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Recent Advances in Quantum Dot – Based Biosensor for Antibiotic Detection

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ABSTRACT
Antibiotics are a category of chemical compounds used to treat bacterial infections and are widely applied in cultivation, animal husbandry, aquaculture, and pharmacy. Currently, residual antibiotics and their metabolites pose a potential risk of allergic reactions, bacterial resistance, and increased cancer incidence. Quantum dots (QDs) are regarded as an ideal material for use in the development of antibiotic detection biosensors. In this review, we characterize different types of QDs summarize the trends in QD-based antibiotic detection.

KEYWORD: Biosensor, Quantum dots, Optical biosensor, electrochemical biosensors.

I. INTRODUCTION

Antibiotics, considered as "wonder drugs," are chemical compounds used to treat bacterial infections and are widely applied in clinical medicine, cultivation, animal husbandry, and aquaculture [1,2] Besides the large use of antimicrobial drugs in human medicine, these compounds are also extensively employed for the prophylaxis or treatment of infections in plants and domestic (dogs, cats) and food-producing animals (livestock, horses, pigs, goats, sheep, etc.) [3,4,5] Antibiotics were seldom applied in crop production (e.g., in China) [6] and sometimes (e.g., CAP) as a disinfectant agent in aquaculture toprevent diseases [7] while around 63,150 tons of antibiotics are consumed alone in the veterinary sector, the global use of antimicrobials in animals being double compared to humans [8] Antibiotics used in humans, plants, and animals are only partially metabolized and can therefore be introduced in the environment through various excretion pathways in complete or resolved forms, such as wastewater discharge, agricultural land runoff, or human excreta[1,9,10]. For example, it was found that the concentrations of erythromycin, sulfamethoxazole, and trimethoprin were 0.10-16.6 ng/L in the offshore waters of the Yellow Sea and the Bohai Sea [10]. The widespread and continuously growing use of antibiotics has led to the contamination of various matrices such as human body fluids, food products (e.g., meat and derivatives, eggs, dairy products), beverages (e.g., milk, drinking water) and environmental resources (e.g., surface and ground waters, soil, sediments) with these parent drugs as well as with their metabolites[3] Antibiotics can enter the environment directly from the pharmaceutical producers (including research laboratories and industrial production) as contaminated after their use in human or veterinary medicine (excreted through urine wastewaters or and feces or discarded as domestic or hospital waste) [3] or from agricultural activities (e.g., from animal farms, soils enriched with manure) [12,13,6] , runoff from agricultural land including aquaculture [7] Residual antibiotics in the environment can cause negative effects, including damaging the ecological health of water and causing abnormal growth of water organisms and imbalance of ecosystems [14].Residual antibiotics and antibiotics resistance have become a global challenge and focus of attention [15]. To overcome these challenges, the straightforward monitoring of antibiotics is highly desirable to reduce potential environmental contamination and ecological health risks from antibiotic pollution [16]. Regular consumption of water or food containing residues of antibiotics or their metabolites posses various health problems (tiredness, headache, diarrhea, muscles pain, blurred vision, hypertension[11], allergic reactions, cancer [13] and AMR, which means that the microorganisms (viruses, bacteria, parasites and fungi) underwent transformations so that they no longer react to antibiotics [17]. Besides affecting human and animal health and also increasing the mortality rate [18,19]

These pathogens often invade the human body via food intake and cause serious harm[20].in order to reduce human, animal and ecological health risks due to antibiotic contamination, there is

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an increasing need for the development of simple, rapid and reliable methods[21,22] for detection Therefore, rapid detection has become top priority in food safety[20] there are many methods for the detection of bacteria, including traditional culture and counting, immunological detection, molecular biological detection, biosensors and emerging detection technologies [20] They are widely used in pharmaceuticals, biosensors, biology, real-time tracking, multi-color labeling, and imaging [23,24,25] In recent years, quantum dots (QDs) have been recognized as an ideal material for the development of biosensors for antibiotic detection. QDs are a type of novel fluorescent nanomaterial consisting of inorganic nuclei with organic molecules in the nanoscale range of 1-10 nm applied to the surface of the nucleus [23,26]. These materials usually consist of carbon, silicon, cadmium selenide, cadmium sulfide, or indium arsenide and emit fluorescence when excited by a light source [27].

II. METHOD OF DETECTION

Rapid detection has become top priority in food safety there are many methods for the detection of bacteria including traditional culture and counting, immunological detection, molecular biological detection, biosensors and emerging detection technologies [20]

3.1 Traditional culture counting

The traditional culture counting method includes pre-enrichment, selective isolation, biochemical identification and serological identification. The whole process takes 4–5 days, the detection limit is >104 colony forming units (CFU)/mL[28,29] and can reach 15–150 CFU/mL after pre-concentration[20]. Because of the advantages of high reliability, low cost and stability, this method is considered to be the basic method for detection of pathogenic bacteria [20,30]

3.2. Immunological detection

Immunoassays work by detecting specific binding of antigen and antibody [28]. At present, the most widely used immunoassay techniques include enzyme-linked immunosorbent assay, immunomagnetic beads (IMBs) and immunochromatography. The immunological method is highly specific, sensitive and easy to operate, and can detect multiple pathogens in 15 min. The detection limit is 104–105 CFU/mL[31]

3.3. Molecular biological detection

Molecular biology can be divided into two kinds of techniques: temperature change amplification and isothermal amplification. The polymerase reaction has the characteristics of high sensitivity, high specificity, simplicity and speed, and it is widely used in the detection of food-borne pathogens. However, these methods require skilled technicians, expensive devices and complex programs, which limit their field applications [31]

3.4. Biosensor

Biosensors are defined as analytical devices that use biological/biochemical reactions to detect target analytes. They are sensitive to biomaterials and convert the concentration of biomaterials into electrical or optical signals by using biomaterials as recognition element.[32,33]

In order to overcome the shortcomings of the above methods , efforts have been made to develop a fast, sensitive and simple food-borne pathogen detection method for accurate detection. Recently, biosensors have become a more intelligent choice for the detection of food borne pathogen because of their specificity, high selectivity, low detection limit, and the advantages of simple operation, low cost, and ease of use [34]

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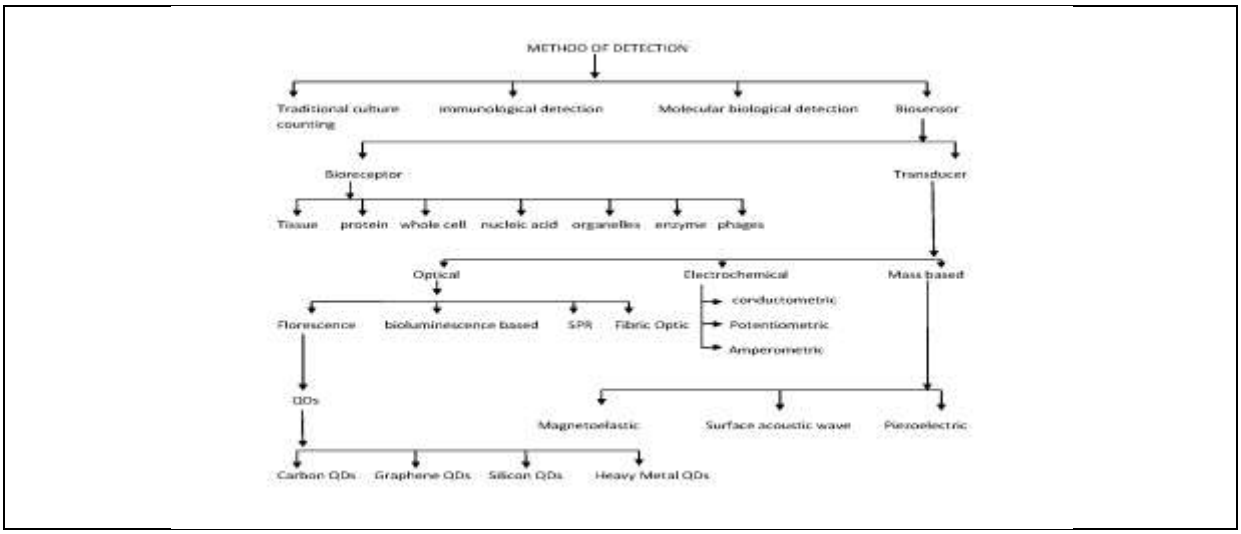

Fig.no.1 Method Detection

Biosensor is an instrumentation that comprises two key elements in close proximity: a transducing device and a recognition element with a supporting material. The recognition element consists of two affinity-pairing partners (antibody/antigen, enzyme/substrate, receptor and its specific ligand , or living cells and an analyte that binds specifically to them), one of which is immobilised [35]

III. TYPE OF BIOSENSOR

Biosensors are generally divided into three main types, namely: (A) electrochemical biosensors; (B) mass-based biosensors; and (C) optical-based biosensors. Common biosensors include electrochemical biosensors, optical biosensors and so on [32, 33]

A. Electrochemical biosensor

An electrochemical biosensor fixes the specific recognition element on the signal converter, applies a certain voltage to the electrode for electrochemical reaction, and traces the analysis of pathogenic bacteria [36]

Electrochemical sensors (potentiometric, amperometric, impedimetric and conductometric) measure the electrical potential difference (electromotive force, EMF) caused by an interaction between an analyte and the membrane/sensor surface. There is proportionality between the electrical potential difference and the logarithm of the electrochemically active concentration of the material. Electrochemical biosensors provide high specificity with rapid analysis at a reasonable cost[37]. There exist four types of electrochemical biosensors, namely potentiometric biosensors, amperometric biosensors, conductometric/capacitive biosensors and impedimetric biosensors [35].

a. Potentiometric-based biosensors sense changes in pH and ion concentrations upon the antigen/antibody interaction.
b. Amperomertic -based biosensors sense the difference in current potentials during redox reactions when antigen/antibody pairing occurs.
c. Conductometric/capacitive biosensors sense the change of electrical charge in a solution under constant voltage. This method is not recommended because of poor signal-to-noise ratio.
d. Impedimetric-based biosensors sense changes in impedances upon antigen/antibody interaction.

B) Optical biosensors

Optical biosensors mainly rely on the measurement of absorbance, including fluorescence and Raman scattering. The combination of fluorescent sensors and specific recognition elements can be used for quantitative analysis by the intensity of the fluorescent signal after capturing pathogenic bacteria [36] Fibre-optic biosensors are considered as optical biosensors since they use the reflective properties of light to sense numerous analytes simultaneously. Fibre-optic biosensors consist of a core (n1), cladding (n2) and jacket (n3), each with a different refractive index. The core and cladding are critical for light transmission. Fibre-optic biosensors are excellent

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for their high specificity, practicality (due to the absence of a reagent in contact with the optical fibre), and cost effectiveness [37].

a) Quantum dots (QDs)

Quantum dots (QDs) are fluorescent semiconductor nanocrystal[38] , with controllable photoluminescence properties and significant quantum effects[39,40] . They have many excellent optical properties, such as a wide and continuous excitation band, a narrow and symmetrical emission band, good light stability, stability against photobleaching, adjustable emission wavelength and long fluorescence [41, 42,43] A biosensor based on QDs combined with antibodies and aptamers can be successfully used in the detection of pathogenic bacteria and can reduce the interference of other compounds in complex samples[39]

IV. CLASSIFICATION

a) Carbon QDs

Carbon QDs (CQDs) are small fluorescent carbon nanoparticles with diameter less than 10 nm [44]. CQDs are being used in various field of application such as bioimaging , medical diagnosis , biosensing, chemical sensing ,photocatalysis and photovoltaic device[45] Compared with traditional fluorescent dyes, CQDs have excellent fluorescence properties, including photo stability, light bleaching resistance and nonscintillation[46] CQDs are being synthesized in two routes ,namely the top -down and the bottom-up routes such as arc-discharge method, ablation of a carbon target, chemical oxidation of soots , electrochemical oxidation of graphite rod ,thermal route, microwave route and supported synthesis [47,48,49] they are admixture of predominant sp2 hybridized carbons and sp3 diamond-like carbon [50] In addition CQDs can engender optical excitation as result of pi-plasmon absorption in the core carbon nanoparticle rather than band gap absorption of the quantum confinement effect [51,52,53].

b) **Graphene based**

Graphene is honey comb like structure formed with single thick planer carbon sheet [54]. It is a two-dimensional (2D) nanomaterial properties are similar to those of semimetals and is found to be stable under suitable conditions [55]. Graphene has been utilized in biosensors because of its numerous advantages which include a high electron transfer rate, large surface area, its ability to immobilize molecules and increased electrical conductivity [56]. In recent years, novel sensing platforms are in high demand for immobilizing biomolecules, such as DNA, antibodies, antigen, etc. for creating highly sensitive and selective biosensors [57,58]. There are numerous graphene based sensors which have been developed for detection of cancer markers [59], pathogen detection [60,61], and early diagnosis of various other deadly diseases[62]. Several implantable devices have also been reported for the real time measurement of glucose levels in diabetic patient, respiration rate, heart rate, body temperature, electrocardiogram signals, etc .[63] Graphene quantum dots are a relatively new class of material, which are derived from both carbon dots (CD) and graphene [64]

GQDs are synthesized by various methods such as nanolithography [65,66], acidic oxidation, hydrothermal or solvothermal[67,68] , sonication-assisted[69,70], selective plasma oxidation[71] and photo-Fenton reaction[72] technique. GQDs have also been used for the development of photoluminescence based sensor. Blue and green are the common photoluminescence colours observed in the GQDs [73]. GQDs generally have a smaller size and higher crystallinity, such that the graphite in-plane lattice distance is 0.18-0.25 nm and its interlamination distance is 0.32-0.34 nm or larger for distinct diffraction planes [74].

c) Heavy metal QDs

Heavy metal QDs are semiconductor nanocrystals with particle size less than 10 nm, and are synthesized by raw materials containing heavy metal elements. QDs have good fluorescence properties of the new nanomaterial, but with heavy metal synthesis of QDs for biosensor applications has potential toxicity of different degrees[75] such as changes in cell morphology, decrease of cell vitality, the appearance of autophagy and changes in gene expression[76,77,78]. Heavy metal QDs have many disadvantages, so the QDs of composite materials are developing continuously. If the new QDs can avoid these disadvantages and provide more competitive performance, they will have great potential in biosensor and pathogenic bacteria detection applications [79]

d) **Composite QDs**

Composite QDs are semiconductor nanocrystals with diameters of 1–10 nm [80] . QDs synthesized by composite materials can improve their original properties, such as water solubility, excellent photoluminescence, chemical stability and biocompatibility , etc [81]. Many studies have

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shown that the core/shell structure can reduce the toxicity of QDs containing heavy metal elements. QDs based on composite materials show superior performance, which provides a wide range of attractive opportunities for pathogen detection [82].

e) Silicon QDs

Silicon quantum dots (Si-QDs) are semiconductor Si nanoparticles ranging from 1 to 10 nm Silicon quantum dots are metal-free biologically compatible quantum dots with photoluminescence emission maxima that are tunable through the visible to near-infrared spectral regions. Si-QDs are biologically compatible and do not contain heavy metals (e.g., cadmium, indium, lead). The biological compatibility of these materials has been carefully studied both in vitro and in vivo. During in vitro studies, Si-QDs have been found to exhibit limited toxicity in concentrations up to 72 µg/mL in HeLa cells[83] and 30 µg/mL in epithelial-like cells (MDA-MB-231).[84] In vivo studies assessing biological compatibility of SiQDs have been undertaken in mice[85] and monkeys (rhesus macaques),[86] Si QDs can be created via different synthetic means, including electrochemical etching, ultrasonic/microwave synthesis, gasphase laser light pyrolysis , chemical/photochemical reduction ,thermal recovery of silicon oxides, Zinc salt metathesis, and disintegration in a supercritical solvent [87]. Si QDs have potential applications in the biological field because silicon exhibits good biocompatibility, and silicon-based materials are typically abundant, cheap, and nontoxic [88,89]. Moreover, Si QDs exhibit excellent biodegradation properties, water solubility, and strong quantum effects, making them applicable in biological fields [88,89]

V. HOW TO RECOGNISED ANTIBIOTIC

The analysis of anti-bacterials , for example, in environmental waters is usually performed by HPLC-MS or HPLC-MS/MS. Other methods, such as UV or fluorescence spectroscopy or electrochemical detection are of minor importance due to their lower sensitivity. The recent detection of antibody by biosensor technique .The two main techniques for recognizing antibiotics are the use of aptasensors and the use of antibody-mediated binding processes. Aptasensor can be defined as RNA- and DNA-immobilized aptamers (oligonucleic acids), which cause the binding of the analyte of interest to their respective 3D structure through ionic interaction, vander Waals forces or hydrogen bonds resulting in measureable signals[90] aptamer- based biosensors are limited in their practicality due to the challenges in synthesizing aptamers with appropriate affinity and selectivity. One possible solution involves synthesizing aptamers that are resistant to cell degradation [91]. The second mechanism for the recognition of antibiotics involves antibiotics detection using antibody-mediated binding processes. This type of binding can be performed at the surface of the sensor for direct detection of the antibiotics or by inverting the assay and detecting the binding of antibody-spiked samples onto immobilized antibiotics in the context of a competitive assay [90]

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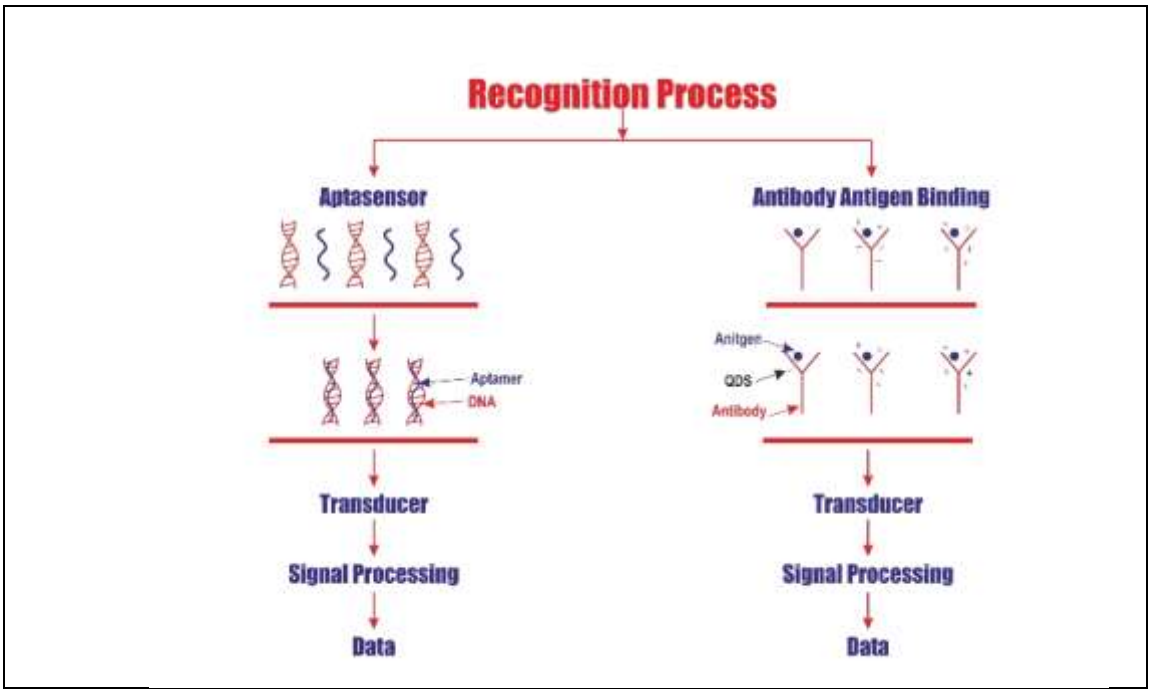

Fig.no.2 Recognition Process

VI. APPLICATION

QDs have gained a tremendous application in biological area. In the area of bio imaging QDs are being used as a contrast agents in the in-vivo and ex-vivo living cell targeting .

1. biosensors , QD tagged with antibodies can detect various disease or tumor cells (Streptavidine-QDs were used to detect Her2 cancer markers on the surface of SK-BR-3 human breast cancer cells via a biotinylated secondary antibody to human and a humanized antibody to Her2
2. Some proteins can be recognized by peptides; hence some peptides are used for QDs functionalization for cell targeting/labelling.
3. QQDs have long term stability in-vivo and also due to their brightness they are ideal candidate for live animal targeting and imaging.
4. Two-photon excitation confocal microscopy was used to image blood vessels in live mice that had received QDs by intravenous injection, showing that higher contrast and imaging depth can be obtained at a lower excitation power than with organic dyes.
5. QDs could be lit up by electron or hole donor enzymes through chemiluminescence
6. Quantum dots are promising candidate for wide range of applications and future technologies, some of the proposed applications are defense and anti-counterfeiting by injecting QDs into fabric, liquid mixtures, polymer matrix to produce unique validation signatures.

VII. CONCLUSION

Without a doubt antibiotics are of great importance in our daily life but, unfortunately , they also have negative effects on the health of living organisms and consequently at an economical level too. In order to reduce the risks generated by uncontrolled or excessive antibiotic consumption, one main way is to monitor their concentration in different matrices. These aspects lead to the increasing need to develop analytical devices and methods for the reliable detection of these compounds.In this review, we summarized the features of different types of QDs and their applications in antibiotics detection. First,the significance of antibiotics detection was described in detail, the variety used for the detection of antibiotics were briefly generalized and summarized, including comments, the limits of detection, and matrices, and the instances for the detection of antibiotics based on QDs were reviewed. Different quantum dots have different properties they are also size dependent. They are used as cell labeling -targeting, imaging and in drug delivery. QDs have played significant roles in antibiotics detection, serving as internal references,

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energy donors, carrier vehicles, target-sensitive dyes, reference dyes, and recognition units in sensing systems. Ability of QD based sensors to recognize target antibiotics, realizing the monitoring of antibiotics of interest in complex sample matrices. The field of biosensors consists of a broad spectrum with high potential for growth in the near future.

VIII. FUCTURE SCOPE

Cell and tissue-based biosensors consist of genetically engineered proteins that are infused into cells ex vivo or in vivo .Biosensors are used for marine applications for detection of eutrophication using nitrite and nitrate sensors. Various sensors based on nucleic acid hybridization detection have been developed for organism detection Applications of nanomaterials in biosensors provide opportunities for building up a new generation of biosensor technologies. Nanomaterials improve mechanical, electrochemical, optical and magnetic properties of biosensors and are developing towards single molecule biosensors with high throughput biosensor arrays. Future work should focus on clarifying the mechanism of interaction between nanomaterials and biomolecules on the surface of electrodes or nanofilms and using novel properties to fabricate a new generation of biosensors.

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