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Recent Approaches in Quantum Dots Application for Biological System

Fauziah Marpani[a,b,*], Syazana Mohamad Pauzi[a], Fauziah Othman[a], Amirah Syakirah Zahirulain[a], Nur Hashimah Alias[a,b], Muhammad Shafiq Mat Shayuti[a,b], Nur Hidayati Othman[a,b]

[a]School of Chemical Engineering, College of Engineering, Universiti Teknologi MARA, 40450 Shah Alam, Selangor Darul Ehsan, Malaysia
[b]Catalysis for Sustainable Energy and Water Nexus Research Group, School of Chemical Engineering, College of Engineering, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia
fauziah176@uitm.edu.my

Quantum dots are semiconductor nanoparticles with optical and electronic (optoelectronic) properties that vary with size and composition. They distinguish themselves from traditional fluorescence dyes due to their high visibility, long-lasting, size-tuneable, and narrow luminescence. Quantum dots are being used for a wide range of biological applications, including fluorescent assays for drug development, disease detection, single protein monitoring, and intracellular reporting. This mini review will focus on the overview of bioconjugation techniques which include the covalent and non-covalent conjugation of quantum dots surface to the active functional groups of carboxyl, amine, thiol, epoxy, hydroxyl and aldehyde. The various type of bioconjugation should be carefully selected based on the application of the quantum dots and the critical criteria of a biocompatible quantum dots will be also discussed. Recent application of quantum dots in biological system in bioimaging, bioanalytical, biosensing and drug delivery were laid out. The future outlook and the reality of quantum dots application in biological system were highlighted as the conclusion of this mini review.

1. Introduction

Quantum dots (QDs) are semiconducting nanocrystalline materials made up of 100 to 10,000 atoms within 2-10 nm in diameters. QDs exhibit size unique optical properties which can convert a spectrum of light into different colors depending on its size, because of variations in band gap energy produced by quantum confinement effects. When illuminated by ultraviolet (UV) light, electrons are promoted from lower energy state (valence band) to the upper energy state (conduction band). The movement of electrons produced an electron-hole pair. When the electron (negative charge) and hole (positive charge) recombined, energy is released in the form of photon. The effect of quantum confinement allows QDs to be tailored to specific energy band gap based on the particle size. Greater band gap energy in smaller QDs results in higher energy photons being emitted (blue shifted), and vice versa. QDs are composed of variety of semiconductor properties material typically from group II-VI (CdSe, CdTe, CdS, ZnO and Zn), III-V (GaN, GaP and InP) and IV-VI (PbSe and PbS) elements in the periodic table. Progress in the synthesis of QDs over the years has expanded to include the transition-metal dichalcogenides, perovskites, and carbon (Cotta, 2020). One of the most utilized properties of QDs is their photoluminescence (PL). PL excitation and emission wavelengths can be altered by controlling the size of QDs, changing the surface properties, or through the introduction of dopants, such as nitrogen or boron, into the carbon lattice (Chung et al., 2019). Other properties of QDs include high photostability, high quantum yield and high molar extinction coefficients, which is about 10 to 100 times higher than those of organic dyes (Samir et al., 2012). They also emit narrow symmetrical bright light at specified wavelengths spanning from ultraviolet to infrared. QDs are superior in chemical inertness, simplicity of production, resistance to photobleaching, low cytotoxicity, and excellent biocompatibility making them applicable in biological applications such as

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bioanalytical and bioimaging, biosensors and drug delivery which will be discussed in detail in the following sections.

2. Bioconjugation techniques

Bioconjugation of quantum dots is a chemical strategy to form a stable covalent link between two molecules, at least one of which is a biomolecule. The formation chemistry is either covalent (Figure 1) or non-covalent bonding. Biomolecules in this context include proteins such as structural proteins (e.g., collagen), enzymes, antibodies, carriers (e.g., myoglobin, receptors; peptides for examples cell penetrating peptides, enzyme inhibitors, glutathione, nucleic acids such as RNA, DNA, DNAzymes, ribozymes; fatty acids such as carbohydrates and lipids and all related component of these biomolecules families (Sapsford et al., 2013). The first attempt to conjugate QDs to biomolecules was performed by Bruchez et al. (1998) and Chan and Nie (1998), and has since been greatly exploited in a variety of imaging, immunoassays, and DNA sequencing techniques. Bioconjugation of QDs are crucial in biological applications to widen the function of QDs. Ideal surface ligands desired for biological applications must fulfil the following criteria for an enhanced biocompatibility and solubility in aqueous media, improve QDs surface properties regarding fluorescence or emission characteristics and targeted drug delivery (Karakoti et al., 2015). The following are the characteristics of an ideal surface ligands: (i) high affinity for the QD surface; (ii) colloidal stability over a wide pH range and at high salt concentration; (iii) small final hydrodynamic diameter (Dh); (iv) minimal non-specific adsorption in biological environments; (v) minimal toxicity; (vi) inexpensive and commercially available; (vii) functional groups for subsequent conjugation with biological molecules; and (viii) availability of functional groups.In order to regulate size and avoid agglomeration, QDs are often manufactured using high temperature methods in organic solvents and subsequently stabilized by hydrophobic groups like amines or phosphines. Nevertheless, this will result to low solubility in aqueous media. To improve solubility, hydrophilic ligands can be functionalized onto the surface of QDs. There are three main strategies to replace or overcoat the QDs with hydrophilic ligands which is ligand exchange, surface silanization and amphiphilic combination (Foubert et al., 2016).

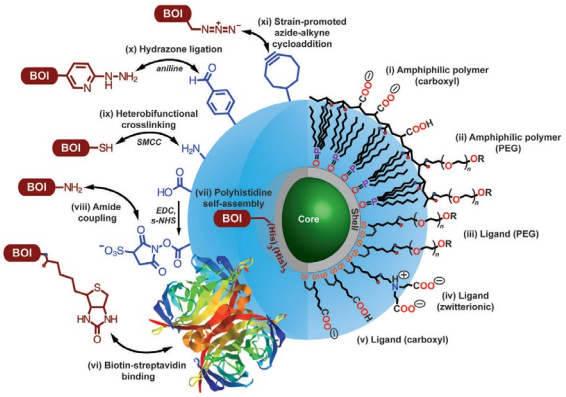

Figure 1: Overview of the chemistry of core-shell QDs with different coatings and methods of conjugating biomolecules of interest (Petryayeva et al., 2013)

Basically, the structure of most QDs consist of two critical surface ligands which is the anchoring group and hydrophilic groups. A stable bond between the QD and the ligands is created by the anchoring groups' interactions with the QD surface. To induce solubility in aqueous media, the hydrophilic groups are required. Ligand exchange involved the removal of original hydrophobic coating and replaced with hydrophilic molecules. The molecules are polymers that contain bifunctional anchor groups, such as amines ($–NH_2$), thiols (–SH), hydroxyls (OH), or carboxyls (–COOH) to provide anchoring branch to secondary biomolecules (such as drugs and antibodies) and improve solubility. These functional anchor groups are known to have strong affinity with Zn and Cd, the most common metals present on QD surfaces.

The second strategy is based on encapsulation of QDs with their original hydrophobic ligands in different carrier matrix for example amphiphilic polymers such as poly(maleic anhydride) copolymers, polyelectrolytes (poly-acrylamide) and biopolymers like DNA (Speranskaya et al., 2014), which is the most commonly used, polymeric microbeads (Han et al., 2001) or liposomes (Beloglazova et al., 2013). Unlike the first method, this technique made no replacement of the native ligands. The native hydrophobic chain is hybridized with the amphiphilic ligands (from the carrier matrix) and the hydrophilic segments lengthened from the QDs surface ensuring solubilization in aqueous media.

Lastly, is surface silanization technique via hydrolysis of silane molecules forming siloxane network on QDs surface. Silanization involved initial ligand exchange with (3-mercaptopropyl) trimethoxysilane to form nucleation sites on the QD surface. Silane molecules such as tetraethoxysilane will grow on the nucleation sites forming shell-like features by reverse microemulsion method or hydrolysis and condensation.

3. Quantum dots application in biological system

3.1 Bioimaging

The early development of quantum dots (QDs) was in the biological imaging field for its superior properties in enhancing the produced imaging through improving brightness, photostability, optoelectronic properties and multiplexing capability. Many aware that cancers have greatly impacted people's lives. The inaccuracy of early-stage detection of cancer was due to over-diagnosis, less sensitivity, less specificity human markers and low compliance of the current screening method. The recent development of biomarkers coupled with nanoparticles may improve the sensitivity of early-stage cancer screening (Tabish et al., 2021). Cancer biomarkers are the biological molecules resulted from cancer progress and synthesized by the tumor cells or human tissues. One of the detection methods that have been implemented is in-vivo molecular imaging, apart from fluorescence and luminescence and light scattering. This molecular imaging utilized broad range of imaging units that are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Position Emission Tomography (PET), ultrasound and optical imaging (Ye et al., 2018). Although QDs were initially used for bioimaging before they were improved and further utilized in immunoassay application, possible toxicity may occur pertaining to in-vivo imaging (Goryacheva et al., 2015). The recent discovery of the ability of QDs cell penetration and division with new cells has been seen as an opportunity to upgrade and improve the current in-vivo detection. QDs were modified to be used for in-vitro cell imaging for molecule exploration and molecule assessment for treatment of chronic diseases (Chatterjee et al., 2014). Introduction of metal ions into the carbon quantum dots (CQDs) may improve the issues with cytotoxicity of the QDs in bioimaging application while providing superb photoluminescence (Lin et al., 2018).

3.2 Biosensor

QDs have a wide properties and advantages as biosensing materials; broad emission spectra (450 to 1500 nm) by tailoring their size, shape and composition (Resch-Genger et al., 2008), broad absorbance bands allow the photoexcitation of QDs of different sizes or compositions by a single wavelength (Freeman and Willner, 2012) and the high resistance to photobleaching enables long-term services in vitro and in vivo imaging (Wegner and Hildebrandt, 2015). In the development of biosensor, QDs are commonly used to modify electrode surfaces for an improvement in the critical features like reproducibility, selectivity and sensitivity (Mansuriya and Altintas, 2020). Additionally, QDs are utilised for signal amplification by serving as nanocarriers for catalysts, nanozymes, detecting bioreceptors, and electroactive labelling components (Campuzano et al., 2019). Development of QDs based biosensor in detecting bioanalyte involved several steps; i) selection suitable bio-recognition tools for target analyte; ii) selection of suitable reporter detecting the presence of analyte and the recognition event; iii) labeling of the bio-recognition agents with the reporter; and iv) integration of the sample and analyte detection with the chosen read-out system (Martynenko et al., 2017). In this section, emphasized is given to graphene quantum dots (GQDs). Compared to the conventional QDs such as PbS, CdTeSe/CdZnS, CdTe/CdSe and CdHgTe, GQDs are regarded as excellent biocompatibility, high fluorescence property and non-toxic. Optical biosensors, electrochemical biosensors, photoelectrochemical (PEC) and QD-based electrochemiluminescence (ECL) enzymatic biosensors are among the biosensors developed with GQDs. So far, only a few biosensors that use CQDs or GQDs have been published, but the number of contributions is expected to grow rapidly.

An optical biosensor is a compact analytical device that incorporates a biorecognition sensing feature with an optical transducer system. The goal is to generate a signal proportional to the concentration of a measured material (analyte). As biorecognition components, the optical biosensor may use a variety of biological materials such as antigens, enzymes, antibodies, receptors, whole cells, nucleic acids, and tissues. Recently, a QDs-based optical biosensor was developed to detect propafenone (Wang et al., 2020). Propafenone is commonly used in the treatment of heart rhythm disorders such as atrial and ventricular arrhythmias. The chemical compound is combined with QDs to form ion-association complex. Experiments confirmed high selectivity of the biosensor with LOD 0.96 ng/mL of propafenone could be detected. In an attempt to detect lysozyme for early diagnosis cancers, molecular imprinted polymer CdTe QDs were synthesized. It can detect lysozyme in human serum and chicken egg white with the limit of detection 3.2 μg/mL.

Electrochemical biosensing involving GQDs can be categorized as electrochemical enzymatic biosensing, electrochemical immunosensors, electrochemical nucleic acid biosensors and aptasensors. GQDs served as electrode modifiers in the construction of enzyme biosensors to retain the functionality of the immobilised

enzyme, strengthen the electrochemical signal, and allows for the wiring of enzyme redox-center due to the nanoscale dimension of GQDs (Campuzano et al., 2019).
Biosensor based on enzyme is a combination of electrochemiluminescence (ECL) and enzyme technology. ECL is a process by which an additional voltage causes electrochemical energy to be transformed into radiant energy at the surface of electrodes. The ECL luminophore is produced in the process of the electrochemical reaction, and consequently, luminescence signals can be detected as the analysis results. Given the benefits of QDs, several different types of enzyme-based biosensors have been established that combining the benefits of ECL and QDs. The first ECL investigation of QDs was reported in 2002, and its optical and chemical characteristics were determined by obtaining the ECL signal from silicon nanocrystals (Ding et al., 2002). GQDs have been used as electrode materials and labels in the field of electrochemical affinity sensors, mostly in immunosensors and nucleic acid sensors for determining DNAs and microRNAs, but rarely in aptasensors. In the field of cardiology, heart attack or myocardial infarction in human can be detected rapidly with the development of an ultrasensitive cardiac troponin I antibody conjugated GQD and polyamidoamine nanohybrid modified gold electrode-based sensor as shown in Figure 2 (Bhatnagar et al., 2017).

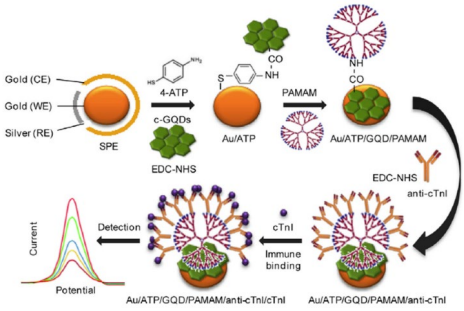

Figure 2: Assembly of an Au/GQD/PAMAM nanohybrid electrode used to create an electrochemical immunosensor for the determination of cTnI (Bhatnagar et al., 2017)

The optical properties of QDs allow these nanomaterials to be used in photoelectrochemical biosensors (PEC), where electron transfer occurs only at the electrode when photo irradiated. The principle working mechanism of PEC is by the photocurrent signal produced during the binding between the target analyte and bioreceptor, which is correlated with the energy and charge transfer of the PEC reaction upon light irradiation between the photoactive agent and electron donor/acceptor moieties. In contrast to optical and electrochemical sensors, photoelectrochemical (PEC) GQD sensors studies are limited.

3.3 Drug delivery

In drug delivery context, QDs can be targeted at single organs, such as the liver with more preciseness than conventional drugs. The perfect model of QD nano-carrier materials for drugs must have appropriate preparation and purification techniques, should have no reaction with drugs, shows good biocompatibility and low toxicity, high drug loading capacity and encapsulation efficiency, obtained a certain mechanical strength and stability and suitable particle size and shape and adequate residence time in vivo (Zhao and Zhu, 2016). The QD nano-carrier drug delivery system has the probability to provide prior diagnosis, detection, and targeted therapy of explicit disease locations. Furthermore, QD nano-carrier systems for medicines can enhance drug stability, increase in vivo dissemination time, improve targeted absorption, and enhance drug delivery and metabolism. As sensing and tracing probe in drug delivery, QDs luminous characteristics promote real-time monitoring and sensing capabilities to aid in medication administration. Certain real-time monitoring features aid in understanding the in vitro and in vivo synergy of these QDs with target cells. The features include monitoring the exchange of QDs between cells, drug translocation through microtubules, membrane-bound receptor diffusion, receptor-mediated signal transduction, endocytic uptake, and viral behaviour within target cells (Nair et al., 2020). In relation to conventional nanostructures that have inadequate light sensitivity, QD allows for simple surface treatment with various antimicrobial mediators and can cope with the rising antibiotic resistance of bacterial infections. Various methods, including photodynamic inactivation, can be used to limit the spread of these viral infections. QDs with photosensitizer properties brighten visible light by producing microbial reactive oxygen species from molecular oxygen (ROS). These ROS respond non-specifically with viral or cell components, causing significant destuction and inactivating a broad type of microorganisms including bacteria, fungus, viruses, and parasites. As a result, antibiotic-resistant bacteria are finally inactivated in the same way as their drug-prone equivalents and cause nonspecific harm to ROS, indicating that resistance to QDs is improbable (Nie et al., 2020). Multi-drug resistance is the primary barrier in clinical cancer therapy, preventing

anticancer medicines from accumulating inside tumour cells, resulting in decreased drug delivery and low drug intensities in targeted cells (Zhou et al., 2010). A type of protein functioned as drug transporter called P-glycoprotein is responsible of multi-drug resistance in various tumour cells. P-glycoprotein functions as a transmembrane efflux pump, transporting its substrates from inside to outside of the cell. Through the inhibition of P-glycoprotein, QDs can reduce drug resistance. Inhibiting P-glycoprotein function and preventing drug efflux from target cancer cells could be accomplished with a water-soluble nano crystalline CdTe QDs capped with negative charges 3-mercapitalpropionic acid, which would effectively enable the accumulation of the antitumor agents daunorubicin in drug-resistant leukaemia cells.

Targeted drug delivery for diagnosis and therapy of cancer is focussing on candidate ligands such as folic acid (Zhao and Zhu, 2016). Folic acid has a high affinity for the folate receptor, which is abundantly expressed in most tumour cells, including ovarian cancer, cervical cancer, endometrial cancer, breast cancer, colon cancer, lung cancer, nasopharyngeal carcinoma choroid, and ependymal cell tumour cells (Chaudhury and Das, 2015). A folate-modified theragnostic (FL/QD-TK) was created by covalently coupling an HSV-TK suicide gene with near-infrared fluorescent CdSeTe/ZnS core/shell QDs. FL/QD-TK demonstrated highly selective tumour imaging as well as significant suppression of FR-overexpressed Bel-7402 mice xenografts without causing systemic damage (Shao et al., 2015). As the tumour diagnosis materials, Wang et al. demonstrated real-time monitoring of cellular absorption using a ligand modified GQD loaded with DOX to improve selective cell labelling for targeted drug administration (Wang et al., 2014). Folic acid complexes combined with radioactive elements have been used to diagnose ovarian cancer clinically (Yoo and Park, 2004). Some researchers believe that the release and therapeutic effects of medicines in folic acid complexes remain inadequate in tumour tissues, thus further study is needed before it can be employed in clinical cancer treatment.

4. Conclusions and future outlook

QDs have piqued the interest of researchers in recent years due to their distinctive and tunable photoluminescence characteristics, excellent physicochemical features, great photostability, strong biocompatibility, and compact size. The most recent advances in the biological applications of QDs in terms of bioimaging, biosensing, drug delivery and bioconjugation are discussed in this mini review. Even though QDs have shown impressive progress in biological applications, there are unavoidable consequences such as biocompatibility and toxicity due to the presence of heavy metals. Heavy metals, even at micro doses exert a harmful effect on human beings and environment. Meanwhile, non-containing heavy metals QDs are widely investigated for cancer treatment, gene delivery, imaging and drug delivery. Nevertheless, the information about biosafety is inadequate to understand the interaction between QDs and biomolecules such as DNA for example. The exact effect of the size and concentration of QDs on the translocation through the lipid membrane are also ambiguous. One of the efforts to reduce toxicity is by surface functionalization and doping of QDs with organic coatings which makes them biocompatible. More research is required to unravel the interaction of QDs with cells and also the future in vivo application of these nanomaterials. Although many functionalized QDs are now available, the research data does not give exact parameters regarding their characterization, size, number of functionalized groups per QD, and other critical properties of the nanomaterials, limiting their potential usage. To customize the properties, it is necessary to first understand their interaction process as well as the active sites or defects on the surface that impede the formation of GQDs. To increase the quantum yields of GQDs, it is critical to regulate the manufacturing and modification procedures. In terms of QDs reproduction, one of the major drawbacks that prevent QDs to be used regularly in research centres and clinical diagnostic facilities may be the lack of homogeneity and reproducibility between commercially available QDs batches. Since the particle size of nanoparticles affects the photoluminescence of QDs, the size of the particles must be carefully controlled for consistent features and effective applications. In addition, the vast quantity of wastes and byproducts must be properly managed in the wide-scale production.

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