Ethernet, wireless sensor network (WSN), and radio frequency identifications (RFID) are the most frequently used communication technologies that enable IoT devices in food industries. Some applications include a study by Seo et al. (2016) in detecting the vibrio species in actual samples via Wi-Fi network of an immunosensor system using a pocket-sized CMOS image sensor (CIS); the detection of food adulterants in a smart monitoring system device with embedded IoT technology (Gupta and Rakesh 2018); the monitor of the sausages production process using a platform based on IoT through video surveillance technology, sensor networks and GPS (Hu et al. 2011); and a low-cost IoT solution for real-time tracing and monitoring food safety during transportation (Maksimovic et al. 2015).

For IoT-based biosensors using smartphones as a device, the adoption of smartphone-based biosensors related to food safety, proposed in the literature, is trending recently. Some recent studies are Man et al. (2021), Sivakumar and Lee (2021), Wang et al. (2019), Shan et al. (2019), Su et al. (2017), Zhang and Liu (2016), Zhang et al. (2019), Guo et al. (2019), Zhang et al. (2018), Zeinhom et al. (2018a, b), Jung et al. (2020). Figure 13.1 shows a schematic overview of one instance of a smartphone-based biosensor in the food safety domain.

13.2.1.3 Social Media

In this era of big data, social media as another source of food safety can be potentially utilized. In the study by Shan et al., the authors reported that social media has been used and positively impacted two-way communication between consumers and public organizations in the food safety area. The adoption of Facebook, Twitter, and YouTube is already in place, bringing new opportunities to food organizations' interactions with the public (Shan et al. 2015). Meyer et al. has

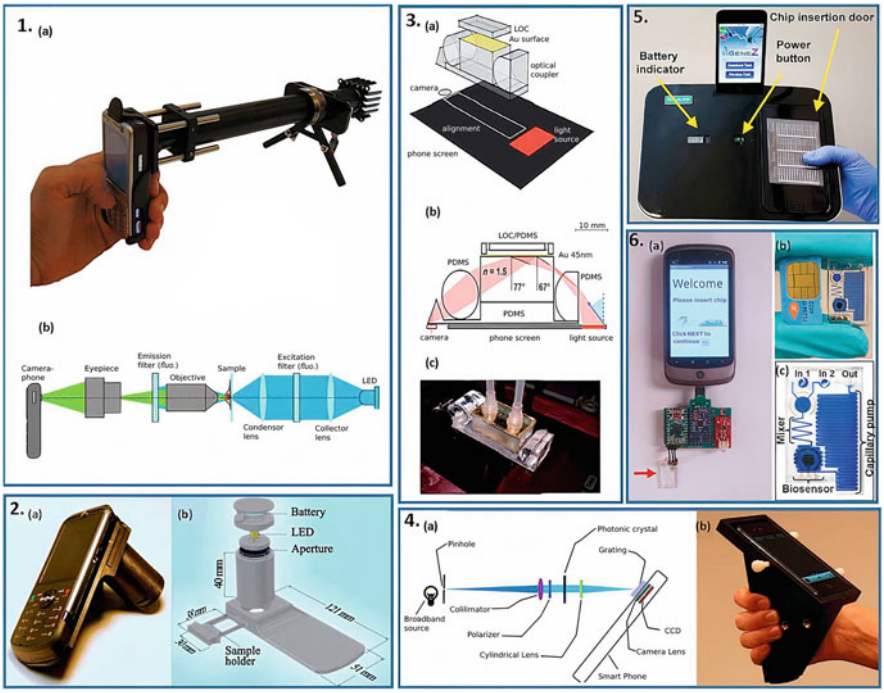

Fig. 13.1 A sample of smartphone-based POC biosensor (Copyright, Elsevier, Roda et al. 2016)

reported some initial insight from a web mining and social media analysis of Wikipedia and Twitter, respectively, to monitor health and food-related issues that can lead to a potential outbreak (Meyer et al. 2015).

13.2.2 Preparation Before Big Data Processing

Storing big data requires a data platform that can handle its main 3Vs properties. Storage design for big data is supposedly able to collect with good performance, voluminous data (volume) produced in various formats (variety) at variable speed (velocity) by multiple sources of data. For reliable transfer and delivery of files, a transferring software is essentially required to be used before processing takes place.

13.2.2.1 Big Data Storage

For data storage, traditional data management systems such as MySQL and Oracle are insufficient to handle big data. Big data requires next-generation technology such as a relational database called NoSQL database and computational technologies framework for storing data. Examples of open-source NoSQL as a platform for data storage and processing purposes are MongoDB (**http://www.mongodb.com/**), Cassandra (**http://www.cassandra.apache.org/**), and HBase (**http://www.hbase.**

apache.org/). Open-source software frameworks such as Hadoop (https://www.hadoop.apache.org/), Spark (http://spark.apache.org/), and MapReduce (http://www.01.ibm.com/software/data/infosphere/hadoop/mapreduce/).

13.2.2.2 Big Data Transferring

Big data originated from different sources need to be migrated into a NoSQL cluster, i.e., a processing unit in NoSQL. This transferring task requires software such as Aspera Data transferring (http://asperasoft.com/), Talend (https://www.talend.com/resource/big-data-transfer.html), Elasticsearch (https://www.elastic.co/), Hive (https://hive.apache.org/), and Apache Flume (http://flume.apache.org/).

13.3 The Prominent Roles of Big Data in Food Safety

In addition to studies related to big genomic data and biosensor data, studies that involved data in various formats sourced from social networks, geospatial, and online illness reports were also conducted in the food safety research area.

13.3.1 Transformation of Screening Techniques for Specific DNA or RNA Sequences in Food Pathogen

Collection and analysis of big data from a large number of actual samples can revolutionize the techniques in rapid screening of food pathogens, such as whole genome sequencing and next-generation sequencing. Specific genomic information and the occurrence information of pathogenic strains can be collected following any foodborne illnesses. Analytics of those data will enable rapid detection of foodborne pathogens accurately and evaluate the risks of food contamination. For instance, in Park et al. (2018), the authors discussed molecular-based methodologies, including several types of polymerase chain reaction assays and whole genome sequencing involving next-generation sequencing platforms to detect Salmonella strains in foods.

13.3.2 Transformation of Biosensor-Based Method of Food Pathogen Detection

Biosensors are easy to operate and require no sample pre-enrichment. The typical biosensors used for the detection of food pathogens are optical, electrochemical, and mass-based biosensors. IoT-based biosensors have been revolutionized by big data such it has motivated some advancements of components to biosensing technology, including data collection, analytics, and networking technologies (see Sect. 13.2.1.2 for definitive studies).

13.3.3 Complementing Genomic and Biosensor Data

Apart from genomic information, actual dynamics of sources of contamination or adulteration can also be genuinely captured and obtained in combination or singly from social network information to identify GMO food (Ji et al. 2019); from geospatial information to identify the wholesalers involved in the distribution of contaminated food (Doerr et al. 2012); and from online illness reports that complement traditional surveillance systems by providing near real-time information on foodborne illnesses, its related foods and locations (Nsoesie et al. 2014).

13.4 Data Analytics in Food Safety

After storing and moving the data to the processing unit in NoSQL or other platforms, the data are then ready to be analyzed. Analytics methods such as data mining and machine learning can be adopted for gaining insights from the food safety data.

13.4.1 Big Data Visualization

Data visualization can discover hidden patterns, trends, and correlations through a graphical illustration of the dataset that could provide instant critical insight and a summary about the big data. Some open-source language or platforms that can be explored for visualization are R language (**http://cran.r-project.org/**), Cytoscope **http://www.cytoscape.org/**), GraphViz (**http://www.graphviz.or/**). Moreover, there exist commercial platforms too that can be utilized, such as IBM Many Eyes (**http://www-01.ibm.com/software/analytics/many-eyes/**), Tableau (**http://www.tableausoftware.com/**) and PanXpan (**https://www.panxpan.com**).

13.4.2 Data Mining and Its Application in Food Safety

The most common methods in data mining are anomaly detection used for sensing any abnormalities is observed over time, association learning for analyzing whether occurrences are happening together either in pairs or larger groups, cluster analysis for recognizing distinct groups, classification for categorizing labeled data, and regression for making predictions based on models. Data mining has the potential to be used for analytics in food safety applications. In the study by Wang and Yue, data mining was found effective in finding food safety pre-warning rules for an IoT-based system for identifying food safety risk in advance and providing decision support information to maintain food safety (Wang and Yue 2017). Wang et al. (2015a, b) introduces the concept of big data mining and big data mining methods for handling big data in food safety.

13.4.3 Machine Learning and Its Application in Food Safety

Machine learning, a branch of artificial intelligence, is an analysis that can build mathematical or computational models by itself, without human intervention. It can identify patterns in data, learn from the data, and adapt itself for future analysis.

For food safety applications, several machine learning methods have been used, such as in rapid detection of foodborne pathogens using kernel principal component analysis and decision tree (Yan et al. 2021), in food safety early warning and monitoring system using extreme learning machine in the Raman spectroscopy (Geng et al. 2017), for identification and quantification of bisphenol mixtures using support vector machine (SVM) (Sun et al. 2021) and in the prediction of chemical acute contact toxicity on honey bees via six machine learning methods including SVM (Xu et al. 2021). In Zhu et al. (2020), the authors have used artificial neural networks (ANN), SVM, relevance vector machine (RVM) for the intelligent analysis of Carbendazim data from their nanosensors. The authors of Bertani et al. (2020) have used detection of aflatoxins B in grained almonds using fluorescence spectroscopy. Tarazona et al. (2021) studied some applications of neural networks, random forests, and extreme gradient boosted trees to predict and control the risks associated with these toxigenic fungi and mycotoxins in food. Feng et al. (2021) have used XGBoost, Random Forest, and lightGBM for the prediction of suspect screening of pesticides. Li et al. (2021a, b) have employed extreme learning machines to determine insecticide deltamethrin by spectral data fusion of UV–vis and NIR analyses. In Estelles-Lopez et al. (2017), the authors have used some machine learning regression methods in predicting meat spoilage from multi-spectral images and metabolic profiles. For detecting histamine in seafood, Tan et al. (2019) have used SVM for their works. The authors of Golden et al. (2019) have compared the application of random forest and gradient boosting machine (GBM) methods for predicting *Listeria* spp.

Meanwhile, the works of Hussain et al. (2020) involved SVM in the classification of pathogens; Mangmee et al. (2020) have proposed a classification tree in detecting non-typhoidal Salmonella (NTS) in the broiler industry; Wei et al. (2020) have applied ANN in detecting carmin in black tea; and Cox (2021) involved classification and regression trees (CART), random forest ensembles, partial dependence plots, and Bayesian network learning algorithms in their works to detect the presence of Salmonella contamination risks in young chicken slaughterhouses. In Zhang et al. (2020, 2021), their applied machine learning methods is the random forest, used to determine the food dye indigotine in cream via near-infrared spectroscopy technology; and in Leggieri et al. (2021), the authors have used ANN for rapid detection of aflatoxin B1 and fumonisins in maize. Furthermore, in Bouzembrak and Marvin (2019), the authors have applied a Bayesian network approach to study the impact of climatic factors, agricultural factors, and economic factors on the occurrence of chemical food safety hazards in fruits and vegetables; in Bouzembrak and Marvin (2016), Marvin et al. (2016), Bayesian network modeling was used in predicting food fraud type via food fraud notifications reports; and in Beaudequin et al. (2015), the authors have provided a scope review of 15 published articles that adopt the

Bayesian network for microbial risk assessment. Lastly, in Esser et al. (2015), the Bayesian network and ANN were used to model microbial growth for safe food production.

13.5 Big Data Analytics of Biosensor Data

Big data analytics can revolutionize rapidly foodborne pathogens' detection and evaluate the risks of food contamination before making decisions. However, the massive digital raw data from food safety archives might be challenging to analyze using traditional analytical tools, including machine learning techniques.

13.5.1 Deep Learning and Its Trending Applications

Deep learning is a subset of machine learning, and deep learning reduces the importance of feature engineering seen in traditional machine learning. Figure 13.2 depicts the relationship between artificial intelligence, machine learning, and deep learning.

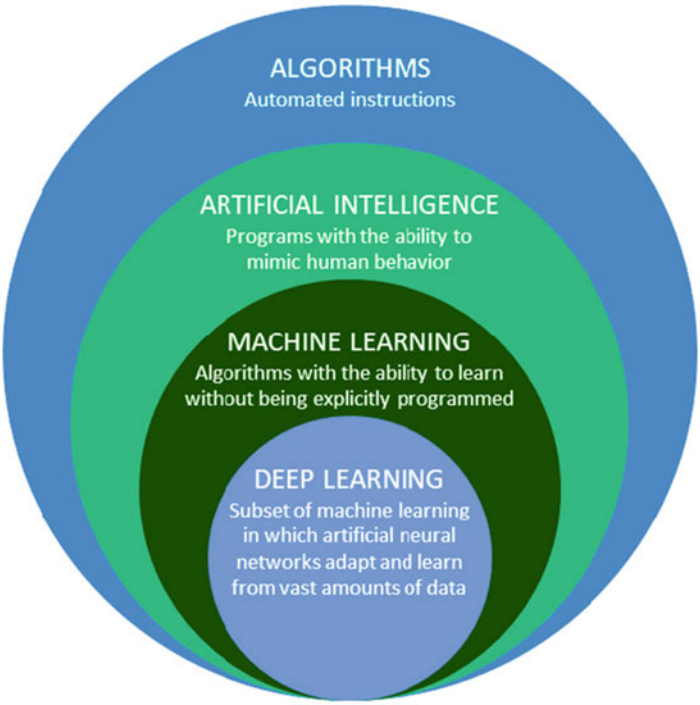

Fig. 13.2 Visualization of the algorithm, artificial intelligence, machine learning, and deep learning (Copyright, Springer, Vrana and Singh 2021, Licenses: CC BY-ND 4.0)

The utilization of deep learning algorithms is triggered by the emergence of high-performance computing such as GPU modules and the availability of extensive and high-quality labeled data. Its broad application ranges from the medical field (Castiglioni et al. 2021; Zhao et al. 2019), cybersecurity (Dixit and Silakari 2021), biosensing (Panganiban et al. 2021; Mehrani et al. 2020), civil engineering (Tong et al. 2020; Avci et al. 2021), bioinformatics (Pomyen et al. 2020), financial studies (Ozbayoglu et al. 2020), and so forth.

There are abundant deep learning algorithms and their variants that could be adopted in the field of biosensors. These include popular algorithms such as Convolutional Neural Networks (CNN), Recurrent Neural Network (RNN), Denoising Autoencoder (DAE) Networks, Deep belief networks (DBNs), and Long short-term memory (LSTM). However, this chapter focuses on the most widely used algorithm, CNN, among the various deep learning algorithms.

13.5.2 Rising of Deep Learning and Its Applications in Food Safety

Machine learning has computationally modeled the complexity of food safety with high precision. However, deep learning is required for large and complex biosensor data and outperforms traditional machine learning algorithms.

The application of deep learning in the food safety domain starts to develop in recent years. The authors of Pradana-López et al. (2021) have applied convolutional neural network (CNN) in their study to verify the quality and safety of ground coffee. In Wu et al. (2019), the authors applied CNN to identify and quantify counterfeit sesame oil via 3D fluorescence spectroscopy. Similarly, the works in Jiang et al. (2019) involved CNN, too, in detecting postharvest apple pesticide residues. Meanwhile, the author of Geng et al. (2019) has moved from machine learning to a deep learning method called deep radial basis function neural network for early warning modeling of complex food safety inspection data to predict and analyze food risk. The authors of Kang et al. (2020a, b), on the other hand, have shown the superiority of stacked auto-encoder-based soft-max regression (SR) methods via label-free hyperspectral 21 microscope imaging (HMI) method of Non-O157 Shiga toxin-producing *Escherichia coli* (STEC) serogroups. The authors of Kang et al. (2020a, b) have utilized a long-short term memory (LSTM) network, deep residual network (ResNet), and one-dimensional convolutional neural network (1D-CNN) in their studies to classify foodborne pathogens via hyperspectral microscope imaging.

On the other hand, in Tetila et al. (2020), Inception-v3, Resnet-50, VGG-16, VGG-19, and Xception deep learning architectures have been adopted in a study to detect and classify soybean pests via UAV images. Lastly, in Yu et al. (2019), the authors explored the stacked autoencoders-based feature extraction method in predicting TVB-N content in Pacific white shrimp (*Litopenaeus vannamei*) via hyperspectral images.

13.6 Convolutional Neural Network (CNN or ConvNet)

The first CNN, called Neocognitron, was introduced in 1979 by Fukushima (1980) and was publicized by LeCun in 1989, where he combined CNN with an algorithm for supervised learning of artificial neural networks called backpropagation (Lecun et al. 2015).

This section details CNN that could potentially be adopted when analyzing biosensor data. The aim is to provide enough insights into how this algorithm work and how it could be matched for the different type of biosensors.

13.6.1 CNN and Its Designed Application

CNN is the most widely used deep learning model and is popularly being used for image analysis as it can preserve the spatial structure of an image. It is commonly used for feature learning in some known applications that include video classification (Karpathy et al. 2014), image classification (Maggiori et al. 2017), image recognition (Simonyan and Zisserman 2015), musical instrument recognition (Han et al. 2017), visual document analysis (Simard et al. 2003), face detection and recognition (Lawrence et al. 1997), sentence classification (Zhao and Wu 2016), speech recognition (Dahl et al. 2012), and on.

13.6.2 The General Concept of CNN

A standard CNN consists of three layers, i.e., convolution layers, pooling layers, and fully connected layers, as presented in Fig. 13.3. Conceptually, a CNN, just like

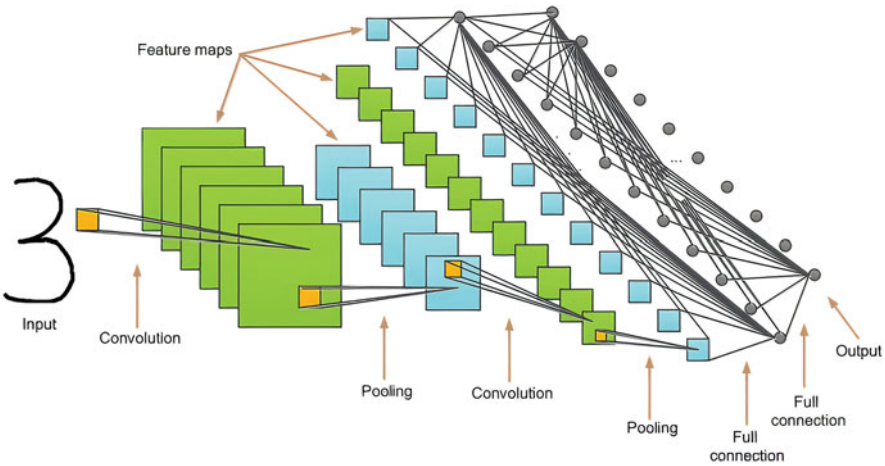

Fig. 13.3 A simple CNN architecture (Copyright, Elsevier, Li et al. 2016)

some other artificial neural network, consists of an input layer, hidden layers, and an output layer. However, in a CNN, the hidden layers include layers that perform an operation called convolution. For instance, in image processing, filters of those convolutional layers can individually detect specific simple geometric patterns within an image, such as edges, circles, and so forth. Then in the deeper convolutional layers within the same network, their filters can detect specific, advanced objects such as nose, tentacles, etc. A complicated object such as a specific bacteria structure could be detected in a much deeper network layer.

13.6.3 The Self-Learning and Self-Training Feature of CNN

Usually, for deep learning, the image is preprocessed before being fed into a standard deep learning algorithm. Rodrigues et al. (2020) detail six preprocessing techniques, such as histogram equalization. Preprocessing aims to reduce the data dimensionality, reducing the amount of data to be analyzed; while maintaining the amount of information in the image. However, CNN is different from a standard learning network such that it itself, without human intervention, defines the extraction of features from simple geometric patterns to advanced patterns by its convolutional layers to classify its input. Thus, without prior knowledge, the network learns to optimize the convolution kernels or filters independently. Thus, CNN allows the direct image input to be fed into its specialized neural network system to detect some patterns and images. As an original input image is fed, it goes through numerous convolutional layers, and learning or training is defined independently by itself, just similar to the preprocessing procedure in standard deep learning with regards to extracting some features.

13.6.4 The Convolution Operation that Gives CNN Its Name

Generally, a CNN receives direct input and generates direct output via deep learning on a set of features to be captured for extraction. As the system receives the direct image, a filter or kernel performs a convolution operation on the image input, which transforms the image and makes it able to detect some patterns. A convolutional layer can have few specified filters where each filter can be considered as a small matrix with a specified row and column numbers that have randomly generated random numbers as its element. As a result of the convolution operation performed by the filter on the first subset of the original image (top left corner), a single value is generated and stored as the first element of a matrix of convolved values. The convolved value is usually generated by applying the dot product of the filter with the subset of area. The filter then slides into another subset adjacent to the previous subset such that it centers this another subset and generates another single value. The process is repeatedly done until all possible subsets/subareas within the entire image area are covered or convolve by the filter to sub-output the weight sharing. The final result is a resultant matrix or a feature map for that particular convolutional

operation. From several random convolution operations by all the filters within the layer, the resultant respective feature maps are then stacked among themselves as shown in Fig. 13.4 and mathematically represented as a matrix form, too, just like the original representation input.

Mathematically speaking, in this layer, feature maps from previous layers are convolved with kernels. The kernels' output goes through a linear or nonlinear activation function, such as hyperbolic, tangent, sigmoid, Softmax, identity, rectified linear functions. The convolution operations form the output feature maps. In general, the output of the current layer is given by:

$$x_j^l = f\left(\sum_{i \in M_j} x_i^{l-1} * k_{ij}^l + b_j^l\right)$$

where x_i^{l-1} is the previous layer output, k_{ij}^l is the kernel for the present layer, and b_j^l is the current layer's biases. M_j represents a selection of input maps. For each output map x_j^l, an additive bias b_j^l is given. As the input maps are convolved with different kernels, their corresponding output maps generated are different too. The output maps finally go through a linear or nonlinear activation function, as mentioned above.

13.6.5 The Subsampling Layer Inside CNN Architecture

Pooling operation is typically added into a CNN as a subsampling layer after a resultant matrix is obtained, i.e., a pooling layer follows after a convolutional layer. When added to a neural network, pooling is intended to reduce the dimensionality of the input image by reducing its previous convolutional layer's output, i.e., the feature map's dimension obtained after convolution. Operationally, it is done to down-sample all the obtained feature maps, by which a set of adjacent nodes generate one output node. The two common types of pooling used are max-pooling operation and average-pooling operation. However, max-pooling is widely used than the other pooling type. Figure 13.5 illustrates both pooling operations. Firstly, a pool filter, i.e., a defined small size matrix with randomly generated elements and a defined stride, i.e., the distance that the pool filter gets to move as it slides across the image, is set. From starting with the first subarea (top left corner) of the entire area/subset of the entire matrix, a maximum value is extracted among all the subset values, stored as the first element in a resultant matrix, making up a matrix of maximum values. Then the same filter is slide over according to the defined stride value, and then the max operation is performed on the subset or pool of values and stored too inside the resultant matrix. Similar to the convolution process, the pooling process is repeated until the edge of the input matrix is reached, bringing the filter to proceed down to the beginning of the next row. It is repeated further until all the subareas of the entire input area are processed. A new set of down-scaled feature maps is obtained after covering all feature maps generated, as shown in Fig. 13.5.

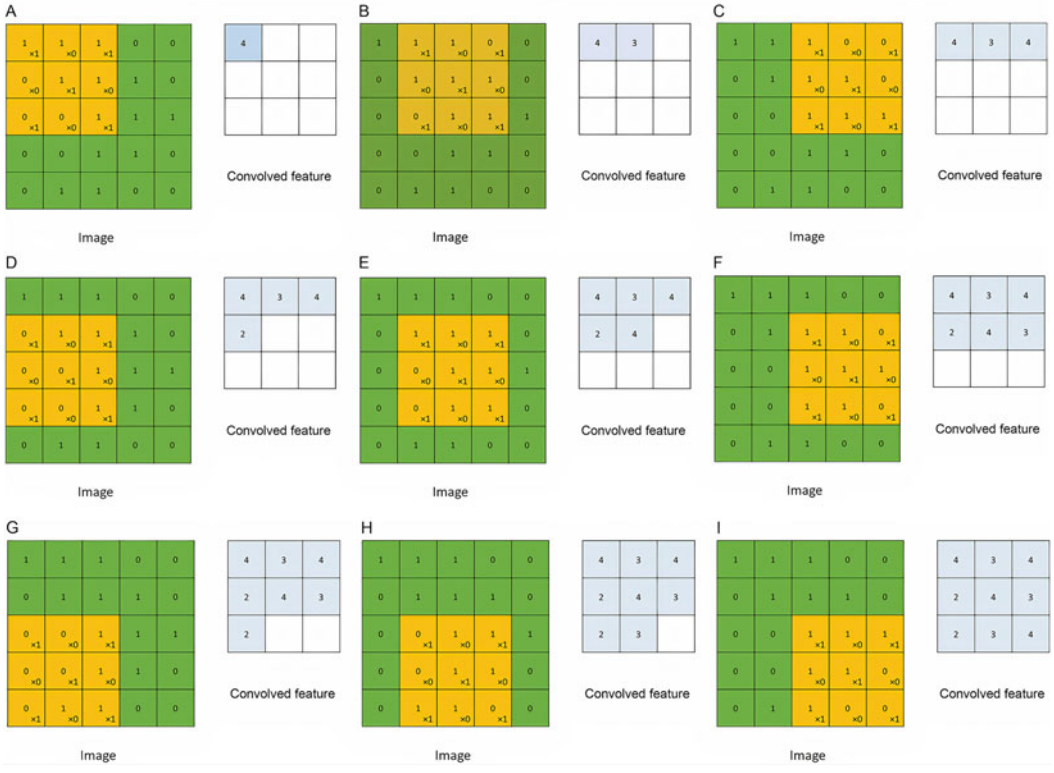

Fig. 13.4 2D convolution example: yellow shows the filter weights and green shows input (Copyright, Elsevier, Fathi and Maleki Shoja 2018)

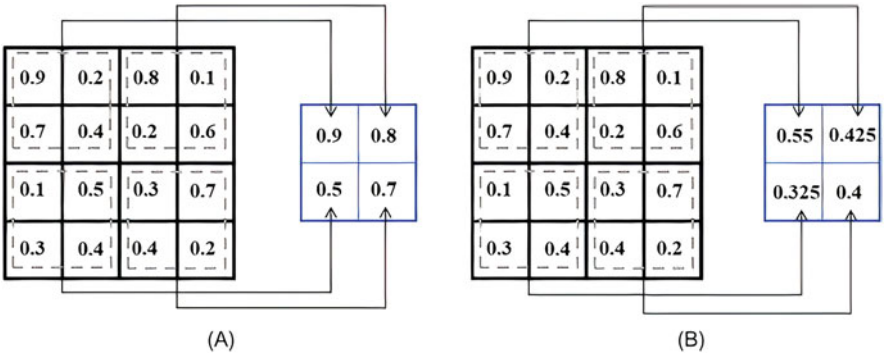

Fig. 13.5 An example of (**a**) max-pooling and (**b**) average-pooling operation (Copyright, Elsevier, Ranjbar et al. 2020)

13.6.6 Multiple Convolutional Layers in Deeper Layers

Multiple convolutions can be performed further until a final set of feature maps is obtained. This set has lost its spatial integrity data or gets reduced in dimension yet contains rich information in multiple feature maps. This final set of feature maps are then fully connected to the output. Training of CNN is similar to other deep learning neural networks with backpropagation of error. Pooling has reduced the resolution of the given output of the convolutional layer, and the network is processing through a larger area of the image at a time going forward, reducing the number of parameters in the network and consequently reduce the computational load. Additionally, pooling might help to reduce overfitting. The max-pooling ideology is that CNN is picking up the highest values in each subset that are seen as the most activated or said to be dominant and preserve the highest values going forward and discarding the lower values of the convolutional output that are not as activated.

13.6.7 CNN Models and Frameworks for CNN Development

Most deep CNNs consist of the main set of the convolution layer, the subsampling layer, dense layers, and the soft-max layer. Usually, they consist of stacks of several convolutional layers and max-pooling layers followed by fully connected and SoftMax layers at the end. In Alom et al. (2018), the authors detail some popular state-of-the-art CNN models such as AlexNet, VGG, GoogLeNet, Dense CNN, and FractalNet.

For architecture designs and implementation, some popular deep learning frameworks suitable for designing CNN are Caffe, DeepLearning4j (DL4j), Torch, Neon, Theano, MXNet, TensorFlow, and Microsoft Cognitive Toolkit (CNTK). The license, core language, supported interface language, and framework support of CNN are summarized by Pouyanfar et al. (2018).

13.6.8 Applications of CNN in Food Safety

CNN is designed to process data in the form of multiple arrays, for instance, 1D for signals and sequences, including language; 2D for images or audio spectrograms; and 3D for video or volumetric images (Lecun et al. 2015). It is mainly used for image data analysis, thus has potential for some utilization in optical biosensing systems integrated with colorimetry, fluorescence, and surface plasmon resonance.

In food safety, examples are Izquierdo et al. (2020), Torrecilla et al. (2021), in which the authors have tested CNN for the analysis and classification of different thermographic images of pure and adulterated extra virgin olive oil; Nasiri et al. (2020), where the authors have proposed automatic sorting system for unwashed eggs based on CNN; and Wu et al. (2019), in which the authors have explored CNN to recognize food contaminating beetle species. Other studies include identifications of adulterated vegetable oil (Wu et al. 2021); minced mutton adulteration (Zheng et al. 2021); moldy peanut kernels as oil raw material (Liu et al. 2020); fraudulent mixtures of rice (Estrada-Pérez et al. 2021); sugar adulteration identification of honey (Li et al. 2021a, b); pesticide residue (Jiang et al. 2019; Zhu et al. 2021a, b); safe and unadulterated ground coffee (Pradana-López et al. 2021); counterfeit sesame oil (Wu et al. 2020); various foodborne pathogens, i.e., *Campylobacter jejuni*, *Escherichia coli*, *Listeria innocua*, *Staphylococcus aureus*, and *Salmonella typhimurium* (Kang et al. 2020a, b); and impurities in juglans such as leaf debris, paper scraps, plastics craps and metal part (Rong et al. 2020).

13.6.9 Beyond CNN's Intended Application

Tensorflow's function conv1d and conv2d are general functions that can be used on any data with spatial features. The functions see the data as an array of floating points instead of image/audio/text. Further, Sharma et al., in their studies, have proposed a methodology to transform non-image data to an image for convolution neural network architecture, named DeepInsight (Sharma et al. 2019).

That additional virtue of CNN means its applications for analytics of food safety databases are not restricted to available online databases, bioimaging data, and biosensing data; but also for integrated food complaint reports or social network data such as suspected food poisoning, foreign matter in food, or observed unhygienic food handling. Text fragments such as "bulging lid on canned food" and "the chicken dish was served hot" can be labeled as "negative" and "positive," respectively. To date, no study attempts to apply CNN for text classification in the food safety domain. However, they are applied for such tasks, and examples are in the classifications of patient portal messages (Sulieman et al. 2017); and building quality complaints (Zhong et al. 2019).

13.7 Conclusion and Future Outlook

Biosensors are proper POCT, point-of-need detection, or point-of-use analysis that could be used not only for medical or health benefits but also to control and monitor the global food supply chain. The success of new applications and approaches in food safety, such as the use of smartphones in foodborne pathogens, development of next-generation sequencing in rapid screening of food pathogens, the introduction of nanotechnology in the smartphone-based biosensor, combining data from a wide variety of data sources, reliable storage of big databases, use of geospatial data and illness report in the analysis of food safety risks, use of social media as an information source, beneficial analytics of complaint reports or incident reports that could provide early warning of a potential outbreak, and precise detection of food contaminants using deep learning will strongly influence the future use of big data tools and technologies.

The integration of a nano-biosensor with a smartphone could revolutionize biosensor technology for rapid communication in cases of a foodborne illness outbreak. With the adoption of deep learning as the data-analytical method, large and complex biosensors data could be analyzed without any need for feature engineering or labeling of data yet with high-quality results even for unstructured data. Among the various deep learning methods, CNN is successfully applied to images. As discussed, CNN could also be utilized for the non-image input. It is hoped that full integration of biosensors, nanotechnology, and smartphones could be advanced further with CNN's capability to analyze both image and non-image data. CNN can solely do data analytics of various data generated by smartphones with built-in capability of biosensing and bioimaging and data gathered from databases and social networks. For future works, the prediction of any continuous data from the food biosensors can be explored, which can be done by adding a regression layer at the end of the CNN. It is also suggested that text analytics of complaints be integrated into the databases of biosensing or bioimaging systems and online databases related to food safety. This comprehensive tool will then have potential in in-field detection of food contaminants through analytics of biosensor data and text complaints with available support from emerging cloud computing architecture for large and complex data storage and processing. Hence, the availability of an extensive database of biosensors data generated from users' smartphones might rapidly address concerns and issues in food safety and therefore facilitate accurate decisions.

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Aptamer-Based Miniaturized Technology for Drug Analysis

14

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Abstract

Recently, the development of sensitive, economical, and accurate devices gets more attention to many clinical and analytical laboratories. The miniaturized analytical system, with particular benefits of low cost and portability, has made attracting attention with the growing requirements for point-of-care (POC) testing. Miniaturized biosensors based on various materials (e.g., aptamer, nanomaterials) have an important role in analytical fields because of their high sensitivity, portability, ease of operation, and analysis in a short time. This chapter will review developments on various types of miniaturized aptasensors based on nanomaterials with focus on drug analysis.

Keywords

Aptamer · Aptasensors · Drug analysis · Miniaturization · Point of care

14.1 Introduction

Biosensors have been defined as analytical devices that incorporate a biological sensing element with a physical/chemical transducer for detecting the specific analytes (Perumal and Hashim 2014). The biological reorganization tools are applied to direct interaction with the specific target. These biosensing elements can be generally categorized as enzyme, aptamer, antibody, and DNA (Han et al. 2010). Among these biological elements, more attention has recently been paid to aptamers. Aptamers are short synthetic single-stranded DNA or RNA and peptide molecules

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that can bind to their specific targets with high affinity and selectivity similar to an antibody–antigen interaction (Saberi et al. 2020). Hence, aptamers are known as artificial chemical antibodies with key advantages over antibodies including stability, easy to prepare, low cost, easy to modify and non-immunogenic (Kong and Byun 2013; Zhou et al. 2016). Also, the preparation of aptamers is less expensive, simpler, and reproducible than the synthesis of antibodies and could be automated. Nevertheless, the selection step of the aptamer by the SELEX approach could be strict and time consumer (Gaudin 2020). Due to these positive properties, aptamers are being applied in the biosensing methods.

In recent years, a variety of biosensor based on aptamers have been developed and used for routine analysis such as medical analysis, food safety and clinical diagnosis. Nevertheless, growing a simple, quick, portable, highly selective, and sensitive biosensor is a considerable challenge. The development of microtechnology has given a new perspective for designing devices of biosensors using downsizing and providing controllable systems (Derkus 2016). The miniaturized systems offer several advantages of portability, low cost, reducing the reaction time and reagent consumption and samples in comparison to traditional systems (Chan et al. 2013). With these special benefits, the problems of conventional analytical procedures can be removed by applying miniaturized devices outside the laboratory. The miniaturized devices can be categorized into small hand-held apparatuses, bench-top devices, and intelligent detection platforms (Yang et al. 2019). In three of them, applied technologies have been improved and refined to provide devices with easier-to-use and advancements in analytical performance. The first group is based on methods of state-of-the-art microfabrication, which preparation of the sample, analysis steps and signal detection are being performed automatically. Qualitative or quantitative measurements can be offered by these devices for a wide spectrum of analytes. The second devices are scaled-down models of central lab equipment which have been diminished in size and complexity. In third devices, coupling of the capabilities of smartphones and portability of biosensors provides rapid, low cost, and easy-to-operate platforms for numerous applications. A smartphone can be coupled by optical or electrochemical biosensors and microscopic imaging sensors (Price et al. 2010; St John and Price 2014).

Nowadays, a trend to miniaturized analytical devices has gained more attention by growing requirements for point-of-care (POC) technology. POC testing is devoted to performing any diagnostic tests and therapy assistance outside the traditional laboratory and close to where the clinical cares are delivered. These tests compared with tests based on laboratory are cost-effective and user-friendly analytical instruments for fast quantitative or semi-quantitative measurements without no sample preparation, no previous knowledge needed for analysis (Baryeh et al. 2017).

In the sensing field, nanomaterials-based biosensor presented great potentials in the detection of trace analytes due to unique catalytic, electrical, chemiphysical characteristics of nanomaterials, for example, high specific surface area, high adsorption capacity and reactive capability, and other interesting features that can only be seen on the nanoscale, not on the bulk. Various nanostructured materials can

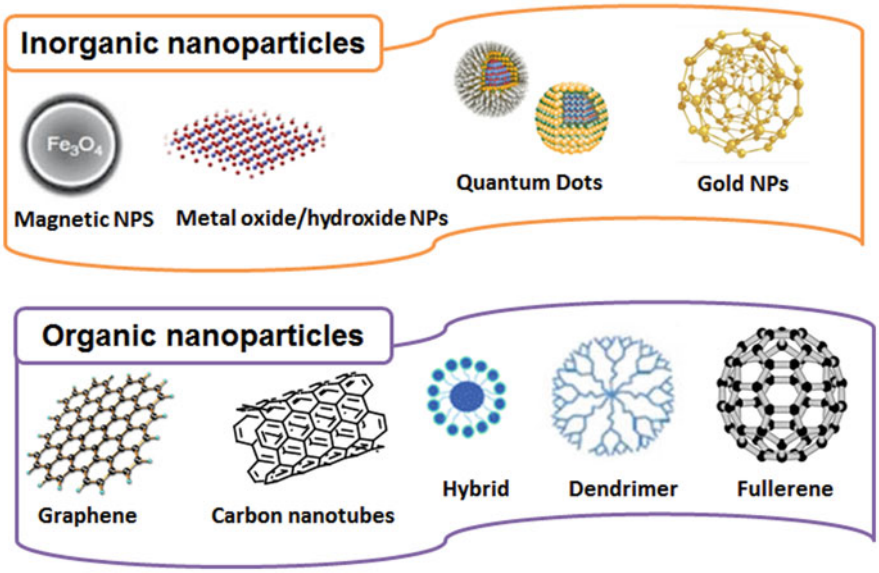

Fig. 14.1 Basic classification of nanomaterials: inorganic nanomaterials and organic nanomaterials

be generally categorized into two classes: (1) inorganic (non-carbon) nanomaterials like noble metals-based nanoparticles (NPs), metal oxide/hydroxide nanosheets and transition metal chalcogenide (TMC); (2) organic (hydrocarbon) nanomaterials such as carbon-based nanomaterials, polymer NPs, dendrimers, and hybrid NPs (Jeevanandam et al. 2018). Figure 14.1 displays the schematic illustration of the nanomaterials categories. There are various strategies for producing nanostructured materials containing physical approaches (for example physical vapor deposition, laser ablation, and flash spray pyrolysis), chemical methods (for instance sol-gel processes, hydrothermal method, thermal decomposition, and chemical vapor deposition), photochemical procedures (such as photodeposition) and electrochemical methods (such as electrodeposition, anodic and cationic oxidation) (Chen and Holt-Hindle 2010; Dhand et al. 2015).

Noble metallic nanomaterials, carbon nanomaterials, and quantum dots (QDs) have been more applied in the miniaturized aptasensors. Here, they are briefly described. *Noble metallic nanomaterials:* (e.g., Au, Ag, Pt, and Pd) are a significant class of nanomaterials that their chemical, physical, and electrochemical properties depend on their shape and size. Fabrication of biosensing platform with these nanoparticles offers a great potential of increasing both sensitivity and selectivity due to high surface areas, the dimensional similarities of noble metal nanoparticles with biological molecules and, facilitating the electron transfer by their conductivity (Vinci and Rapa 2019). *Carbon nanomaterials:* have gained certain attention owing to their remarkable structural and physical characteristics. These properties include good conductivity, low cost, high stability, facile surface functionalization that offer

various advantages, for example, chemical stability, high electrical conductivity, biocompatibility, high surface-to-volume ratio, and robust mechanical strength (Rauti et al. 2019). Advance in constructing types of carbon-based nanostructures and modification of surface has increased interest in applying these nanomaterials in an extensive range of areas including optical and electrochemical (bio)sensing applications (Adhikari et al. 2015). *QDs:* semiconductor NPs are made from the periodic groups II–VI, III–V, and IV–VI (Kazemifard et al. 2020). They present not only the bulk metal oxides properties but also, have unique optical, photochemical, catalytic, and electronic characteristics such as high band-gap, good photostability, narrow and symmetric emission spectra (Ensafi et al. 2017a). The hybrid of nanomaterials with miniaturized aptasensors can improve the sensing performances and introduce reliable and robust devices for effective analysis.

Until now, enormous aptasensor based on nanomaterials have been widely employed to monitor a variety of drugs such as illicit drugs (Mao et al. 2020) like amphetamines (Saberi et al. 2018) or cocaine (Mokhtarzadeh et al. 2015); thrombin (Jamei et al. 2020); insulin (Ensafi et al. 2017b); vitamins (Heydari et al. 2020) and antibiotics (Mehlhorn et al. 2018). Nevertheless, the number of miniaturized aptasensors-based nanomaterials for monitoring drugs is limited. The purpose of this chapter is to overview advances in the development of miniaturized aptasensor with different nanomaterials for sensitive and quick detection of various drugs. Depending on read-out techniques, the miniaturized aptasensors were studied into electrochemical and optical analytical methods. The latest advance of microtechnology in the use of drug aptasensors like paper-based devices, microfluidics, and lateral flow are lighted.

14.2 Miniaturized Aptasensor Based on Electrochemical Methods

Electrochemical analysis is an attractive approach due to offering inherent miniaturization compatible with novel microtechnologies, high sensitivity, and low cost (Wang 2002). Miniaturized electrochemical (MEC) sensors are a class of analytical platforms that have been operated for detecting trace amounts of target molecules by recording variations of the electrochemical signal. In addition to the advantages of miniaturized systems, MEC sensors provide simple instrumentation, easy to operate, high sensitivity and selectivity, least sample pretreatment, and short analysis time (Zhang et al. 2020). Currently, there have been considerable efforts in developing different devices based on MEC sensors to analyze target analytes at trace levels in several fields, including drug and medical monitoring. Electrochemical methods used to characterize and quantify the signal include cyclic voltammetry (CV), differential pulse voltammetry (DPV), square wave voltammetry (SWV), amperometry, chronoamperometry, linear sweep voltammetry (LSV), and electrochemical impedance spectroscopy (EIS) (Rezaei and Irannejad 2019).

Several electrochemical sensors have been developed based on the miniaturized devices. Here, they will be mentioned briefly (Zhang et al. 2020). (1) Paper-based

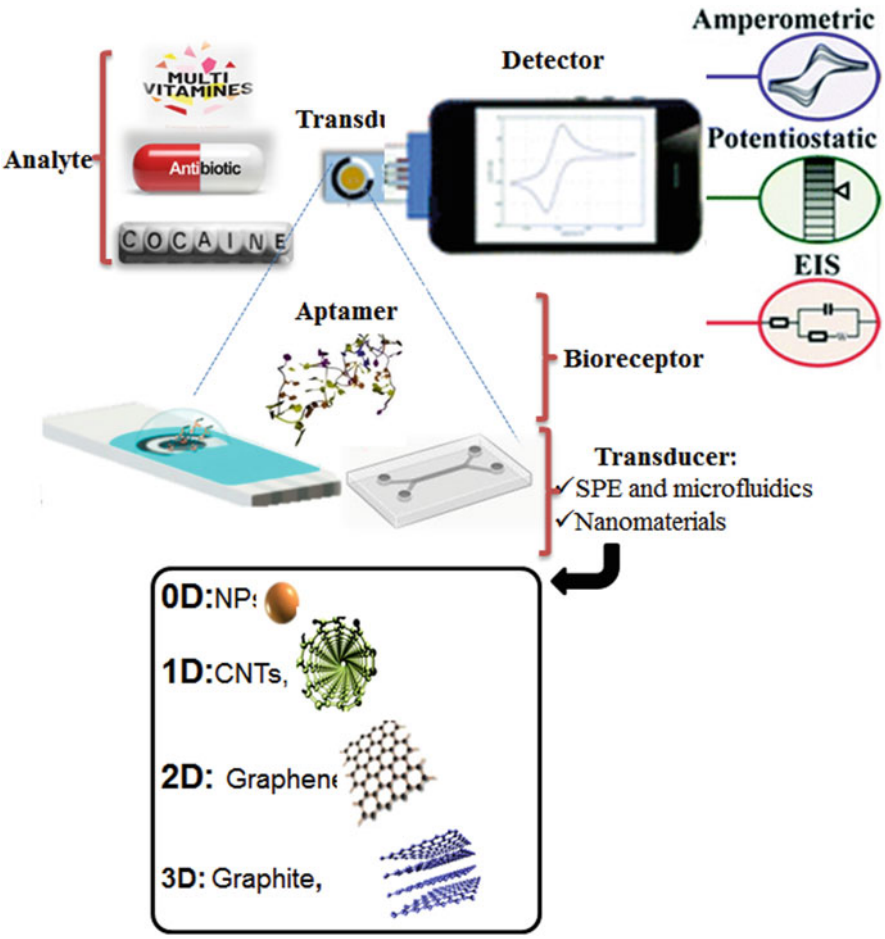

Fig. 14.2 Schematic representation of a miniaturized electrochemical aptasensor

electrochemical sensor: analytical devices based on paper have been popular for sensing applications since the mid-1960s (Li et al. 2015). Using paper as a simple and reliable platform offers simplification of instrumentation, cost reduction and incorporation of functionality. (2) Microfluidics-based electrochemical sensor: in these sensors, microfluidic channels were utilized to control fluid flow, reduce sample/reagent consumption and improve portability and flexibility (Sun et al. 2014). (3) Screen-printed electrode-based sensor: using screen-printed techniques in electrochemical sensors makes them more appropriate for numerous analytical purposes that provides the potential for miniaturizing and excellent uniformity (Tudorache and Bala 2007). Figure 14.2 shows a schematic design of an electrochemical miniaturized aptasensor that composed of bioreceptors (aptamer) contact

with transducer modified with nanomaterials and detector (e.g., smartphone, watch, etc.).

14.2.1 Electrochemical Aptasensor Based on Microfluidics

Microfluidics technology is a developing revolution in laboratory testing that combines the advantages of integration, automation, and miniaturization to many research fields. Using microfluidic technology in lab-on-a-chip devices allows to construct several microchannels on a single chip for controlling fluids in amounts as low as a few picoliters. The smaller dimensions and volumes of microfluidic channels allow all tests to be done with less sample than what might be used (Mazaafrianto et al. 2018). Coupling a microfluidic system with an electrochemical aptasensor exhibits some benefits low detection limits, improved sensitivity and high specificity (especially in real samples) (Wang et al. 2010). In the following, some applications of microfluidic electrochemical aptasensor for drug detection are reviewed and summarized in Table 14.1.

Cocaine is a strong stimulant that affects the brain, directly. Also, cocaine causes users to feel happy, energized and mentally alert (Nakayama et al. 2016). A microfluidic device based on electrochemical aptasensor was fabricated using three-electrode systems-on-chip based on Au-Ag dual-metal array for small molecules analysis. In the sensing approach, chronocoulometry method is applied because it is more accurate than other electrochemical methods to detect the signal of an electrostatically trapped redox marker. AuNPs have favorable electronic properties, a large surface area and good biocompatibility that was used to enhance the sensitivity of the aptasensors. Cocaine was chosen as a model that a linear relationship between response and logarithmic concentration of cocaine was obtained 0.1–26.3 μM and 0.07 μM as a detection limit (Du et al. 2011). Thrombin is used to prevent and stop bleeding whenever oozing blood and minor bleeding from microvessels is accessible (Lomax and Traub 2009). A microfluidic device modified with aptamer was fabricated for the determination of thrombin by Wang et al. (2010). Device applied poly (diallyldimethylammonium chloride)/AuNPs multilayers assembled on poly (methyl methacrylate) microchannel for immobilizing aptamers. This film showed good stability. A linear response range was achieved from 1–100 pM and a detection limit was 1 pM.

14.2.2 Electrochemical Aptasensor Based on Paper

Paper has been broadly used as a platform for analytical platforms due to its properties including portable, low cost, disposable, and compatible with biological samples (Li et al. 2019a, b). Paper-electrochemical aptasensor has gained special attention due to their high specificity, quantitative capability and low response time (Wang et al. 2019). According to the recent advances in nanotechnology, paper material, and instrumental miniaturization, tremendous progress is witnessed in

Table 14.1 Summary of the application of miniaturized aptasensor based on nanomaterials in drug analysis

Analytes	Strategy	Nanomaterials	LOD	Linear range	Ref
Cocaine	Electrochemical/SPE	Dendrimer/AgNPs	333 amol L^{-1}	1 fmol L^{-1} to 100 nmol L^{-1}	(Roushani and Shahdost-fard 2018)
Epirubicin	Electrochemical/SPE	AuNPs/ Fe3O4@SiO2	0.04 μM	0.07–21.0 μM	(Hashkavayi and Raoof 2017)
Chloramphenicol	Electrochemical/SPE	Gold nanocubes	0.10 μM	0.25–6.0 μM	(Bagheri Hashkavayi et al. 2015)
Kanamycin	Electrochemical/SPE	AuNPs	9.4 nM	0.05–9.0 μM	(Zhu et al. 2012)
Chloramphenicol	Electrochemical/SPE	AuNPs	1 nM	1–1000 nM	(Yu et al. 2020)
Amoxicillin	Electrochemical/SPE	AuNPs/MWCNTs	0.015 μM	0.2–10 and 10–30 μM	(Muhammad et al. 2016)
Thrombin	Electrochemical/SPCE	AuMNPs	0.07 pM	0.5–100 pM	(Zhao et al. 2013)
Chloramphenicol	Electrochemiluminescent/SPCE	QDs/L-AuNPs	0.03 nM	0.1–120 nM	(Feng et al. 2016a, b)
Thrombin	Electrochemical/SPGE	AuNPs/QDs-Si	0.1 ng mL^{-1}	1–50 ng mL^{-1}	(Li et al. 2012)
Diethylstilbestrol	Electrochemiluminescent/SPCE	MMIPs/QDs	0.1 pg ml^{-1}	0.3–1.0 × 10^5 pg mL^{-1}	(Jiang et al. 2017)
Dopamine	Electrochemical/microfluidics	MWCNTs	NR	NR	(Mathault et al. 2015)
Cortisol	Electrochemical/microfluidics	AuNPs	10 pg/mL	30 pg/mL to 10 μg/mL	(Sanghavi et al. 2016)
Lysozyme	Electrochemical/SPCE	rGO Amino-MSNs	2.1 fmol L^{-1} 4.2 fmol L^{-1}	10 fmol L^{-1} to 200 nmol L^{-1} 20 fmol L^{-1} to 50 nmol L^{-1}	(Jamei et al. 2019)
Kanamycin	Fluorescence/microfluidics	AuNPs	0.3 pg·mL^{-1}	0.8 pg·mL^{-1} to 10 ng·mL^{-1}	(He et al. 2019)
Neomycin	Fluorescence/microfluidics	GO	153 nM	0–3.5 μM	(Zhang et al. 2015)
Thrombin	Colorimetry/microfluidics	AgNPs	20 pM	20–5000 pM	(Zhao et al. 2016)
Vitamin D3	Colorimetry/paper-microfluidics	AuNPs	NP	NP	(Weng et al. 2018)
Vitamin D3	Electrochemical/μEs	GQD-Au	0.70 nM	1–500 nM	(Wadhwa et al. 2020)
Cocaine	Electrochemical/SPCE	AuNPs/GO	1 nM	1–500 nM	(Jiang et al. 2012)
Thrombin	RIFTS/microfluidics	OEPSi	8.21 nM	10–1000 nM	(Yu and Wu 2019)

(continued)

Table 14.1 (continued)

Analytes	Strategy	Nanomaterials	LOD	Linear range	Ref
Tryptophan	Potentiometry/SPE	MWCNT	1.0×10^{-12} M	1.0×10^{-11} to -1.0×10^{-4} M	(Majidi et al. 2016)
Progesterone	Lateral flow	AuNPs	5 nM	NP	(Alnajrani and Alsager 2019)
Ascorbic acid	Electrochemical/SPE	$Cu(OH)_2$ nanorods		0.0125–10 mM	(Raveendran et al. 2017)
Estradiol	Electrochemical/paper	AuNPs	5 pg mL^{-1}	10 pg mL^{-1} to 500 ng mL^{-1}	(Ming et al. 2019)
Enrofloxacin	Lateral flow assay/??	AuNPs			(Tian et al. 2020)
Ampicillin	Lateral flow assay	AuNPs	185 mg/L	NR	(Kaiser et al. 2018)
Kanamycin	SERS/microfluidics	AuNPs/GO	0.75 nM	1–100 nM	(Nguyen et al. 2019)
Cocaine	Lateral flow assay	AuNPs	10 μM	NR	(Liu et al. 2006)
Kanamycin	Lateral flow assay	AuNPs	0.0778 nM	1–30 nM	(Liu et al. 2018a, b)
Oxytetracycline	Scattering/microfluidics	PS	100 ppb	100–104 ppb	(Kim et al. 2010)
Oxytetracycline	Electrochemical/offset printing	SWCNTs	2.5 nM	20–325 nM	(Yildirim-Tirgil et al. 2019)
Oxytetracycline	Reflectance-based colorimetry	AuNPs	1 nM	1 nM to 1 μM	(Seo et al. 2015)
Tetracycline	Electrochemical/SPCE	Fe_3O_4	1.0 nM	1.0 nM to 1.0×10^7 nM	(Shi et al. 2017)
Chloramphenicol	Electrochemical/SPCE	GelB nanospheres	0.183 nM	0.30–2.0 nM	(Hamidi-Asl et al. 2015)
chloramphenicol	Colorimetric/microarrays/ smartphone	AuNPs	5.88 nM	0–450 nM	(Wu et al. 2019)
Thrombin	Fluorescence/microarrays	GO	0.001 nM	NR	(Jung et al. 2013)

LOD limit of detection, *SPE* screen-printed electrode, *QDs* quantum dots, *AuNPs* gold nanoparticles, *MWCNTs* multi-wall carbon nanotubes, *AgNPs* silver nanoparticle, *GO* graphene oxide, *RIFTS* reflective interferometric Fourier transform spectroscopy, *OEPSi* pen-ended porous silicon, *SPCE* screen-printed carbon electrode, *SPGE* screen-printed gold electrodes, *QDs-Si* quantum dots-coated silica nanosphere, *AuMNPs* Fe_3O_4/Au magnetic nanoparticles, *MMIPs* magnetic molecular imprinting polymers, *GQD* graphene quantum dot, *Amino-MSNs* amino-mesosilica nanoparticles, *PS* polystyrene microspheres

miniaturized electrochemical aptasensors based on paper for the detection of analytes in clinical and medical applications (da Costa et al. 2015). Here, some determined drugs by this method were mentioned and listed in Table 14.1.

de Oliveira and coworkers fabricated an electrochemical device based on paper for the quantification of multiplex targets. The device consisted of two electrochemical cell parts detached by hydrophobic wax barriers, and SPEs deposited straightly over the paper surface. The platform was used to simultaneous analysis of caffeine, paracetamol, and ascorbic acid in drugs. Detection limits were obtained 0.04 mmol L^{-1} for paracetamol, 0.40 mmol L^{-1} for ascorbic acid, and 0.22 mmol L^{-1} for caffeine (de Oliveira et al. 2019). Kanamycin is a bactericidal antibiotic that has been used to treat many microbial infectious diseases. Also, it has a significant role in bacterial therapy. Many side effects including kidney toxicity, loss of hearing, and allergic reactions can be caused by this drug (Ha et al. 2017b). To detect kanamycin, a wireless potentiometric aptasensor was fabricated based on freestanding graphene paper. A graphene paper was applied as a biocompatible device to immobilize aptamers by π-π stacking interaction. A catalytic recycling reaction based on the adoption of the nuclease was introduced to improve the sensitivity. An ultra-low detection limit of 30.0 fg/mL was reported for kanamycin (Yao et al. 2019).

14.2.3 Electrochemical Aptasensor Based on SPEs

Screen-printed electrodes (SPEs) have been broadly applied for developing electrochemical sensors and improving their performances because of ease, cost-effectiveness, and production speed by thick-film technology. The SPEs surface can be simply improved by nanomaterials and biomolecules to attain a variety of improvements (Beitollahi et al. 2020). The integration of their downscaled size and the potential to link them to portable instrumentation allows the on-site analysis of analytes. Further, SPEs can prohibit several common obstacles of classical electrodes, such as tedious cleaning processes and memory effects (Taleat et al. 2014). Over the last years, several papers have been consecrated to improve the high-efficiency electrochemical aptasensors based on SPEs, to be applied in the detection of drugs (summarized in Table 14.1). For example, a label-free aptasensor was described by Zhan et al. for electrochemical detection of tetracycline (Zhan et al. 2016). Tetracycline is a kind of antibiotic that is applied to treat a variety of bacterial infections like urinary tract, skin or chest, typhus fever and acne (Liu et al. 2018a, b). The composite film of rGO/Fe3O4/sodium alginate immobilized-aptamer was applied to modify the surface of SPEs. DPV method monitored the interactions of aptamer with tetracycline using the electrochemical probe thionine. Tetracycline was quantified in the range between 1 nM to 5 μM concentration with 0.6 nM as the detection limit. Codeine or 3-methylmorphine is a painkiller medication. It has been generally prescribed to relieve mild to moderate pain (Van Hout et al. 2018). Yang and coworkers reported an aptasensor based on SPEs modified with polyamidoamine dendrimers (PAMAM) and AuNPs for codeine detection (Niu et al. 2016). Chitosan (CHIT) was used to immobilize PAMAM. The aptamer was

conjugated on the electrode modified with AuNPs/PAMAM/CHIT. Using SPEs, Codeine was quantified in a linear range from 1×10^{-12} mol L^{-1} to 1×10^{-7} mol L^{-1} and the detection limit was obtained 3×10^{-13} mol L^{-1}. In another work, Amouzadeh et al. fabricated an electrochemical aptasensor based on mesoporous carbon and 1,3,6,8-pyrenetetrasulfonate-modified SPEs for determination of insulin (Tabrizi et al. 2018). Insulin is a protein hormone that is used as a medication to control high blood glucose (Silver et al. 2018). The mechanism of the electrochemical aptasensor is based on the variation in adsorbed methylene blue signal on the surface of modified SPEs. After binding insulin to its aptamer on the electrode surface, methylene blue was desorbed and the signal was changed. Insulin was found in the concentration range from 1.0 fM to 10.0 pM with a 0.18 fM detection limit. A portable EIS aptasensor based on screen-printed carbon electrodes (SPCEs) was described by Sharma's group to detect Kanamycin (Sharma et al. 2017). Using diazonium coupling mechanism for immobilizing aptamer provides uniform surface modification, high sensitivity, and more stability. The aptasensor found a linearity 1.2–75 ng mL^{-1} and detection limit 0.11 ng mL^{-1}. Also, Gan's group presents an electrochemiluminescence aptasensor array based on a SPCEs for determination of malachite green (MG) and chloramphenicol (CAP), simultaneously (Feng et al. 2015). The SPCE is composed of two carbon working electrodes (WE1 and WE2). CdS-QDs attached MG complementary strand and luminol-Au NPs conjugated CAP complementary strand were employed to modify WE1 and WE2, respectively. Cyanine dye as a quencher of QDs and chlorogenic acid as a quencher of luminol-AuNPs labeled aptamers. Linear ranges can be obtained by this strategy for MG and CAP, 0.1–100 nM and 0.2–150 nM accompanied by limits of detection of 0.03 nM and 0.07 nM, respectively.

14.3 Aptasensors Based on Optical Techniques

During the past years, various optical assays have been established for screening different analytes including fluorescence, colorimetry, surface-enhanced Raman scattering (SERS), chemiluminescence, and surface plasmon resonance (SPR). Optical-based aptasensors have been drawn tremendous notice owing to their abilities in terms of allowing direct label-free, quick response, easy operation, real-time detection, and easily realized mobile phone imaging and visualization (Feng et al. 2014; Zhou et al. 2020). To enhance figure of merits such as the sensitivity and selectivity, a variety of nanomaterials can be serving as probes or functional materials in optical-based aptasensors (Yuan et al. 2012). Different miniaturized aptasensors based on optical techniques have been developed including, microfluidic strips, paper-based, microarrays, and other interface-based microdevices. In the following parts, several miniaturized aptasensors based on the above techniques are categorized to colorimetric technique, fluorescence, and other techniques and discussed (Fig. 14.3). More examples of these optical aptasensors were listed in Table 14.1.

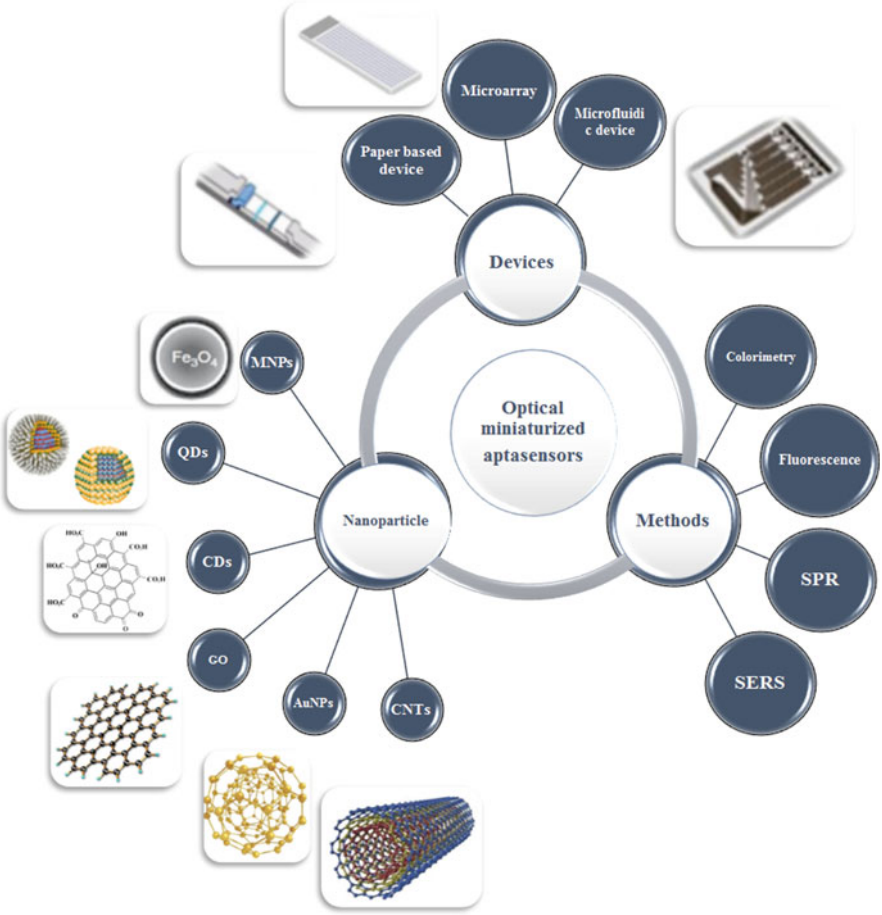

Fig. 14.3 Schematic representation of a miniaturized optical aptasensor

14.3.1 Colorimetric Techniques

Over last few decades, detection based on colorimetric method have become popular because it is a more suitable strategy for miniaturized aptasensors especially POC testing. This technique has been given more attention concerning drug analysis due to its merits, such as ease of use, simplicity, amenability, low cost, and even visualization of results by the naked eye or numerous commercial devices such as smartphones and flatbed scanners (Khan and Song 2020). The mechanism of colorimetric detection using nanomaterials is commonly based on their inherent optical or catalytic properties (Zhao et al. 2016). Here, some applications of miniaturized aptasensors based on colorimetric methods were mentioned for drug detection. For example, Epinephrine belongs to a group of drugs called alpha and beta adrenergic agonists (sympathomimetic drugs). It was used in a variety of

therapies including treating life-threatening allergic reactions; treatment of mucosal congestion of rhinitis, hay fever, and acute sinusitis; resuscitation of cardiac arrest following anesthetic events and relaxing the uterine muscle and inhibition of uterine contractions (Simons 2004). Seal and coworkers reported a label-free colorimetric aptasensor for detection of epinephrine based on interactions between epinephrine and aptamers conjugated with AuNPs. The effect of different parameters has been investigated to improve the performance of aptasensor in terms of selectivity and sensitivity. A detection limit was obtained 0.9 nM (Saraf et al. 2017).

Dopamine is a class of catecholamine neurotransmitters that have an important role in the endocrine, cardiovascular, and central nervous systems. When substantia nigra cells are damaged, the amount of dopamine produced was decreased. Dopamine was prescribed for treating cardiac output, low blood pressure and improving blood flow to the kidneys (Wightman et al. 1988). A paper-based colorimetric platform was designed by Nuchtavorn et al. for dopamine determination. The sensing was based on a redox reaction of 3,3′,5,5′-tetramethylbenzidine (TMB)-silver nitrate. The blue color solution was produced from the oxidized TMB. The blue color was faded by the addition of dopamine. The aptasensor has been able to measure dopamine in a linear range of 1–8 mM with 0.57 mM as a detection limit (Manmana et al. 2019).

In another study, a paper microfluidic device has been developed using AuNPs and aptamer for the colorimetric detection of cocaine. The paper device generates a detectable color change visualized by the naked eye or camera. The images were analyzed by y Image J software. The visual LOD for the method and based on camera were 2.5 g and 2.36 g, respectively (Wang et al. 2018a, b). A paper chip was developed based on a colorimetric aptasensing assay for kanamycin detection. The sensing mechanism is based on adsorption of aptamers on AuNPs surface caused to the dispersion of gold NPs that by addition of target, AuNPs aggregated due to binding kanamycin with aptamers. Kanamycin was measured as low as 3.35 nM (1.95 ppb) via the naked eye and using techniques of RGB color analysis (Ha et al. 2017a).

14.3.2 Fluorscence Techniques

Among luminescence detection methods, methods based on fluorescence detection are by far the most broadly employed in sensing techniques especially in microfluidic devices due to their ease of implementation (Lafleur et al. 2016). The fluorescence-based method offers benefits of high selectivity, low detection limits and an extensive range of fluorophores available for labeling biomolecules (Lafleur et al. 2016). Some fluorescence-based aptasensors in microfluidic applications are summarized here and in Table 14.1. For example, Lin and coworkers developed a microfluidic biosensor based on aptamer for cocaine detection. The device is composed of a microchamber filled with aptamer-conjugated microbeads that act as a sensing surface combined with a temperature sensor and an on-chip heater. A Förster resonance energy transfer (FRET) mechanism was used which FAM and Dabcyl

were used as a fluorophore-quencher pair. Cocaine was measured in four orders of magnitude linear response in μM to nM concentrations. The detection limit is achieved lowered to 10 pM (Hilton et al. 2011). Also, He et al. (2020) used aptamer and magnetic tripartite to fabricate a microfluidic chip aptasensor to identify kanamycin, aflatoxin M1, 17β-estradiol (E2), simultaneously that here, determination of kanamycin is reported. Using magnetic nanocomposites functionalized with multi tripartite DNA structure can be realized structure changing of aptamers for recognition of targets and eliminating the complex matrix effect of the real sample by appropriate separation via magnetic beads. Kanamycin was detected as low as 0.32 pg mL^{-1}.

14.3.3 Other Optical Techniques

In addition to the above-mentioned methods, other optical techniques including SERS, chemiluminescent, SPR, can be applied in miniaturized aptasensors. Some applications of these methods in drug detection are presented in Table 14.1 and explained here. Singh presented a microfluidic aptasensor based on surface plasmon resonance for insulin detection. The device applied an antibody conjugated magnetic NPs for capturing insulin molecules and surface immobilized plasmon enhancing QDs for amplification of the signal. a linear dynamic range was obtained 0.8–250 pM and the detection limit was 800 fM (Singh 2020).

Theophylline is a group of methylxanthine family that is generally utilized as a respiratory stimulator and bronchodilator in the treatment of respiratory diseases such as asthma or weight loss and lethargy (Wang et al. 2018a, b). Nanopore thin-film aptasensor was fabricated with a microfluidic interface for detection of theophylline. The anodicaluminum oxide nanopore surface was functionalized by the RNA aptamer. The optical signal (interference fringes) was changed by binding theophylline to the aptamer. The aptasensor can found theophylline as low as 0.2 μM concentration (Feng et al. 2016a, b). Li et al. developed a conceptual nanoplasmonic method based on high-resolution images of dark-field microscopy (DFM) and latent fingerprints (LFPs) to detect cocaine in LFPs using aptamer-conjugated AuNPs as a probe of imaging and recognition. The localized surface plasmon resonance (LSPR) of AuNPs attached to LFPs was recorded by DFM, which producing a colorful image of LFPs. Cocaine was identified ranging from 150 ng to 30 mg (Li et al. 2013).

14.4 Lateral Flow Assay

The lateral flow test strips have been noticed for POC devices that are used for visual detection and semiquantitative, or even quantitative analysis of different analytes. These tests are economic, simple and normally results were shown in around 5–30 min. Lateral flow assay is carried out using a strip whose various parts are laminated on a backing. These parts include a sample pad, the sample is dropped on this area;

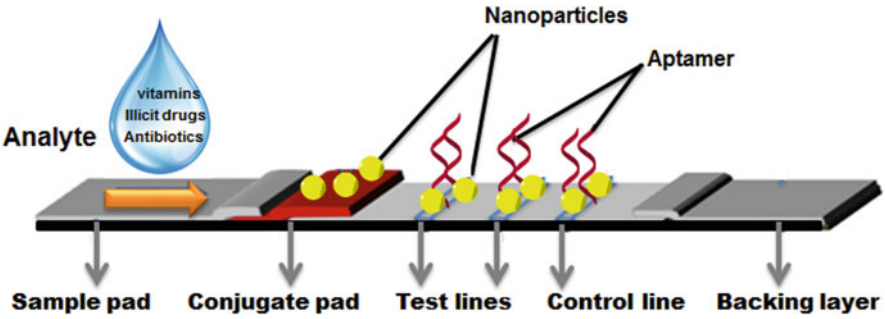

Fig. 14.4 Illustration of lateral flow aptasensor based on nanoparticles for drug analysis

membrane (nitrocellulose), includes test line and control line; conjugate pad, which labeled molecules for biorecognition are dispersed; and absorbent pad, acts as sink at the end of the strip (Bahadır and Sezgintürk 2016; Sajid et al. 2015). The lateral flow assays have been coupled with detection techniques including colorimetry, fluorescence, electrochemistry, and Raman (Li et al. 2019a, b). Incorporation of NPs with aptamers provides an effective strategy to increase the performance of lateral flow assays. A schematic diagram of lateral flow platform based on aptamer and nanoparticles is illustrated in Fig. 14.4.

Here, some applications of this test were reported in drug analysis. For example, a lateral flow strip assay has been fabricated using conjugating aptamer to AuNPs surface for rapid detection of cortisol. AuNPs play as a color probe that adsorption aptamer on AuNPs surface enhances stability against salt-induced aggregation. By the addition of cortisol to the system, change in the conformation of aptamers have resulted from cortisol binding which was accompanied by aggregation and color change. The portable device exhibited a linear range between 8 and 140 ng/mL. A limit of detection was obtained 1 ng/mL (Dalirirad and Steckl 2019). In another study by Dalirirad and Steckl, a lateral flow assay using the aptamer and AuNPs was investigated for the detection of dopamine. The mechanism of detection is based on duplex dissociation. In the presence of the analyte, the aptamer undergoes conformational changes leading to the aptamer dissociation from the duplex. A red band was produced by the duplex aptamer conjugated with AuNPs and dopamine using the hybridization of the conjugated aptamer and its immobilized complementary strand on the test zone. A detection limit was estimated 50 ng/mL with 52–480 ng/mL as a linear range (Dalirirad and Steckl 2020).

14.5 Conclusion and Future Outlook

During the past years, studies have been directed toward the development of aptamer-based sensors for drug analysis due to high specificity binding with the target analyte and good stability compared to antibody-based sensors. With advances in the fields of lab-on-a-chip technology and nanostructure materials, the

combination of aptasensors to numerous forms of miniaturized devices such as microfluidics or paper-based platforms modified with nanomaterials offers promising solutions in the sensing challenges especially in POC tests. These systems have some advantages including portability, improved sensitivity, low sample volume and reduced response time. This chapter has attempted to offer an overview of examples of miniaturized aptasensors based on different signal transductions for qualitative detection, semi-quantification to quantitative analysis of drugs. Table 14.1 summarizes a variety of aptasensors in terms of the target analytes, nanomaterials and the detection methods of platforms. There are still drugs that do not possess matching aptamers with high specificity and affinity. So, the success of the miniaturized devices for aptamer-based biosensing will depend on the discovery of novel aptamers for the drug analyte.

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