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Recent advances in nanomaterial-based biosensors for antibiotics detection

Lingyi Lan, Yao Yao, Jianfeng Ping, Yibin Ying*

School of Biosystems Engineering and Food Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, PR China

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ABSTRACT

Antibiotics are able to be accumulated in human body by food chain and may induce severe influence to human health and safety. Hence, the development of sensitive and simple methods for rapid evaluation of antibiotic levels is highly desirable. Nanomaterials with excellent electronic, optical, mechanical, and thermal properties have been recognized as one of the most promising materials for opening new gates in the development of next-generation biosensors. This review highlights the current advances in the nanomaterial-based biosensors for antibiotics detection. Different kinds of nanomaterials including carbon nanomaterials, metal nanomaterials, magnetic nanoparticles, up-conversion nanoparticles, and quantum dots have been applied to the construction of biosensors with two main signal-transducing mechanisms, *i.e.* optical and electrochemical. Furthermore, the current challenges and future prospects in this field are also included to provide an overview for future research directions.

1. Introduction

1.1. The dangers of antibiotics

It is well known that antibiotics are used for treating diseases and promoting animal growth worldwide. With their capability to enhance growth rates and improve feed efficiency, antibiotics have been extensively applied to human and veterinary medicine (Ur Rehman et al., 2015). Generally, antibiotics can be classified into seven groups, *i.e.* tetracyclines, macrolide antibiotics, aminoglycosides, peptide antibiotic, lincosamides, streptogramins, and β-lactam antibiotics. However, antibiotics are able to be accumulated in human body by food chain, which may produce negative influence on human health even at low concentrations, such as hearing loss, toxicity to organs, and so on (Aghdam et al., 2016). In addition, the abuse of antibiotics has improved the frequency of resistance genes, which may result in a decrease in the efficiency of diseases treatment (Leibovici et al., 2016). Furthermore, the development of antibiotic-resistant bacteria is likely to spread to other microbial populations, posing a potential threat to human and animal health (Sapkota et al., 2007). Hence, the control of antibiotics is extremely important to protect human health and safety.

1.2. Conventional detection methods

In the past decades, numerous efforts have been made to develop analytical methods for qualitative/quantitative determination of antibiotics. Chromatographic methods including thin-layer chromatography (TLC), gas chromatography combined with mass spectrometric (GC-MS) (Posyniak et al., 2003), gas chromatography coupled with electron capture (GC-EC), and high-performance liquid chromatography (HPLC) (Blanchaert et al., 2013), are the most conventional detection methods for antibiotics. However, the inherent disadvantages of chromatographic methods such as the expensive apparatus and time-consuming have limited their wide applications. Except chromatographic methods, capillary electrophoresis (CE), diode array (DA), flame ionization (FI), and enzyme-linked immunosorbent assay (ELISA), are also successfully established for the detection of antibiotic residues with accuracy and precision, but still face some drawbacks such as complicate sample pretreatment process and the requirement of highly trained technical personnel (Chauhan et al., 2016). Therefore, a sensitive, selective, convenient, robust, and rapid detection method for antibiotic residues for human health and safety is highly desirable.

Biosensors appear to be suitable alternative or complementary analytical tools for the detection of antibiotics due to their advantages of high selectivity, rapid detection, and *in-situ* applications. Recently, there is a growing rise in the fabrication of antibiotic biosensors. Here, we summarize the current research literature on nanomaterial-based biosensors for antibiotic residues detection. Our aim is to give the readers a complete concept about the state-of-art of nanomaterial-based biosensors for the detection of antibiotic residues and expect more nanomaterials as well as more biosensing strategies be enrolled into this research field that create really workable biosensing devices serving for human world.

* Corresponding author.
E-mail address: ybying@zju.edu.cn (Y. Ying).

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2. Nanomaterials in antibiotic biosensors

Nanomaterials have been widely used for the construction of biosensors in view of their excellent electronic, optical, mechanical, and thermal properties. They are recognized as one of the most attractive materials for opening new gates in the development of next-generation biosensors. With their high surface area to volume ratio, great electronic conductivity, excellent magnetic and physicochemical properties (Wang et al., 2010), different kinds of nanomaterials (including carbon nanomaterials, metal nanomaterials, magnetic nanoparticles, up-conversion nanoparticles, and quantum dots) have been successfully applied to develop numerous biosensors for antibiotics detection. In this section, the basic properties of these five types of nanomaterials used in antibiotic biosensors are discussed.

2.1. Carbon nanomaterials

Carbon nanomaterials, including carbon nanotubes, carbon nanofibers, fullerene, graphene quantum dots, and graphene, are obtaining a lot of attention for their extraordinary properties (Yang et al., 2015). Among them, carbon nanotubes and graphene are the most commonly used carbon nanomaterials in biosensors for the detection of antibiotics.

2.1.1. Carbon nanotubes

Carbon nanotubes (CNTs), one-dimensional (1D) carbon nanomaterials, are sp^2 hybridized carbon atom rolled graphene sheets that were discovered by Iijima in 1991 (Iijima, 1991). Since their discovery, CNTs have gained enormous attention due to their unique mechanical, thermal, and electronic properties. For example, their great mechanical flexibility, fast electron transportation, excellent electrochemical stability, and unique thermal conductivity make them very attractive materials in the application of electrochemical biosensors (Lawal, 2016). Moreover, CNTs can be easily functionalized with various chemical groups which are able to connect the biomolecules (*e.g.* protein and nucleic acid) or organic molecules (Katz and Willner, 2004). In the past decades, CNTs-based biosensors have been extensively used for the detection of antibiotics.

2.1.2. Graphene

Graphene, two-dimensional (2D) carbon nanomaterials, is a sheet of sp^2 bonded carbon atoms that are arranged into a rigid honey comb lattice, exhibiting the highest mechanical strength among the known materials, extraordinary electron transfer capabilities, excellent electrical conductivity, ultra-large specific surface area, unprecedented pliability and impermeability, and favorable biocompatibility (Ping et al., 2015). Since its discovery in 2004, graphene has been successfully applied into various fields, such as catalysis, energy storage, sensor, and electronic devices. In addition, graphene can be easily oxidized into graphene oxide (GO), which contains many hydrophilic groups such as hydroxyl, epoxy, carbonyl, and carboxyl groups (Loh et al., 2010). These hydrophilic groups make GO aqueous dispersibility and easy to be functionalized with biomolecules, which are highly important features in biosensor applications.

2.2. Metal nanomaterials

Metal nanomaterials are a class of functional materials with unique physical and chemical properties, which are closely related to their size, composition, shape, and structure. Great progress has been made in the synthesis of novel metal nanocrystals and their potential applications in diverse fields such as in catalysis, electronics, sensors, and medicine. With their high specific surface area, excellent electron transfer kinetics, and plenty absorption sites to antibodies, enzymes and antigen, metal nanomaterials have attracted extensive attention in the development of electrochemical biosensors for antibiotic detection (Sozer and Kokini, 2009). In addition, metal nanomaterials, especially gold nanoparticles (AuNPs), possess a distinctive phenomenon termed as surface plasmon resonance, in which any change/alteration in the size, shape, or geometry of particles alters the local electron confinement that is thereby reflected in the absorption maxima and color of colloidal solution (Saha et al., 2012). In the past decades, optical biosensors based on AuNPs have been successfully developed for antibiotics detection.

2.3. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) have gained an increasing attention in the development and applications of biosensors recent years. Enormous efforts have been made to develop MNPs because of their particular characteristics such as large surface area, high mass transference, unique physicochemical properties, biocompatibility with biomolecules, and easy production (Akbarzadeh et al., 2012; Reddy et al., 2012). MNPs display superparamagnetic property below 50 nm size and perform best at 10–20 nm, making them a suitable choice in magnetic fields when quick response is required (Netto et al., 2013). Moreover, MNPs are able to be integrated into the transducer materials, attracting analytes in the samples by an external magnetic field (Rocha-Santos, 2014). Compared to non-MNPs-based strategy, biosensing strategy based on MNPs has many merits including improved sensitivity, lower detection limit, less noise, and quicker analysis (Justino et al., 2013).

2.4. Up-conversion nanoparticles

Up-conversion nanoparticles (UCNPs) are a novel class of luminescent materials that transform the near infrared radiations (lower energy) into visible radiation (higher energy) (Wang et al., 2011). It has been paid significant attention in various fields due to their low background noise, high photo stability, low toxicity, and great penetration of signals in tissues with low absorption (Zhang et al., 2016). These advantages make them a better choice in comparison to down-conversion fluorescent materials, such as organic fluorescent dyes and inorganic quantum dots. Generally, they are used as fluorescent labels combined with biorecognition molecules for antibiotics detection in the optical biosensing systems (Wang et al., 2005).

2.5. Quantum dots

As semiconductor nanocrystals, quantum dots (QDs), including CdS, ZnS, and CdTe, display unique optical and electronic properties, such as high luminescence, long-term photo stability, resistance to photo-bleaching, broad absorption bands, and size-tunable, narrow, symmetric emission (Bonilla et al., 2016), which make QDs very attractive in analytical chemistry. Moreover, QDs provide the convenience of conjugation to aptamer/antibody without affecting either their emission properties or aptamer/antibody specificity (Stanisavljevic et al., 2015).

3. Nanomaterial-based biosensors for antibiotics detection

3.1. Optical biosensors

Optical detection comprises of transducers that can capture signals produced by the interactions of biorecognition element with target analyte and can transform them into optical signals (Yoo and Lee, 2016). In the past years, optical biosensors have been extensively used in antibiotics detection owing to their advantages such as simplicity of operation, convenience, and sensitivity (Adrian et al., 2009). The introduction of nanomaterials into optical biosensors have enabled the ultrasensitive and label-free strategies in antibiotics detection. According to the optical signal transducing mechanism, the nanoma-

Table 1
Summary of nanomaterial-based optical biosensors for the detection of antibiotics.

Biosensor type	Analytes	Nanomaterials	Bioreceptors	Linear range	LOD	Ref.
Fluorescent	oxytetracycline	GO	aptamer	25–1000 μg L^{-1}	25 μg L^{-1}	(Tan et al., 2016)
	chloramphenicol	MNPs, UCNPs	aptamer	0.01–1 ng mL^{-1}	0.01 ng mL^{-1}	(Wu et al., 2015)
	kanamycin	AuNPs	aptamer	0.5–20 nM	321 pM	(Ramezani et al., 2016)
	kanamycin	UCNPs	aptamer	0.01–3 nM	9 pM	(Li et al., 2014a)
	kanamycin	SiNPs	aptamer	2–60 nM	612 pM.	(Khabbaz et al., 2015)
	streptomycin	AuNPs	aptamer	_	54.5 nM	(Taghdisi et al., 2016)
	streptomycin	CdTe QD	antibody	0.01–25 ng mL^{-1}	5 pg mL^{-1}	(Song et al., 2015)
	tetracycline	CdTe QD	antibody	0.01–25 ng mL^{-1}	5 pg mL^{-1}	
	penicillin G	CdTe QD	antibody	0.01–10 ng mL^{-1}	5 pg mL^{-1}	
Colorimetric	oxytetracycline	Fe_3O_4 MNPs	enzyme	50–1000 nM	26 nM	(Wang et al., 2016)
	tetracycline	Fe_3O_4 MNPs	enzyme	100–1000 nM	45 nM	
	doxycycline	Fe_3O_4 MNPs	enzyme	50–1000 nM	48 nM	
	streptomycin	AuNPs	aptamer	_	73.1 nM	(Emrani et al., 2016)
	oxytetracycline	AuNPs	aptamer	0.025–1 μM,	25 nM	(Kim et al., 2010b)
	tetracycline	AuNPs	aptamer	10^{-3}–45.8 nM	45.8 nM	(He et al., 2013)
	kanamycin	AuNPs	aptamer	10–150 nM	25 nM	(Song et al., 2011)
	aminoglycosides	AuNPs	aptamer	1–100 nM	1.0 nM	(Derbyshire et al., 2012)
	chloramphenicol	AuNPs	aptamer	1–120 nM	451 pM	(Abnous et al., 2016)
	amoxicillin	AuNPs	_	0.3–4.5 μM	0.15 μM	(Akhond et al., 2015)
CL	chloramphenicol	MNPs	aptamer	0.01–0.20 ng mL^{-1}	0.01 ng mL^{-1}	(Hao et al., 2015)
ECL	tetracycline	SiNPs	_	1–100 μM	0.23 μM	(Chen et al., 2014)
	oxytetracycline	SiNPs	_	0.1–100 μM	0.10 μM	
	chlortetracycline	SiNPs	_	1–100 μM	0.16 μM	
SPR	fluoroquinolone	AuNPs	antibody	_	0.07 μg L^{-1}	(Fernandez et al., 2012)
	erythromycin	MIP	_	6.8–68.1 μM	0.40 μM	(Sari et al., 2016)
	amoxicillin	MIP	_	0.1–2.0 ng mL^{-1}	0.022 ng mL^{-1}	(Yola et al., 2014)

MIP: molecularly imprinted polymer.

terial-based optical biosensors for antibiotics detection can be classified into four types: fluorescent, colorimetric, chemiluminescent, and surface plasmon resonance biosensors (Table 1).

3.1.1. Fluorescent biosensors

The fluorescent biosensors with fluorogenic probes are becoming increasingly popular due to their inherent advantages, such as operation convenience, rapid hybridization kinetics, and ease of automation (Kim et al., 2011). Such probes usually consist of a fluorophore and a quencher to form a Förster resonance energy transfer (FRET) pair, in which the distance-dependent fluorescence quenching is elaborately designed for biomolecular recognition detection (Hirata and Kiyokawa, 2016). Nanomaterials have been used as novel fluorescent biosensing platforms on the basis of their unique optical and electronic properties. Over the past two decades, there has been an explosion of interest in the design of novel nanoprobes by coupling nanomaterials with biomolecular recognition events for sensitive detection of antibiotics (Table 1).

Among the large family of nanomaterial-based quenchers, GO is the most usually used nanomaterials in view of its water solubility, excellent fluorescence quenching ability, and ease of synthesis. For example, Tan et al. designed a GO hydrogel-based fluorescent method for oxytetracycline detection (Tan et al., 2016). The GO hydrogel was prepared by physically mixing GO sheets, adenosine, and aptamers together, in which the adenosine and aptamer work as the co-cross-linkers to connect the GO sheets and then form the three-dimensional macrostructures. Under the optimal conditions, the developed fluorescent biosensor exhibits a linear range of 25–1000 μg L^{-1} with a limit of detection (LOD) down to 25 μg L^{-1}. Moreover, they applied this detection method for oxytetracycline in real water samples with excellent accuracy.

Apart from GO, other nanomaterials, such as UCNPs and AuNPs, can also be incorporated into fluorescent biosensors for antibiotics detection. For instance, an aptamer-based fluorescent biosensor was developed to detect chloramphenicol using MNPs and UCNPs (Wu et al., 2015). Under the optimal conditions, the linear detection range is found to be 0.01–1.0 ng mL^{-1} and a LOD of 0.01 ng mL^{-1} is achieved. Furthermore, this proposed biosensor was successfully applied to measure chloramphenicol in contaminated milk samples. Li et al. reported a sensitive fluorescent biosensors based on UCNPs for the detection of kanamycin (Li et al., 2014a). In their experiment, UCNPs were used as the energy donor and graphene sheets as the energy acceptor (Fig. 1). The amine-modified kanamycin aptamer could be attached to hexanedioic acid-modified UCNPs on the basis of an EDC-NHS protocol. In the absence of kanamycin, the UCNPs-aptamer conjugates are adsorbed onto graphene surface through π–π stacking

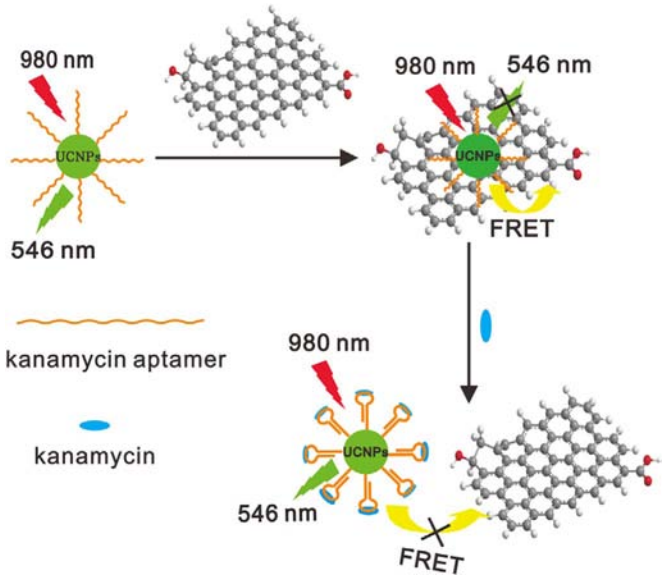

Fig. 1. Schematic illustration of the kanamycin aptasensor on the basis of FRET from aptamer- linked UCNPs to grapheme (Li et al., 2014a).

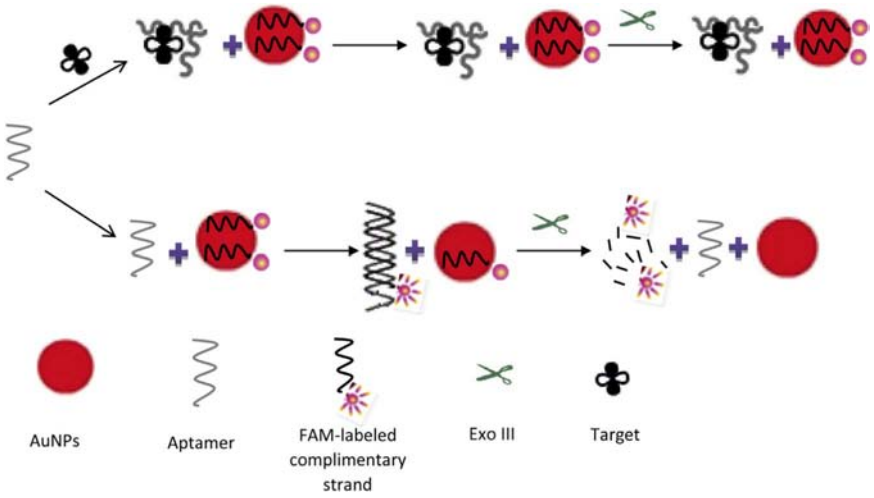

Fig. 2. Schematic description of Kanamycin detection based on Exo III-based fluorescence assay (Ramezani et al., 2016).

interaction and thus bring the UCNPs (energy donor) and graphene (energy acceptor) in close proximity, resulting in the quenching of UNCPs emission. After the introduction of kanamycin, the structure of aptamer would change into a hairpin structure due to the binding reaction between aptamer and kanamycin. While the hairpin structure possesses low affinity to graphene, leading to the dissociation of aptamer from graphene surface, and finally the FRET process was blocked. As expected, a quite low LOD of 9 pM was achieved for kanamycin detection.

In order to improve sensitivity, the incorporation of nucleic acid-related enzymes into the detection process is commonly used. For example, Ramezani et al. proposed an ultrasensitive fluorescent aptasensor for kanamycin detection based on exonuclease III activity (Exo III), dye-labeled complimentary strand of aptamer, and AuNPs (Ramezani et al., 2016). As shown in Fig. 2, in the presence of kanamycin, aptamer binds to its target and the complimentary strand remains on the surface of AuNPs, resulting in a weak fluorescence emission. In the absence of kanamycin, aptamer binds to its complimentary strand to form a double-stranded DNA (dsDNA). The formed dsDNA leaves the surface of AuNPs. Upon addition of Exo III, aptamer is recycled from dsDNA and the cycle goes on, leading to a very strong fluorescence emission. With this enzyme amplified strategy, the developed biosensor shows a LOD down to 321 pM.

3.1.2. Colorimetric biosensors

Colorimetric methods have gained great interest because of their inherent advantages including simple preparation, quick detection, and no need for complicated apparatus. Colorimetry has commonly been applied for analytical applications since it can be detected with only the naked eyes through a color change (Gopinath et al., 2014). In view of these properties, colorimetric biosensors are very popular among the optical biosensors for antibiotics detection (Table 1). There are two types of nanomaterial-based colorimetric biosensors, *i.e.* colorimetric biosensors based on the inherent optical properties of nanomaterials (such as plasmonic AuNPs) and colorimetric biosensors based on the catalytic properties of nanomaterials (such as Fe_3O_4 MNPs).

Generally, colloidal AuNPs are employed in the solution-based biosensors and the color change can be detected through AuNPs aggregation. For example, Emrani et al. proposed a colorimetric aptasensor on the basis of dsDNA and AuNPs to detect streptomycin (Emrani et al., 2016). The dye-labeled complementary strand dsDNA remains stable when streptomycin is absent, leading to the aggregation of AuNPs by addition of NaCl. As a result, the solution color changes from red to blue. When streptomycin is added, the streptomycin aptamer binds to its target and consequently the dye-labeled complementary strand leaves the aptamer and adsorbs on the surface of AuNPs. The AuNPs are well-dispersed and remains stable against NaCl-induced aggregation with red color. Under the optimized conditions, the developed colorimetric aptasensor shows high sensitivity towards streptomycin detection with a LOD of 73.1 nM. A colorimetric sandwich aptasensor based on an indirect competitive enzyme-free method for detection of chloramphenicol was reported by Abnous et al. (Abnous et al., 2016). As illustrated in Fig. 3, in the absence of chloramphenicol, the AuNPs (colorimetric probes) bind to the well through a sandwich structure, *i.e.* aptamer-biotin-streptavidin-biotin, leading to a sharp red color in the well. Upon the addition of chloramphenicol, a huge amount of biotin-modified aptamers bind to free chloramphenicol molecules and would be removed from the well by washing. As a result, a little AuNPs bind to the well, leading to a faint red color in the well (Fig. 3). The fabricated biosensor exhibits a LOD as low as 451 pM for chloramphenicol detection.

Another colorimetric biosensing strategy is based on the catalytic activity of nanomaterials. In this type biosensor, the inherent peroxidase-mimicking activity of Fe_3O_4 MNPs are commonly used. For example, a novel colorimetric biosensor for tetracycline determination based on the Fe_3O_4 MNPs was reported by Wang et al. (Wang et al., 2016). In their biosensor design, tetracycline molecules have a strong tendency to complex with Fe (II) or Fe (III) on the surface of Fe_3O_4 MNPs owning to the multiple O- and N-containing moieties. The obtained complexation of Fe_3O_4 MNPs and tetracycline molecules could lead to the accelerated catalyzing H_2O_2-mediated oxidation of 3, 3′, 5, 5′-tetramethylbenzidine (TMB) by Fenton chemistry. As a result, more obvious color change of solution can be found compared to the similar detection system without tetracycline molecules. They applied this detection strategy to colorimetric biosensing of oxytetracycline, tetracycline, and doxycycline with LODs of 26 nM, 45 nM, and 48 nM, respectively. Moreover, this method was successfully applied for the determination of oxytetracycline content in drugs with satisfactory results.

3.1.3. Chemiluminescent biosensors

Chemiluminescence (CL) is the emission of light on the basis of chemical reactions. Generally, chemiluminescent reactions are multi-step oxidation reactions with fast reaction kinetics (Giokas et al., 2010). Chemiluminescent detection method is extensively applied to different fields, especially in optical biosensing systems. It plays a powerful and important role in analytical technique due to its advantages including high sensitivity, wide dynamic range, low-cost as well as operational simplicity (Cho et al., 2014). Compared to the fluorescence, CL has the merits such as no requirement for an external light source, and longer life time than that of fluorescent ones (Li et al., 2014b). Recent years, chemiluminescent biosensors combined with nanomaterials have been

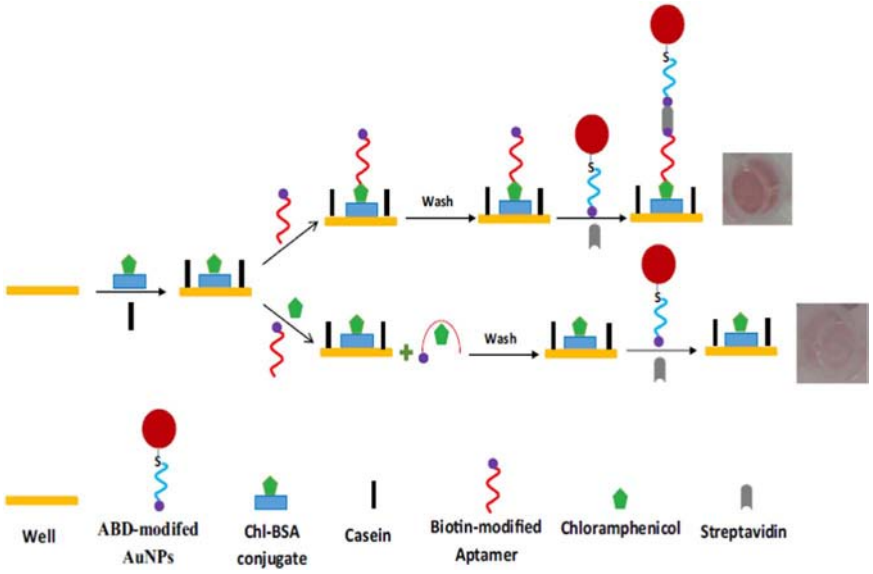

Fig. 3. Schematic illustration of chloramphenicol detection based on a sandwich colorimetric assay (Abnous et al., 2016).

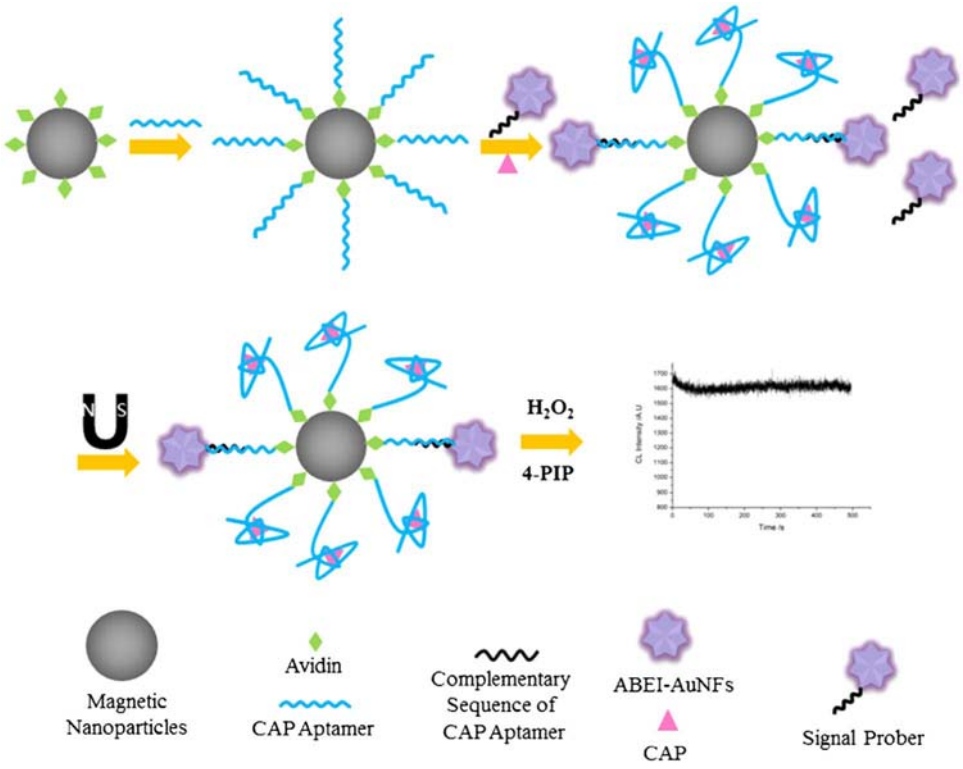

Fig. 4. Schematic illustration of fabrication process of the CL biosensors for chloramphenicol detection (Hao et al., 2015).

studied extensively (Table 1). For example, Hao et al. reported a novel chemiluminescent aptasensor to detect chloramphenicol in milk using MNPs as capture probes and flower-like gold nanostructures (AuNFs) as signal probes (Hao et al., 2015). The aptamer-conjugated MNPs can bind with both chloramphenicol and the signal probes (Fig. 4). When chloramphenicol is added, the aptamer would bind to it because of the stronger interaction. Then, the unbound signal probes are released to the external magnet. As a result, with the increase of chloramphenicol concentration, the concentration of the signal probes decreases. On the basis of this competitive format, the linear range is 0.01–0.20 ng mL^{-1} and a LOD of 0.01 ng mL^{-1} in buffer is achieved. This highly sensitive and easily operating method can be successfully applied to detect chloramphenicol in milk.

Electrochemiluminescence (ECL) is another effective detection method that combines the advantages of electrochemistry with the sensitivity of CL. It is a chemiluminescent reaction caused by an electron transfer reaction at the electrode surface, resulting in an excited state of photon emission (Miao et al., 2016). This electrochemical process can be controlled by the applied potential. Recent years, nanomaterials including quantum dots, CNTs, silica nanoparticles (SiNPs), and metal nanoparticles (Roda et al., 2016) have been used to improve the performance of ECL biosensors, which makes ECL a good choice to develop novel biosensors for the detection of antibiotics (Table 1). For example, Chen et al. proposed an ECL biosensor based on a $Ru(bpy)_3^{2+}$-doped silica nanoparticles (Ru-SiNPs)/Nafion film modified electrode for the detection of tetracyclines

(Chen et al., 2014). After being prepared by a water-in-oil microemulsion method, the Ru-SiNPs were then immobilized on the glassy carbon electrode (GCE) with the help of Nafion film. Interestingly, they found that the presence of tetracyclines can enhance the ECL response of the modified electrode. The results reveal that the linear range is 1–100 μM for tetracycline, 0.1–100 μM for oxytetracycline, and 1–100 μM for chlortetracycline. The LODs are 0.23 μM for tetracycline, 0.10 μM for oxytetracycline, and 0.16 μM for chlortetracycline, respectively. In addition, this ECL biosensor also showed wonderful repeatability and stability, which lead to its application in analyzing the antibiotics content in drugs.

3.1.4. Surface plasmon resonance biosensors

Surface plasmon resonance (SPR) is the phenomenon of oscillation that exists at the interface between two materials which can be induced by both electrons and photons (Situ et al., 2010). It is very sensitive to the refractive index of the dielectric that is attached to the metal surface. Since the refractive index is the inherent feature of all materials, any dielectric attached to the metal surface is able to be detected. Based on this principle, the SPR biosensors usually immobilize various biological compounds including antibody, enzyme, and nucleic acid on the surface of metal (Rajan et al., 2007). Analytes can be detected directly relying on the SPR response to the binding reaction. In the past decades, SPR biosensors have attracted extensive attention in antibiotics detection due to their compact design, low-cost, and more importantly their ability to realize the label-free and real-time analysis (Homola, 2003) (Table 1).

For example, Fernández et al. reported a SPR immunosensor based on antibody-nanogold probes for sensitive detection of antibiotic residues (Fernandez et al., 2012). The antibody-nanogold probes were prepared by covalent attachment of the antibodies to the PEGylated nanoparticles *via* the active ester method (Fig. 5a). Then, they developed three different biosensing strategies to evaluate the performance of antibody-nanogold probes-based SPR biosensor (Fig. 5b). Results show that the antibody-nanogold probes-based SPR biosensor possesses a LOD as low as 0.07 μg L^{-1} for fluoroquinolone antibiotic residues detection. In addition, they also developed a portable six channel SPR biosensor on the basis of the plasmon of gold diffraction grating surface for simultaneous detection of multi-antibiotics in milk samples. Three common antibiotics, *i.e.* enrofloxacin, sulfapyridine, and chloramphenicol, were chosen as the models. Under the optimized conditions, the LODs of these three antibiotics are 0.30 μg L^{-1}, 0.29 μg L^{-1}, and 0.26 μg L^{-1}, respectively. Moreover, the developed multi-channel SPR biosensor can be used for antibiotics detection in real milk sample without clean-up steps.

Later, Yola et al. developed a SPR biosensor based a molecular imprinted nanofilm for the detection of amoxicillin (Yola et al., 2014). Firstly, the gold surface of SPR chip was modified with allyl mercaptane. Then, the amoxicillin imprinted nanofilm was generated on the allyl mercaptane modified gold surface. Under the optimized conditions, the linear range is found to be 0.1–2.0 ng mL^{-1} and the LOD is 0.022 ng mL^{-1}. Furthermore, the developed imprinted nanosensor was applied to the chicken egg and human plasma samples for the determination of amoxicillin. Recently, a new SPR biosensor for rapid detection of erythromycin based on molecular imprinted nanoparticles was reported by Sari et al. (Sari et al., 2016). With the combination of mini emulsion polymerization, molecular imprinting, and SPR techniques, the developed biosensor could detect erythromycin in the range of 6.8–68.1 μM with a LOD of 0.4 μM.

3.2. Electrochemical biosensors

Electrochemical biosensors are the most common and frequently used biosensors among various types of biosensors, since the chemical reactions may lead to changes in measurement of electrons or ions, which have an effect on electrical parameters of solutions. Nanomaterial-based electrochemical biosensors are prominent for antibiotics detection owing to their privileged merits including high sensitivity, selectivity, low cost, and easy operation (Wang et al., 2015). Based on the different type of transducers, electrochemical biosensors can be classified into amperometric, impedimetric, voltammetric, and photoelectrochemical biosensors (Table 2).

3.2.1. Amperometric biosensors

Amperometric biosensor works behind the principle that analyte concentration is linear to the transferred electrons (Tomassetti et al., 2015). It evaluates the amplitude of a reduction or oxidation flow at a given particular potential during a fixed period of time (Hayat et al., 2014). Many nanomaterials have been incorporated into amperometric biosensors for improved detection of antibiotics (Table 2). For example, Kim et al. proposed an amperometric immunosensor based on carboxyl functionalized CdS QDs for the detection of chloramphenicol (Kim et al., 2010a). As shown in Fig. 6, the AuNPs were formed on the surface of the GCE through electrochemical deposition. Then the conducting polymer was coated onto the AuNPs using the potential cycling method, and another layer of AuNPs were physically deposited on the polymer layer. Thereafter, an amine-terminated dendrimer was covalently immobilized on the conducting polymer through the formation of amide bonds between the polymer and the dendrimer. After this attachment, CdS QDs interacted with amine-terminated dendrimer through covalent bonding between the carboxylic acid groups of CdS QDs and the amine groups of the dendrimer, and finally antibody was immobilized onto the CdS QDs surface. Under the optimal conditions, this immunosensor exhibits a linear range from 50 to 950 pg mL^{-1}, with a LOD of 45 pg mL^{-1}. Furthermore, the amperometric immunosensor was used in real meat samples for the analysis of chloramphenicol.

Wei et al. reported a label-free amperometric immunosensor based on graphene sheet-Nafion/thionine/Pt nanoparticles (GS-Nf/TH/Pt) modified electrode for the detection of kanamycin (Wei et al., 2012). The anti-kanamycin antibody was immobilized onto the GS-Nf/TH/Pt *via* electrostatic adsorption. As an electron transfer mediator, the electroactivity of TH was significantly improved due to the excellent electron-transfer ability of GS and Pt. Furthermore, due to the large specific surface area of the Pt and GS, kanamycin antibody can be easily adsorbed onto the modified electrode which could greatly increase the loading amounts of antibody. As a result, the developed immunosensor shows improved performance for kanamycin detection with a LOD of 5.74 pg mL^{-1} and a wide linear range from 0.01 to 12.0 ng mL^{-1}. In addition, this immunosensor was employed to the determination of kanamycin in animal derived foods with satisfactory results.

3.2.2. Impedimetric biosensors

Electrochemical impedance spectroscopy (EIS) is a label-free technique that is highly sensitive to changes/interactions at a surface. It has the ability to extract information about electrochemical features of the electrochemical system effectively, such as double-layer capacitance, diffusion impedance, charge transport processes and solution resistance (Lindholm-Sethson et al., 2010). Over the past few years, EIS has played an important role in biosensing for various antibiotics due to their high sensitivity and rapid detection times (Conzuelo et al., 2013) (Table 2). For example, Zhu et al. proposed a label-free aptasensor using EIS technique for the detection of kanamycin based on a screen-printed electrode (SPE) modified with a self-assembled conducting polymer/AuNPs nanocomposite (Zhu et al., 2012). SPE has always been used in the electrochemical biosensors due to its easy fabrication, low-cost, and miniaturization. Here, the SPE was used as electrode substrate for coating the nanocomposite through an electropolymerization process. Then, aptamer was immobilized onto the electrode through the covalent bonding between the $-NH_2$ groups of aptamer and the –COOH groups on conducting polymer. According to the results, it can be concluded that the incorporation of AuNPs to SPE

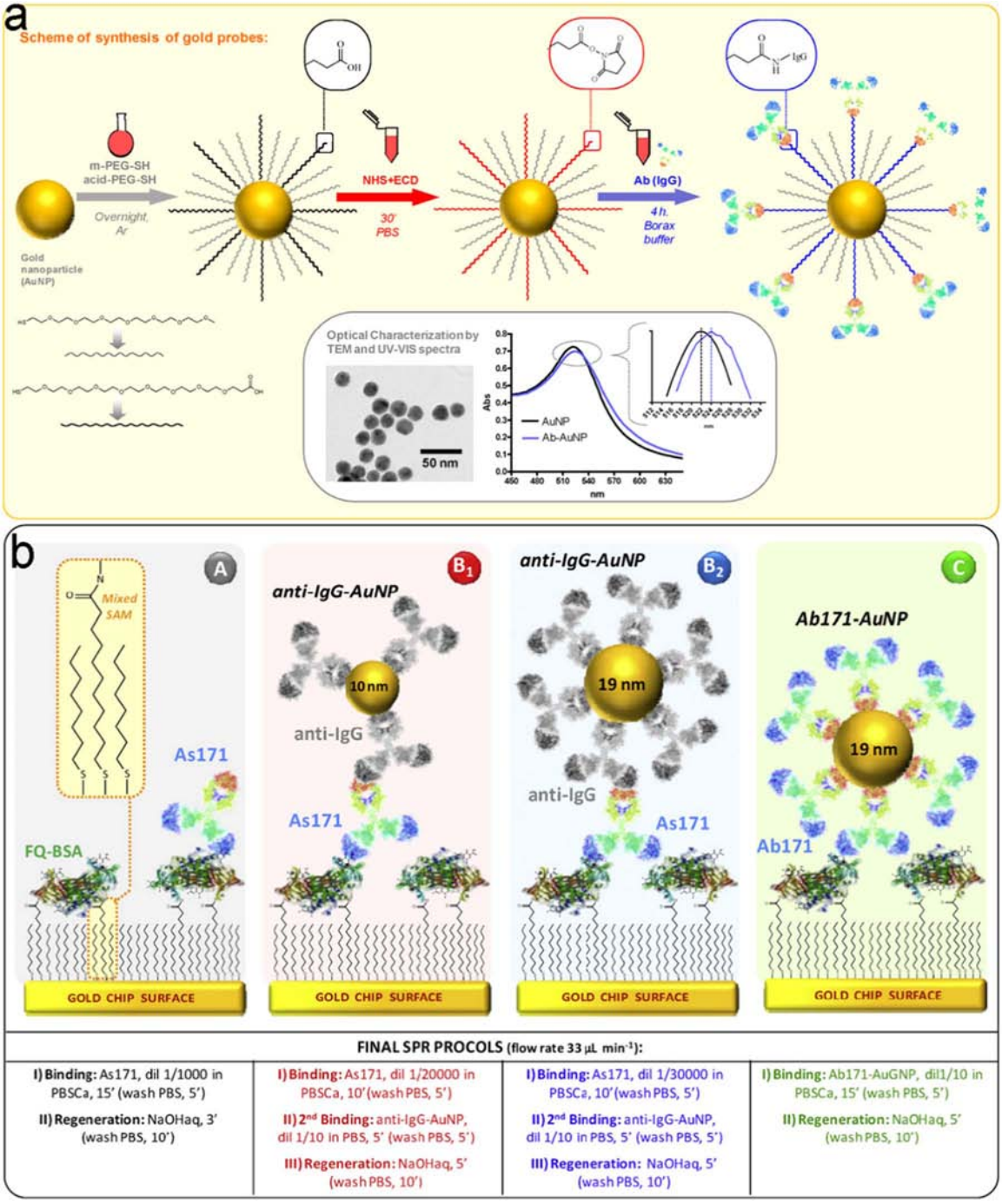

Fig. 5. (a) Schematic illustration of fabrication process of the antibody-nanogold probes. (b) Schematic illustration of the detection process of the antibody-nanogold probes-based SPR biosensor (Fernandez et al., 2012).

could greatly increase the analytical performance. The results show a linear range from 0.05 to 9.0 µM with a LOD of 9.4 nM for the detection of kanamycin.

Later, Liu et al. reported an electrochemical immunosensor for the detection of tetracycline based on gold electrode-modified carboxyl-Fe_3O_4 MNPs by chitosan as linker (Liu et al., 2016). The carboxyl-Fe_3O_4 MNPs were used to accelerate the electron transfer and to immobilize the anti-tetracycline monoclonal antibody onto the electrode surface. Compared to the bare gold electrode, the electron transfer resistance shows an obvious decrease for the MNPs modified gold electrode. The decrease in electron transfer resistance demonstrates that the attached MNPs could facilitate the electron transfer kinetics and hence improve the sensitivity of the impedimetric immunosensor. Under the optimal conditions, the fabricated immunosensor shows a linear response to the concentration of tetracycline in the range from 0.08 to 1 ng mL^{-1} with a LOD of 0.0321 ng mL^{-1}. Furthermore, this impedimetric immunosensor was successfully applied to the detection of tetracycline in milk sample.

3.2.3. Voltammetric biosensors

Voltammetry works behind the principle of measuring current flowing produced by the working electrode. The working electrode is immersed in a solution containing electroactive species that can be analyzed by varying potential (Chillawar et al., 2015). The ability to easily identify the analyte by its voltammetric peak potential makes it extremely sensitive and selective. There are three main types of

Table 2
Summary of nanomaterial-based electrochemical biosensors for the detection of antibiotics.

Biosensor type	Analytes	Nanomaterials	Bioreceptors	Linear range	LOD	Ref.
Amperometric	penicillin G	AuNPs	enzyme	10–50 nM	4.5 nM	(Goncalves et al., 2014)
	chloramphenicol	CdS QDs	antibody	50–950 pg mL^{-1}	45 pg mL^{-1}	(Kim et al., 2010a)
	kanamycin	Nanoporous gold	antibody	0.02–14 ng mL^{-1}	6.31 pg mL^{-1}	(Zhao et al., 2011)
Impedimetric	kanamycin	CP/AuNPs	aptamer	0.05–9.0 μM	9.4 nM	(Zhu et al., 2012)
	penicillin	GR-Fe_3O_4 MNPs, PEDOT-AuNPs	aptamer	0.1–200 ng mL^{-1}	0.057 ng mL^{-1}	(Zhao et al., 2016)
	tetracycline	CS-Fe_3O_4 MNPs	antibody	0.08–1 ng mL^{-1}	0.0321 ng mL^{-1}	(Liu et al., 2016)
	tetracycline	Fe_3O_4 MNPs	antibody	10^{-6}–10^{-14} M	3.8×10^{-15} M	(Jahanbani and Benvidi, 2016)
Voltammetric	tetracycline	MWCNTs	aptamer	0.01–50 μM	5 nM	(Zhou et al., 2012)
	tetracycline	AuNPs	_	10^{-5}–10^{-3} M	0.52 μM	(Asadollahi-Baboli and Mani-Varnosfaderani, 2014)
	kanamycin	Ag@Fe_3O_4, TH-GS	antibody	0.05–16.0 ng mL^{-1}	15 pg mL^{-1}	(Yu et al., 2013)
	kanamycin	GR-TH/HNP-PtCu	aptamer	_	0.42 pg mL^{-1}	(Qin et al., 2016)
	chloramphenicol	Fe_3O_4 MNPs-AuNPs	aptamer	10^{-3}–100 ng mL^{-1}	0.33 pg mL^{-1}	(Chen et al., 2016)
	streptomycin	GR-Fe_3O_4-AuNPs	aptamer	0.05–200 ng mL^{-1}	0.028 ng mL^{-1}	(Yin et al., 2017)
PEC	kanamycin	GO	aptamer	1–230 nM	0.2 nM	(Li et al., 2014c)
	oxytetracycline	BiOI-GR	aptamer	4–150 nM	0.9 nM	(Yan et al., 2015)
	chloramphenicol	N-GQDs	aptamer	10–250 nM	3.1 nM	(Liu et al., 2015)

CP: conducting polymer; CS: chitosan; PEDOT: poly(3,4-ethylenedioxythiophene); GR: graphene; TH-GS: thionine mixed graphene sheet; N-GQDs: N-doped graphene quantum dots.

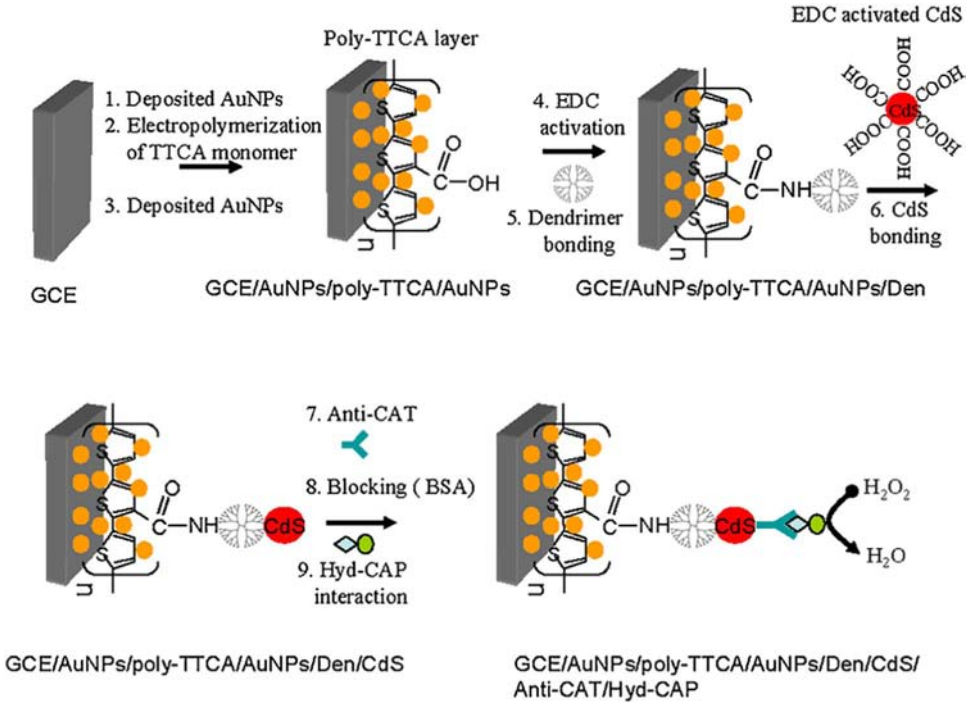

Fig. 6. Schematic illustration of the fabrication of chloramphenicol immunosensor based on AuNPs/Den/CdS modified conducting polymer (Kim et al., 2010a).

voltammetric techniques including cyclic voltammetry (CV), square-wave voltammetry (SWV), and differential pulse voltammetry (DPV) (Batchelor-McAuley et al., 2015). These methods are all widely used in the electrochemical biosensors for the detection of antibiotics (Table 2).

Qin et al. (2016) proposed an electrochemical aptasensor using DPV technique for the detection of kanamycin based on thionine functionalized graphene (GR-TH) and hierarchical nanoporous PtCu (HNP-PtCu) (Fig. 7). In this study, GR-TH composite acted as a suitable charge-transfer bridge to facilitate the electron-transfer rate, while HNP-PtCu alloy could immobilize more aptamers and promote the electron-transfer kinetics. According to the results, there were no redox peaks obtained at the bare GCE. However, after modification of GR-TH/GCE with HNP-PtCu, the peak current was largely increased. Under the optimal conditions, the proposed aptasensor exhibits a high sensitivity and a wider linearity to kanamycin in the range from 5×10^{-7} to 5×10^{-2} μg mL^{-1} with a LOD of 0.42 pg mL^{-1}. Moreover, this voltammetric aptasensor was successfully applied to the determination of kanamycin in animal derived food.

Zhou et al. (2012) reported an electrochemical aptasensor based on multi-walled carbon nanotubes (MWCNTs) using CV and DPV techniques for the detection of tetracycline. The carboxyl functionalized MWCNTs was used to immobilize the anti-tetracycline aptamer and to construct the aptasensor. The interaction between the aptamer and tetracycline was investigated by the electrochemical probe of $Fe(CN)_6^{3-/4-}$. After the pretreated GCE was modified with MWCNTs, the shape of the CV changed significantly, which was as twice as the bare GCE, suggesting that the introduction of MWCNTs played an important role in the increase of the electroactive surface area and

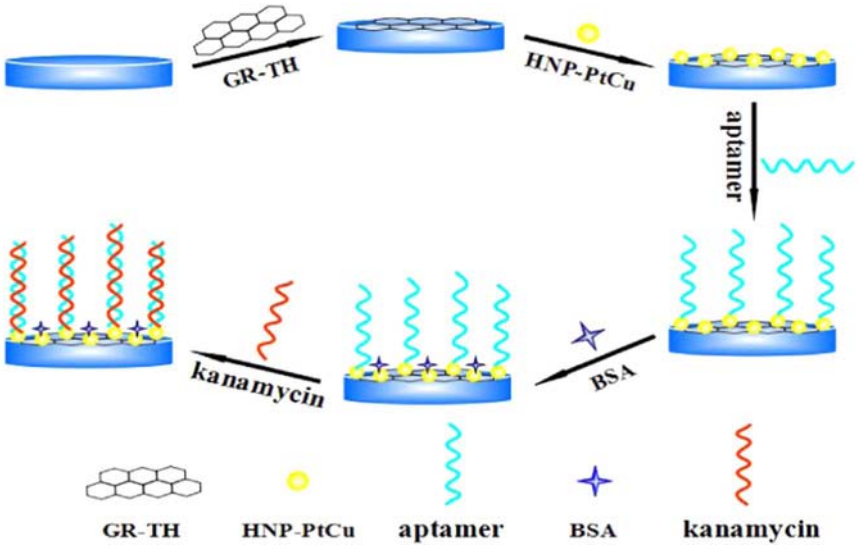

Fig. 7. Schematic illustration of the fabrication of the kanamycin aptasensor (Qin et al., 2016).

conductibility of the aptasensor. Under the optimal conditions, the linear range is found to be 1×10^{-8} to 5×10^{-5} M with a LOD down to 5×10^{-9} M. Furthermore, the aptasensor was successfully applied to the determination of tetracycline in spiked milk samples.

3.2.4. Photoelectrochemical biosensors

Photoelectrochemical (PEC) biosensor works on the basis of the combination of the PEC oxidation and specific biorecognition (Shi et al., 2016). It shows greater performance than traditional optical and electrochemical biosensors because it combines the advantages of them. During the past few years, analytical methods based on PEC biosensors have been paid a growing attention due to their significant advantages such as simple apparatus, easy miniaturization, fast response, reduced background signal, and ultrahigh accuracy (Li et al., 2016). Recently, incorporating functional nanomaterials are widely used to enhance the performance of PEC biosensors for antibiotics detection (Table 2).

Li et al. (2016) proposed a PEC aptasensor for specific detection of kanamycin. In their experiment, water-dispersible graphite-like carbon nitride (w-g-C_3N_4) was used as photoactive material and aptamer as the biorecognition element (Fig. 8). They also found that the incorporation of GO into w-g-C_3N_4 (GO/w-g-C_3N_4 nanocomposite) could improve the visible light photocurrent response. The kanamycin aptamer was able to be immobilized on the surface of GO/w-g-C_3N_4 nanocomposite *via* π–π stacking interaction. The linear range towards kanamycin is from 1 to 230 nM with a LOD down to 0.2 nM. Moreover, the developed PEC aptasensor performed excellent reproducibility and high stability.

Yan et al. reported a 'signal-off' PEC aptasensor based on BiOI-graphene nanocomposite for the detection of oxytetracycline (Yan et al., 2015). In their study, BiOI was used to produce a cathodic photocurrent signal and the anti-oxytetracycline aptamer as the recognition element. The photocurrent response of BiOI could be amplified by the doped graphene. In the presence of oxytetracycline, the photocurrent decreases due to the specific capture of oxytetracycline by aptamer. The linear range towards oxytetracycline is from 4.0 to 150 nM and the LOD is found to be 0.9 nM.

3.3. Other biosensors

Surface-enhanced Raman scattering (SERS) is a powerful technique that has been extensively applied to biosensors. It is a useful tool to

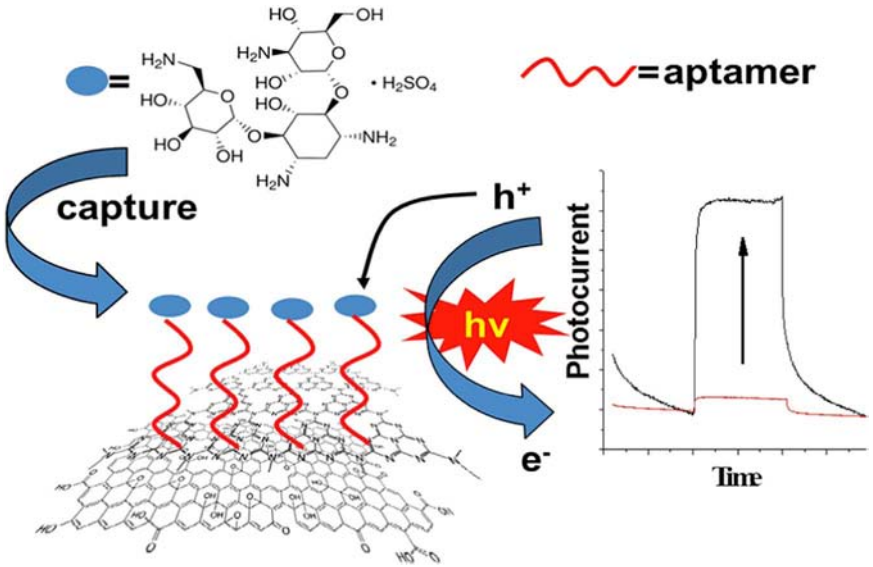

Fig. 8. Schematic illustration of PEC aptasensing of kanamycin (Li et al., 2014c).

amplify Raman signals by using nanomaterials such as gold nanostructures, silver nanostructures, and so on (El-Said et al., 2016). Generally, the characteristic spectral signals stem from the Raman nanotag adsorbed on the surface of the SERS substrates, and the enhancement comes from the excitation of localized SPRs, which are the collective oscillations of conduction electrons of metallic nanoparticles in the electromagnetic field (Jiang et al., 2016). Recently, SERS-based biosensors with simplicity, rapidity, and high sensitivity have been gained great interest in antibiotics detection. For example, Yang et al. proposed a SERS biosensor based on competitive immunoassay and magnetic separation for accurate and sensitive detection of chloramphenicol (Yang et al., 2016). In their study, functionalized AuNPs were labeled with the Raman reporter molecule. In the presence of chloramphenicol, a competitive reaction occurs between free chloramphenicol and above AuNPs for conjugating with antibody-modified MNPs. The results indicates that this developed SERS biosensor was highly sensitive and selective for chloramphenicol detection, with a LOD of 10 pg mL^{-1} and a wide concentration range from 1 to 1×10^4 pg mL^{-1}. Moreover, the SERS-based magnetic biosensor could be applied for the quantitative analysis of chloramphenicol in water with no sophisticated sample processing.

Piezoelectric biosensors have been commonly applied to measure concentration of analytes such as volatile compounds, cancer markers and small molecules for a long time. The principle working behind is the piezoelectric effect that occurs in quartz crystal (QC) without a center of symmetry (Skladal, 2016). When pressure is applied to QC, its lattice is deformed in such a manner that a dipole moment arises in the molecules of QC, generating a signal. Recently, nanomaterial-based piezoelectric biosensors have been fabricated for antibiotics detection. For example, Karaseva et al. proposed a piezoelectric biosensor using nanoparticulate molecularly imprinted polymers (NMIPs) for the detection of penicillins (Karaseva et al., 2016). The NMIPs obtained by precipitation polymerization were used to form a receptor layer at the surface of the piezoelectric chip in a direct format. The application of NMIPs could lead to a mass increase upon binding, which can be analyzed by detuning the resonance frequency of the device. Moreover, as recognizing element, NMIPs could significantly increase the area available for binding targets, and thus increase the sensitivity. In this study, the linear range is found to be 0.1–0.5 μg mL^{-1} for penicillin G, and 0.1–1.0 μg mL^{-1} for ampicillin with a LOD of 0.04 and 0.09 μg mL^{-1}, respectively.

4. Conclusion and prospects

This paper gives an overview about recent advances in developments and applications of nanomaterial-based biosensors for antibiotics detection. It provides the basic properties of carbon nanomaterials, metal nanomaterials, MNPs, UCNPs, and QDs, which have been widely used in antibiotic biosensors. Two main signal-transducing mechanisms in nanomaterial-based antibiotic biosensors, *i.e.* optical and electrochemical, are present in detains. Interestingly, many label-free, one-step analysis, and regent-free strategies have been established with the help of nanomaterials. However, to implement these nanomaterial-based antibiotic biosensors for real sample detection, it is necessary to figure out the main aim of the application. For qualitative and semi-quantitative preliminary detection, where sensitivity is not a major concern, the fluorescent biosensors can prove to be a suitable choice. However, fluorophotometer is required in this case. To avoid this, one can choose colorimetric biosensors, known as the simplest and fastest detecting assay. But it suffers from low sensitivity and the interference from the background color of sample. For some antibiotics that need to be detected at very low concentrations, more sensitive and accurate methods are required. In that case, electrochemical methods, such as amperometric, voltammetric, and impedimetric, are the suitable choices even they need complex sample pretreatments. Therefore, each kind of antibiotic biosensor possesses its own advantages and disadvantages (Table S1, Supplementary table). In addition, there are several commercially available biosensors for antibiotics detection. For example, Biacore Company developed a series of SPR biosensors for food analysis, *i.e.* Biacore 3000, Biacore A100/T100, and Biacore T200/4000, which can be used to detect sulfonamides residues in milk samples. Two chemiluminescent biosensors, *i.e.* the Microarray Chip Reader System 3 (Darmstadt, Germany) and the Evidence Investigator System (Randox, UK), were developed for the detection of antibiotic residues in milk and honey samples, respectively. Even with this developments, biosensors for antibiotic detection are potential markets need to be established urgently and the research in this field is still relatively immature in development compared to other biosensing fields. Many technical hurdles still need to be addressed, including the biocompatibility of nanomaterials with the biorecognition molecules, the influence of non-uniform nanomaterials (*i.e.* due to shifts in size or shape of nanomaterial) on the performance of biosensing devices, the effective connections between organic/inorganic nanomaterials and biorecognition molecules, and the cross interference within the antibiotics (due to the little difference in their molecular structure, *e.g.* tetracycline, oxytetracycline, and chlotetracycline).

An important challenge in nanomaterial-based antibiotic biosensors is the practical application, *i.e.* on-site analysis of analytes in real world, complex environments. That is, the final goal of all the biosensing devices should face to the end user. Unfortunately, till now the innovation is restricted to the laboratory scale and it has not reached to end user who badly needs a smart quick biosensing reliable tool. Therefore, an effective technology, enabling rapid production of large amounts of nanomaterial-based biosensors with high-quality specifications and relatively low cost, is still highly desired. Such a technique is the prerequisite for the successful commercial application of any biosensing devices. Future efforts should focus on developing multifunctional nanomaterials and making the antibiotic biosensors more robust. What's more, for further application in real samples, the biorecognition elements should also be improved, since they should be tolerant to real environmental conditions. Nevertheless, we expect the research in nanomaterial-based antibiotic biosensors will still continuous hot and eventually become effectively routine analysis tools that could meet various challenges.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2017.01.007.

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