Indian Journal of Biochemistry & Biophysics
Vol. 59, December 2022, pp. 1171-1175
DOI: 10.56042/ijbb.v59i12.67291

A review on synthesis of quantum dots and their biomedical applications

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Received 28 September 2022; *revised 10 October 2022*

Quantum Dots (QDs) are ultra-fine nanometer-sized semiconductor particles with a core-shell structurepossess both electrical and optical properties. Their unique ability to emit pure, monochromatic light on being exposed to light makes them extremely versatile in their applications. The color of the light emitted directly depends on their size and shape. Smaller QDs emit shorter wavelengths, closer to the violet end of the visible light spectrum (~380-450 nm), while larger QDs emit longer wavelengths *i.e* in reddish spectrum (~620-750 nm).

Owing to their "tunability", QDs can be exploited in a wide range of fluorescent, photonic, and electrochemical applications. QDs represent elements mainly from Group II-VI (*e.g*., CdSe) or Group III-V (*e.g*., InP) with the resultant optical and electronic properties of the quantum dots being somewhere between bulk semiconductor material and individual atoms or molecules. Besides applications in energy and photonics, they are under extensive investigation and development for use in disease diagnosis and therapy, specifically in the area of controlled drug delivery, biosensing and imaging. This review surveys the progress of research explores their properties, synthesis, applications, delivery systems in biology, and their toxicity.

Keywords: Band gap, Nanobiotechnology, Nanomaterials, Semiconductor, Quantum dots

Introduction

Nanomaterials are of interest to us due to their unique physical, chemical and optical properties that arise because of their large surface area, extremely small size, shape, structure, *etc*[1]. Over the last decades, quantum dots have gained widespread attention especially due to their optical properties such as broad and strong absorption, narrow and symmetric emission and strong luminescence[2]. They can be classified on the basis of number of dimensions that are significant in the macroscale: zero dimensional, *i.e*., all of the dimensions are in the nanoscale range (example: nanoclusters, nanospheres, *etc*.) one dimensional (example: nanowires, nanofibers, *etc*.), two dimensional (example: nanolayers, quantum well, *etc*.) and three dimensional (example: dispersions of nanoparticles, bundles of nanowires, *etc*.)[3]. Quantum dots are a special type of nanomaterials that are tiny enough to be treated as a point. They exhibit electronical and optical properties that are intermediate between bulk semiconductors and individual molecules[4]. The most common commercially available quantum dot includes a cadmium selenide nanocrystalline semiconductor core with a zinc sulphide capping layer along with a polymer layer over it[5].

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In 1981, Quantum dots were first produced by Russian physicist Alexey Ekimov[6] of the Vasilov State Optical Institute inside a glass matrix followed by Lois Brus[7] who synthesized QDs in a colloidal suspension in 1983.Today, Cadmium has been the most extensively researched material to make QDs as its synthesis is easily achieved by the synthetic route[8]. For an isolated gaseous atom, we define the term "ionization energy" which refers to the amount of energy a ground state atom must absorb to let go the most loosely bound electron resulting in a positive ion. Analogous to that, we have the term "Charging Energy" associated with quantum dots that defines the amount of energy that a quantum dot needs to absorb to emit a single electron from the dot.Besides biomedical uses, quantum dots have also been widely researched for electronics and energy storage applications[9] (Fig. 1).

Synthesis and characterization

Both top-down and bottom-up approaches are used to synthesize QDs, with the most common ones being Molecular Beam Epitaxy[10,11], hot injection method[12,13], X-Ray Lithography[14,15] and plasma synthesis[16].

MBE is a perfect example of Nanotech. To start the synthesis process, we take a material called substrate which can be any of the commonly known

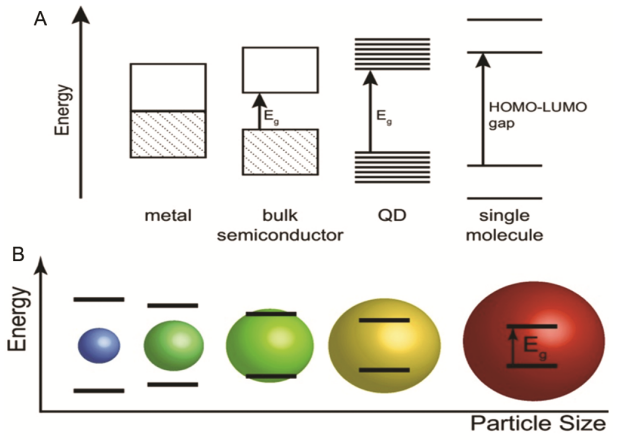

Fig. 1 — (A) Diagrammatic illustration of the band structures of metals, bulk semiconductors, quantum dots (QDs) and single molecule; and (B) Schematic representation of the change in QD band gap and photoluminescence emission wavelength, or color, with increasing particle size

semiconductors: silicon, gallium arsenide and germanium. The substrate after being chosen is heated to a very high temperature which is different for every material. MBE machines consist of complex circuits for heating and accelerating atoms or molecules that are targeted at the substrate maintained at ultra-high vacuum conditions which upon landing, condense. In this way, the crystal grows very slowly – one atomic layer at a time.

Hot injection method is an important commercial method for synthesis of monodisperse colloidal quantum dots. In this method, we produce homogenous nuclei by quickly injecting organometallic reagents into a hot solvent. This way, CdSe QDs[17], QLEDS that electrically excite QDs[18] and toxicity free indium phosphide (InP) quantum dots have been created[19].

The most common green synthesis route for QDs made of Carbon is hydrothermal synthesis[20]. The conditions required in this include pressurized autoclave vessels, temperatures way above the boiling point of water (120-240°C) with the whole reaction taking somewhere between 3 and 12 h to complete[20]. The solvent used in the reaction should be water in hydrothermal case but can be replaced by a renewable substance in other routes which can simultaneously act as solvent and source of carbon atoms (*e.g.*, walnut oil)[20]. Carbon dots can also be synthesized using neem leaves *via* the hydrothermal route[21]. The benefits of green synthesis are that the process is usually much safer to execute due to less hazardous chemicals involved, are cost-effective and generally produce environmentally safe byproducts[22].

As far as characterization is concerned, the optical properties of obtained QDs can be studied using UV-visible spectroscopy and photoluminescence spectroscopy[23]. Since the optical properties are actually dependent on the QDs' size, we can employ the conventionally used characterization techniques in Materials Science to study the size and structure of quantum dots such as Atomic Force Microscopy, Scanning Electron Microscopy, X Ray Diffraction analysis and Transmission Electron Microscopy. X-ray photoelectron spectroscopy, FTIR and Surface-Enhanced Raman Spectroscopy[24] have additionally be used to characterize graphene QDs and other dots.

Drug delivery

Conventional drug delivery systems that are known to us in daily life such as syrups, tablets *etc*. although are effective against common remedies but do suffer from poor bioavailability and uncontrolled drug release in the body which reduces their effectiveness against life threatening conditions and increases side effects.[25] Nanoparticles on the other hand are under intensive investigation to develop controlled drug delivery systems as they have better bioavailability, target specificity, controlled drug release in the body and they reduce the dosing frequency since the medicine with DDS can be present for long period of time in the body[25].

The most important advantage of developing drug delivery vehicles as compared to researching more efficient drugs is the time saved in improving disease treatment: it may take 10-15 years for a drug candidate to pass through the important clinical trials before it can be licensed and distributed in the market. Meanwhile, nanoparticles can be loaded with drugs which have already proven their efficacy against serious pathogens and tumor cells while reducing side effects caused by a drug[26].

It is, however, important to note that nanomedicines also undergo rigorous clinical trials to make sure they are safe and an effective treatment option to maintain the safety of the patients. Quantum Dots can used as drug delivery vehicles for therapy against Cancer[27], Tuberculosis[28], Neurodegenerative conditions[29], *etc*. while executing traceable targeted delivery.

One of the most import proposed mechanisms to justify using nano drug delivery systems include the Enhanced Permeability and Retention Effect[30,31]. In 1986, Matsumura and Maeda coined the term EPR when they noticed in their research that

neocarzinostatin, an anti-cancer protein when conjugated to a polymer matrix, tends to accumulate in tumor tissues as compared to accumulation demonstrated by free neocarzinostatin. By using tumor-bearing mice in their work, they were able to demonstrate that the concentration of the anti-cancer protein was 5 times higher in tumor areas as compared to the blood stream over the course of 19 to 72 h. This observation is attributed to one of the 10 hallmarks of cancer cells – they induce angiogenesis. The new blood vessels formed to feed the tumor cells are leaky. Nano drug delivery vehicles enter tumor tissue through the permeable tumor vasculature and retain their due to poor lymphatic drainage of the new blood vessels[32]. Thus, quantum dots hold huge potential in becoming a part of successful chemotherapy against cancer.

QDs in biosensors

Quantum dots are increasingly being used in manufacturing of biosensors due to their unique and promising properties such as size-tunable emission spectrum, decent photostability, high brightness and distinctive photoelectrochemical behavior[33]. Antibiotics, humanity's best defense against malignant bacterial infections are not only used to treat humans but also find their applications in agriculture, animal rearing and aquaculture. Excessive use of antibiotics in these sectors lead to environmental pollution due to the residual medicine that if it were to enter a human body may cause allergic reactions in certain individuals, lead to evolution of antibiotic resistant bacteria and even increase incidences of cancer[34]. Thus, it is important to develop biosensors to monitor the level of residual antibiotics to prevent adverse ecological effects and quantum dots are considered an ideal material for manufacturing them due to their low cost, high sensitivity and quick analysis[34]. Sensors utilizing quantum dots have also been created as a defense against biological and chemical warfare.[35]For a sensor to be considered a biosensor, it must have a "biorecognition" part like an enzyme that can interact with a bioanalyte. Current research in optical biosensors is focused on developing new materials to improve the biorecognition part of biosensors which may contain nanoparticles. Better biorecognition parts of optically active materials such as quantum dots will make them an attractive choice for colorimetric biosensors.[35]Scientists at the Seoul National University in 2015 developed graphene quantum dots based fluorescent sensor that was able to detect *anthrax* biomarkers within 8 seconds, and demonstrated that the detection properties of the GQDs were size dependent[36]. QD based nano-biosensors have also been developed for early diagnosis of dangerous conditions such as lung cancer. Here, the sensors detect the circulating miRNAs which may be utilized as a biomarker for presence of lung cancer cells[37].

***In vivo* imaging**

There are many upcoming technologies that keep enabling deeper visualization and insight into the biological world. Fluorescence techniques are widely used in the life sciences such as in monitoring cell movement in an organism, DNA detection and observing how the immune system works in humans. They are based on a very important property of atoms and molecules due to which they absorb light of a certain wavelength and then emit light after returning to ground state that has a longer wavelength (ergo less energy). The time lag between absorption and emission of light is referred to as fluorescence lifetime.

The drawbacks of organic dyes that are used as fluorescent labels include the lack of applicability in an experiment that requires multiple colour tracking, a limiting excitation range and broad emission spectra[38,39]. These issues are inherent in the chemistry of organic fluorophores. The first imaging applications of semiconductor quantum dots for use as fluorescent label were described in 1998[40,41]. Their advantages include the convenient absorption behaviors that shifts towards shorter wavelengths and a roughly symmetrical narrow emission band[40,41]. They allow images to be taken for longer period of time[42] and are available in many well-separated colors[42] making it easier to implement them in studies requiring tracking of multiple cells. Due to biocompatible nature of silicon quantum dots as well as their environment friendly nature, they have been used as fluorescent probes for medical imaging[43].

Photodynamic therapy

PDT, as the name suggests is a type of two-stage treatment for diseases that involve some light-responsive medicine which can destroy malignant cells in the body post light activation. PDT can be a part of a patient's treatment plan along surgical

removal, radiation therapy or chemotherapy in cases of certain cancers and pre-cancers[44].

The first step of the therapy involves intaking a photosensitizer (Photofrin, Levulan, *etc*.) which can be administered orally, through an intravenous line or in case of Levulan, applied directly on the skin depending on location of the tumor. After 1 to 3 days, the drug should have been removed from most healthy cells and only be retained in the tumor cells. The second part involves the actual application of light at photosensitizer. This is a simpler process if skin cancer is being treated since the doctors just apply the light directly at cancer but for tumors in the lung, throat, intestine *etc*., an endoscope needs to be inserted in the body which contains a fiber optic cable that applies the light for excitation of photosensitizer. The activated photosensitizer in the presence of oxygen then generates reactive oxygen species which damage the nearby cells causing cell death[45].

Quantum Dots are being considered to play the role of photosensitizers in PDT. Quantum dots upon treatment with radiation generate reactive oxygen species[46] making them a substitute for traditionally used photosensitizers. Jiayi Chen and fellow researchers tested the photoactivity of graphene quantum dots made of single layers of carbon atoms by monitoring their ability to generate ROS when they undergo light activation with promising results.[47]Another interesting result out of that study was that QDs should not be paired with a different type of photosensitizer as they can inhibit their photoactivity[47].

Conclusion

As discussed in the paper, Quantum Dots can be used in various ways in the clinic. Their unique optical and electrical properties can be harnessed as a means to treat and diagnose life threatening conditions. They have already been implemented to be used *in vitro* for detection of cancer biomarkers, studying the tumor microenvironment, fluorescent labelling of cells, *etc*. Many QDs are being tested in clinical trials against diabetes, cancer, tuberculosis *etc*. and they are expected to become a part of routine medicine in the future.

It is important to note however, that the clinical challenges in administering quantum dots in terms of quantifying doses, developing synthesis methods that produce a very homogenous population of quantum dots and understanding their biotoxicity mechanisms must be overcome before further applications can be considered. Nevertheless, their advancement would revolutionize medicine and change our daily life by bringing us closer to a world where nanotechnology and biotechnology have converted science fiction to reality.

Conflict of interest

The author declares no conflict of interest.

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