

Aqueous Continuous Flow Synthesis of Cadmium Chalcogenide Quantum Dots: Opportunities and Challenges

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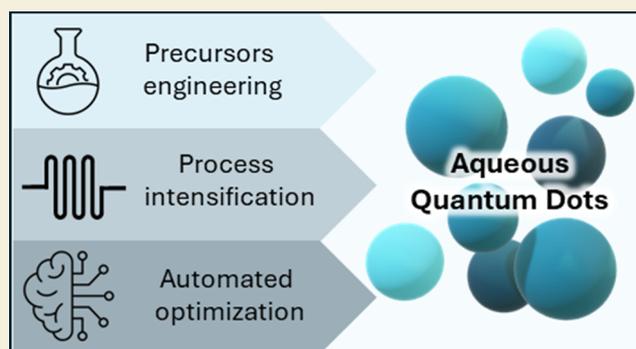
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ABSTRACT: Cadmium chalcogenide quantum dots (CdX QDs, X = S, Se, Te) are among the most extensively studied semiconductor nanocrystals due to their size-tunable optical properties and wide potential applications in optoelectronics, bioimaging, and sensing. While early syntheses relied on high-temperature organometallic routes in organic solvents, the demand for safer, greener, and more biocompatible approaches has driven increasing interest in aqueous-based methods. These two strategies differ substantially in terms of precursor chemistry, surface passivation, and control over nanocrystal quality. In parallel, continuous flow technology has brought transformative assets to the field, offering precise reaction control, scalability, and reproducibility, which are essential for both fundamental studies and industrial translation. This review summarizes the evolution of CdX QDs synthesis, contrasting organic and aqueous batch approaches, and focuses on recent advances in aqueous continuous flow strategies. Finally, we highlight perspectives on the integration of automated machine learning and artificial intelligence approaches with continuous flow, which may accelerate the discovery, optimization, and scalable production of high-quality QDs for next-generation technologies.

KEYWORDS: quantum dots, continuous flow, aqueous, microfluidic, nanocrystals, cadmium chalcogenides



1. INTRODUCTION

Quantum dots (QDs) are a unique class of semiconductor nanocrystals that have fascinated researchers since their discovery in the late 1980s, culminating in the 2023 Nobel Prize in Chemistry.^{1–3} With diameters typically in the range of 2–10 nm, smaller than the exciton Bohr radius, they show pronounced quantum confinement effects. This results in discrete, size-dependent electronic states and an energy bandgap that widens as particle size decreases, giving rise to tunable photoluminescence and redox properties.^{4–6} Such features, coupled with their high photoluminescence quantum yield (PLQY), photostability, and versatile surface chemistry, have established QDs as enabling materials for applications in photocatalysis,^{7–10} drug delivery and bioimaging,^{11,12} as well as in optoelectronics and energy devices.^{13–15} Traditionally, QDs are composed of a semiconductor core, often coated with an additional semiconductor shell, and stabilized by an outer layer of organic ligands that ensure colloidal stability and facilitate charge mobility (Figure 1). In recent years, however, the field has expanded to include more complex architectures, such as alloyed nanocrystals, advanced core–shell configurations, and doped quantum dots.¹⁶

Cadmium chalcogenide QDs (CdX, X = S, Se, Te) have been especially prominent in these developments owing to their well-understood electronic structures, wide spectral tunability, and relative synthetic accessibility. Nevertheless, their preparation is not without challenges. Conventional syntheses in organic solvents, such as the hot-injection and heat-up methods, allow good control over size distribution, crystallinity, and heterostructure formation. Yet, they are hindered by issues of toxicity, high-temperature operation, limited scalability, batch-to-batch reproducibility and difficulties in adopting automated or continuous manufacturing. These are among the many bottlenecks that complicate both industrial translation and sustainable development. The need for precise control over nucleation and growth demands tight temperature, mixing, and feeding protocols, which are often batch-dependent and sensitive to operator conditions.

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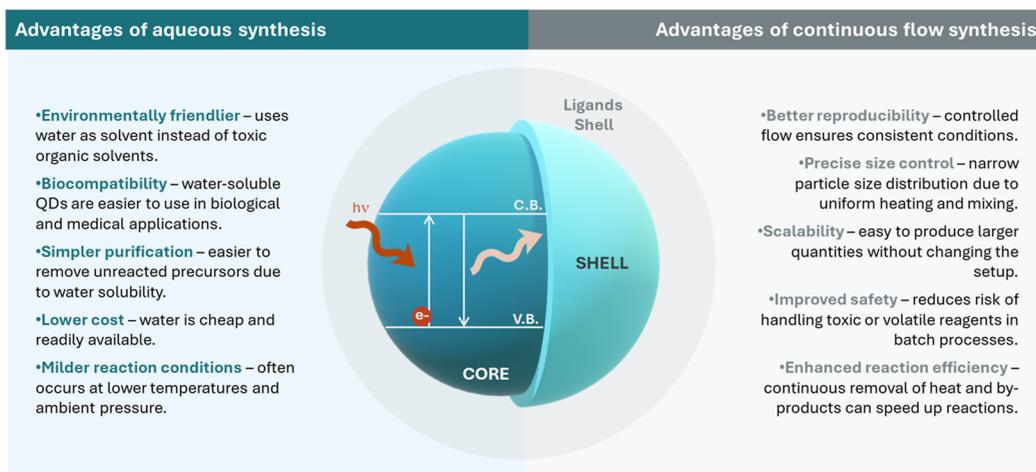


Figure 1. Simplified typical structure of QDs (V.B. = valence band, C.B. = conduction band and e^- = electron) with advantages of their synthesis in aqueous medium and in continuous flow.

Alongside these organic routes, aqueous syntheses have a long history, dating back to the pioneering work of Henglein and Fendler, and have since grown into a central branch of colloidal nanochemistry.^{17–21} Although organic solvent methods often yield higher PLQYs and fewer defects, aqueous strategies remain highly appealing due to their sustainability, scalability, intrinsic safety and compatibility with biological and environmental applications. In particular, the use of water-soluble ligands, including biomolecules, has opened up possibilities for direct biofunctionalization and even biosynthetic approaches.^{22–25}

In recent years, significant progress has been made in expanding the scope of aqueous synthesis. Chiral ligands have been introduced to impart size-dependent optical activity,²⁶ and nucleic acids have been employed to direct the formation of QDs with programmable and biocompatible surface chemistries.^{27,28}

While high-quality III–V and Pb-based nanocrystals still rely on organic methods, many II–VI systems are now achievable through both aqueous and nonaqueous routes, with water-based approaches becoming increasingly competitive.²¹

Aqueous environments bring additional complexity, as factors such as pH, ionic strength, and solvation strongly affect precursor chemistry and surface passivation.²¹ Nevertheless, these conditions can be harnessed to build heterostructures and even core/shell QDs with performances approaching those of organic counterparts.²⁹ Ongoing work in understanding nucleation, growth, and ligand interactions continues to enhance the quality of the resulting nanomaterials, moving the field closer to rational, application-driven design.

The earliest aqueous synthetic protocols involved simple precipitation reactions between ionic precursors in the presence of stabilizing additives. Early stabilizers included micelles, polymers, and phosphates, and these strategies were quickly extended from CdS to other chalcogenides such as ZnS, PbS, Cd₃P₂, Zn₃P₂, Cd₃As₂, and CdTe.²¹ The introduction of thiol ligands was a decisive advance, as they proved exceptionally effective at stabilizing surfaces and enabled the isolation of ultrasmall CdS clusters with molecular-level precision.^{30–32} The methodology was then broadened to CdSe and CdTe, the latter becoming particularly important due to its narrow bulk band gap (1.43 eV vs 2.45 eV for CdS). As mentioned, initial aqueous CdTe syntheses relied on Cd²⁺ and Na₂Te in the presence of polyphosphate,³³ later improved by adding thioglycerol (TGL)

as a costabilizer.³⁴ A significant step forward was achieved by Rogach and colleagues, who used TGL or mercaptoethanol to obtain size-controlled CdTe QDs, although the PL efficiencies remained low (<3%).³⁵ Gao's group advanced the field by introducing mercapto acids such as thioglycolic acid (TGA) and mercaptopropionic acid (MPA), which produced CdTe with PLQY of 18% and 38%, respectively, and long-term colloidal stability.^{36,37} Optimization of these protocols subsequently raised PLQYs to 50–80% and enabled access to a variety of anisotropic structures, including nanorods, nanowires, nanotubes, ribbons, and nanosheets.^{38–42}

Advances in processing techniques further strengthened aqueous approaches. Hydrothermal conditions enhanced long-term stability, while microwave heating enabled faster, more reproducible syntheses with improved uniformity and photo-physical quality, reducing reaction times from hours to minutes.^{43–46}

As mentioned, the epitaxial growth of shells in water presents challenges that are distinct from core nucleation. Although aqueous synthesis of CdSe/CdS, CdTe/CdS, or multishell CdTe/CdS/ZnS QDs has been demonstrated, achieving high-quality shell growth requires careful ligand and precursor control to avoid undesirable homogeneous nucleation, hydrolysis, or uncontrolled growth, challenges that stem from the aqueous medium itself.^{47,48} In aqueous environments, the higher dielectric constant and weaker ligand binding can further complicate growth, increasing the risk of surface etching or ripening. Yet, strategies such as thiolate-assisted precursor stabilization and the in situ generation of chalcogenide species have enabled successful aqueous core/shell structures.^{49,50} For example, water-soluble CdTe/CdS have been prepared via stabilization using dual capping ligands (adenosine 5'-monophosphate and thiopropionic acid).⁵¹ Optimized precursor design and passivation strategies therefore remain central to advancing high-quality aqueous core/shell Cd-chalcogenides.

What began as simple precipitation methods has thus matured into a versatile synthetic platform. Mercapto acid-based strategies, first optimized for CdTe, have since been extended to a broad spectrum of chalcogenides, including CdX, ZnX, PbX, HgX, AgX, CuInS₂, and AgInS₂.²¹ This body of work has firmly established aqueous synthesis as a mainstream route for high-quality QDs. Nevertheless, batch processes still face challenges

in reproducibility, scalability, and precise control over nucleation and growth.

To address these limitations, continuous flow chemistry has emerged as one of the most effective strategies for nanomaterial synthesis, enabling access to QDs with improved uniformity and tunability.^{52,53} By allowing fine regulation of reaction parameters, flow systems not only enhance reproducibility but also improve safety through controlled handling of hazardous or toxic substances, while supporting more sustainable production.^{54,55}

A notable example was provided by Jensen and co-workers, who engineered a stainless-steel tubular microreactor for the continuous preparation of QDs.⁵⁶ Their design incorporated a gas–liquid flow regime, which suppressed the parabolic residence time distribution typical of laminar flow and thereby produced nanocrystals with a remarkably narrow size distribution.

As said, continuous flow reactors and microfluidic platforms offer multiple intrinsic advantages that directly address many of the drawbacks of batch methods for the production of QDs:

- Improved mixing, heat, and mass transfer: In small channels or coils, diffusion times and convective flows are controlled more precisely. This allows sharper delineation between nucleation and growth phases, reducing the overlap that often broadens size distributions in batch systems.^{57–59}
- Better reproducibility and narrower polydispersity: Because the reactor environment is fixed and decoupled from operator handling, batch-to-batch variation is reduced. Flow synthesis inherently ensures that every particle experiences the same history of temperature, concentration, and flow conditions.^{60–62}
- Scalability and continuous production: Flow systems allow prolonged, uninterrupted operation, enabling high cumulative yields without repeated manual intervention. Scalability to larger scales can be addressed through either numbering up (operating several identical flow reactors in parallel) or scale-out (higher flow rates in larger internal volume flow reactors). This is especially advantageous for industrial translation.^{62–65}
- Modularity, inline monitoring, and automation: Flow reactors easily integrate with real-time analytical probes (UV–vis, fluorescence, Raman, Infrared), feedback loops, and machine-driven optimization. This enables adaptive control and potentially closed-loop optimization of synthesis.^{66,67}
- Safety, confinement, and reduced waste: Because flow reactors handle small reaction volumes continuously, hazards (e.g., hot reagents, evolving gases, toxic precursors) are confined, and heat or pressure excursions are easier to manage. Also, reaction byproducts and unreacted precursors can be handled downstream continuously, reducing waste and simplifying purification workflows. Moreover, microfluidic QDs syntheses often discard the need for inert gas protection or glovebox handling, as sealed channels reduce oxygen sensitivity, improving safety and reducing complexity.^{66,68}

However, translating batch protocols into flow is not straightforward: clogging, fouling, precursor solubility, mixing times, and reactor design all pose obstacles. Moreover, transfer of optimized batch conditions to flow is often nontrivial and may

require reoptimizing of process parameters, solvent systems, and precursor delivery schemes.⁶³

Given these trade-offs, aqueous continuous flow synthesis of CdX QDs presents a compelling but underexplored area. By combining the sustainability and biocompatibility of water with the precision, reproducibility, and scalability of flow systems the field has an opportunity to push QDs production toward truly robust, large-scale, greener manufacturing (Figure 1).

Before delving into the synthesis of CdX QDs, it is important to acknowledge that, despite being among the most widely studied and best-performing QDs to date, the toxicity of Cd-based materials remains a critical concern. Their synthesis typically requires stringent experimental conditions, involves hazardous raw materials, and poses potential environmental risks, all of which may limit their commercial development. As a result, developing more environmentally friendly synthetic methods and identifying nontoxic alternatives have become major priorities in the field.

In this review, we start by comparing classical batch synthesis in organic solvents and in water and continue by summarizing the current state of aqueous continuous flow syntheses of CdX QDs discussing challenges in developing this emerging strategy. Although we chose to focus on Cd-based systems as a mean to improve the overall sustainability of their preparation, it is also worth noting the ongoing efforts aimed at developing safer, Cd-free materials, often using similar flow-based technologies. A brief discussion of aqueous continuous-flow syntheses of Cd-free QDs (including carbon and In-based QDs) is provided at the end of Section 3. Finally, we highlight perspectives for future integration of advanced tools such as machine learning and automated process control, which may accelerate the rational design of high-quality, sustainable QDs.

2. BATCH SYNTHESIS OF CDX QDS: ORGANIC VS AQUEOUS ROUTES

As mentioned in the introduction, among the various types of QDs, CdX QDs remain among the most widely produced, despite concerns regarding their toxicity.³ These QDs are particularly valued for their narrow and tunable emission and excellent optical properties, such as high PLQY and narrow FWHM (full width at half maximum).^{16,69} Batch synthesis can be performed in several ways, with protocols generally divided into solvo-/hydrothermal and hot-injection methods, which differ primarily in the order of reagent addition. In solvo- or hydrothermal syntheses (using organic solvents or water, respectively), the reagents are mixed at room temperature and the temperature is then gradually increased to generate the monomers.^{70,71} A subcategory of these methods is microwave-assisted synthesis, where the reaction mixture is heated using microwaves.^{72,73} By contrast, in hot-injection methods the solvent and/or one thermally stable precursor is first heated to a high temperature, followed by the rapid injection of the remaining precursors.⁷⁴ In Figure 2 an example for the synthesis of CdSe using the hot-injection method is illustrated.

Owing to these thermal requirements, solvothermal methods are generally more suitable for aqueous precursors, whereas organic solvents are typically preferred for hot-injection approaches.

From a chemical standpoint, the synthesis of CdX QDs is, in principle, as simple as reacting a Cd²⁺ precursor with a X²⁻ one (where X = S, Se, or Te) in the presence of ligands in the chosen solvent. In practice, however, solubility is a key parameter to consider, since both precursors and ligands must dissolve in the

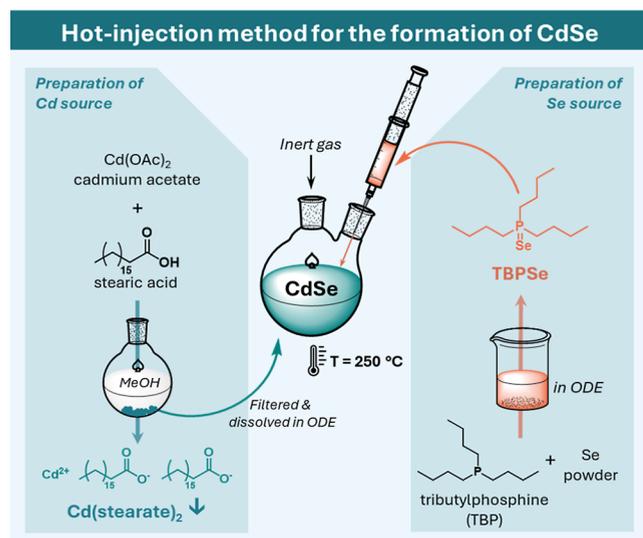


Figure 2. Example of a hot-injection synthetic protocol for the preparation of CdSe in an organic solvent (ODE = octadecene). The experimental protocol is from ref 78.

selected solvent. The resulting nanocrystals are accordingly soluble in either water or organic solvents; however, when a different solubility profile is required for the intended application, postsynthetic surface modification strategies such as ligand exchange can be employed to adjust the dispersibility of the QDs.^{75–77}

The following sections explore recent advances in the batch, bottom-up synthesis of CdX QDs, with emphasis on the differences between protocols in organic solvents (Section 2.1) and aqueous routes (Section 2.2). For each approach, the choice of cadmium and chalcogen precursors, as well as the ligands, is discussed.

2.1. Organic Solvent-Based Synthesis

The pioneering work in QDs synthesis using organic solvents was reported by Bawendi et al. in 1993, who developed the hot-injection protocol that remained the gold standard for QDs preparation until the early 2000s.² Subsequent advances, notably the addition of a shell to the CdX core, significantly enhanced PLQY.⁷⁹

Organic-solvent-based syntheses are typically conducted under harsh conditions, with reaction temperatures reaching up to 350 °C in hot-injection protocols. Consequently, these methods rely on high-boiling-point, weakly polar or nonpolar solvents such as octadecene (ODE), trioctylphosphine oxide (TOPO), fatty acids (e.g., stearic acid, lauric acid, oleic acid (OA), myristic acid), and hexadecylamine (HDA), some of which can act also as ligands. The structures of the main solvents used to prepare CdX, together with the principal ligands, cadmium sources and chalcogen precursors are illustrated in Figure 3.

Among cadmium precursors suitable for organic solvent-based syntheses, the first widely used source was dimethylcadmium ($\text{Cd}(\text{Me})_2$). In the above-mentioned work from Bawendi and co-workers, indeed $\text{Cd}(\text{Me})_2$ was used as the precursors to obtain CdS, CdTe and CdS nanocrystals as small as 1.2 nm.²

However, $\text{Cd}(\text{Me})_2$ has several drawbacks, such as its extreme toxicity, pyrophoric nature, and tendency to decompose in the presence of TOPO at high temperature to form insoluble

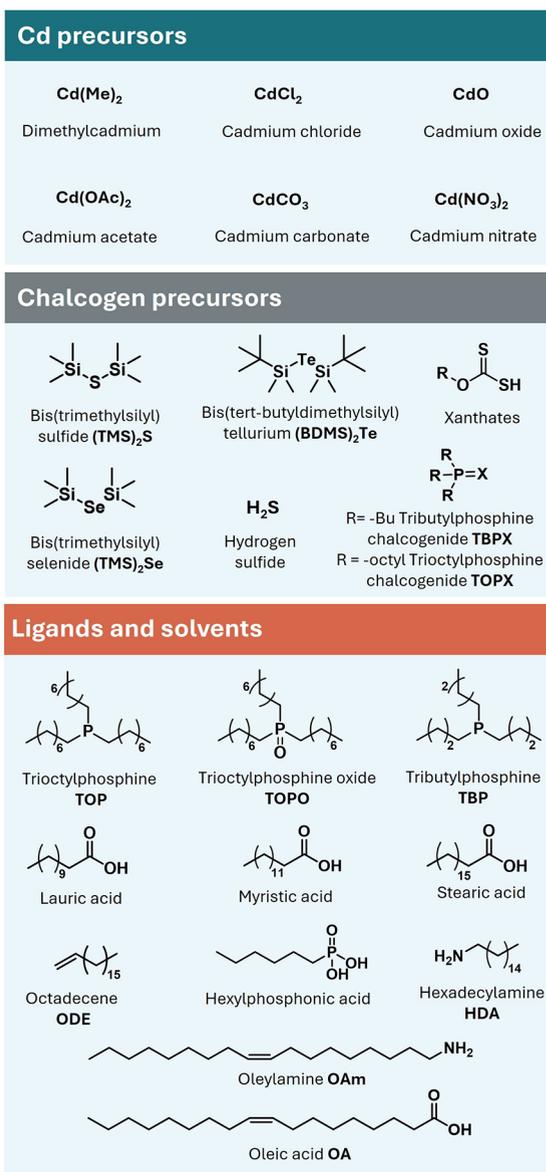


Figure 3. Structures of typical Cd precursors, chalcogen precursors (X = S, Se, Te), ligands and solvents used for the synthesis of CdX QDs in organic solvents.

metallic cadmium. For these reasons numerous efforts have been done to find safer alternatives.⁸⁰

Peng and co-workers extensively investigated alternative and greener cadmium precursors for the colloidal synthesis of CdX QDs.^{81–83} A typical example is their work of 2001 where they explored safer, cheaper, and more accessible synthetic routes to CdSe while maintaining high optical quality.⁸² Their goal was to replace the hazardous and expensive reagents used in conventional organometallic syntheses, with more benign and practical alternatives.

The authors investigated more than ten different solvent and ligand systems, using combinations of fatty acids, amines, phosphine oxides (both technical-grade and pure TOPO), and phosphonic acids, often mixed in varying ratios. As cadmium sources, they tested cadmium acetate ($\text{Cd}(\text{OAc})_2$), cadmium oxide (CdO), and cadmium carbonate (CdCO_3), while selenium was supplied as trioctylphosphine selenide (TOPSe), prepared by dissolving elemental selenium in trioctylphosphine.

Reactions were conducted under inert atmosphere using hot-injection procedures at temperatures between 250 and 360 °C, followed by controlled growth to tune the nanocrystal size. The resulting CdSe exhibited narrow size distributions and tunable diameters (1.5–25 nm). Importantly, Cd(OAc)₂ was identified among the most versatile precursors, and that fatty acids served as effective ligands and solvents for promoting uniform growth. In contrast, precursors containing strong-acid anions or thiolates were found to degrade optical quality, likely due to defect formation.

Other works then described the preparation also of CdS, CdSe and CdTe from CdO, Cd(OAc)₂, and CdCO₃.^{80–82,84} Currently, common cadmium precursors include CdCl₂ and Cd(NO₃)₂ as well as the already mentioned CdO, Cd(OAc)₂, and CdCO₃.^{78,82,85–89} Although these salts and oxides are considerably safer and easier to handle than Cd(Me)₂, they are also less reactive, which complicates burst nucleation and reduces the reproducibility of forming small QDs. In contrast to Cd(Me)₂, which rapidly releases reactive Cd species due to weak Cd–C bonds, cadmium salts and oxides are more stable and form stronger interactions with coordinating ligands or anions. This stabilizing effect slows precursor decomposition, limiting the instantaneous availability of free Cd²⁺ and resulting in slower nucleation kinetics and lower reproducibility. In general, the strength of the Cd–ligand interaction plays a decisive role in reaction kinetics and particle size distribution: stronger bonds favor gradual, diffusion-controlled growth and monodispersity, whereas weaker or more labile bonds lead to faster, less controlled growth and broader size distributions.⁹⁰

Chalcogen precursors have been introduced through several strategies to provide X^{2–} species in organic solvents. Early approaches employed silylated chalcogenides such as (TMS)₂S, (TMS)₂Se, and (BDMS)₂Te.² However, the high reactivity and poor controllability of bis(trimethylsilyl)-based compounds led to a shift toward phosphine-mediated methods, where elemental chalcogens are reduced in situ by organo-soluble phosphines such as trioctylphosphine (TOP) or tributylphosphine (TBP).^{82,84,87,89,91–99} For instance, CdTe QDs capped with stearate groups have been prepared from cadmium stearate and TOPTe in *N*-oleylmorpholine at 280 °C.¹⁰⁰ The obtained nanocrystals showed good stability, high crystallinity, narrow size distribution, and clear size-dependent optical properties. In a work by Cao et al., the use of TBPSe or Se powder as chalcogen precursors produced CdSe QDs of spherical or tetrahedral shape, respectively.⁸⁹

Elemental sulfur or selenium can also be directly used as chalcogen sources in organic solvents.^{84,88,101,102} To become reactive, S and Se must be thermally activated by heating in nonreductive solvents such as ODE above their melting points (115 °C for sulfur, 221 °C for selenium), where they undergo dismutation or chain fragmentation. The high melting point of Te (450 °C), however, makes elemental Te impractical for QDs synthesis. A notable phosphine-free route for CdSe nanocrystals that relies on elemental selenium dispersed in ODE was reported by Peng et al.¹⁰³ In this method, finely powdered Se is suspended in ODE, which upon heating provides a highly reactive yet “green” precursor. This approach avoids toxic TOPSe while maintaining excellent control over nucleation and growth. The Se-ODE precursor owes its reactivity to the thermal fragmentation of selenium rings and chains into short-chain species stabilized in the solvent. Spectroscopic studies confirmed this transformation, which makes Se-ODE an effective selenium source for CdSe QDs.¹⁰⁴

Gaseous precursors such as H₂S are also sometimes used, particularly for shelling CdSe or CdTe with CdS or ZnS, though they are less suitable for core synthesis because of slow mass transfer during nucleation.^{99,105} Direct H₂S gas is more often employed in aqueous or biomimetic syntheses rather than in hot-injection, organic-solvent protocols (see Section 2.2). Reports of CdX cores prepared directly with gaseous H₂S in organic solvents are rare due to the hazardous nature of H₂S and the difficulties of handling it at high temperature.

Another option, mainly explored in solvothermal syntheses, is the use of cadmium–chalcogen complexes such as cadmium xanthates.^{106,107} For example, Efrima et al. reported the reaction of cadmium salts with alkyl xanthates to yield stable cadmium–xanthate complexes that incorporate both Cd and S moieties. Upon thermal decomposition in alkylamine solvents (e.g., oleylamine), these precursors release cadmium and sulfide in a controlled fashion, enabling the growth of high-quality, monodisperse CdS QDs. This single-source strategy eliminates the need for separate Cd and S reagents, simplifies the reaction scheme, and offers size control through the choice of xanthate ligand, solvent, and temperature.¹⁰⁷

Ligands play a crucial role in stabilizing CdX nanocrystals, requiring functional groups capable of binding to the nanoparticle surface along with nonpolar moieties to ensure solubility in organic media. Amphiphilic molecules are typically used (e.g., fatty acids, hexylphosphonic acid, HDA).^{85,86,97,103,105,106,108} In practice, QDs surfaces are passivated by a mixture of species, including not only intentionally added ligands but also precursor byproducts. Early generation precursors such as Cd(Me)₂ or silylated chalcogenides tend to produce volatile byproducts, while later-generation systems leave behind nonvolatile cadmium carboxylates or phosphonates that remain coordinated at the surface. Phosphine-based chalcogen sources can oxidize after delivering the chalcogen atom to generate L-type ligands, whose binding efficiency depends on steric factors such as the Tolman cone angle.¹⁰⁹ The final ligand shell composition has profound effects on both the photoluminescence and crystalline structure of the nanocrystals.¹¹⁰

Despite its long-established foundations, the organic-phase synthesis of Cd-chalcogenide QDs remains an active and rapidly evolving research area, with ongoing advances in precursor chemistry, ligand design, and reaction engineering continually refining material quality and synthetic control.^{111–116} In Table S1, a summary of the organic solvent-based methods for the synthesis of CdX QDs is reported. The type of metal and chalcogen source, ligands and solvents are stated together with maximum reaction temperature, size of the dots and PLQY.

2.2. Water-Based Synthesis

The aqueous synthesis of CdX QDs dates back to the early 1980s, when CdS precipitation was first achieved on colloidal silica, which acted as both stabilizer and support.¹¹⁷ Although these initial attempts did not produce nanocrystals small enough to be associated with quantum confinement, subsequent work relying on water-soluble copolymers such as styrene/maleic acid and sodium polyphosphate enabled the observation of pronounced blue shifts relative to bulk CdS.^{30,118} In the 1990s, the introduction of diverse precursors and stabilizers expanded the scope and improved size distribution control, paving the way for more advanced aqueous protocols.

A distinctive feature of aqueous CdX QD synthesis, compared to organic routes, is the central role of pH control. Most aqueous strategies rely on thiol-containing ligands (e.g., TGA, MPA,

TGL) to simultaneously stabilize Cd^{2+} in solution and passivate the nanocrystal surface.^{119–121} The degree of thiol deprotonation, and thus the strength of Cd–thiol coordination, is highly pH-dependent, making alkaline adjustment a critical parameter. The Cd–thiol complexes used as precursors are generally stable and reactive only in a moderately alkaline environment, and most protocols therefore adjust the solution to $\text{pH} \approx 8–11$ using NaOH. By contrast, when buffer systems are employed instead of NaOH, the restricted buffering range and competitive ligand interactions often result in reduced PLQY and broadened optical features.^{122,123} Importantly, the selected pH must strike a balance between ensuring deprotonation of stabilizing ligands for efficient surface binding, enhancing precursor reactivity, and limiting side reactions.³⁰

In Figure 4, the structures of typical ligands, cadmium and chalcogen precursors used for the aqueous preparation of CdX QDs are reported.

The availability and the preparation of water-soluble chalcogen precursors represent the most challenging aspects

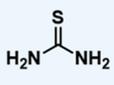
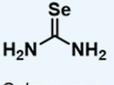
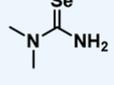
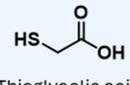
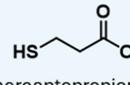
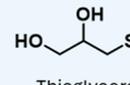
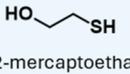
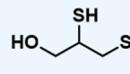
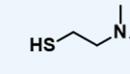
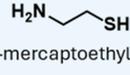
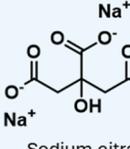
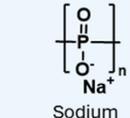
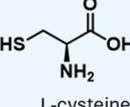
Cd precursors		
$\text{Cd}(\text{ClO}_4)_2$ Cadmium perchlorate	$\text{Cd}(\text{OAc})_2$ Cadmium acetate	CdCl_2 Cadmium chloride
Chalcogen precursors (details in Figure 6)		
H_2X Hydrogen chalcogenide	Na_2X Sodium chalcogenide	NaHX Sodium hydrogen chalcogenide
 Thiourea TU	 Selenourea SeU	 N,N-dimethylselenourea
Ligands		
 Thioglycolic acid TGA	 3-mercaptopropionic acid MPA	 Thioglycerol TGL
 2-mercaptoethanol	 2,3-dimercapto-1-propanol	 2-(dimethylamino)ethanethiol
 2-mercaptoethylamine	 Sodium citrate Cit	 Sodium polyphosphate
 L-cysteine		

Figure 4. Structures of typical Cd precursors, chalcogen precursors (X = S, Se, Te) and ligands used for the aqueous synthesis of CdX QDs.

of aqueous synthesis. Sulfur sources are commercially available in diverse forms, including Na_2S , which provides highly reactive sulfide ions, and thiourea (TU), which offers lower reactivity and thus greater control over crystal growth.¹²⁴ Thiol/thiolate ligands, commonly used to stabilize cadmium precursors, can under thermal or annealing conditions partially decompose or convert to polysulfide/ H_2S species.¹²⁵ Those sulfur-containing decomposition products may be incorporated into the particle, promoting local sulfide formation, improved crystallinity, and surface passivation; examples include aqueous CdTe/CdS formation via thiol decomposition and reports of thiolate-driven CdS shelling in hot syntheses.^{126–128} In addition to thiol-mediated sulfur, several studies have demonstrated the use of H_2S as a direct sulfur source for CdS core formation. For instance, Ozdemir et al. report a bioinspired chemical cycle that generates H_2S in situ, which reacts with Cd^{2+} in aqueous solution to nucleate and grow size-tunable CdS QD cores (Figure 5).¹²⁹ Similarly, bacterial production of volatile sulfur

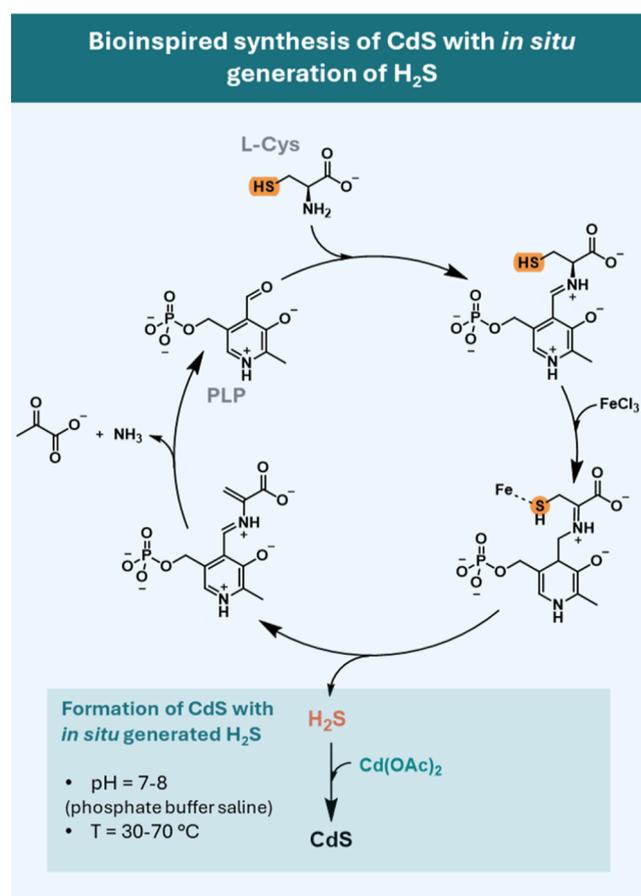


Figure 5. In situ generation of H_2S using pyridoxal 5'-phosphate (PLP) and L-cysteine (L-Cys) for the formation of CdS in water. Adapted from ref 129.

compounds, notably H_2S , supplies S^{2-} for extracellular and intracellular formation of CdS nanocrystal cores.¹³⁰ Musić and co-workers described a classical method in which H_2S gas is bubbled into an aqueous $\text{Cd}(\text{OAc})_2$ solution at room temperature, yielding nanosized CdS core particles.¹³¹

Commercial selenium precursors for aqueous CdSe synthesis are more limited than sulfur sources and are most commonly selenourea (SeU) or *N,N*-dimethylselenourea, both of which are water-soluble and thermally/chemically labile to produce Se^{2-}

under alkaline or heated conditions.^{132–135} For example, Pan et al. used SeU in a two-phase (toluene/water) autoclave route to prepare OA-capped CdSe cores, reporting PLQYs up to 35%.¹³⁶ SeU-type precursors are relatively slow to decompose, which can limit rapid nucleation compared to reactive organic-phase precursors such as TOPSe. In addition to organoselenium sources, a significant number of aqueous CdSe syntheses rely on inorganic selenium precursors. Sodium selenide (Na_2Se) and sodium hydrogen selenide (NaHSe) can be generated in situ by reducing elemental Se with NaBH_4 under alkaline conditions, providing a highly reactive Se^{2-} source (Figure 6).^{136–138}

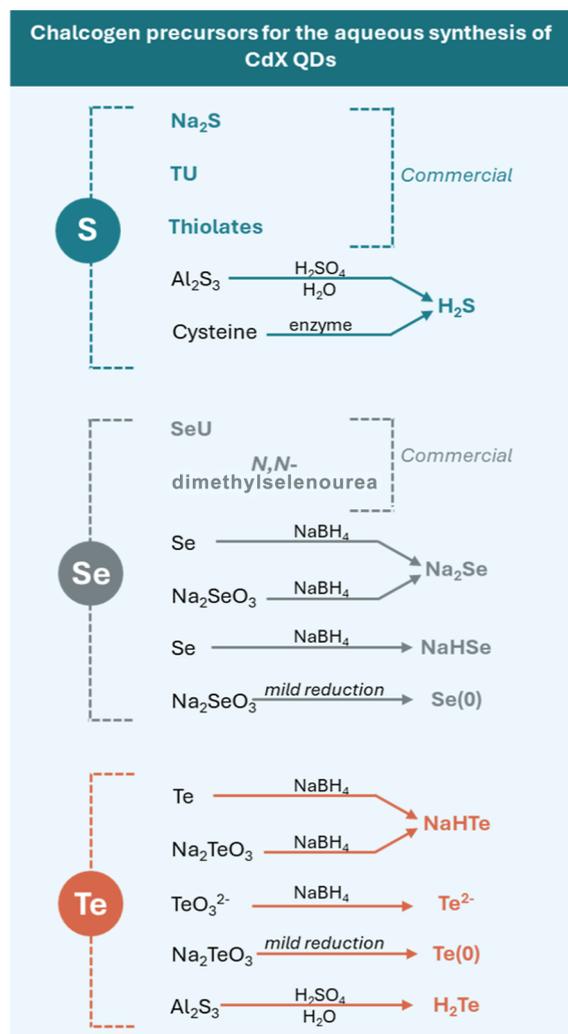


Figure 6. Overview of the main chalcogen precursors for aqueous synthesis of CdX QDs. Both commercial and in situ generated precursors are reported.

Sodium selenosulfate (Na_2SeSO_3), prepared by dissolving Se in sodium sulfite solution, has also been widely used as a safer and more controllable Se^{2-} donor.^{136,139} Se(IV) salts (selenite/selenate) can also be reduced to Se^0 or Se^{2-} and be exploited in aqueous syntheses and biogenic routes.^{140–142} Mild reducing agents, like ascorbic acid, can also be used in substitution to NaBH_4 , to produce reactive Se species.¹⁴² These inorganic routes avoid organic phosphines, but typically require strict pH control and stabilizing thiols to suppress uncontrolled precipitation and to obtain luminescent, monodisperse CdSe nanocrystals.

Tellurium precursors are not commercially available, so CdTe synthesis requires in situ generation of reactive Te species (Figure 6). Typically, Te^{2-} is produced by reduction of Te^0 or Te(IV) salts, such as Na_2TeO_3 or K_2TeO_3 , with NaBH_4 under alkaline conditions to produce sodium hydrogen telluride (NaHTe), a reactive telluride ion source.¹⁴³ This method has been employed in various studies to synthesize CdTe.^{144,145} For instance, Zuo et al. prepared NaHTe from Te powder and NaBH_4 and used it as a precursor to prepare water-soluble multicolored fluorescent CdTe QDs, achieving high PLQY.¹⁴⁶ Recently ammonia has also been reported as an effective reducing agent to obtain CdTe using Na_2TeO_3 as the chalcogen precursor.^{147,148}

Direct use of H_2Te gas is rare due to its extreme toxicity and poor solubility; when employed, it is typically generated in situ or bubbled through basic cadmium solutions to form soluble telluride salts.^{149–151} These strategies allow controlled Te delivery in aqueous media, enabling nucleation and growth of CdTe while avoiding unstable, preisolated Te^{2-} compounds. Figure 6 reports the most common commercial chalcogen precursors together with the synthetic strategies to prepare them in situ.

A general consideration in selecting chalcogen sources is the balance between precursor reactivity and reaction temperature: highly reactive species may be oxidized by water at elevated temperatures, becoming ineffective for CdX formation (Figure 7).^{47,62,152}

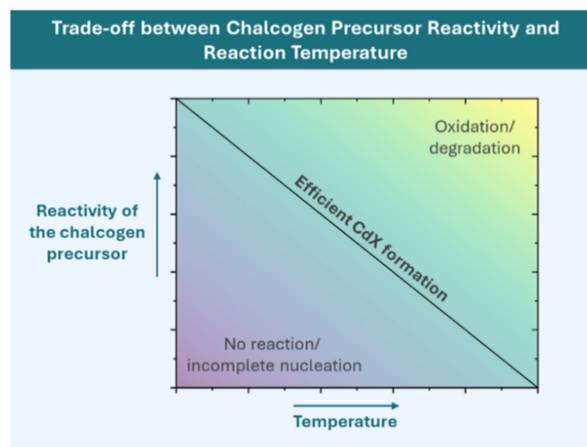


Figure 7. Trade-off between chalcogen precursor reactivity and reaction temperature in aqueous CdX QD synthesis. Highly reactive precursors require lower temperatures to prevent oxidation, while less reactive ones need higher temperatures for efficient nucleation. The optimal region represents balanced conditions for controlled CdX formation.

As mentioned earlier, the synthesis of CdX QDs in aqueous media typically requires basic conditions. Under these circumstances, insoluble $\text{Cd}(\text{OH})_2$ readily precipitates, and ligands play a crucial role in mitigating this challenge. To stabilize the reaction, strongly binding, water-soluble ligands are needed, with anionic X-type ligands (e.g., thiolates, phosphates, or carboxylates) being the most commonly employed.^{43,153,154} The binding strength of surface ligands, indeed, strongly influence nucleation and growth kinetics of QDs (Figure 8).^{21,39,155,156}

In a notable study, Weller and co-workers systematically investigated thiol-capped CdTe QDs and demonstrated that each ligand exerts a distinct influence on PLQY, surface charge,

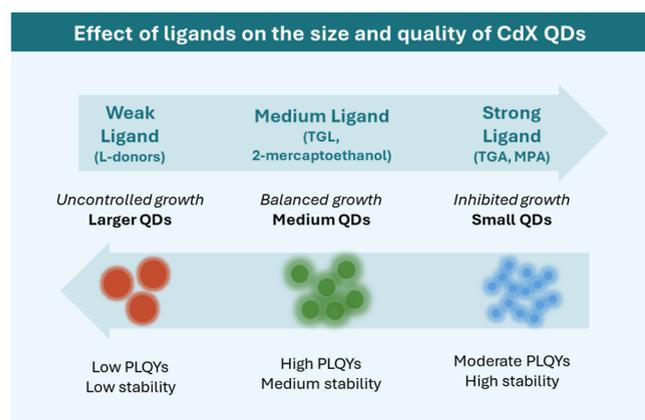


Figure 8. Correlation between the choice of the ligands, the size and the quality of the obtained CdX QDs.

and colloidal stability.¹⁵¹ Common examples of such ligands include TGA,¹⁵⁷ TGL,¹⁵⁸ MPA,^{159,160} and 2-mercaptoethanol,¹⁶¹ as well as hydrophilic polymers such as sodium polyphosphate or poly(vinyl alcohol), which provide additional steric stabilization.^{162,163} Importantly, the ligands used during aqueous synthesis often remain as the final biocompatible surface ligands, eliminating the need for postsynthetic ligand exchange in biorelated applications.¹⁶⁴

Neutral donors (L-type) such as alcohols, amines, and phosphines can also coordinate to Cd²⁺; however, they provide weaker stabilization and are generally insufficient to prevent Cd(OH)₂ precipitation.¹⁶⁴ Recently also biomass derived ligands/stabilizers, such as castor oil, have been proved efficient for the preparation of CdTe QDs.¹⁶⁵ Finally, cadmium counteranions (e.g., acetate, chloride) themselves act as surface ligands and influence both nucleation and growth kinetics.

Generally, the aqueous synthesis of CdX involves:

- 1) preparing a Cd-ligand solution at proper pH;
- 2) introducing the chalcogen source (Na₂X, NaHX, or H₂X);

- 3) aging the reaction mixture under reflux at ~100 °C (lower temperatures are possible with highly reactive precursors, higher temperatures have also been employed using autoclaves).

Ligands interact with metal ions both before and after QDs formation, making their affinity crucial for size control. Strong ligands suppress growth, while weak ligands lead to uncontrolled growth (Figure 8).¹⁵⁰

Although early aqueous CdX syntheses generally produce smaller core sizes than organic methods, which in turn limits PLQY, optimized aqueous protocols (careful ligand choice, alloying, core/shell growth or postsynthetic passivation) have raised ensemble PLQYs up to ~50–80%.^{38,40–42} Aqueous conditions, indeed, impose extra constraints (hydrolysis, Cd(OH)₂ formation, stronger surface trap formation in polar media) and commonly rely on short, anionic ligands (thiols, phosphonates, carboxylates) that are essential for colloidal stability but can be less effective at eliminating surface traps than the careful ligand engineering possible in organic syntheses. These factors make it harder to reach organic-phase near-unity PLQYs (~90–98%) in strictly aqueous syntheses.^{166,167}

However, in one recent example, Wang, Shen and co-workers developed a one-step aqueous synthesis to obtain CdTe/CdSe QDs with PLQY up to 80.5%.³⁸ In their methodology, the simultaneous addition of Te and Se sources passivates the defects of CdTe while suppressing the overgrowth of CdSe shell, obtaining core–shell structure with small size and high PLQY.

Another work reported the influence of the nature of thiol-type capping ligands on the optical properties of CdTe synthesized in aqueous media.⁴¹ The comparison of MPA, TGA, TGL, and glutathione revealed that the PLQY, along with other properties, strongly depend on the type of surface ligand. The obtained PLQY ranged from 38% to 73% depending on the chosen thiol and the reaction time.

In Table S2 an overview of the aqueous methods for the synthesis of CdX QDs is reported. The type of ligand, metal and chalcogen source are shown together with the pH, maximum reaction temperature, size of the dots and PLQY.

Table 1. Comparison of Batch Aqueous and Organic Solvent-Based Synthesis of CdX QDs

aspect	aqueous synthesis	organic solvent synthesis
solvent	water at controlled pH (7–12)	high-boiling organic solvents
Cd precursors	readily available hydrated salts. Risk of Cd(OH) ₂ precipitation; mitigated by thiolate complexation	organometallic or pretreated cadmium complexes. Often require custom preparation for compatibility
chalcogen precursors	S: Na ₂ S, thiourea, thiolates, H ₂ S (commercial) Se: Selenoureas (commercial) or in situ generated Se ²⁻ sources Te: none available, require in situ generation	-TOPX or TBPX; - elemental S or Se; -H ₂ S; -silylated chalcogenides; -Cd-chalcogen complexes
Ligands	common examples: TGA, MPA, mercaptoethanol, mercaptoethylamine, hydrophilic polymers (sodium polyphosphate, PVA). Cd counteranions also act like ligands	hydrophobic, longchain ligands: phosphines, thiols, amines, carboxylates
reaction conditions	- normally reflux at ~100 °C; - lower T with highly reactive precursors; - higher T using autoclaves	hot-injection at high temperature (200–350 °C)
particle size	typically small cores due to slow precursor reactivity	larger, more tunable sizes with better monodispersity
PLQY	generally <80%. Improvements with core–shell	can reach >90% with optimized core–shell structures
Pros	- water is safe, cheap, biocompatible; - directly employs commercial Cd salts; - suitable for biomedical applications	- high-quality QDS - better control over size, shape, and PLQY; - widely used for display/lighting applications
cons	- lower PLQY, smaller sizes, slower growth kinetics - requires pH and precursor solubility control	- toxic and sensitive reagents; - less biocompatible; - postsynthetic ligand exchange for water solubility

Aqueous Continuous Flow Conditions				Organic Continuous Flow Conditions				
Ref	Cd	Chalcogen	Ligand		Cd	Chalcogen	Ligands/Solvents	Ref
180,181	CdCl ₂	Na ₂ S	MPA	CdS	CdCl ₂	S	OAm	89,176
179,188	Cd(NO ₃) ₂	Na ₂ S	Sodium polyphosphate		CdO	ODE-S	OA	53
55,187	Cd(NO ₃) ₂	Na ₂ S	MPA					
190	Cd(NO ₃) ₂	Na ₂ S	---					
57	Cd(OAc) ₂	TCEP=S	MPA	CdSe	CdO	TOPSe	ODE/OA/ODE+OA	53,168 171,175
191	Cd(NO ₃) ₂	NaHSe	---		CdO	TOPSe	OA+OAm+lauric acid	167
57	Cd(OAc) ₂	TCEP=Se	MPA		Cd(OAc) ₂	TOPSe	OA+ODE+dodecylamine	169
183	Cd(OAc) ₂	NaHSe	MPA		Cd(OAc) ₂	TOPSe	TOPO+stearic acid	170
182	CdCl ₂	NaHSe	L-cysteine		CdMe ₂	TBPSe	TOPO+TBP	174
					Cd-pentanedionate	TOPSe	OA+OAm+squalane	172
185	Cd(NO ₃) ₂	NaHTe	MPA	CdTe	CdO	SeO ₂	OA+ODE	52
57	Cd(OAc) ₂	TCEP=Te	MPA		CdO	TOPTe	OA+OAm+lauric acid	167
183	Cd(OAc) ₂	NaHTe	MPA		CdO	TOPTe	OA+ODE	168
186	CdCl ₂	NaHTe	Glutathione					

Figure 9. Literature protocols to access CdX with flow processes. For each chalcogen (S, Se, Te), the precursors and ligands are summarized according to the reaction medium (organic/aqueous).

While aqueous synthesis of CdX QDs still lags behind organic routes in terms of PLQY and overall optical performance, it offers clear advantages in other aspects. The use of water as solvent facilitates scalability, reduces costs, and eliminates the need for high-boiling, often hazardous organic media. Moreover, aqueous protocols align better with current sustainability goals and regulatory frameworks, particularly within the EU, where directives increasingly emphasize hazard reduction, safer chemical alternatives, and waste minimization.⁵ These aspects make aqueous synthesis a promising pathway for greener and more compliant large-scale QDs production, even if further optimization is required to match the photophysical properties achieved in organic systems. A comparison of the preparation of CdX QDs in organic solvents and in water is reported in Table 1.

Building on these considerations, an important next step is to assess not only the choice of solvent, but also the synthetic strategy itself. In particular, the comparison between batch and continuous-flow approaches in aqueous media provides critical insight into how scalability and reproducibility can be further advanced. These aspects are discussed in the following section.

3. AQUEOUS CONTINUOUS FLOW SYNTHESIS OF CDX QDS

The continuous-flow synthesis of CdX QDs has attracted growing attention to improve synthetic control and achieve scalable production. Compared with conventional batch methods, flow reactors offer superior reproducibility through well-defined mixing, precise temperature management, and tunable residence times, which allow more uniform nucleation and growth.^{52,168} This typically results in narrower size distributions, higher reproducibility, and the possibility of in-line monitoring, making flow chemistry an attractive alternative for QDs production.^{3,55,68,169–173} Early studies focused mainly on nonaqueous syntheses in high-boiling coordinating solvents, which provide good control but limit biocompatibility and scalability in green contexts.

Among nanosized semiconductors, type II–VI QDs, and more specifically CdX QDs, have been extensively studied.¹⁷⁴ Their hot-injection synthesis is particularly amenable to translation into flow conditions, as rapid thermal exchange enables sharper temperature gradients than those achievable with batch methods. Furthermore, the synthesis of CdX QDs involves the use of harmful reagents: microfluidics is employed to reduce the risks by limiting the amount of reagent reacting at a given moment. Additionally, the reagents are usually pumped from a closed container, preventing the operator from exposure.

CdSe QDs have been among the first to be synthesized using microfluidics demonstrating the advantages brought by the technique such as the preparation of monodisperse nanocrystals with narrow emission spectra and higher PLQY.^{68,175} In a recent paper CdS QDs were continuously synthesized using an impinging jet mixer: the setup was able to deliver monodisperse 2.7 nm nanocrystals at a production rate of more than 5 g/min.⁶⁴

Various types of chalcogen sources have been transposed into microfluidics, such as TOPX,^{2,58,176–182} TBPX,^{183,184} or those chelated by the solvent itself (such as octadecene⁵⁸). Similarly, the cadmium precursors followed the same trend as observed in batch: early syntheses were carried out using Cd(Me)₂.¹⁸⁴ Subsequently, the precursors evolved toward less toxic compounds, prepared ex situ (e.g., Cd(OAm)₂ from CdCl₂ and OAm or Cd(OA)₂ from CdO and OA).^{57,185,186}

These organic-phase systems established the general principle that flow chemistry can deliver reproducible, scalable, and tailorable nanocrystals. However, the reliance on toxic and pyrophoric reagents as well as nonbiocompatible solvents has motivated the development of greener, aqueous alternatives.

Aqueous synthesis offers several advantages, such as biocompatibility, no additional ligand exchange steps, and lower reaction temperatures. However, aqueous protocols often lead to broader size distribution and lower quantum yield.^{187,188} Moreover, the relatively limited number of reports using aqueous protocols suggests that they are more cumbersome compared to their organic counterparts.

One of the challenges in synthesizing QDs in water lies in the preparation of a suitable reduced chalcogen source, which is essential for initiating the transfer to the cadmium precursor. Most reported protocols involve an *ex situ* preparation of the chalcogenide source in batch, which could potentially lead to its decomposition. These protocols typically rely on the reduction of native chalcogens with ionic reductants such as NaBH_4 to give air-sensitive ionic chalcogenides such as Na_2S ,^{189–191} NaHSe ,^{192,193} or NaHTe .^{193,194} Their decomposition prevents a seamless scale-up that continuous flow aims to offer.

Figure 9 report examples of the various precursors used in the aqueous and organic protocols to obtain CdX in continuous flow. Reports on the aqueous preparation of QDs in flow often lack photoluminescence data, suggesting that the resulting optical properties are poorer or, at best, comparable to those obtained in batch.¹⁷¹ Nevertheless, the advantages offered by water continue to push researchers to develop suitable continuous-flow aqueous protocols for preparing CdX. Furthermore, the introduction of a BPR downstream facilitates high-pressure syntheses, including hydrothermal conditions, within microfluidic platforms.

Two main technological approaches for the continuous aqueous preparation of CdX can be distinguished: droplet-based microfluidics and homogeneous micro/mesofluidic reactors, with more recent extensions into hydrodynamic cavitation (HC) systems.

Several studies have demonstrated the use of droplets as confined microreactors to achieve controlled and reproducible synthesis. Yan and co-workers reported a continuous chemical aerosol flow method for the fabrication of CdTe/CdS/ZnS core–shell–shell nanocrystals.¹⁹⁵ In this integrated process, an ultrasonic nebulizer coupled to a quartz tube furnace (200–300 °C, under nitrogen flow) generated CdTe/CdS intermediates, which were subsequently overcoated with ZnS in a secondary low-temperature (~80 °C) setup. The resulting particles displayed narrow photoluminescence features tunable between 525 and 567 nm and a PLQY exceeding 45%, with production rates approaching 0.1 g h^{-1} .

Some years later, another study further demonstrated the versatility of droplet reactors, using picoliter droplets as individual reaction vessels.¹⁹⁶ To form the droplets, mineral oil was used as the continuous phase and an aqueous solution of the Cd and Te precursors. By fine-tuning local temperatures by as little as 1–2 °C, they were able to produce multicolor, water-soluble CdTe QDs within approximately 1 min, highlighting the ultrafast and precise control offered by droplet microfluidics. In addition to ultrafast color-varying syntheses, droplet-based microfluidic platform capable of multistep nanoparticle synthesis on millisecond time scales has also been reported.¹⁹⁰ Aqueous reagents are introduced as plugs in an immiscible carrier fluid, mixed via winding microchannels, and then sequentially merged with further reactive streams within the same droplet. They used this scheme to generate colloidal CdS and CdS/CdSe core–shell nanoparticles, maintaining the reaction confined to droplets to avoid aggregation on channel walls. The fine temporal control and reagent merging provide tighter control over nucleation and shell growth, improving uniformity and reproducibility in QDs size and structure. This concept was later simplified using a water–oil digital droplet reactor (Figure 10).⁶⁰ This approach, relying on aqueous precursors such as cadmium nitrate and MPA, enabled CdS synthesis under ambient conditions. Enhanced mixing in a helical droplet mixer produced highly uniform nanoparticles

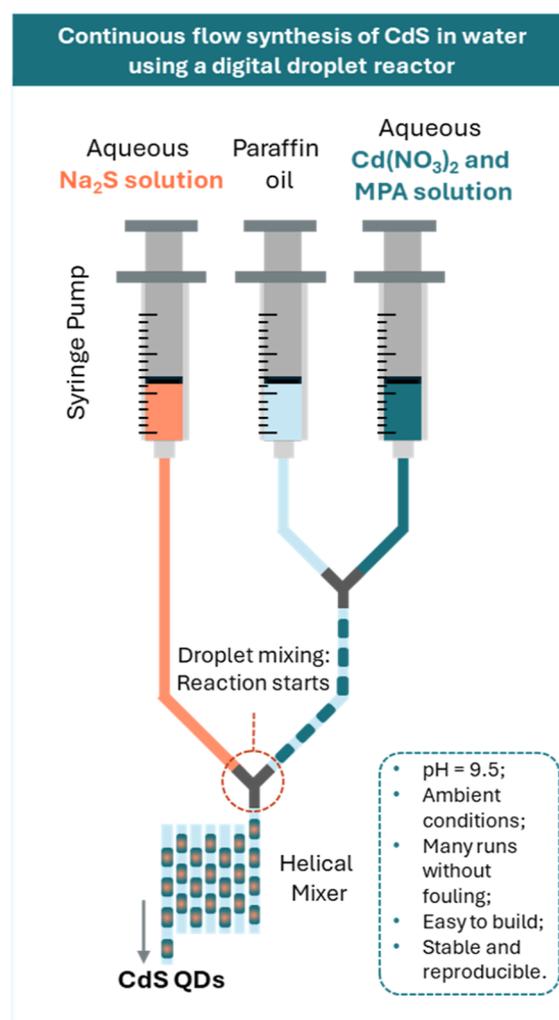


Figure 10. Digital water–oil droplet-based continuous reactor for the aqueous production of CdS QDs. Adapted from ref 60.

($3.05 \text{ nm} \pm 6.3\%$), confirming the reproducibility and mild reaction conditions achievable with droplet microfluidics.

In parallel, several studies have investigated continuous homogeneous micro- and mesofluidic reactors for aqueous CdX QDs. In a recent work from Monbaliu and co-workers, tris(2-carboxyethyl)phosphine chalcogenides (TCEP = X) have been introduced as innovative chalcogenide transfer agents for the continuous preparation of CdS, CdSe, and CdTe QDs in water (Figure 11).⁶² The microfluidic process was then implemented in a commercial mesofluidic reactor capable of flow rates up to 80 mL min^{-1} , with real-time monitoring by Raman and in-line ^{31}P NMR spectroscopy and optimization via design of experiments. This work represents a notable step toward scalable, biocompatible production under continuous flow.

In a 2022 study, a microjet reactor was also used to prepare $\text{Cd}_{1-x}\text{Zn}_x\text{S}$ and CdS/ZnS core/shell QDs in water in a continuous manner.¹⁹⁷ Due to the short mixing times compared to nucleation in the microjet reactor, supersaturation is reached everywhere at once and all nuclei were formed synchronously from homogeneous solution, resulting in a narrow particle size distribution. The resulting QDs were stable, monodisperse and crystalline.

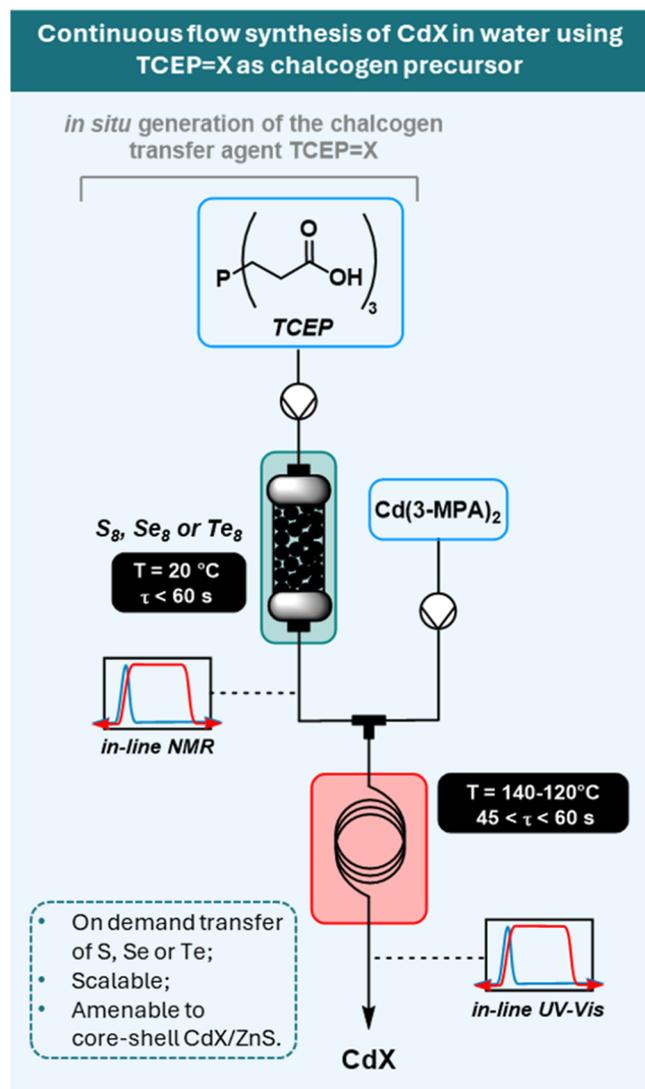


Figure 11. Concatenated continuous flow setup for the production of tris(2-carboxyethyl)phosphine chalcogenides (TCEP = X) and its use as a chalcogen precursor to prepare CdX in water. X = S, Se, Te. Adapted from ref 62.

The preparation of CdX, in particular CdS, has been explored also with oscillatory flow mixing in serpentine microchannels as a mean to overcome clogging in conventional microreactors.¹⁹⁸ Using oscillatory forward–reverse pumping, enhanced advection and mixing in larger channels was achieved, validated by computational fluid dynamics and by experiments. QDs with a smaller and more uniform size in respect to those obtained by laminar flow alone were observed, underscoring the benefits of oscillatory flow for reproducibility and size control.

Another type of microreactor was recently used by Bodas et al. for the synthesis of CdTe QDs in water.¹⁹⁹ The nanocrystals were produced in a custom polydimethylsiloxane microreactor, using mathematically derived process parameters to optimize conditions with >95% accuracy. The resulting QDs exhibited narrow emission (540–550 nm, FWHM \approx 40 nm), high PLQY (\sim 61.5%), and good photostability.

Earlier contributions reported the use of a continuous flow micromixer to prepare aqueous CdS¹⁸⁹ and educational modules have also demonstrated the accessibility of these

technologies, bringing microreactor-based aqueous CdX synthesis into teaching laboratories.¹⁹³

More recently, HC has emerged as a powerful continuous method for aqueous nanomaterial production. In this approach, rapid pressure drops in Venturi-type reactors generate microbubbles that collapse to release localized energy, driving nucleation and growth. Qi and co-workers reported the preparation of CdS QDs using an HC reactor optimized at 12 h cycle time, 3.0 bar inlet pressure, and a 2.0 mm throat.²⁰⁰ The resulting nanocrystals were blue-emitting with narrow size distribution, large Stokes shift, and high PLQY. In 2025 this method was extended to CdSe QDs, achieving highly stable particles as small as 1.83 nm, with an 87 nm Stokes shift and long fluorescence lifetime (1255 ns) (Figure 12).²⁰¹ These studies underline the scalability, low energy demand, and reproducibility of HC-based systems for continuous aqueous QDs production.

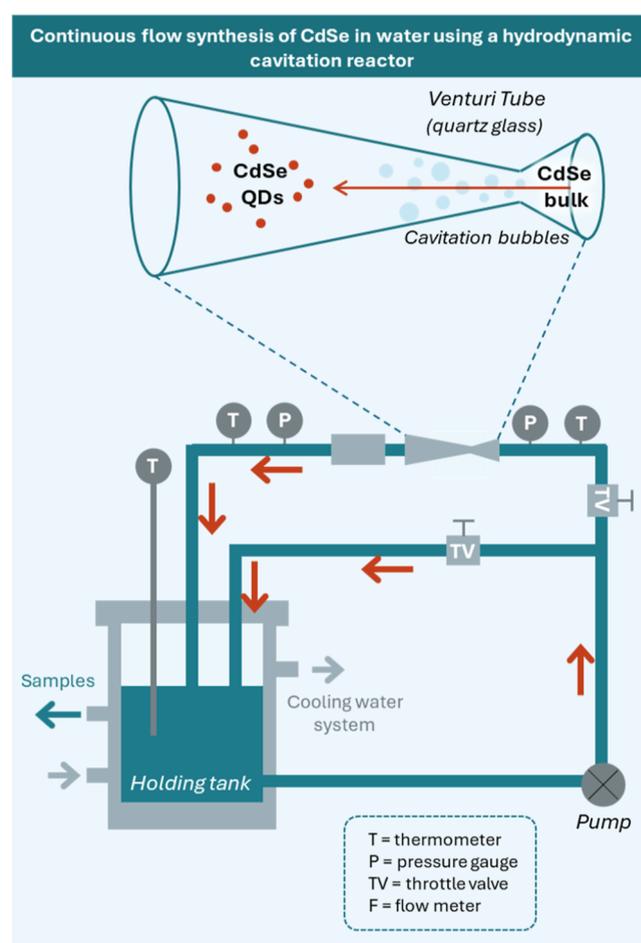


Figure 12. Structure diagram of HC reactor and Venturi tube for the aqueous continuous production of CdSe. Adapted from ref 201.

Taken together, these works illustrate the versatility of continuous-flow technologies for the aqueous synthesis of CdX QDs. Droplet microfluidics offers ultrafast, highly controlled reactions ideal for fine-tuning emission, while micro/mesofluidic reactors enable process intensification, monitoring, and scalability. Hydrodynamic cavitation adds an emerging dimension, combining continuous operation with straightforward scale-up. Collectively, these strategies merge the environmentally friendly conditions of aqueous synthesis with

Table 2. Recap of the Aqueous Continuous Synthesis of CdX QDs^a

entry	core	reactor type	T (°C)	size (nm)	PLQY (%)	procedure details	ref
1	CdTe/CdS/ZnS	chemical aerosol flow	200–300	2.5	<45	flow rate = 1.5 mL/min	195
2	CdTe	picoliter droplet microreactor	81.5–91	1.4–2.6	n.a	flow rates: water = 10 μ L/h oil = 30 μ L/h residence time = 66s	196
3	CdS and CdS/CdSe	droplet (plug) microreactor	r.t.	n.a	n.a	reaction time = 5 ms – 1 min	190
4	CdS	water–oil digital droplet reactor	r.t.-230	3.05	n.a	residence time = 9–45 min flow rate = 220–1000 μ L/min	60
5	CdX & CdSe/ZnS	micro and mesofluidic flow reactor	120–200	3.31–4.0	<51	residence time = 45–60 s	62
6	CdS	micromixer chip	r.t.	3.2–12	n.a	flow rate = 10–300 μ L/min	189
7	Cd _{1-x} Zn _x S and CdS/ZnS	microjet reactor	30–90	1–3	n.a	flow rate = 40 g/min	197
8	CdTe	polydimethylsiloxane microreactor	90–200	5–15	61.5	flow rate = 21–500 μ L/min	199
9	CdS	oscillatory microreactor (serpentine microchannel)	n.a	11.3	n.a	particle residence time = 0.42–1.66 s flow rate = 125–501 mL/min	198
10	CdS	hydrodynamic cavitation reactor	60	1.38–1.50	<47.1	cycle time = 6–12 h	200
11	CdSe	hydrodynamic cavitation reactor	r.t.-160	1.83	n.a	flow rate = 29.25 m/s	201

^aThe type of reactor used and some synthetic details are reported together with reaction temperature range, size of the dots and PLQY. n.a. = not available.

the engineering strengths of flow chemistry, marking a clear improvement over conventional batch approaches.

Continuous aqueous strategies, indeed, offer precise control of precursor addition, mixing, and growth kinetics in real time, producing colloidally stable, luminescent QDs with higher reproducibility and reduced need for postsynthetic processing. Table 2 reports some examples of aqueous continuous flow synthesis of CdX with details on the used setup and on the obtained nanocrystals.

Other types of QDs, such as InP QDs, carbon dots, or ternary QDs (e.g., CuInS₂ or AgInS₂), have also been successfully synthesized and applied under aqueous continuous-flow conditions.^{202–209}

For example, CuInS₂ QDs have been produced using a microwave-assisted continuous setup, where rapid and homogeneous heating enabled the formation of high-quality luminescent nanocrystals under fully water-based conditions.²⁰⁸ Similarly, AgInS₂ and AgInS₂/ZnS QDs with PLQYs up to 83% have been synthesized using a fully aqueous flow apparatus.²⁰⁹ Continuous hydrothermal platforms have also been employed for the preparation of carbon quantum dots, where efficient flow-based carbonization generated bright, water-dispersible nanodots subsequently applied for metal-ion sensing.²⁰⁷ Although many InP QDs syntheses still rely on organic-phase precursors, continuous approaches have significantly improved nucleation–growth separation, size distribution, and optical performance, underscoring the broader trend that continuous processing, whether aqueous or organic, enhances the uniformity and scalability of cadmium-free QDs.^{203,205}

These examples further demonstrate that flow chemistry in water can achieve scalable production while minimizing the use of toxic solvents and reagents. Insights and methodologies developed for one type of QDs are often transferable to other systems, highlighting the broader potential of aqueous flow approaches for environmentally friendly nanomaterial synthesis.

4. CONCLUSIONS, OPPORTUNITIES AND FUTURE DIRECTIONS

Aqueous continuous-flow synthesis of CdX QDs represents a crucial step toward the sustainable and scalable production of these nanomaterials. While traditional batch routes in organic solvents have delivered high-quality QDs, their reliance on toxic reagents, limited reproducibility, and challenges in scaling up constrain translation beyond the academic laboratory. In contrast, water-based continuous-flow platforms combine environmental compatibility with intrinsic process advantages such as modularity, reproducibility, and in-line monitoring. This makes them uniquely suited to bridge the gap between academic discovery and industrial production, positioning aqueous QDs as the next Frontier for sustainable nanomaterials in optoelectronics, photonics, and biomedicine.

Future opportunities for aqueous continuous-flow synthesis of chalcogenide QDs lie at the intersection of technical refinement, industrial translation, and digital automation. On the technical side, one of the most pressing challenges is the identification of ligands that can maintain long-term colloidal stability in water. While earlier droplet-based and homogeneous microfluidic studies demonstrated reproducible CdS, CdSe, and CdTe QDs with narrow emission and high PLQYs,^{62,189,195,196} instability over extended operation remains a critical bottleneck. Developing multifunctional ligand shells, capable of both stabilizing surfaces and preventing hydrolytic degradation, would help close this gap. Another technical need is the integration of antifouling coatings within micro- and mesofluidic channels. For example, Bhargava and co-workers noted reactor fouling as a concern in their digital droplet reactor for the synthesis of CdS and CdSe.⁶⁰ To mitigate the problem the devices were flushed with paraffin oil after runs so they could be reused without fouling. Clogging clearly remains one of the biggest obstacles to the scale-up of the continuous production of QDs, particularly when nucleation is rapid and particle loading increases.^{198,210,211} Tailored surface chemistries, whether polymeric or inorganic, could mitigate nanoparticle deposition, extend reactor lifetimes, and reduce downtime. In parallel, in-line optical monitoring methods such as real-time fluorescence and absorption spectroscopy would enable unprecedented

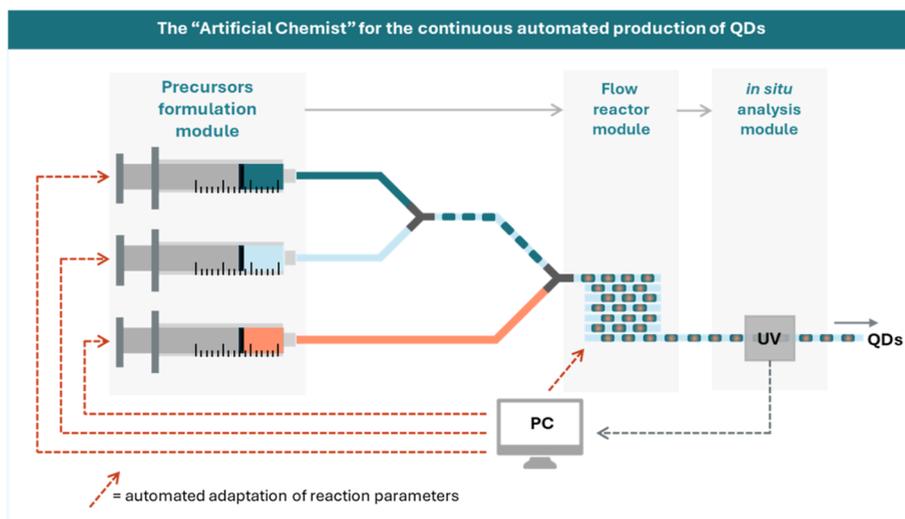


Figure 13. Diagram of the modular smart fluidic microprocessor designed for autonomous exploration and optimization of colloidal QD synthesis routes. Adapted from ref 213.

control over nucleation and growth. Coupling synthesis with real-time PL or Raman diagnostics would provide the missing link for adaptive control.⁶²

From an industrial perspective, aqueous continuous-flow technologies hold clear advantages. Pharmaceutical and biotechnology sectors already operate under water-based, sterile, and modular process environments, making integration of aqueous QDs synthesis both natural and scalable. Compared to traditional batch processes in toxic organic solvents, aqueous platforms promise easier regulatory approval and alignment with existing good manufacturing practice frameworks. The work of Monbaliu and colleagues on mesofluidic protocol to obtain CdX in water, illustrates how industrially relevant reactors can achieve controlled, high-throughput production with in-line analytical validation.⁶² As the demand for biocompatible luminescent probes grows, particularly for imaging in biological tissues, the convergence between water-based chemistry and clinical manufacturing workflows will make aqueous QDs uniquely positioned for translational applications.

A third and rapidly emerging direction involves automation through artificial intelligence (AI) and machine learning (ML). These approaches take advantage of modular and reconfigurable flow platforms that integrate precursor delivery, controlled reaction conditions, and real-time diagnostics, enabling high-throughput experiments with immediate feedback on QDs properties.²¹²

Within this area, Abolhasani and colleagues have carried out extensive work on automated synthesis of multiple classes of QDs, ranging from Cd-based to lead halide perovskites. Their efforts make use of autonomous flow reactors that allow synthetic parameters to be tuned on the fly through AI-guided decision-making, resulting in reproducible protocols and improved material quality. In particular, they introduced closed-loop systems such as the “Artificial Chemist,” specifically developed to accelerate materials discovery by continuously adjusting reaction conditions based on real-time optical signals and predictive modeling (Figure 13).²¹³ One notable application was an automated microfluidic platform for biphasic CdSe QDs synthesis and ligand exchange, which improved control over segmented flow and minimized particle adhesion to channel walls.²¹⁴

More recently, the same group developed “AlphaFlow”, a reinforcement learning-based self-driving platform built from modular fluidic units that can autonomously navigate complex multistep synthetic routes.²¹⁵ Using CdSe/CdS core-shell QDs as a model, AlphaFlow was able to independently identify optimal reagent sequences, producing nanocrystals with enhanced optical performance even without predefined chemical order. Further advances include a modular microfluidic reactor with AI-driven optimization for lead halide perovskites, capable of simultaneously controlling up to ten parameters to accelerate synthesis of ten distinct QDs types.²¹⁶ In addition, the “Smart Dope” platform combined digital twin simulations with closed-loop experimentation to streamline the synthesis of multication-doped lead halide perovskites, enabling both rapid optimization of existing protocols and on-demand discovery of novel reaction pathways.²¹⁷

Beyond these examples, some reviews and perspectives highlight the broader promise of AI/ML and automation in colloidal nanomaterials. Munyebvu and co-workers stress that the vast multidimensional parameter spaces typical of QDs syntheses demand data-driven workflows; they propose modular flow platforms with in situ diagnostics to build standardized, rich data sets for reproducibility and accelerated optimization.²¹⁸ Bayesian optimization, surrogate modeling, and reinforcement learning are also being presented as effective tools to map optical signals to structural and functional properties of QDs.²¹⁹ The importance of robust data curation, model validation, and transferability across laboratories is also highlighted in the context of nanomaterials in general, emphasizing how continuous flow reactors with integrated sensing can accelerate process development, minimize fouling, and improve scalability.^{220–222} At the same time, more targeted studies, such as the automated production of CdSe but also perovskite and PbS QDs, illustrate how computational and engineering strategies can provide precise control over nucleation, growth, and passivation in flow.^{223–226} Also carbon QDs have been synthesized with similar strategies using ML to predict photoluminescence behavior and optimize synthetic conditions.²²⁷ More generally, future directions point toward the convergence of high-throughput experimentation, closed-loop

control, and robotics as the foundation for reproducible nanomaterial discovery.^{228,229}

In the case of aqueous chalcogenide QDs, AI- and ML-driven methods are still rarely explored, even though these systems are particularly well suited for such approaches. Water-based synthesis involves a complex interplay of parameters, including pH, ligand choice, residence time, mixing rate, and temperature, that create a multidimensional space where automated optimization could be especially powerful. Closed-loop systems that integrate in-line PL or absorption readouts with reinforcement learning or predictive models, could autonomously tune conditions to yield optimal size, surface passivation, and optical properties of QDs. These arguments align closely with recent discussions of autonomous discovery pipelines, where flow chemistry is described as a natural enabler of data intensification and scalable optimization.^{222,230}

In conclusion, aqueous continuous-flow synthesis of chalcogenide QDs not only enables environmentally benign processing but also provides a pathway toward reproducible, scalable, and industrially relevant nanomaterials. Technical advances in ligands, antifouling strategies, and in-line monitoring will lay the foundation, while integration with AI and ML promises to transform optimization into a closed-loop, autonomous process (Figure 14). By uniting sustainability

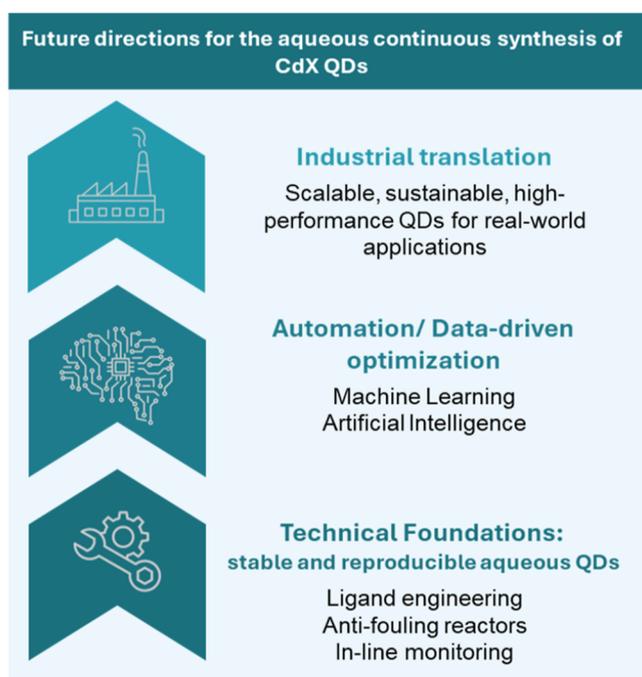


Figure 14. Perspectives for the continuous aqueous synthesis of CdX QDs. Technical advances in ligands, reactor coatings, and in-line monitoring establish the foundation; AI/ML integration enables closed-loop optimization; together these elements enable reproducible, scalable, and sustainable production suitable for industrial translation.

with automation and scalability, aqueous continuous-flow approaches could redefine QDs manufacturing, bringing high-performance materials from the academic laboratory into industrial production and real-world applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.5c01449>.

Tables with an overview of the batch protocols to obtain cadmium chalcogenides quantum dots in organic solvents and in water (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

AI, artificial intelligence
 BPR, back pressure regulator
 CdX, cadmium chalcogenides
 Cit, sodium citrate
 FWHM, full width at half-maximum
 HC, hydrodynamic cavitation
 HDA, hexadecylamine
 MA, mercaptoethylamine
 ML, machine learning
 MPA, mercaptopropionic acid
 MR, nuclear magnetic resonance
 OA, oleic acid
 OAM, oleylamine
 ODE, octadecene
 PL, photoluminescence
 PLQY, photoluminescence quantum yield
 QDs, quantum dots
 SeU, selenourea
 TBP, tributylphosphine
 TBPX, tributylphosphine chalcogenide
 TCEP, tris(2-carboxyethyl)phosphine
 TCEPX, tris(2-carboxyethyl)phosphine chalcogenide
 TGA, thioglycolic acid

TGL, thioglycerol
TOP, trioctylphosphine
TOPO, trioctylphosphine oxide
TOPX, trioctylamine chalcogenide
TU, thiourea
UV-vis, ultraviolet-visible

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