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Quantum dots and their potential biomedical applications

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Abstract. Quantum dots (QDs) are semiconductor-based nanocrystals. These nanoparticles have exhibited their unique optical and electronic properties. With these characteristics, QDs attracted scientists' interest in biomedical areas such as bioimaging, drug delivery and biosensors apart from other applications like photocatalysis, light-emitting, and solar cells in recent years, and plenty of QDs and QD-based materials have exhibited their unique properties in their applications of biomedical areas. Nevertheless, the potential toxicity of QDs becomes the limitation of QDs' application in biomedical areas. The toxicity of QDs might come from: the toxicity core material of QDs; the toxicity substances from the surface of QDs; the free radicals or reactive species released from QDs; the biological environment induced QDs' toxicity. In this article, we review the properties of QDs, the applications of QDs in different biomedical fields, how QDs cause toxicity, and how to reduce or prevent QDs' potential toxicity. In the future, we expect the improvement and further application of QDs in biomedical areas.

Keywords: Quantum dots, biomedical applications, toxicity, nanomaterials

1. Introduction

Quantum dots (QDs) are semiconductor-based nanocrystals with ultra-small size. Their size is in the range of 2-10nm, while compared with materials in the nano range (1-100nm), it is like a single point or dot. It is considered zero-dimensional [1]. These ultra-small nanoparticles usually preferred the elements from groups II-VI, III-V and IV groups [2]. QDs were first reported in 1980s on the research of semiconductors, and then QDs exhibited their first bioimaging application in 1998 [3, 4]. Currently, QDs have shown their applications in photocatalysis, light-emitting, solar cells, sensors, and biomedical.

Most of the QDs, the structure of them consists of semiconductor nanocrystals with a bandgap semiconductor shell and components of brunches from elements in II-VI, III-V and IV groups, such as the SiO_2 is utilized as shell material, while CdTe, CdS, PbSe, ZnSe, or CdS were utilized as core materials. This structure makes QDs overcome the surface deficiency and increases the quantum yield [5, 6]. Also, some of the natural organic atoms could be applied by making them absorb on the QDs' surface and proceeded as covering specialists [7-9]. What needs to be concerned is that some of the QDs are based on single elements, for example, the carbon dots (C-Dots), which are regarded as a new choice for semiconductor materials, are exhibiting their potential for their applications in plenty of fields [10-12]. Kumar's team has synthesized a kind of graphene quantum dot-based material for sensing, bioimaging and energy storage applications [13].

For quantum dots, their different properties depend on their size. As the range of QDs is 2-10nm, the surface area to volume ratio and surface to bulk atom ratio of QDs have a markable increase. The

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properties like absorption or emission wavelength, solubility, transparency, color, catalytic behavior, conductivity, melting point, etc., only depend on the size of QDs, and it makes the difference in QDs' behaviors. Apart from QDs' surface to volume ratio, QDs' electronic and optical properties are contrary to their bulk materials. The energy levels of QDs are not continuous but are quantized, that is, discrete. Therefore, the QDs exhibit their quantum confinement effect [1, 14]. In addition, the oscillation of valance electrons in QDs excited by incident light makes QDs show different color, which is called localized surface plasmon resonance (LSPR). The properties of QDs, like conductivity, dispersible nature, catalytic behavior, and optical properties, are determined by the surface properties of QDs [1]

With these characteristics, QDs have attracted the attention of scientists in the last few decades. QDs also show great potential in biomedical applications. However, the toxicity of QDs becomes the limitation of QDs' application. In this report, we will discuss the biomedical applications of QDs, then we will pay attention to how the toxicity of quantum dots will be exhibited.

2. QDs in bioimaging

Since magnetic resonance imaging (MRI), optical imaging, and nuclear imaging are becoming more and more considerable in biological systems [15], how to improve these technology's performance, such as their sensitivity, resolution, complexity, acquisition time, and operation cost are needed to be considered [16]. Traditional dyes are broadly utilized in bioimaging, but they still have some drawbacks that limit their development. For traditional dyes, some of the organic dyes are unstable not only under photo-irradiation, but also under environmental factors like pH. Besides, the small excitation of traditional dyes will make the result become inaccurate. What's more, it is a challenge for traditional dyes to detect multiple detection channels [17]. Compared with traditional dyes for bioimaging, QDs take advantage of their unique electronic properties and optical properties, such as their high quantum yield, high brightness, high extinction coefficient, high stability against photobleaching, and intermittent fluorescence signals (blinking) [18, 19]. The different sizes of QDs also make the optical properties of QDs become tunable.[20]. With these exciting features, QDs are broadly used as fluorescent probes for biomedical imaging [21]. Shi's team synthesized a single layer of MoS_2 QDs modified with glutathione. Biomedical imaging characteristics of GSH-MoS2 QDs were tested through in vitro and in vivo tests. The in vitro test yielded a blue fluorescence in the cytoplasm of SW480 cells, indicating the internalization of GSH-MoS_2 QDs into SW480. On the other hand, the in vivo test showed a high contrast enhancement between pre-injection and post-injection of QDs in mice, causing the periphery of the tumor to turn blue [22]. Gongalsky's team synthesized water-dispersible Si-based QDs by laser ablation. The in vitro test of these QDs in CF2Th cancer cells shows different color under different magnitude scales. It could be considered a novel contrast agent for photoluminescent bioimaging [23]. For biological tissues, the poor transformation of visible light through them makes it difficult for fluorescence imaging to observe them. To detect the tissues, QDs are utilized for conducting deep-tissue optical imaging by using the NIR (near infrared) window. (700-1700nm) [24, 25]. Osifeko and Nyokong's team synthesized a kind of nanoparticle combined with QDs, magnetic nanoparticles and gold nanoparticles (GNPs), their product shows an increase in fluorescence quantum yield for phthalocyanines in QDs and GNPs and a general decrease in fluorescence quantum yield for all nanoparticles [26].

3. QDs in drug delivery

Currently, the trend that QDs are utilized in drug delivery is gradually increasing. QDs not only show their outstanding optical and electronic properties in bioimaging, but they can also be utilized in drug delivery. For drug delivery, QDs show the features like their ease of fabrication, capability of conjugation to a wide variety of drugs, tuned physico-chemical properties. What's more, their outstanding optical properties make QDs become traceable while delivering drugs [5, 27]. Besides, as QDs have intense and stable fluorescence for detecting cancer, it could be possible for QDs to be used as drug carriers to support cancer detection [1]. The fluorescence of QDs could be detected easily, which allows scientists to map the drug distribution process of QD-derived complexes. Moreover, scientists

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found that mammalian cell lines could uptake the QDs efficiently. QDs are targeted to different cellular organelles [28-30]. According to these mentioned features, QDs show their potential in drug delivery. Liu et al. synthesized PEGylated MoS_2 QDs for traceable and pH-responsive chemotherapeutic drug delivery [31]. Apart from that, graphene QDs (GQDs) are utilized as a new QDs-based drug delivery system. To make drug delivery systems become more efficient, scientists have started paying more attention to the close relationship between drug delivery and drug release. Besides, scientists are trying to develop new methods for improving drug delivery and release efficiency to improve therapeutic effects [32]. GQDs show their properties such as their low toxicity, large surface/ volume ratio and their massive capabilities of surface functionalization, which make them possible to be utilized in drug delivery. Vahedi's team synthesized graphene quantum dots (GQDs) modified with hyaluronic acid (HA) to carry curcumin (CUR). The HA-GQD could be used as an excellent anticancer drug (CUR) carrier, and it shows anticancer properties on HeLa (Henrietta Lacks) cell lines [33]. In another GQD-based drug delivery system, GQDs were attached to doxorubicin (Dox) and the selective self-guiding molecule arginine-glycine-aspartic acid (RGD). This delivery system shows pH-dependent features as the release of Dox shows pH-dependent, which makes the system become a well-controlled drug delivery system. The addition of self-guiding ligand RGD peptide makes the modified GQDs show the better effect on the anticancer properties. The result shows the Dox-RGD-GQDs are more effective in killing cancer cells compared to MC3T3-EI cell line [34].

4. QDs in biosensors

Biosensors are systems that can produce a measurable signal in response to the biological process in question. The unique optical properties of QDs make QDs incorporated into the biosensor systems to integrate selectivity, efficiency, accuracy, and high detection sensitivity into a single system [35]. The biosensors containing QDs show their potential in various areas, such as diagnostic, toxicological, and follow-up medical applications [36, 37]. With these features, QDs have been used for new methods for the identification of biologically relevant molecules recently [38]. Also, biosensors synthesized by biotechnology in combination with nanotechnology are needed to solve biological and environmental problems [39, 40]. Shen and Xia synthesized carbon QDs modified with boronic acid moieties and utilized biosensors for testing the blood glucose level. The result shows the CQD biosensor could detect the lowest blood glucose level in 1.5μM [41]. Andreadou's team utilized CdTe QDs corporate with magnetic beads for detecting Leishmaniosis antigens. The lowest concentration of Leishmania DNA that the biosensor could detect is 3125ng/ μL [42]. Yang's team reported a biosensor for detecting the clofazimine and protein's interaction. In this report, researchers synthesized CdZnSeS/ZnS alloyed core/thick-shell QDs that were modified with multifunctional polymer ligands, and they were used as energy donors for Förster resonance energy transfer (FRET) applications [43].

5. Toxicity of QDs

Although QDs exhibit their characteristics in biomedical fields, the toxicity of QDs has become one of the greatest challenges for QDs' biomedical applications. The potential toxicity of QDs usually comes from four parts: the toxicity materials used in the particle core; [44, 45]. the potentially toxic substance from the surface of the QDs; [45, 46, 47]. the free radicals or reactive species generated from excitation; and the tissue and nano-colloid interaction in biological environments [48, 49]. The most used heavy metal element for producing QDs is cadmium [50], which is usually covered by a zinc sulfide shell (ZnS) or crosslinked with a stable polymer coating [51, 52]. The cadmium core shows its potential toxicity to the human body by releasing cadmium ions (Cd^{2+}) from QDs. The mechanism of the toxicity of QDs is investigated by researchers [53-57], the results indicated that the toxicity of QDs caused by the Cd^{2+} released from the QDs was distributed in the cytoplasm and induced the generation of ROS.

The size of QDs needs to be considered as well. The research showed that when the size of QDs is less than 2.5nm, they may damage the lung [58]. Choi's team also conducted research on the relationship between hydrodynamic diameter and the toxicity of CdSe/ZnS QDs. The result showed that the average hydrodynamic diameter of QDs around 8-10nm can skip this issue. When the size of QDs is less than

5.5nm, the QDs could be more easily eliminated through the urinary excretion, and they will cause damage in kidneys through glomerular filtration, while the size is over 15nm, there were almost no QDs that could be absorbed by the human body [59].

The coating materials of QDs could also become a potential toxicity source to the human body. Usually, the coating of QDs is synthesized to reduce the toxic substance released from the QDs. However, on some occasions, the coating material might be more toxic than the core material. Hoshino's study showed the QDs capped with tri-octyl phosphine oxide (TOPO) are cytotoxic and genotoxic. When removing the TOPO from QDs, the toxicity of QDs is reduced [60].

Besides, the toxicity of QDs is caused by photolysis and oxidation. When the QDs are under the condition of oxidative and photolytic, the possible toxic capping material or core might be toxic to the human body. A study showed that under 254nm UV wavelength, the thiol coated CdSe QDs showed photochemical instability [61].

To reduce the toxicity of QDs for further biomedical applications, various approaches have been taken to minimize the toxicity of QDs. Most of the coating of QDs could reduce the toxicity of the QDs' core, so adding a protective shell is still a valid approach to reducing QDs' toxicity. Apart from adding a shell, QDs can be passivated, or bio conjugated by modifying QDs with antibodies, polymers, or some nanoparticles [62]. It is reported that PEGylation of QDs is regarded as a common approach for QDs' passivation and adjusting the QDs' biodistribution as well as extending the QDs' effective duration in the blood circulation [63]. Besides, scientists have found a new approach to QDs' passivation, which is encapsulating QDs in phospholipid micelles. The micelles' properties support this approach by making QDs still keep their unique optical properties and protecting the QDs' surface simultaneously [64]. Besides, adding ligands for QDs' structural stability and solution [65], and replacing the QDs' core material with heavy metal material to the material without toxicity could also reduce the toxicity of QDs. Recently, graphene QDs have been broadly used in biomedical fields. Compared with common QDs, graphene has no toxicity, which makes it a novel material in the biomedical area.

6. Conclusion

Since the quantum dots were first reported, quantum dots (QDs) have been drawing researchers' attention in many different fields. According to this review, QDs possess plenty of their advantages, like their characteristic optical and electronic properties; their high surface to volume ratio; and they have been regarded as new kinds of novel nanomaterials in biomedical areas. QDs possess exceptional potential in biomedical areas such as bioimaging, drug delivery, and biosensors. Scientists have extensively researched how to apply QDs in these areas. To indicate the specific applications of QDs in biomedical areas, several QDs and QD-based substances have been mentioned. Moreover, to improve the functions of QDs and QD-based materials, modifications on these materials have been applied on QDs so that it would be possible to apply the QDs in biomedical research as bioimaging, drug delivery, and biosensors.

Although the QDs have exhibited their properties in biomedical areas, the toxicity associated with QDs has limited their widespread use. QDs' toxicity is caused by their inherent physicochemical properties and environments which induced the free radicals released from the QDs. Studies on the toxicity of QDs by scientists have been continued during the past few years. Before the QDs are utilized in biomedical fields, systematic analysis, and comprehensive evaluation of QDs should be held. Before QDs could be broadly utilized in biomedical fields, there were still many difficulties on QDs' applications in human body. Continuous research on QDs in biomedical areas will be greatly improved with the rapid development of biotechnology and nanotechnology, which will pave the way for their successful application.

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