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State-of-the-Art and Trends in Synthesis, Properties, and Application of Quantum Dots-Based Nanomaterials

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Quantum dots (QDs) with a nanoscale size range have attracted significant attention in various areas of nanotechnology due to their unique properties. Different strategies for the synthesis of QD nanoparticles are reported in which various factors, such as size, impurities, shape, and crystallinity, affect the QDs fundamental properties. Consequently, to obtain QDs with appropriate physical properties, it is required to select a synthesis method which allows enough control over the surface chemistry of QDs through fine-tuning of the synthesis parameters. Moreover, QDs nanocrystals are recently used in multidisciplinary research integrated with biological interfaces. The state-of-the-art methods for synthesizing QDs and bioconjugation strategies to provide insight into various applications of these nanomaterials are discussed herein.

1. Introduction

Quantum dot (QD) nanoparticles have made an indelible impression on various fields including chemistry, physics, and biomedical sciences. These nanoparticles, which are made up of metallic or semiconductor materials, typically range from 2 to 10 nm,[1] are composed of ≈10^2–10^4 atoms[2] and possess tunable optoelectronic properties.[3] In addition, their shape can be precisely controlled by adjusting the duration, temperature, and ligand molecules used in their synthesis.[2b,3] Colloidal QDs have been widely studied over the past two decades both in fundamental and practical research, resulting in significant advances in their synthesis.[4]

The biomedical analysis should be investigated based on a specific and sensitive detection of target biomolecules with appropriate reproducibility. Fluorescence-based detection strategies are well-suited to meet these expectations.[5] These methods have been used to study biological phenomena by considering experimental parameters such as excitation, emission wavelength, and intensity of the fluorescent signal generated. To detect down to the single-molecule level, a number of eminent properties of QDs including fluorescence life-time, photochemical stability, fluorescence quantum yield, and emission anisotropy provide high resolution (nanoscale) and significant sensitivity.[5a]

QDs have been found as alternatives to organic and fluorescent dyes and are now becoming widely used in biotechnology and the medical field (**Table 1**).[6] Parameters such as highly sensitive detection and practical usability can also be considered as important factors, which make these fluorescent nanoparticles desirable tools for studying biological phenomena.[7] QDs may be used to develop the next-generation of biological labels that could overcome the limitations of conventional organic dyes and other fluorophores.

The photophysical properties which make QDs interesting as compared to classic organic dyes are i) the size-tunable fluorescence emission, which can be generated for any specific wavelength and symmetry, and ii) the broad absorption and narrow emission spectra, which generally makes them ideal for simultaneous detection of multiple fluorophores.[9] Furthermore, high resistant photobleaching capabilities of QDs, in contrast with organic fluorophores, make these nanoparticles suitable candidates to be applied for continuous monitoring of fluorescence.[7,10] Additionally, due to the large molar extinction

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coefficients and high quantum yields of these nanoparticles, bright fluorescent probes are provided in aqueous solutions.[7,11] QD nanomaterials also have long fluorescence lifetimes ranging from 20 to 50 ns, which allow their signal to be separated and distinguished from those of shorter species such as background or other fluorophores.[7,12] This, in turn, results in increased sensitivity of detection. These advantages can lead to their integration with nanotechnology and biology, triggering major advances in medical diagnostics, targeted therapeutics, and molecular and cellular biology.[8] **Figure 1**A displays a multicolor fluorescence micrograph obtained from a mixture of polymer beads containing hydrophobic QDs and spreading on a glass surface and Figure 1B shows CdTe QDs synthesized by a direct aqueous method in our lab (data not published). It was found that the polymer-enclosed hydrophobic QDs were spatially separated and did not display fluorescence resonance energy transfer. Modification of these polymer beads using biomolecular probes, such as oligonucleotides and antibodies, developed a biofunctionalized microstructure that exhibited excellent potential for molecular recognition and integrated codes for rapid target identification.[13]

Despite all these advantages, QDs-based detection strategies also impose several limitations such as high cost and the use of toxic materials as well as significantly larger size compared to organic dyes. These limitations can prevent the replacement of well-established dye-based tests with QD-based bioassays. The main limitation is that the excitation and emission wavelengths are dependent on the size of QDs, and even a small change in the size leads to significant changes in the wavelengths. Thus, in contrast with most organic fluorophores, the exact wavelengths required for excitation and emission should be empirically determined for any batch of QDs.[7]

Nevertheless, it has been demonstrated that changing the QD alloy composition can adjust the emission wavelengths while preserving the QDs size.[31] Furthermore, organic solvents are used in most of the synthesis approaches where highly monodispersed and homogeneous QDs are produced. The QD nanoparticles fabricated using these techniques should be water soluble for biomedical purposes. Thus, surface treatment and modification are inevitable steps to overcome the difficulties such as toxicity, low stability, and solubility in water.[32] Until now, various methods have been used for the preparation of QDs and these methods can be considered in different classifications. In this review, we focus primarily on current synthetic methods for the synthesis of QDs with a brief description of their applications.

2. Chemical Modification Strategies

Surface modification of nanocrystals is carried out to improve the dispersibility of nanoparticles and reduce the aggregation and precipitation possibility. Moreover, changing the surface chemistry can be useful for further coupling of functional groups.[33] To apply QDs to various biomedical systems, it is important to provide aqueous solubility and surface modification that support bioconjugation. This can be achieved by attaching organic molecules and macromolecules, including proteins and peptides, enzymes, antibodies, carbohydrate, and oligonucleotides, on

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Table 1. Comparison of the conventional dyes and QDs properties.

Property	Conventional dyes	Ref.	Quantum dots	Ref.
Size	Approximately 0.5 nm	[5a]	2–60 nm	[1,15a,14]
Absorption bands	The full width at half height of the maximum in the range of 35 nm (resonant dyes) to 80–100 nm (CT dyes)	[15]	Wide-ranging absorption patterns: narrow emission spectra, and broad excitation spectra, mostly ranging from the first exciton absorption in the visible region toward and into the UV	[14,16]
Molar absorption coefficient [M^{-1} cm^{-1}]	25000–250 000; at longest wavelength absorption maximum	[15a,17]	Size dependent; 100 000–1 000 000	[18]
Fluorescence quantum yield	Between 0.5 and 1.0 for the visible spectrum, between 400 and 700 nm (high fluorescence quantum yield) and 0.05 and 0.25 for the NIR wavelength region, above 700 nm (moderate fluorescence quantum yield)	[15b,17d,19]	Between 0.1 and 0.8 for the visible spectrum, between 400 and 700 nm (high fluorescence quantum yield) and 0.2 and 0.7 for the NIR wavelength region, above 700 nm (high fluorescence Quantum yield)	[20]
Solubilization	Solubility can be significantly increased using sulfonates or other charged groups; steric effects should be avoided by regulation of sulfonation rates	[21]	Depends on chemical surface characteristics; water solubility methods, such as ligand exchanging, surface silanization, or encapsulation, are needed.	[22]
Biofunctionalization	Commercial availability of functionalized dyes, well-established labelling, purification, and characterization protocols, at least possible steric hindrance, some challenges about high label densities and fluorescence quenching issues, hydrophilicity, influence on biomolecule correct function	[5a,23]	Limited numbers of standard approaches about biomolecules labelling of QDs; biofunctionalization methods are typically based on electrostatic conjugation, biotin-streptavidin, covalent cross-linking, polyhistidine tags, and ligand exchange; suffers from limitations such as aggregation due to nonoptimal surface chemistry and binding of several biomolecules to a single QD and biomolecule orientation difficulties	[11,24]
Stability	Can be less photostable than quantum dots; often problematic for NIR-wavelength dyes; reactive oxygen species (ROS) may degrade the dyes	[15b,25]	Outstanding photochemical stability compared with organic fluorophores (stable even after continuous illumination for 14 h)	[5a,6c,26]
Quantification	Effectively applied for quantification in an extensive variety of studies	[27]	QD photo brightening phenomenon may prevent quantification; QD blinking also can affect the results	[28]
Toxicity	Can be cytotoxic; mainly dose used for studies will be significantly lower than the doses associated with toxicity; DNA intercalators can be considered as the major problem	[5a,29]	Can be cytotoxic, $Cd2^{+}$ leaking as one of the main issues of cadmium based quantum dots, cytotoxic surface results from ligands and/or aggregation which is the most reported causes of QDs toxicity, cytotoxic due to the size (nanotoxicity)	[30]

the surface of these nanoparticles to make them suitable for biomedical applications such as imaging, biosensing, and drug delivery systems.[8,34] Common modifications of QDs surfaces are illustrated in **Figure 2**. Depending on the final application, different modifications such as adding thiol groups or polyethylene glycol (PEG) on QDs can be carried out resulting in in the formation of nanoparticles with specific features.

In terms of QD surface modification, different strategies including ligand exchange, amphiphilic polymer strategy (encapsulation), biotin-streptavidin, silanization, etc. are used. For instance, for the polymer-based surface modification of QDs, amphiphilic polymers play a key role. Polymer-based modification strategies can be categorized based on a) interactions of multiple side groups of polymers, as a multidentate compound, with the surface of nanocrystals, b) interaction of polymers with hydrophobic ligands of QDs, and c) polymer attachment to the surface of QDs via functional end groups.[35] Nonetheless, in the polymer-based modification, hydrophobic interactions between a suspended alkyl group and the native ligands of the nanoparticle, such as trioctylphosphine oxide

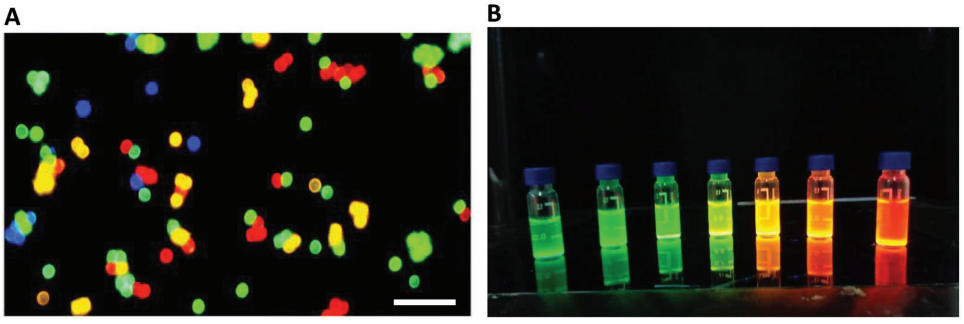

Figure 1. A) Fluorescent micrograph of CdSe/ZnS QD-conjugated beads immobilized on a glass surface coated with polylysine. B) Prepared CdTe QDs by a direct aqueous method. Reproduced with permission.[8] Copyright 2002, Elsevier.

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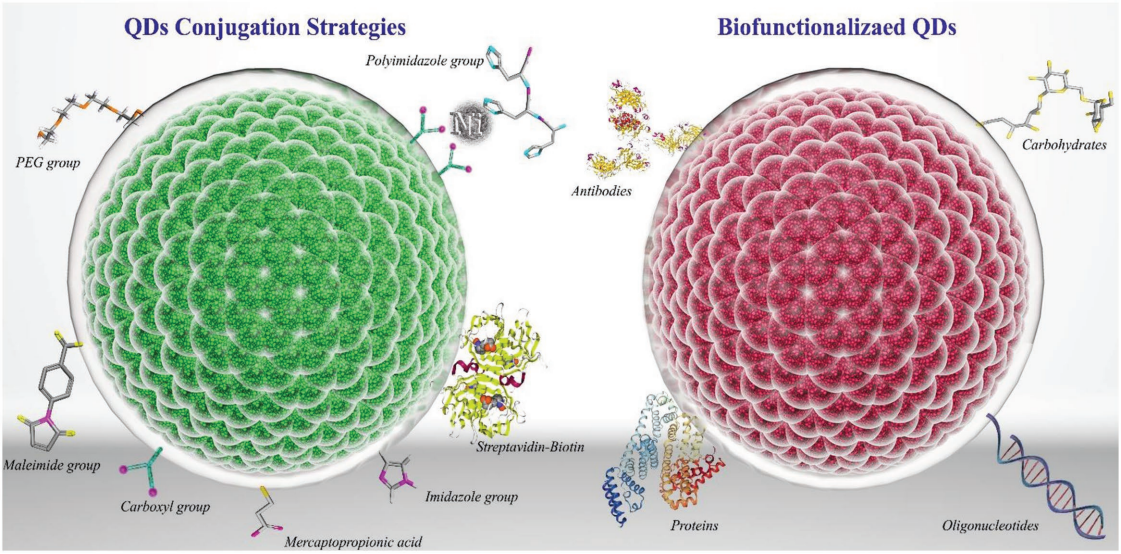

Figure 2. Examples of particular surface modifications of QDs. The shell around the QDs depicts surface coating. Conjugation strategies categorize into hydrophobic interactions and ligand-based modification. Some ligands which can be conjugated include monodentate or bidentate thiols, such as mercaptopropionic acid and dihydrolipoic acid, and also imidazole and polyimidazole groups, such as polyhistidine group. Water solubility of QDs may be mediated by amine groups, carboxyl groups, and functionalized polyethylene glycol (PEG) which can be conjugated to the surface of the coating part. Some QDs bioconjugation strategies include: 1) thiol-based functionalization, 2) polyhistidine tags, and 3) coating surface modification based on electrostatic interactions; 4) modification based on assembly of polyhistidine to carboxyl groups of coated surface mediated by nickel; 5) bioconjugation based on maleimide-activated QDs; 6) active ester-based coupling strategy; 7) conjugation based on biotin-streptavidin. Adapted with permission.[36] Copyright 2010, Elsevier. Figure not to scale.

(TOPO) originated from the synthesis step, result in encapsulation of the QDs by polymers.[36] Modification of QDs surface for binding of biomolecules (proteins and peptides, oligonucleotides, carbohydrate, etc.) can also be achieved with different strategies as summarized in **Table 2**.

3. Organometallic-Based Synthesis

Synthetic procedures are mostly focused on obtaining monodispersed and highly luminescent nanoparticles with desirable surface functionalities. In the 1980s, organometallic precursors were used in the solution-phase synthesis of nanocrystalline particles,[37] followed by the establishment of an applied guidance for QDs synthesis.[38] Moreover, in 1993, a well-regulated method was reported by Murray et al. for nucleation and growth of QDs with narrow size distribution,[39] and in the early 2000s, Talapin et al. and Peng et al. established a method based on hot injection.[40] For the organometallic synthesis of QDs, precursors, surfactants and solvents are required where surfactant molecules may also play the role of solvent.[41] As reported by Steigerward et al.[42] the use of suitable precursors is an imperative stage for QD synthesis. At the growth temperature, precursor molecules, such as organometallic compounds, should be quickly decomposed by the solvent to produce a reactive species needed for nucleation steps and nanocrystal growth. Dimethyl cadmium (Cd $(CH_3)_2$) is an excellent example of a precursor used for QD synthesis and has been utilized to yield CdSe,[43] TOPO, octadecene (ODE), and hexadecylamine organic solvents containing extended alkyl chains. Cd $(CH_3)_2$ may also be used for preparing QDs at high temperatures due to its high boiling point.[44] These hydrophobic organic compounds possess a critical role in the inhibition of bulk semiconductor formation on the QD surface by providing a reaction media in which interaction between these compounds and unsaturated metal molecules occurs. Therefore, the organic ligands-capped nanocrystals can be soluble only in nonpolar hydrophobic solvents, such as chloroform.

Two stages are involved in the synthesis of QD which include: i) the nucleation, where precursors at high-temperatures form reactive monomers, resulting in nanocrystal nucleation; ii) the growth of the created nuclei of the precursor units. To isolate the nucleation and growth of nanocrystals, the temperature should be precisely controlled. Generally, separation of these stages is mainly determined by different factors including mixture temperature, injection procedure, and the concentration gradient.[52] The use of high reaction temperatures, ranging from 150 to 350 °C, facilitates the elimination of crystalline defects and enhance photoluminescence (PL) (**Figure 3**A).[53]

Moreover, surfactant molecules, including nanocrystals and inorganic cores, are enclosed by a monolayer of organic molecules, which may lead to the formation of new materials.[2b,54] Surfactants used for the synthesis of QDs contain two domains including a nonpolar tail and a polar head group. Diffusion properties are affected by the nonpolar tail while binding efficiency is typically influenced by the polar head group.[55] Chemicals with amine groups, phosphine oxides, alkyl phosphonic acids, alkyl phosphines, and fatty acids are examples of organic surfactants that determine the solubility of the nanocrystals.[41] In 2005, Yin et al. reported that adhesion energy, which produces a dynamic solvation, is responsible for the adhesion of

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Table 2. Biomolecule conjugation of QDs.

Surface modification strategy	Biomolecule modification group	Properties	References
Ligand exchange	Thiols, amines, phosphines, carboxylic acids, and pyridines	Primary surface groups such as TOP/TOPO are replaced with functionalized biomolecules, the native ligands can be also covered with other ligands such as hydrophobic molecules, the hydrophobic part can be resistant to hydrolysis or enzymatic degradation. However, it is difficult to control the reaction procedures; it has low quantum yield, low optical and colloidal stability; and variation in number of conjugated molecules per nanocrystal can be deemed as limitations of the proposed strategy	[24b,35,45]
Biotin-streptavidin	Biotin, (strept)avidin	In this strategy, ionic strengths affect the binding between streptavidin and QDs. Aggregation at high ionic strength; low quantum yield, and small number of conjugated oligonucleotide per nanocrystal are other reported limitations	[24a,46]
Silanization	Depends on the modified surface chemistry	Crosslinkers such as tetraethyl orthosilicate (TEOS) are employed. This method has some distinct advantages including high stability in a salted aqueous solution ($>100 \times 10^{-3}$ M) and minimal cytotoxic effects reported in cell studies making it an appropriate matrix for biomedical applications. However, this method suffers from multiple steps of modification, small number of conjugated biomolecules such as oligonucleotide per nanocrystal. Also, photoluminescence (PL) quantum efficiencies can be reduced significantly and aggregation is possible due to interparticle crosslinking	[47]
Amphiphilic polymer strategy	Depends on the modified surface chemistry	Nonpolar parts of polymer and native ligands of QDs are intercalated, crosslinked polymers encapsulate the nanocrystals and their polar and chemically reactive end groups are exposed to outer surface which can be used for bioconjugation, terminating groups are carboxylic acid, amines, maleimide groups, etc.	[35,48]
Based on EDC[a)]	Primary-amine group	All hydrophilic QDs coated by carboxyl groups are activated by EDC, amine-functionalized DNA can react with Maleimide activated nanocrystals. The limitations of this approach include low conjugation yields, aggregation due to excess amount of EDC used, and nonspecific and irreversible binding of DNA backbone to negatively charged surface of QDs	[49]
Based on SIA,[b)] Sulfo-SMCC[c)], and Traut's reagent[d)]	Primary-amine/thiolated groups	Traut's Reagent reacts with primary amines to introduce sulfhydryl groups (thiolation), whereas, crosslinking reagents including SIA and SMCC react toward amino groups to conjugate with sulfhydryl residue in other ligands via their maleimide groups. Limitations include the orientation of biomolecules such as antibodies, and instability of conjugates in the study medium, which may result in aggregation	[50]
Based on sulfo-LC-SPDP[e)]	Primary-amine/thiolated groups	Amino-nanocrystals can react with sulfo-SMCC to change into maleimide activated QDs, biomolecules with amino groups can be activated with sulfo-LC-SPDP to be thiolated. QDs modified with sulfo-SMCC can be conjugated with thiolated biomolecules such as antibodies	[51]

[a)]EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; [b)]SIA: *N*-hydroxysuccinimidyl iodoacetate; [c)]SMCC: succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate; [d)]Traut's Reagent: (2-iminothiolane); [e)]Sulfo-LC-SPDP: Sulfosuccinimidyl 6-[3′-(2-pyridyldithio)propionamido] hexanoate.

surfactant molecules to the nanocrystals surfaces in growth medium and should be considered as one of the determinative factors during the growth stage.[41] In this approach, further chemical modification of the physical properties of nanocrystals can be employed to use in other prospective strategies[56] aiming at the synthesis of nanocrystal-biomolecule conjugations.[57] The synthesis procedure is typically carried out in a three-neck flask connected to a Schlenk line, where reactant injection and the temperature measurement are performed through the necks of the flask (Figure 3B). Nanocrystals are often prepared under an inert atmosphere. To initiate the synthesis of QDs, the organic solvent and surfactant agents are loaded into the flask and, following the solvation, the flask is heated to 150–300 °C for 10–20 min under a vacuum condition to eliminate impurities. Tellurium (Te), selenium (Se), and sulfur (S) are examples of elemental chalcogens, which are added to the reaction media in the presence of a capping agent. In this process, a complex is formed by dissolving the elemental chalcogens in liquid trioctylphosphine (TOP) or tributylphosphine.[55] When the high surface energy of the small particles in the colloidal system promotes their dissolution, redeposition of the material onto the larger particles enable their further growth, which is a phenomenon known as Ostwald ripening. Both the nucleation and the growth processes have important effects on the final particle size and morphology. The most general technique of QD synthesis is based on organometallic precursors. In this technique, the high reaction temperature (between 150 and 350 °C) helps the exclusion of crystalline defects and improves the PL properties. In addition, the size distribution of QDs prepared by this process can be simply optimized through temperature or reaction time.[58]

Using an organometallic strategy, surfactants in the growth stage of the surfactant-aided synthesis of QDs are anchored to the surface of nanocrystals.[59] These agents serve as the surface capping ligands and can control the growth of QDs during synthesis to maintain the appropriate size, stabilize nanoparticles, prevent the aggregation, and influence the solubility of nanocrystals.[60] However, synthesis methods using surfactant

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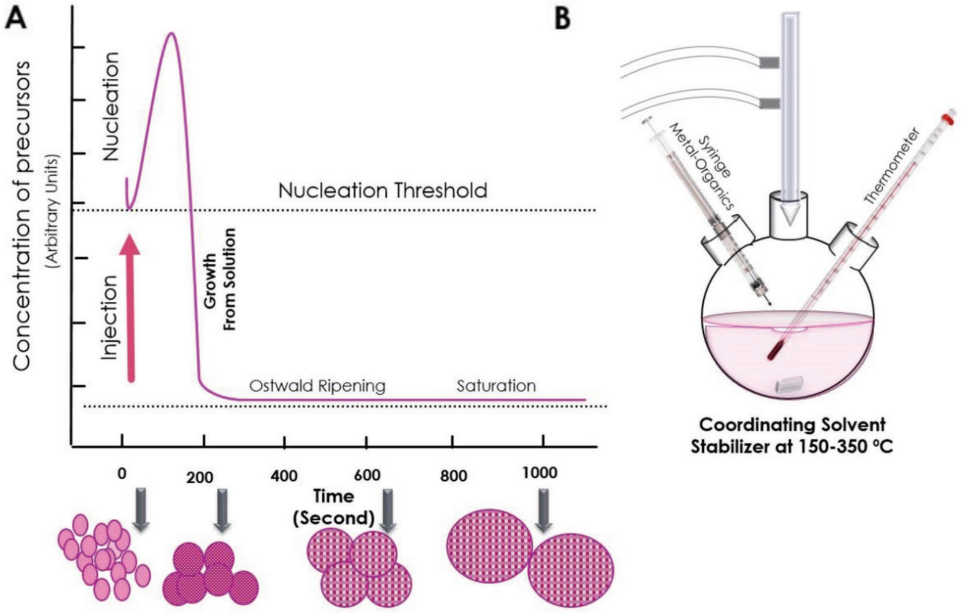

Figure 3. Nucleation and growth stages in the synthesis of monodisperse nanocrystals (the La Mer model). A) During the nanocrystals growth and by periodically sampling aliquots from the reaction media, nanocrystals can be isolated based on size. B) Illustration of the simple machine employed in the synthesis of monodisperse nanocrystals. Adapted with permission.[44a] Copyright 1993, American Chemical Society.

yield QDs with insulating organic ligands on the surface and can prevent charge transport between nanocrystals.[61] To overcome this drawback, these organic ligands can be easily changed in a procedure known as ligand exchange process. This exchanging of surfactants on the surface of nanocrystals facilitates the development of QDs with a wide range of functionalities for specific applications including biomedical applications[41,62] (**Figure 4**).

In optoelectronic devices, transport of charge between nanoparticles is necessary. Therefore, the ideal ligand should exhibit properties such as stable colloids, high conductivity, and stable and facile electronic interactions.[63] Recently, the synthesis and characterization of CdSe QDs developed with ferrocene phosphine and phosphine oxide derivatives as electroactive ligands have been reported.[64] This study reported that the inorganic cores of the nanoparticles were directly conjugated to ferrocene phosphine or phosphine oxide derivatives by their phosphine-oxide functional group. The absence of an intervening alkyl chain spacer minimized the electroactive moiety. These metallocenes were directly bound to the inorganic core of the nanoparticle and consequently, the distance between the nanoparticles and the electroactive moiety was minimized. Meanwhile, the tertbutyl attachment, serving as the alkyl side chain, provided colloidal stability (**Figure 5**). These materials were shown to be acceptable photoexcited hole conductors and photoredox systems.

Nevertheless, high toxicity, high cost, instability of the substances, and high reaction temperatures generally suggest that organometallic approaches are not ideal for the synthesis of QDs. Although organometallic methods have presented promise in fabricating higher PL quantum yield and narrow size distributions, research has been pushed toward more environmentally nontoxic methods.[65]

4. Nonorganometallic-Based Synthesis

Generally, organometallic-based synthesis of QD nanocrystals has resulted in high-quality nanomaterials. Nonetheless, due to high toxicity and the use of expensive and pyrophoric materials as well as an explosive risk, this method still suffers from some serious limitations for wide-range applications.[66] For instance, Cd $(CH_3)_2$ which is an extremely toxic, air, and moisture sensitive complex, has been employed as a precursor in this strategy. These limitations have been overcome by using alternative components such as cadmium oxide (CdO),[67] cadmium acetate (Cd $(Ac)_2$),[68] and cadmium myristate.[41] For example, by using CdO instead of the traditional pyrophoric organometallic complexes, production of high-quality CdSe/ZnSe core/shell QDs has been reported by Reiss et al.[69] and Li et al.[70] Furthermore, Qu et al.[71] have reported successful incorporation of CdO for the synthesis of nanocrystals, including CdSe, CdS, and CdTe.

Moreover, although conventional high-quality CdSe nanocrystal production was considered as a rigid method, high-quality CdSe nanoparticles well synthesized by using one-pot synthesis and some organic solvents (e.g., amines and fatty acids).[73] For example, Flames et al.[72] reported a novel method for rapid synthesis (5–10 min) of monodispersed (3 nm with a size dispersion of 6.7%), phosphine-free, and high yield (80–85%) nonorganometallic CdSe nanocrystals. This method was based on a heterogeneous mixture of Se which was dissolved in ODE and directly injected into a solvent (270 °C) containing CdO dispersed in cadmium carboxylate. Remarkably, no protective atmosphere was required during synthesis as it had no effects on the quality of the end product. In addition, the synthesis procedure could be executed on an automated platform, hence indicating the potential of this strategy for scaling up the synthesis of this type of nanoparticles. Recently,

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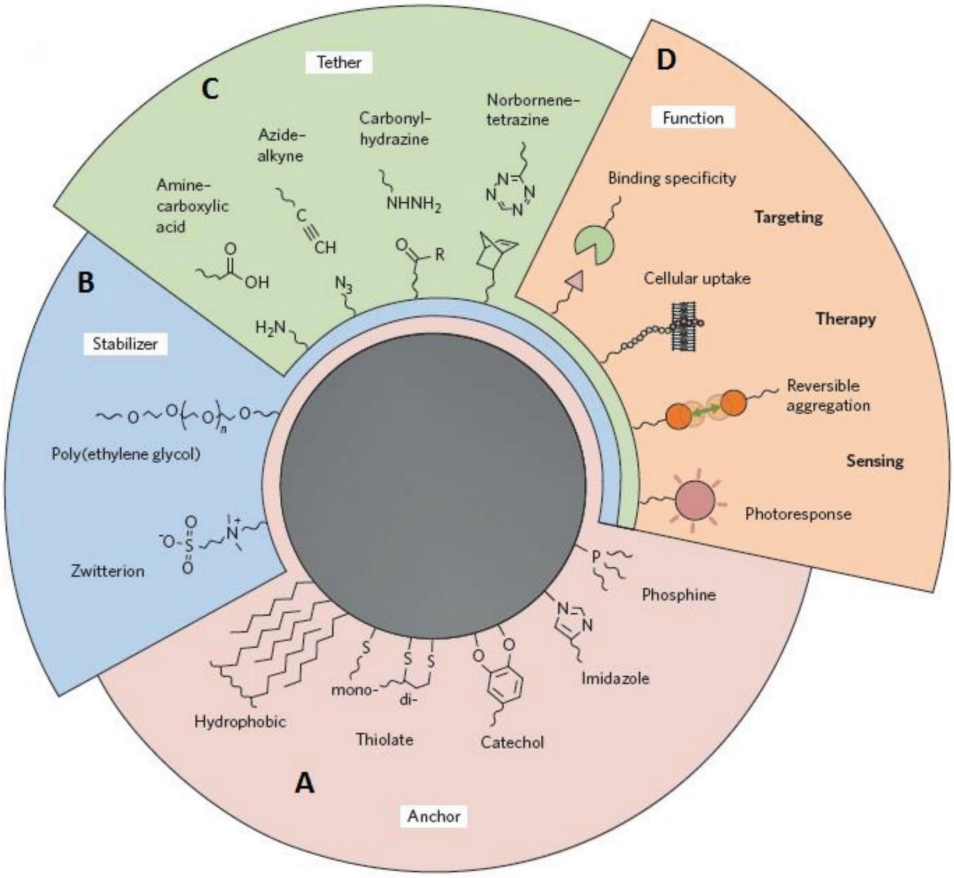

Figure 4. Schematic illustration of ligands used for the synthesis of biocompatible nanomaterials. Generally, these ligands can be categorized into four groups including A) anchors, B) stabilizers, C) capping molecules, and D) the biofunctional units. Anchors act as bridges between capping agents and crystallite by hydrophobic interactions with primary native ligands or by directly binding to atoms of QDs surfaces. Stabilizers such as polyethylene glycol (PEG) prevent nonspecific adsorption as well as give hydrophilicity. Capping molecules can also be used for covalent binding of biofunctional molecules following ligand exchange and the biofunctional units could be used in different diagnostic, therapeutic, and smart targeting systems. Reproduced with permission.[62b] Copyright 2016, Nature Publishing Group.

synthesis of II–VI nanocrystals using a high-temperature strategy has been modified by using single-source precursors.[74] However, purifying these precursors required further synthetic phases. Additionally, nanocrystals synthesized from single-source precursors usually show lesser luminescence emission and occasionally polydispersed particles (**Figure 6**).[75]

5. Microwave-Based Synthesis

The use of microwave electromagnetic irradiation for QDs production can enhance the rate, yield, and scalability. These advantages can originate from a phenomenon named "dielectric heating," where polar materials are heated due to the strong absorption of microwaves.[76] In contrast to convective heating, the whole volume is uniformly heated using dielectric heating. Consequently, thermal gradient effects are reduced, resulting in greater control over the size and optical properties of QDs.[77] By forming a traditional thermal bath where precursors or solvents can be directly heated, the rapid growth of nanocrystals is easily managed based on the polarity differences between the solvent and the precursor. The reaction medium components including precursors, passivating ligands, and solvent as well as several microwave factors such as temperature, time, and power have an important role in controlling the nucleation and growth processes, and therefore the quality of synthesized QDs.[78]

The optical properties depend on applied temperature and power of microwave irradiation. For example, using a higher temperature typically results in larger nanoparticles, characterized by the generation of a solution in red color.[79] Chalcogenide precursors can be considered as the important examples of compounds used for microwave-based synthesis that selectively absorbs the microwave energy and enables instantaneous nucleation and growth of nanoparticles. Hence, QDs can be grown rapidly and controlled by a combination of reactant concentration and microwave power.[80]

Microwave irradiation has also been used for the rapid synthesis of water-soluble CdTe QDs (<5 m) with high fluorescence quantum yields around 40–60%.[81] Furthermore, a new strategy has been reported for the synthesis of CdSe(S) and ZnSe(S) QDs.[82] Qian et al. applied 3-mercaptopropionic acid (MPA) as a ligand to reduce the chemical reactivity of the surface of nanocrystals and to serve as the source of sulfide for high-temperature reactions. Furthermore, InGaP, InP, CdTe,

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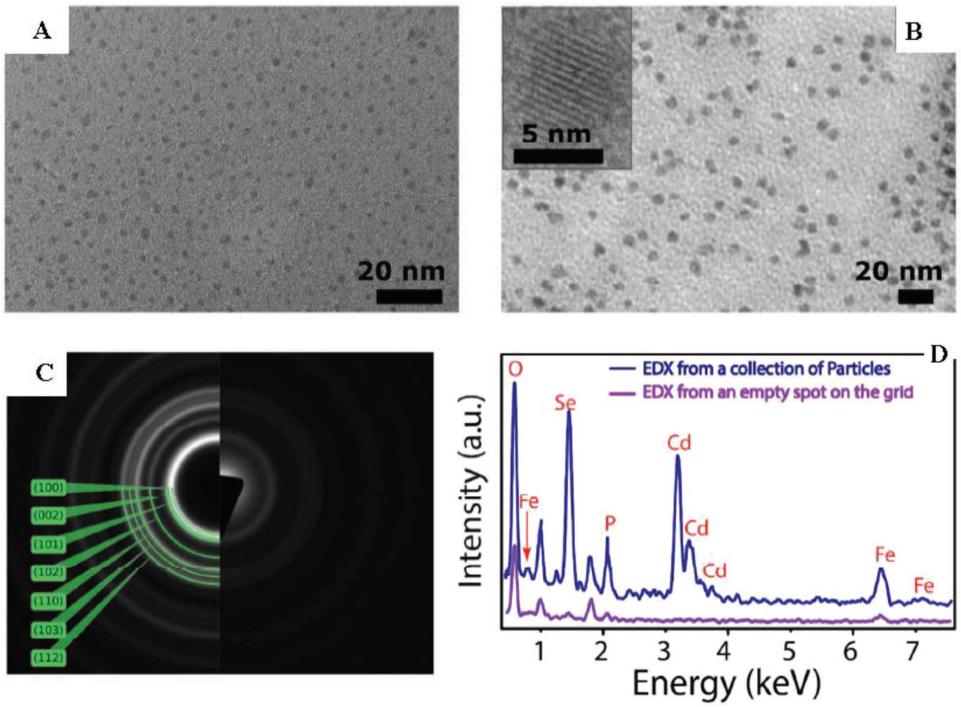

Figure 5. Morphology and chemical composition of the CdSe QDs capped with FcPtBu2. A) Representative low-magnification transmission electron micrograph (TEM) images of nanoparticles capped with ferrocene derivatives including FcP(O)tBu2 with size of 3.5 nm and B) FcPtBu2 with size of 7–7.5 nm. C) Selected area from electron diffraction pattern (SAED) revealing broad diffuse rings as a characteristic of nanoscaled particles. This analysis confirms the high crystallinity and the hexagonal structure of CdSe. D) Energy dispersive X-ray (EDX) analysis of CdSe sample capped with FcP(O)tBu2 composite, showing traces of elements including Cd, Se, Fe, and P (size: 7–7.5 nm). Reproduced with permission.[64] Copyright 2016, American Chemical Society.

CdSe nanocrystals,[83] and CdSe coated with ZnS[84] have been successfully prepared by using a microwave heating strategy.

Recently, synthesis of water-dispersed CdSe/CdS/ZnS core/shell/shell QDs by a simple one-pot microwave irradiation has been reported.[85] As shown in **Figure 7**, CdSe QDs were obtained by a microwave-assisted heating of the vessel containing Se precursor and Na_2SO_3 for 20 min. Then $CdCl_2$ was dispersed in 3-mercaptopropionic acid as a surfactant. In the next step, both prepared Cd and Se precursors were placed into a vessel and heated to 100 °C for 30 s by microwave irradiation. Finally, the high-pressure air was applied to cool down the solution to 50 °C within 2 min to obtain CdSe QDs (emission wavelength at 572 nm). CdSe/CdS core/shell QDs were also prepared by adding the prepared CdSe core QDs to a solution containing Cd precursor, Na_2S, and the surfactant and then it is heated to 100 °C for 5 min. Finally, CdSe/CdS/ZnS core/shell/shell QDs were synthesized by adding the prepared CdSe/CdS QDs into a solution containing $ZnCl_2$, N_2S, and MPA. The mixture was then heated by microwave irradiation for 5 min at 70 °C. In this approach, by applying microwave irradiation, the reaction time was reduced to 30 min and resulted in QDs with a high PL quantum yield and excellent photostability.

6. Microemulsion-Based Synthesis

In microemulsion-based systems, two or more immiscible solutions are generally stabilized by incorporating an amphiphilic agent, resulting in a thermodynamically stable dispersion.[86] Microemulsion procedures are popular approaches for developing QDs at room temperature. They are categorized as either normal microemulsions (i.e., oil-in-water) or as reverse microemulsions (i.e., water-in-oil).[2a] Microemulsion process has been known as an effective method for controlling the growth of narrow size-distributed and nanodispersed inorganic nanoparticles. This high-quality formation is due to the mechanism of QD synthesis in the microemulsion procedures where the newly formed clusters are efficiently stabilized and consequently, uncontrolled growth of the QD crystals is inhibited.[44b,87]

The reverse micelle procedure is currently used for the synthesis of QDs, by which two immiscible liquids, such as polar water and nonpolar long-chain alkanes, form an emulsion.[89] This procedure is generally well accepted for adapting the size and distribution of particles. Moreover, this strategy can be employed for the synthesis of QDs with the same shapes as their nuclei. Water droplets in the nanometer range, dispersed in nonpolar solutions, can be produced by using surfactants.[89] The reverse micelle method is a process where the hydrophilic and hydrophobic groups on opposite ends of the surfactant molecules create small micelle droplets in solution. The hydrophilic ends are accumulated in the center where the reactants are entrapped, resulting solubility in the continuous oil phase. The micelles are vigorously stirred to increase the rate at which exchanges of the entrapped reactants occur, resulting from dynamic collisions.[89]

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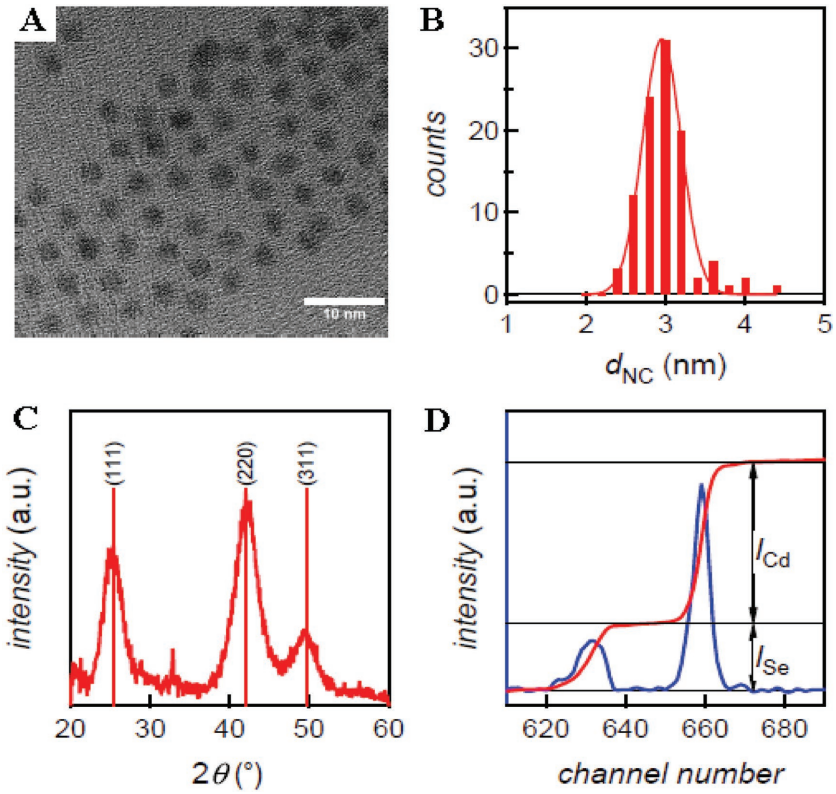

Figure 6. Characterization of CdSe QDs using a one-pot synthesis method. A) Representative TEM image of synthesized nanoparticles. B) Size distribution histogram of the obtained QDs through analyzing 100 different samples with quasi-spherical shape of nanocrystals. C) The X-ray diffractogram (XRD) pattern which shows the synthesized QDs have the crystal structure of zinc blende CdSe. D) Rutherford backscattering spectrum, in which two signals can be attributed to Se and Cd. Reproduced with permission.[72] Copyright 2013, American Chemical Society.

Recently, CdS QDs were synthesized and stabilized in situ in ionic liquid reverse micelles (IL RMs).[88] Briefly, 2-hydroxyethylammonium formate (HO-EAF) and isooctane were emulsified by dioctylsulfosuccinate proliniumisopropylester ([ProC3]AOT), as an amino acid-based surface-active IL, to obtain reverse micelles. Then, to prepare CdS QDs embedded in microemulsions, $Cd(NO_3)_2 \cdot 6H_2O$ and Na_2S were separately dissolved in HO-EAF. Subsequently, this mixture was added to the reverse micelles and was stirred for 12 h. This IL-QDs hybrid system provided excellent control over size of nanomaterials (3.0, 3.4, and 5.7 nm in different ratios including 0.5, 0.7, and 1.0, respectively, and could be used in electroluminescent devices due to its tunable light emission with no need for further chemical treatment (**Figure 8**).[88]

The reverse micelle method has been also used to produce II–VI core and core/shell QDs, such as CdS,[87] ZnS/CdSe,[44b] CdSe/ZnSe,[91] and ZnSe.[92] Furthermore, the reverse micelle-based synthesis of QDs has been employed to make new QD-based barcode systems for detection of cancer biomarkers.[90] By mixing the micellar solutions and the sulfide containing a micellar solution, the encoding elements including Zn^{2+}, Cd^{2+}, and Pb^{2+} were merged into a single QD.

Some advantages of this fabrication method include better control of the size of QDs (facilitated by changing the water to surfactant molar ratio), a narrow distribution of size, and easy dispersion of the QDs. However, this method suffers from some limitations including low fluorescent yield and incorporation of impurities and defects (**Figure 9**).

7. Lab-on-a-Chip Technology-Based Synthesis

One of the main challenges in nanoscience and nanotechnology is the synthesis of colloidal nanocrystals with controlled size distribution. Furthermore, producing pure and monodisperse nanocrystals is considered to be one of the major issues for many nanoscale types of research.[93] Microfluidic systems were originally developed in the early 1990s and have found various applications including medical diagnosis, rapid drug analysis, and performing chemical reactions in the biotechnology, pharmaceutical, and chemical industries.[94]

In 2002, the use of microfluidic devices to prepare nanocrystals was reported for the first time,[95] which provided many prospective advantages in terms of chemical and biomedical applications. These devices provide more control over synthesis reaction, leading to the formation of monodisperse emulsion droplets reaction. In addition, microfluidic-based synthesis of QDs reduces the need for precursor materials, making this approach easily scalable and high throughput. Another important aspect of this approach is that the synthesis reaction of QDs is isolated from contact with the operator and the environment, minimizing potential safety issues due to exposure to toxic chemicals.[96,97]

In terms of the device platforms, both classic lithography-based and capillary-based microfluidic systems have been utilized for the preparation of monodisperse droplets. For scaling up the production, lithography-based systems have great potential. On the other hand, capillary-based microfluidic devices have demonstrated robustness in preparing multiple emulsions for novel material synthesis. Further, capillary-based microfluidic devices have been developed for the encapsulation of different materials, controlling microreactions through confining them, and biosensing.[98] Various types of microfluidic devices are utilized to inject dry powder,[99] to investigate fluid physics[100] and detect gases mixture.[101] However,[101b,c] the immense majority of efforts have been currently focused on continuous flow reactors.[101b,c,168–170] These reactors can be categorized into two types. In the first type, precursor molecules are inserted in simple capillaries, which typically possess an inner diameter of 100–1000 µm. Being chemically inert and capable of withstanding high temperatures without degradation, these capillaries are commonly made from glass and polytetrafluoroethylene. The reagents are added using "tributary" connections joined to other capillaries. Heat-dependent reactions are then started by passing the pre-determined sizes

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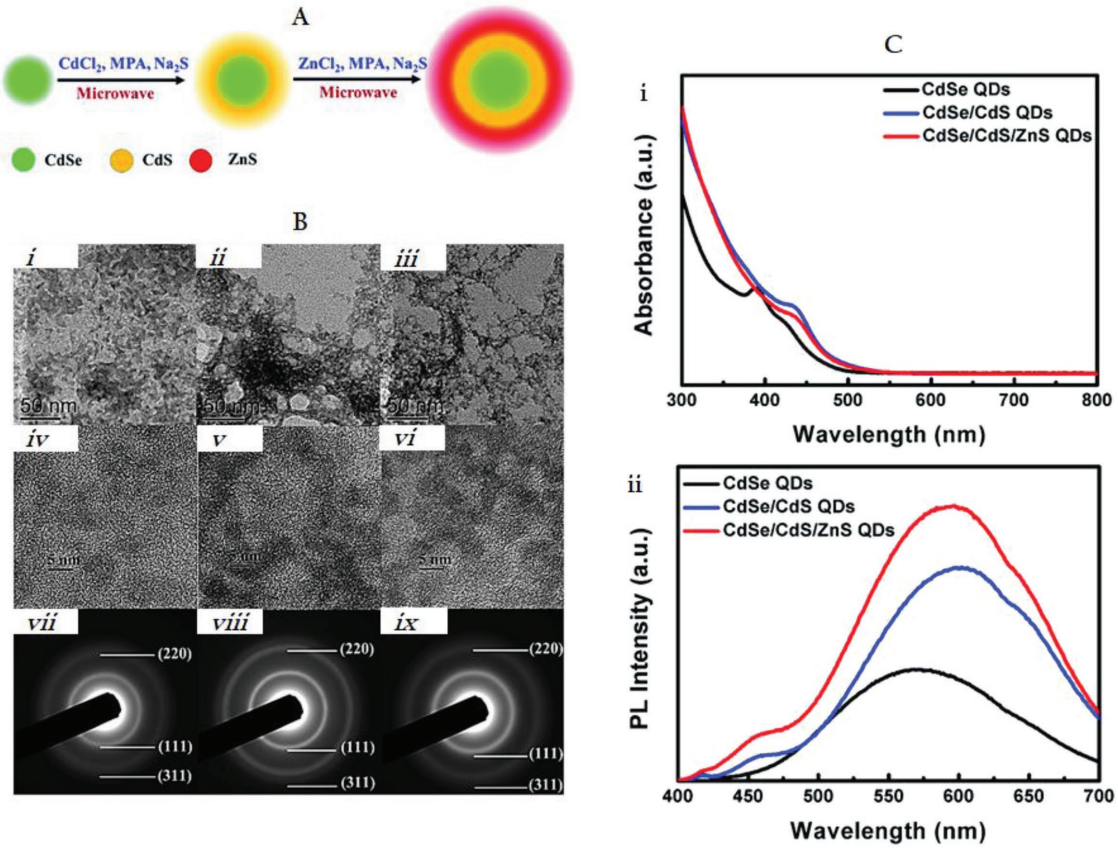

Figure 7. Preparation and characterization of CdSe/CdS/ZnS core/shell/shell QDs. A) an illustration for the microwave-assisted synthesis of core/shell/shell QDs. In this method, water-dispersed CdSe/CdS/ZnS core/shell/shell QDs were synthesized for each component via a simple one-pot microwave irradiation. B) Representative transmission electron microscopy (TEM) images of i–iii) CdSe, CdSe/CdS, and CdSe/CdS/ZnS QDs, iv–vi) high resolution TEM (HRTEM), and vii–ix) selected area electron diffraction (SAED). Generally, prepared QDs show spherical morphology (3.2 nm for CdSe, 3.7 nm for CdSe/CdS, and 3.9 nm for CdSe/CdS/ZnS QDs) and HRTEM analysis reveals lattice planes which extend across the entire particle. Moreover, the SAED images show the same three diffraction plane rings from inner to outer, implying the similar crystal structure to that of bulk cubic zinc blende. C,i) UV–vis absorption and ii) photoluminescence spectra of prepared QDs. Following synthesis of CdSe QDs (excitation: 390 nm, emission: 575 nm), CdSe/CdS QDs was formed which shows 50 nm shifts for UV–vis absorption and 25 nm for PL spectra. By formation of CdSe/CdS/ZnS QDs, they show 5 nm shift compared with CdSe/CdS QDs and PL intensity was increased. Reproduced with permission.[85] Copyright 2015, American Chemical Society.

of the capillaries through heated oil-baths.[93] In the second form of microfluidic devices, a solid host or "chip" is employed to house the channels with widths typically in the range of 100–1000 µm. Synthesis of high-quality QDs often requires high-temperature reactions, which can be achieved using glass or silicon chips.

Kwon et al.[102] reported a continuous microfluidic system for in situ production of ZnSe/ZnS core/shell QDs. In this system, three major sections were designed for mixing the precursor, ZnSe formation, and ZnS shell coating (**Figure 10**). For easy monitoring of the reaction process, plastic has been used by applying a nickel master stamp and microinjection method. As illustrated in Figure 10A, this thermoplastic microreactor was composed of three inlet channels connected to syringe pumps for pumping the precursors and one outlet channel. Figure 10Bi shows the dimensions of microchannels of the device where the reactants are combined. Also, in the zigzagged mixing zone, the reactants are mixed (Figure 10Bii) before entering into the microreactor zone where heat is applied to induce the synthesis reaction. In the small dimension of this device, the flow rate of precursor solutions determines the size of ZnSe/ZnS core/shell QDs with the uniformity and reproducibility. Thus, QD size could be easily tuned by changing the flow rate (Figure 10Biii).

Furthermore, Swain et al.[103] described a strategy for the synthesis of CdSe by using a combinatorial synthesis system using computer-controlled programmable isocratic pumps and online detectors. In this system, various parameters of the process could be manipulated through the programmable computer software. Therefore, the desired size of QDs could be easily achieved, which may overcome the challenges such as economic viability, and efficiency of the development of QDs.

8. Direct Aqueous-Based Synthesis

Aqueous-derived QDs are appropriate for biomedical applications, and their synthesis is commonly safer, simpler, and less

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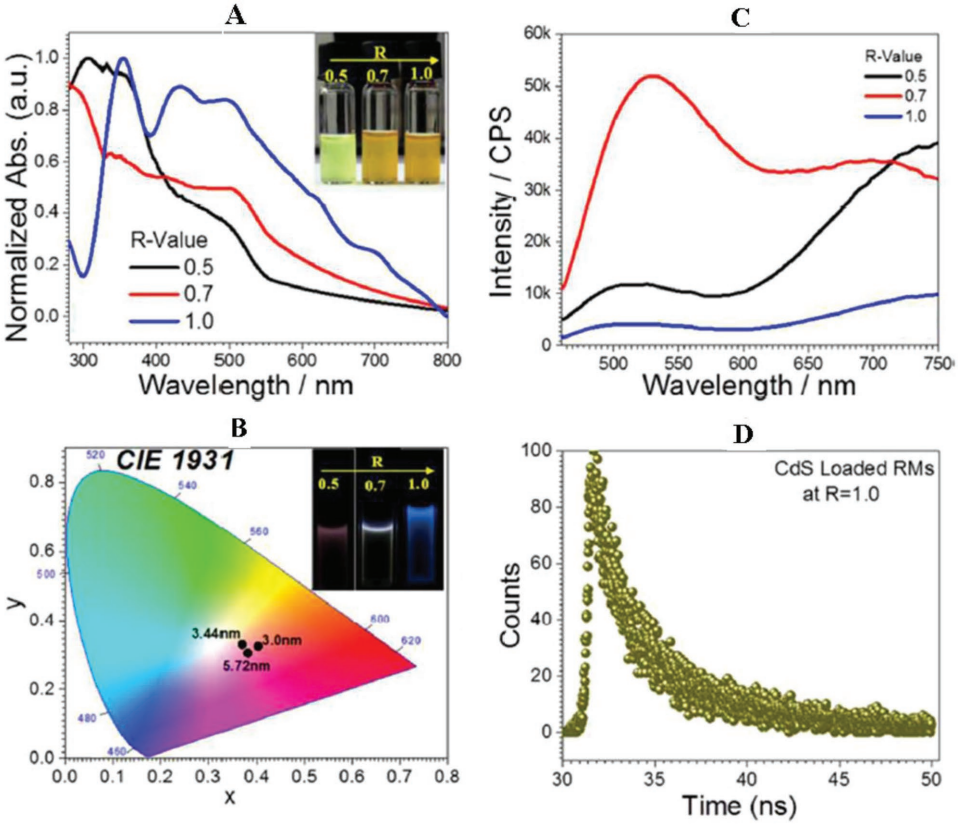

Figure 8. Main properties of CdS QDs. A,B) UV–vis absorption and fluorescence emission spectra of CdS QDs embedded in reverse micelles of microemulsions (excitonic band: 450 nm) at different ratios (0.5, 0.7, 1.0). C) Chromaticity coordinates for the fluorescent microemulsions, showing pinkish white (3.0 nm), yellowish-white (3.4 nm), and bluish white (5.7 nm) regions (in inset images), and D) transient PL decays at trap states of CdS QDs. Reproduced with permission.[88] Copyright 2016, American Chemical Society.

expensive compared to nonaqueous-derived QDs. Recently, the synthesis of water-based nanoscale crystals with thiol capping agents has become increasingly popular as an alternative reductant for the water-based synthesis of QDs.[104] This aqueous-based technique is categorized in two aspects: i) stronger affinity of thiol-ligands for conjugation with the surface of nanocrystals compared with the affinity of trioctylphosphine oxide and ii) nucleation at room temperature with crystal growth at a higher temperature (≈100 °C).[105] Therefore, direct aqueous-based production of QDs can be more appropriate for the controlled synthesis of magic-sized clusters. Magic-sized clusters are intermediates in the synthesis process that are composed of a specific number of atoms in an arrangement that makes them extremely stable structures.[106] Rogach et al. introduced the aqueous-based synthesis of CdTe nanoparticles capped with thioglycerol and mercaptoethanol in 1996.[107] This was followed by Kapitonov and Rogach who reported successful synthesis of thiol-stabilized CdTe QDs and CdSe QDs by using NaHX, where X is Se, Te, etc. and metal salt.[108] Due to the good water solubility, biocompatibility, and passivation effect, biothiols such as cysteine have also been used as stabilizers in the production of II–VI semiconductor nanocrystals.[109]

Based on the classic approach for the synthesis of CdTe, a solution of Cd $(ClO_4)_2$ and thiol stabilizer is treated with H_2Te gas, which is produced by the chemical decomposition of Al_2Te_3 powder by concentrated sulfuric acid. Through this process, nonluminescent CdTe clusters are achieved, and in the next step nonluminescent solutions are heated under reflux at

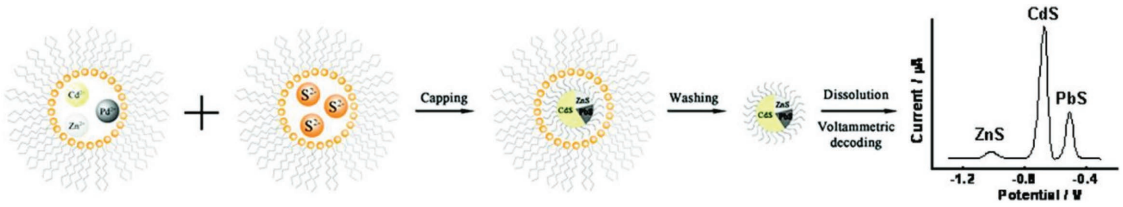

Figure 9. Illustration of reverse micelle-based QDs electrochemically encoded with Zn^{2+}, Cd^{2+}, and Pb^{2+} ions and then decoded by voltammetric stripping method. Reproduced with permission.[90] Copyright 2010, American Chemical Society.

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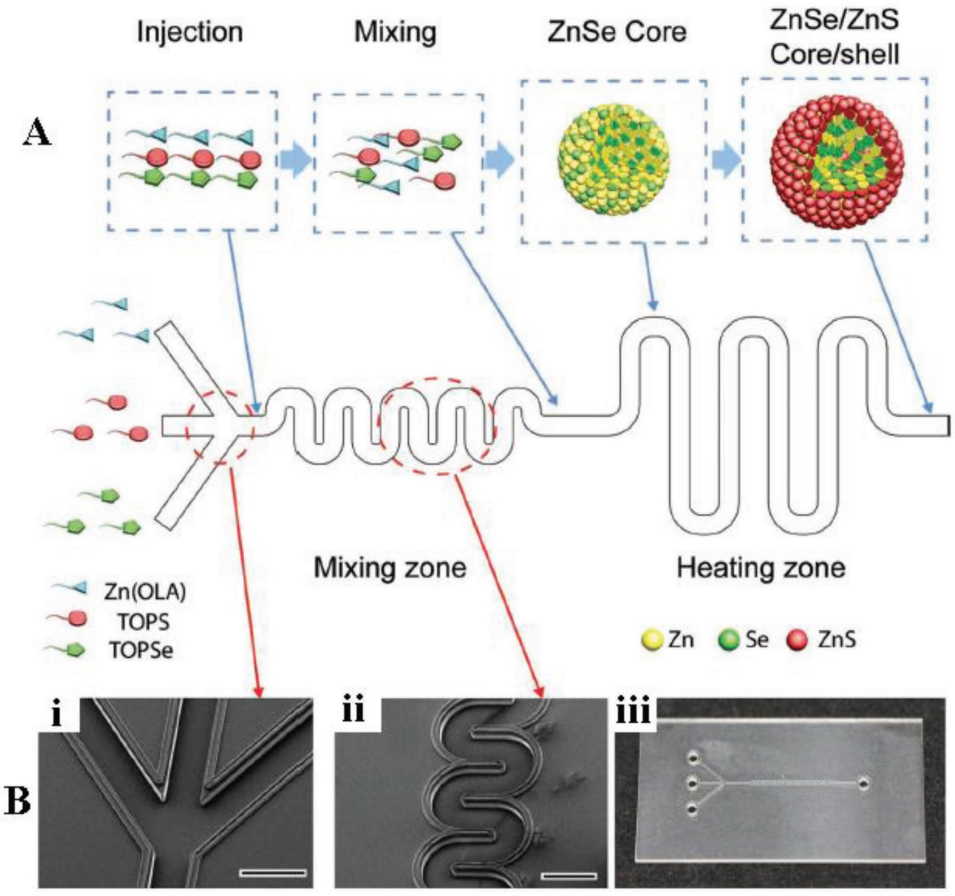

Figure 10. The principle of microfluidic-based synthesis of uniform QDs. A) An illustration of the microfluidics-based synthesis of ZnSe/ZnS core/shell using the continuous-flow thermoplastic microfluidic platform. B) Representative scanning electron microscope (SEM) images from i) inlet and ii) mixing zone and iii) a photograph of the fabricated device. Reproduced with permission.[102] Copyright 2012, John Wiley & Sons, Inc.

100 °C for several h to produce CdTe QDs.[111] Extended reflux times lead to larger QDs, hence the size of nanocrystals can be adjusted by the time given for reflux. To synthesize QDs larger than 6 nm, the addition of a source of cadmium and stabilizer, coupled with higher concentrations of H_2Te are required (**Figure 11**).

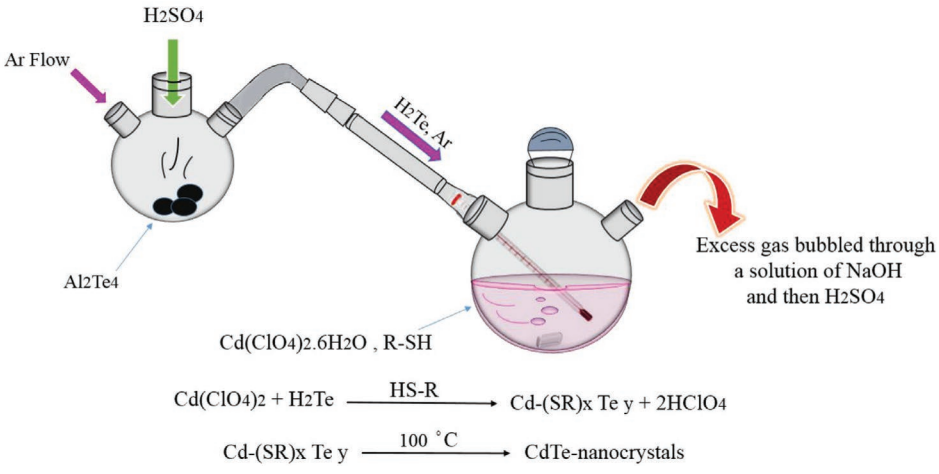

Figure 11. Graphical illustration of water-soluble CdTe QDs synthesis. In this synthesis strategy, H_2Te_2, produced from the reaction between H_2SO_4 and Al_2Te_4, forms CdTe nanocrystals through a two-step reaction. In a similar synthesis route, Selenite salts can be used instead of Telluride salts to produce CdSe QDs. In order to fine-tune the size of the produced QDs, the synthesis condition should be carefully optimized. Adapted with permission.[110] Copyright 1996, John Wiley & Sons, Inc.

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9. Other Synthesis Procedures

9.1. Metathesis, Thermolysis, Dehalosilylation, and Transmetalation Reactions

In recent years, significant progress has been made in the development and application of group III–V QDs. However, increased covalently bonded components in the structure of group III–V QDs results in poor crystallinity. In contrast to group II–VI QDs, the progress on synthesis methods of group III–V QDs is sluggish as a result of poor crystallinity.[112] Moreover, in most group III–V QDs, the growth of nanocrystals required a long time (e.g., up to several days) and yielded particles with a broad size distribution and indistinguishable absorption peaks. In addition, the inherent shortcomings of accessible precursors have also made little improvement in the group III–V QD synthesis.[113] Therefore, large-scale production and commercialization of group III–V QDs can be challenging due to the lag of their synthesis techniques. The following reactions have been commonly considered for the synthesis of group III–V QDs: metathesis,[114] thermolysis,[115] dehalosilylation,[113a,116] and transmetalation.[117] Metathesis reaction, also known as double displacement reaction, is a chemical transformation in which the chemical bonds are exchanged between the reactants, yielding products with similar or identical bond types.[114] In preparation of group III–V QDs, group III–V bonds could be established from Ga- or In-halides as III-based precursors and from alkali nitrides or arsenides as V-based precursors.[118] Reaction systems involving metathesis or single source precursors generally require high temperatures (>400 °C) or several days to complete the reaction. In addition, it is difficult to control the sizes of QDs synthesized using metathesis, which results in polydispersed nanocrystals.[114b]

Thermolysis is a type of endothermic reaction in which the decomposition of a single or dual source material is triggered by heat. In most cases, for the synthesis of group III–V QDs, reactions are conducted by thermally decomposing pre-synthesized solid-state complexes containing both III and V precursors.[115] Additionally, to obtain monodispersed group III–V nanocrystals, reactions are transferred into a solvent with a high boiling point to meet the requirement of high temperature.[119]

The dehalosilylation reaction, which is also referred to as trimethylhalosilane elimination, was introduced by Wells et al. and has been extensively investigated through the removal of various ligands to obtain the group III–V QDs.[120] In this way, group-III halides and group-V organometallic precursors, such as tris(trimethylsilyl)arsine [$As(TMSi)_3$] or tris(trimethylsilyl) phosphine [$P(TMS)_3$], were utilized in a coordinating solvent such as TOP, TOPO, and quinoline.[113a,121] Dehalosilylation reactions resulted in appropriate control over the sizes to yield highly crystalline QDs at lower temperatures and shorter times.[122]

GaN is a classic group III–V QD with a wide and direct band,[123] containing 3.2–3.3 eV for zinc blende bulk GaN at room temperature, which is important for UV optoelectronics.[124] GaN semiconductors possess excellent thermal, chemical, optical properties, and radiation stability; therefore, have the potential to be used for applications in current-injected laser diodes (LDs) and LEDs. Due to a lack of appropriate N-precursors, the synthesis of solution-based GaN QDs was mostly focused on two reactions: metathetical reaction and thermolysis. The metathetical reaction, followed under solvothermal conditions, has been recognized as a feasible wet-chemical approach for GaN QD synthesis.[123,125] However, despite the low reaction temperature and acceptable diameter control, poor solubility of QDs may lead to aggregation. Hence, capping agents such as TOPO seldom have been utilized for the GaN QD synthesis.[126] Additionally, thermolysis reactions, through precursor decomposition at a moderately low temperature, were also employed for the GaN nanoparticle synthesis. In this reaction, single source precursors containing Ga and N with an existing Ga-N bond in a single molecule were utilized.[124,127] To control growth and inhibit agglomeration, different types of amines such as *N, N, N, N*-tetramethyl-1 and 6-hexanediamine (TMHDA) were investigated as surfactant/capping agent, where blue-color photoluminescent Ga-N QDs were achieved through pyrolysis of gallium imide by boiling TMHDA.[127c]

Among the Ga-based III–V semiconductor, GaAs possesses a wide variety of properties and has demonstrated the potential to be used for different applications such as modern optoelectronic devices and solar cells.[128] In metal organic chemical vapour deposition strategy, uniform structures of GaAs, even without crystal defects, can be achieved. However, this high-quality strategy of QD synthesis requires highly toxic precursors such as arsine or pyrophoric materials. Therefore, finding an alternative less toxic and more cost effective wet-chemical synthesis method has recently received significant attention.[117]

A typical wet-chemical synthesis method of GaAs QDs has been reported by Wells et al., which utilized a dehalosylation reaction between gallium salt and [$As(TMSi)_3$].[120] The solvent and precursors played a key role in the morphology, size distribution, and purity of the GaAs QDs synthesized by using a dehalosylation reaction. It was reported that GaAs QDs with a narrow size distribution were obtained through a reaction between $GaCl_3$ and [$As(NMe_2)_3$] in 4-ethylpyridine as a coordinating solvent.[129] Moreover, a novel and simple synthesis of colloidal GaAs nanocrystals based on a transmetalation reaction has been reported.[117] Transmetalation reactions are a class of organometallic reaction where the transfer of organic groups/ligands from one metal to another occurs. This reaction is the underlying principle for preparing various organo-transition metal complexes. Mechanistically, in transmetalation organic group or neutral ligand is transferred from main group metal to transition metal.[130] This wet chemical approach could produce highly crystalline nanomaterials and was shown to yield a narrow size distribution by using reagents with reduced toxicity. Transmetalation of gallium (III) halides with *n*-butyllithium resulted in producing the elemental gallium. Subsequently, GaAs nanocrystals could be achieved by reaction between the elemental gallium species and Mg_3As_2.[117]

InP QDs can also be considered an effective candidate to replace or even surpass CdSe nanocrystals in some applications such as bio-imaging and photodynamic therapy.[131] InP nanocrystals can provide comparable or even preferable emission color to that of CdSe QDs. Notably, unlike cadmium, selenium, or arsenic, it has been demonstrated that InP possesses

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low intrinsic toxicity. InP nanocrystals are also structurally stable, leading to a better optical stability in biological systems.[132] The synthesis of InP QDs has been further investigated in comparison with that for other III–V QDs.[133] Recent investigations report that InP QDs have been fabricated by means of thermolysis of InP-precursor in a hot mixture containing TOPO and TOP.[113a,b] Although it was shown that a dehalosilylation reaction can be utilized for InP QD synthesis, owing to the high reactivity of the phosphorous precursor such as $[P(TMS)_3]$, this reaction is difficult to maintain due to the ultrarapid nucleation, consuming almost all phosphorous precursor.[133,134] Moreover, the uncontrolled mechanism of nucleation leads to the formation of poor size distributions.[135] Classically, a number of indium halides were used as precursors and TOP served as a solvent, stabilizing agent, and phosphorus source.[117] To maintain the reaction under control, carboxylate ligands have been used instead of phosphorous precursors, such as phosphine, to reduce the speed of nucleation. In this strategy, the reduced nucleation allowed for leaving some unreacted precursor for postnucleation growth which led to the production of narrowly sized InP QDs.[135]

9.2. Liquid-Solid-Solution (LSS) Phase Transfer Process

Synthesis of a wide variety of narrow disperse QDs with different chemistries was introduced by Li et al. through LSS phase transfer based on ion exchange.[136] This approach is based on the gradual transfer of the reactants from one phase to another as the reaction progresses, where "general phase transfer" and "phase separation" phenomena occur. Thus, there are three different phases in which separate reactions progress, and at the same time, the reactions occur among the reactants from different phases. In the solid phase, sodium linoleate is present, whereas, in liquid phase ethanol and linoleic are present. In addition, there is a solution phase of water-ethanol containing metal ions. First, metal ions are reduced by ethanol at the interfaces of liquid or solution phases at different temperatures from 20 to 200 °C and at the same time metal-linoleate is conjugated with hydrophobic surfaces in a phase transfer reaction (**Figure 12**). Finally, due to the weight of nanocrystal and also an incompatibility between hydrophobic surfaces of metals and surrounding hydrophilic nature, phase separation can occur and nanocrystals can be simply collected. To yield compounds, such as TiO_2, CuO, ZrO_2, SnO_2, or ZnO, the metal ions dehydrate into oxides in designed reaction circumstances. Alternatively, there is a possibility that metal ions react with anion species such as S^{2-}, or Se^{2-} to form molecules, such as ZnS or ZnSe. Using this method, the size of QDs can be affected by various factors such as temperature, mole ratio, and the length of alkyl chains.[136]

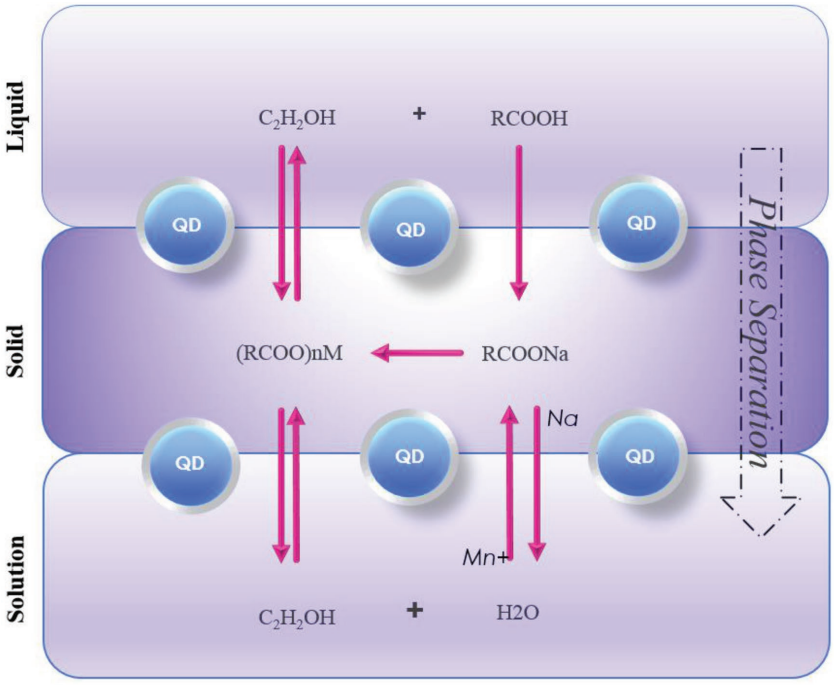

Figure 12. Nanocrystal synthesis based on liquid-solid-solution phase transfer strategy. In this approach, the reactants, which are presented in different phases, are transferred to different phase as the reaction progresses. Adapted with permission.[136] Copyright 2005, Nature Publishing Group.

9.3. Top-Down and Bottom-Up Approaches

QD may be synthesized using either a top-down or bottom-up technique. Generally, in the top-down approaches, such as electron beam lithography and reactive-ion etching, a bulk semiconductor is mixed with water to form QDs.[2a] In contrast, bottom-up or self-assembly techniques may be generally subdivided into wet-chemical and vapour-phase methods.[137]

Generally, top-down strategies include techniques such as lithography-based technique,[138] electrochemical synthesis[139] acidic oxidation-based synthesis,[140] hydrothermal/solvothermal synthesis,[141] and microwave-assisted synthesis.[142] In contrast, bottom-up strategies include methods such as oxidative condensation reactions,[143] self-assembly synthesis of graphene quantum dots (GQDs) based on using hexa-perihexabenzocoronene as a precursor,[144] and using benzene derivatives.[143b]

In wet-chemical approaches such as microemulsion,[87,145] hot-solution decomposition[44a,71,73] and sonic waves or microwaves,[146] the conventional precipitation procedures are involved, in which there is strict control over solutions parameters. The nucleation and limited growth of nanoparticles are two main features of the precipitation stage. However, the nucleation process can be homogenous, heterogeneous or secondary types.[126] In the vapour-phase method, the thermodynamically unstable vapour phase mixtures produce nanoparticles.[147] The vapour-phase synthesis and passivation of luminescent

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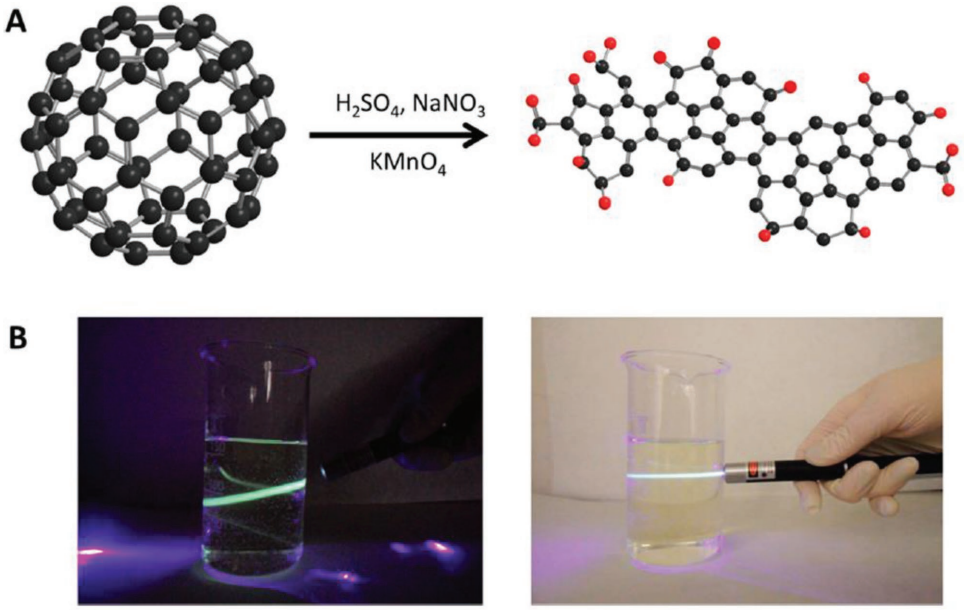

Figure 13. The general properties of GQDs. A) Synthesis of GQDs via oxidation and cage-opening of fullerene C60 induced by strong acid. B) Evaluation of GQDs optical properties: GQDs excited at 405 nm by a blue laser pointer. Reproduced with permission.[155] Copyright 2015, American Chemical Society.

ZnSe nanocrystals have been also reported.[148] This synthesis method of group II–VI QDs demonstrated better compatibility with current operations in the microelectronics industry compared with traditional liquid-phase techniques. Using wet-chemical synthesis methods, a thiol-based passivation process could lead to the well-stable photoluminescence properties of QDs, while the nucleation remained unaffected. This indicates that thiolation can be a suitable passivation method for increasing the quality of the resultant QDs.

Moreover, it is reported that Si substrates can be decorated by using extreme ultraviolet interference lithography technique, 2D hole arrays (2DHAs), and reactive ion etching.[149] 3D well-organized SiGe QDs and 3D QDs arrays (crystals) decorated on Si substrates have been fabricated with extraordinary structural perfection.[149] Both conventional top-down lithographic techniques and bottom-up methods have been widely utilized to develop QDs. However, the growth of self-assembled QDs applied on planar substrates has resulted in random nucleation and relatively broad size distribution. Nonetheless, within the past decade, to avoid basic issues originated from random nucleation, self-assembly pattern of semiconductor nanostructures has attracted extensive attention.[149]

9.4. Graphene QD Synthesis

GQDs are deemed 0D materials, which possess the beneficial characteristics of both graphene and carbon dots (CDs).[150] GQDs have unique properties including good photostability against photobleaching and blinking, and lower toxicity in comparison with semi-conductive nanocrystals, as well as organic fluorophores.[151] In recent years, this new class of nanomaterials has drawn great attention in biomedical field.[152]

Synthesis of GQDs can be categorized into the top-down and bottom-up approaches. In top-down strategies, carbon-derived products such as carbon fibers, graphite or graphene sheets, and carbon nanotubes are cut into nanoparticles. In the bottom-up methods, by contrast, precursors are used to produce GQDs.[154] In 2010, blue photoluminescent (PL) GQDs were synthesized through the hydrothermal cutting of oxidized graphene sheets resulting in GQDs with sub-10 nm sizes, with a quantum yield of 6.9%.[153] Moreover, direct electrochemical synthesis of green-luminescent GQDs, ranging from 3–5 nm, was reported.[154] In this study, filtration-formed graphene film was used as a working electrode and the reaction was carried out in phosphate buffered saline.

More recently, Chua et al.[155] reported a novel method based on top-down wet chemistry approach for the production of GQDs (**Figure 13**). In this method, fullerene C60 or buckminsterfullerene, as a spherical molecule with fused hexagonal and pentagonal structures, was treated with a mixture of strong acid and chemical oxidant inducing oxidation and cage-opening processes (Hummers method). The prepared QDs, with a diameter of ≈1 nm, exhibited the highest luminescence intensity at 460 nm under a 340 nm excitation wavelength. This strategy, due to its simplicity, can be considered for further improvements to integrate into optoelectronics-based devices.

10. Prospective Biomedical Applications of QDs

Nanotechnology is widely being applied in different industrial fields. Nanomaterials could have a game-changing role in non-biomedical applications such as displays. The majority of these nanomaterials have modified in a way to represent the quality expected for a nonbiomedical application. However, this quality

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makes them inappropriate for biomedical applications mainly due to their toxic effects and their incompatibility in biosystems. For example, a disappointing rate of only 0.7% of the administered nanoparticle dose could be delivered to a solid tumor.[156] Consequently, the success rate of nanotechnology in the clinical translation of nanomaterials has been limited.

The reasons for the limited application of nanomaterials in biomedical applications are diverse. However, lack of deep understanding of nano–bio interfaces could be highlighted as one of the main reasons. To address this issue, three main factors should be deeply addressed including: i) the nano parameters, ii) the complexity of biological systems, and iii) the interactions between nano and bio-parameters.[157] The lack of deep studies in terms of the interactions between these three factors has made a considerable inconsistency in nanomedicine data which causes misinterpretations of the current literature and subsequently, poor control over the desired application in the clinical translation of nanoparticles. Therefore, for successful applications of nanomaterials including QDs in a biological context, these three parameters should be optimized appropriately.

QDs show potential as materials to be utilized in three main areas of biological-related applications: imaging,[158] biosensing,[159] and therapeutic applications.[160] Multicolor imaging with QDs typically involves the specific binding of QDs to analytes such as genes and antibodies for cells staining,[161] animal imaging,[162] and tumor biology investigation.[163] QD-labeled DNA probes[24a,164] and antibody molecules[165] are used for targeted detection of nucleic acids and proteins. These fluorescent nanobiostructures are considered the principal components of novel QDs-based optical and electrochemical biosensors. QDs have been used as therapeutic agents in photodynamic therapy[166] as treatments for a number of malignancies and also drug delivery systems.[167] One of the emerging applications of QD-based nanomaterials is theranostic applications where the optical properties and the surface chemistry of QDs play a central role in the simultaneous diagnosis and therapy of diseases such as cancer.[74,76] Also, QDs are being used as a signal enhancer to improve the specificity of molecular techniques.[168]

Depending on specific physicochemical properties originated from the synthesis route and the surface modifications, different types of QDs can find specific applications. In terms of biocompatibility, some synthesis routes offer QDs with minimal environmental and biological toxicity. Thus, these QDs can be used in the environmental analysis and in vivo biosystems. The application of QDs can be also affected by the complexity and the cost of their synthesis as well as their fluorescent stability and electrical properties.

Among the different types of QDs, GQDs possess characteristics required for materials used for biomedical applications, including excellent biocompatibility as well as low-cost and ease of synthesis. One study reported the use of GQDs as a fluorescence resonance energy transfer (FRET)-based tracer of protease activity in the real clinical samples due to their biocompatibility and stable photoluminescence.[152a] Also, their excellent electrical properties allow their use in electrochemical-based nanobiosensors.[152b]

Surface engineering of GQDs opens a new window for further applications in the nanobiosensing field. For instance, tyramine-functionalized GQDs have been utilized by Li N et al.[152c] to profile a range of metabolites as biomarkers for human diseases. Upon exposure to the GQDs, these metabolites induce a tyramine-mediated crosslinking of GQDs that leads to the quenching of their fluorescence.

Replacing the less-stable shell of CdSe QD systems with a more chemically stable shell allowed for the development of l InAs (ZnCdS) QDs where the surface may be readily functionalized. This, in turn, led to designing a new generation of QDs that can be traced using the near-infrared (NIR) spectrum. Application of these NIR-responsive QDs in vivo significantly improved the resolution of images obtained from veins.[169] A novel in vivo imaging modalities has also been designed with the capability of real-time and high-resolution spatial imaging of cancer, neurological, and metabolic diseases.[170] As the synthesis and surface engineering methods continue to evolve, QD-based nanomaterials demonstrate improved performance for use in biomedical applications.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioconjugation, crystallinity, photoluminescence, quantum dots, synthesis

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