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Quantum materials made in microfluidics - critical review and perspective

M. Wojnicki [a,*], V. Hessel [b,c,*]

[a] AGH University of Science and Technology, Faculty of Non-Ferrous Metals, Mickiewicza Ave. 30, 30-059 Krakow, Poland
[b] The University of Adelaide, School of Chemical Engineering and Advanced Materials, Adelaide, Australia
[c] School of Engineering, University of Warwick, UK, United Kingdom

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ABSTRACT

Quantum materials exhibit excellent optical properties. They are applied for displays, sensors, detectors of radiation, as well as in bioimaging and ion detection. Quantum materials change their optical properties depending on their size. Therefore the synthesis of monodisperse quantum materials is a prime goal. Many years ago microfluidics reactors have been proven to be an effective tool to produce functional materials on the nanometer scale and to synthesize nanomaterials with controllable morphology and customized properties. Accordingly, this review focuses on recent progress and perspectives in the microfluidic fabrication of quantum materials. In this paper, examples are shown to demonstrate how quantum materials, including semiconductor nanocrystals, carbon quantum dots, metal nanoparticles (especially metal clusters), rare earth doped nanophosphors, and fluorescent oxide, are fabricated, and their quality and properties are controlled. The review aims to serve as an instruction for the scientific as well as an industry research group interested in the field of quantum materials synthesis and scale-up production.

1. Introduction

1.1. Quantum dots: Advanced materials with a need for advanced processing and tools

Quantum materials are of increasing interest to researchers [1]. This is mainly due to the unusual properties of these materials, which change nonlinearly depending on size. Typical properties of bulk materials can be easily investigated and described on a macroscale by classical mechanics. However, the study of nanomaterials requires a description in the form of quantum mechanics. This is related to the change in the percentage of surface atoms to the total number of atoms in the material. The proportion of surface atoms is crucial for catalysis. Then the material can play a more distinct role, and a further increase in the surface area (size reduction) leads to a situation where the properties of matter may begin to change rapidly. This is the effect of a high surface area over volume ratio [2,3]. The best example are quantum dots. In this case, particles behave as semiconductor nanoparticles which exhibits composition and size-dependent electronic, physical, and optical properties [4]. Also, catalytic properties depend on the size. Therefore interesting, the application is to replace the homogeneous catalysts with supported metallic nanoclusters [5]. Depending on the source, the quantum range is defined as particles in the range: from 2 to 10 nm [6] or from 1.5 to 10 nm [4]. However, other sources give a slightly wider range from 1 to 10 nm [7]. A commonly accepted definition is that quantum dots are a class of nanoparticles with sizes of a few nm. Quantum dots emit light of a specific wavelength when a current is applied or exposed to light.

Regardless of the definition and properties, advanced synthesis methods must be used to obtain quantum materials. This entails the use of different types of reactors and precursors to obtain these materials. Fig. 1 presents how the emission spectra depend on material composition.

Typical quantum materials absorb at short wavelengths and thereafter emit light with larger wavelengths. Part of the energy is converted into heat, and part is radiated as light. So one of the key parameters is the quantum yield of such material. The quantum yield as well as characteristic photoluminescence (PL) highly depends on the number of the cluster atoms and the chemical structure of the stabilizing ligands [8].

As it is shown in Fig. 1, among the well-known quantum materials, gold was also presented. In the last few years, research onto noble metal-based quantum materials has been developing strongly. Gold quantum dots (AuQDs) are a kind of novel fluorescent nanomaterial. AuQDs are

* Corresponding authors.
E-mail addresses: marekw@agh.edu.pl (M. Wojnicki), volker.hessel@adelaide.edu.au (V. Hessel).

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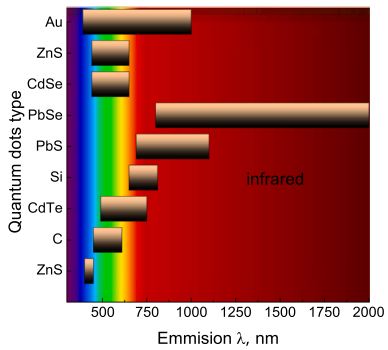

Fig. 1. Quantum materials - light emission range depending on the composition.

generally made up of several to c.a. 100 gold atoms, and it is smaller in size than ~ 2 nm [9]. They have a significant fluorescence intensity [10], low toxicity [11], as well as can form stable water dispersion [12].

1.2. Scope of this review and perspective

This review is up to date and covers modern quantum dot synthesis such as noble metal quantum dots and carbon quantum dots, while the former literature was based on the high-temperature synthesis in microreactors. As a consequence, the material choice was limited, e.g. to cadmium sulfide or cadmium selenide. Modern quantum material choice is much diverse, and our review reflects that; we even point at valuable modern syntheses which so far have not been done in microfluidics, but principally could be. Thus, the nanomaterial itself and its engineering are more in focus than in previous reviews while not compromising the cutting-edge microfluidic technology used to make it. Actually, and as a consequence of the increased material choice considered, our review shows how to use microfluidics in a broader way (than just by heat transfer intensification, meaning high-temperature synthesis).

To summarize, past reviews, like ours, show how flow reactors offer excellent, partly unique processing opportunities and how the latter translates into advanced material properties. Past reviews were governed by a few known material innovations which were “repeated” in microreactors; we like to show the opposite, meaning how processing development can inspire and broaden the materials development. In this sense, we bridge the flow synthesis to the related cyclic reactors, which is not found in earlier literature. Past reviews were interesting typically for one scientific community, whereas we aimed to give relevant information for both material scientists and flow or process engineers. The review is also a perspective - it sets new directions for research and industrial research units.

1.3. Manufacturing of quantum dot materials and use of microreactors

Concerning future manufacturing and its ease, effective and fast methods have been developed. Generally, synthesis methods of quantum materials can be divided into two groups: top-down and bottom-up methods. In the case of the top-down process, the large objects are broken down into small-sized CDs using physical or chemical methods. In the second case, named bottom-up, small molecules are transformed to quantum materials by chemical reaction.

Regarding top-down, the following methods can be listed: laser ablation [13-15], arc discharge [16,17], and finally acidic oxidation (chemical etching method) [18]. In the case of bottom-up, the following methods are frequently used: thermal like microwave-assisted pyrolysis [19,20], hydrothermal (autoclaves) [21-23], solvothermal [24,25], and electrochemical [26-29].

The idea of using microreactors in various fields of chemistry is nothing new but rather can recruit almost three decades of experience [30,31]. A simple flow-through microreactor can function as a gradientless microreactor under appropriate conditions. The concentration of the reactants is significantly equalized due to effective convection, being finalized by molecular diffusion [32,33]. Microreactors have great application in chemical reactions. Among many benefits, two significant advantages are striking, like excellent heat transfer in the case of exothermic or endothermic reactions and enhanced mass transfer [34-37]. The activation energy, as well as the reaction rate for the synthesis of QDs, is low, and accordingly, the application of high temperature is required [38]. Then, the excellent heat exchange properties of microreactors are important, which stem from their large ratio of the reactor surface area to its volume. The weaknesses and strengths analysis of batch versus flow reactor is presented in Table 1.

While this review does not intend to discuss the engineering advances of microreactors in all their details, it is worth shortly focus on their mixing efficiency. Diffusion as such is normally not particularly effective, even in microreactors, as the diffusion coefficient for small molecules in water is in the order of 10^{-5} cm^2/s and corresponding mixing times amount to seconds or even higher; which is much above the needs of nanomaterial synthesis. For very large structures (nanoparticles) and molecules (macromolecules), shape and size also play a role concerning diffusion. Specialty solutions are known to increase the power of diffusion in microreactors, such as bifurcation and focusing (geometric, hydrodynamic). They can provide mixing in the order of milliseconds [39] suited for nanomaterial synthesis [40,41]; yet at the severe expense of increased pressure drop. A much simpler way to increase the mixing efficiency in microreactors is provided by using convection, which is achieved by setting flow rates sufficiently high to increase the Reynolds number. Internal mass circulations combined with stretching and disrupting of fluid lamellae allow then diffusion to be effective. The balance of advantages and disadvantages of batch reactor v.s. the microreactor is shown in Fig. 2.

Cyclic reactors have high operational stability. Moreover, they can be easily adapted to new tasks when technology changes. Unfortunately, when rapid changes, for example, in the temperature in the reactor, are required in order to rapidly supersaturate the solution, it is practically impossible. It is mainly related to the large volume of the reactor in relation to the heat transfer surface. Of course, it is possible to introduce additional cooling/heating elements to the batch reactors. However, it does not change the fact that significant temperature gradients will still be observed in such systems. Only theoretically, batch reactors can be scaled easily. Unfortunately, very often in the case of nanomaterials and quantum materials, such scaling is practically impossible. One of the better examples is the synthesis of trimethoxybenzene, where the influence of the mixing speed on selectivity is clearly visible [42]. In the case of nanomaterials, similar effects are observed. Microreactors are not scaled by increasing size, but by multiplying them. This means that the laboratory conditions are fully transferred to an industrial scale, and a larger scale is obtained by using a larger number of microreactors. It should be noted that most often microreactors are used for highly

Table 1
Comparison of engineering properties batch and flow reactors relevant for nanomaterial synthesis.

Parameter	Flow	Batch
Mass transfer	Fast mixing	Slow mixing
Heat transfer	High	Moderate
Surface area to volume ratio	High	Medium to very small
Operational stability (e.g. avoidance of blockage)	Low	High
Scale-up efficiency	High	Moderate
Flexibility for multi-product (multipurpose) operation	High	Moderate
Automation and process control	High	Moderate

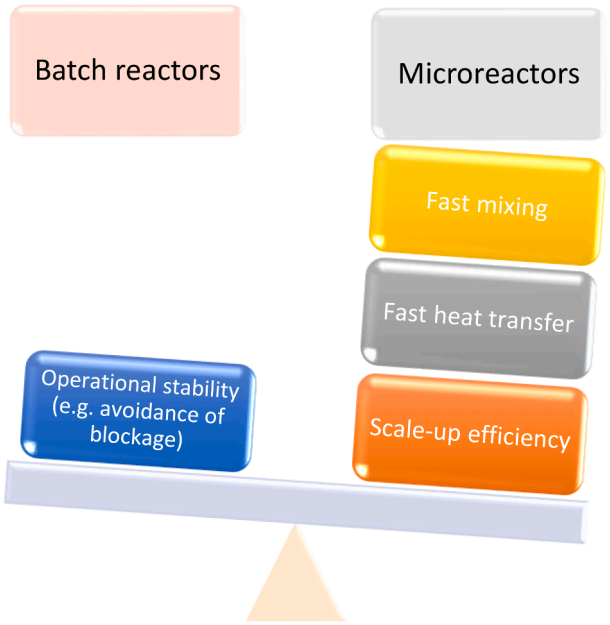

Fig. 2. Balance of advantages and disadvantages of the batch reactor and microreactor.

sophisticated materials, so the production scale is unlikely to ever reach thousands of tons / hour.

A good example of the combined effect of geometric focusing and subsequent convection are interdigital micromixers which have been particularly thoroughly investigated for their mixing properties and systematically been optimized toward a commercial mixing tool [35-37,43]. Accordingly, the mixing qualities of microreactors could be demonstrated for fast reactions demanding even faster mixing, e.g. the reduction of silver(I) nitrate or gold(III) chloride complex with $NaBH_4$. Luty-Błocho et al. [44] have shown how the flow rate through this interdigital micromixer impacts nanoparticles size and size distribution. Under hydrodynamic focusing and downstream convection flows, the good mixing properties of interdigital micromixers improved the synthesis process [45,46].

1.4. Unique chances for quantum dots in continuous flow

Taking into account the fact that in the case of quantum materials, the thickness of a single atomic layer is important for their size ergo properties, properly controlled synthesis conditions are required. The use of microreactors in this area seems to be an appropriate choice. As it was mentioned above, they can provide mixing in the order of milliseconds [35] suited for nanomaterial synthesis [36,37]. Rapid concentration equalization prevents uneven growth [47] of quantum materials. A relevant example is the work of Liu et al. [48]. The paper shows how small differences in the size distribution translate into the properties of the obtained quantum dots. In each of the 9 cases, the dominant fraction is 1 nm, while the position of the maximum emission varies over a wide range from 415 to 615 nm.

This review focuses on recent progress and perspectives in the microfluidic fabrication of different types of quantum nanomaterials. The review aims to serve as an instruction for the scientific as well as an industry research group interested in the field of quantum materials synthesis and scale-up production of those interesting materials.

Metal-based nanoparticles and quantum materials.

The synthesis of nanoparticles can be carried out in many ways. The main challenge is the rapid formation of nuclei. A large number of nuclei favors the formation of small and uniform nanoparticles. To obtain a large number of nuclei, strong metal ion reductants should be used, or the reaction parameters should be rapidly changed to obtain supersaturation quickly. In case of redox reactions, strong reducing agents are used for example $NaBH_4$ [44,49], DMAB [50,51], ascorbic acid [52,53]. Another solution is to assist the reduction reaction with an external source of energy (e.g. radiation).

1.5. Metal-based nanoparticles

Toit et al. [54] used a UV lamp to accelerate the redox reaction between gold(III) chloride complex ions and trisodium citrate (TSC). The process was carried out in a flow reactor. Conventionally, the reduction reaction of Au (III) with sodium citrate is called the Turkevich method [55,56]. The Turkevich method allows to synthesize the gold nanoparticles (AuNPs) with the size range 9–120 nm [56], independent of the process is initiated thermally or by UV irradiation. Also, the application of a microflow reactor did not decrease the size of the nanoparticles significantly. The bottleneck of this process is the low nucleation rate obtained by a weak reducing agent. To speed up the process, higher temperature is required [57].

Panariello et al. [58] have been searching to optimize the reaction conditions, resulting in a method termed the modified Turkevich. They confirmed that the modified method allowed for the synthesis in a batch of ~12 nm monodisperse (residual standard deviation, RSD ~10%) particles, with variability from batch to batch of only ~5%. Its size distribution is quite significant because of the high threshold given for quantum materials. The flow reactor enabled the synthesis of AuNPs with a diameter ~11 nm and RSD ~10%. The precursor conversion and reproducibility between reactor runs is higher than obtained in batch (variability of ~2%). To further speed up the mixing process, micro drops were used [39,59]. In this particular case, the flow reactor did not decrease the RSD of obtained nanoparticles. This may be because plastic tubing was used for the flow-through microreactor. The inner diameter of the tubes was 0.5 mm. It is worth emphasizing here that the Turkevich reaction requires a large amount of energy to be supplied quickly. The use of plastic tubes does not facilitate heat transfer and obtaining a gradient-less system. In such a situation, there may be a slight difference between a cyclic reactor (made of glass) and a flow-through reactor (made of plastic).

Wagner and Köhler [52] synthesized gold nanoparticles in a microreactor with a size range of 5–50 nm. Theoretically, the produced nanoparticles are in the quantum range, but their fluorescence properties have not been investigated. This is a fairly typical case. Depending on the purpose of nanoparticles, their various properties are investigated. Therefore, it may happen that optically interesting materials, although produced, have never been tested for specific applications they might suit. Huang et al. used microreactors for gold nanoparticle synthesis [57]. The influence of many factors was examined, including the capillary material, surface-to-volume ratio (capillary internal diameter 0.3–1.0 mm), average residence time (1.5–30 min), and temperature (70–100 °C) were investigated. Using the Turkevich method, nanoparticles with a size of 1.9 ± 0.2 nm are obtained. In our opinion, these nanoparticles with a high degree of probability should show PL. Unfortunately, such studies have not been carried out by the authors. Thus, a new area is visible that is worth exploring, taking into account the quantum properties of noble metal nanoparticles synthesized by the Turkevich method. The preliminary conditions for the synthesis have already been defined by the authors.

1.6. Noble metal quantum dots

Noble metal quantum clusters (NMQCs) are an intermediate step between isolated noble metal single atom structure and nanoparticles. The NMQCs have a size below 1 nm and are core-sized clusters composed of a group of atoms. The size of these individual nano-objects is comparable to the Fermi wavelength of an electron (Broglie's wavelength of an electron at the Fermi energy, ca. 0.5 nm for Au or Ag) [60].

This results in molecular-like species properties such as discrete electronic structure as well as HOMO-LUMO transition-based photoluminescence [61-63]. Those materials possess interesting photonic, chemical, and physical properties. Photoluminescence of bulk metals is not observed because of nonradiative decay and the nonappearance of an energy gap [64]. In the case of noble metals, the emission color can be controlled not only by size but also by NMQCs composition (see Fig. 3).

Frequently proteins are used for noble metal quantum cluster synthesis. It is well known that proteins are large molecules (compared to nanoparticles). For this reason, they can effectively screen interactions between metal clusters, in contrast to much smaller structures such as citrates (applied in Turkevich method). This opens potential applications in biology and medicine. It is obvious that the properties of such materials will strongly depend not only on metal atoms but also on the structure of applied proteins. Therefore there is potential in bioimaging applications and censer targeted treatment [65].

One of the best examples of the application of NMQCs in bioimaging using protein-gold nanoclusters on human immune system mimetic cells [66]. For the synthesis bovine serum albumins (BSA) and human serum albumins (HSA), as well as lysozyme (LYZ) and gamma globulin (γG) immunoproteins, were applied as reducing and stabilizing agents of the Au nanohybrids. The obtained cluster emits at λ_{em} = 560 nm with a quantum yield of 5%. The size of the received NMQCs was not specified.

The toxicity of Au-NMQCs was studied considering their ability to induce inflammation in the cells [67]. LYZ-, HAS-, BSA- and γG- Au-NMQCs applied at high concentrations induce physiological changes in COLO-720 L and HUT-78 cells. This result is in contrast to the studies conducted for citrate-stabilized Au NPs [67]. This shows the large influence of the properties of the quantum material itself.

Cytotoxicity studies of Au-NMQCs have been described in [11]. Regardless of the type of proteins, all synthesized Au NMQCs possess intense red emission (λ_{em} ~ 650 nm) and have a similar size of core (ca. 1.4 nm). In this case, the quantum yield (QY) was determined for all applied proteins, being in the range of 3.8% to 5.4%, respectively, for the lysozyme from chicken egg and bovine serum albumins.

The synthesis of Au-NMQCs does not have to be difficult and complex. Ungor et al. have synthesized red-emitting gold nanoclusters for rapid fluorescence sensing of tryptophan metabolites and developed a single-step, synthesis protocol [68]. Red-emitting (λ_{em} ~ 645 nm) NMQCs were obtained using γ-globulin. In this case, immunoprotein γ-globulin was a combined reducing and stabilizing agent. The size of the core is d = 1.5 ± 0.3 nm, and the QY amounts to 4.4%. Obtained Au-NMQCs were exhibiting high sensing properties against tryptophan metabolites.

The control of the optical properties of Au-NMQCs has been investigated by Csapó et al. [69] at the example of sub nanometric sized (d < 2 nm) Au NCs having blue or green photoluminescence (λ_{em} = 470–500 nm). The photoluminescence can be fined tuned by setting the molar proportion of Au(III) and L-tryptophan. Details are shown in Table 2.

Fluorescent and size-tunable gold quantum dots were synthesized by

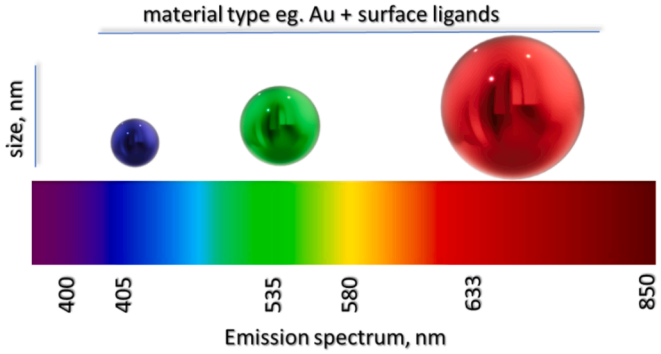

Fig. 3. Correlation between QDs emission color, size, and material type.

Table 2
Optical properties for different Au-NMQCs and AuQD.

Au-NMQCs / AuQD composition/size	λ_{em}, nm	QY, %
Molar ratio Au(III):L- tryptophan 1:1	497	1.1
Molar ratio Au(III):L- tryptophan 1:5	486	1.3
Molar ratio Au(III):L- tryptophan 1:15	472	1.7
Gold cluster Au5	385	70
Gold cluster Au8	455.8	42
Gold cluster Au13	510	25
Gold cluster Au23	751	15
Gold cluster Au31	879	10

Zheng et al. [70]. The Au-NMQCs were obtained by reduction of gold salts (e.g., $HAuCl_4$ or $AuBr_3$) within aqueous PAMAM solutions. Depending on the gold cluster size, different optical properties were obtained (see Table 2). As the size of the cluster increases, the quantum yield decreases.

Au-NMQCs were also investigated as a selective fluorescent sensors for different metal ions: Fe^{3+} [71], Hg^{2+} [72], Cu^{2+} [73], *etc*. A one-pot green synthesis method of Pt-NMQCs was described for the preparation of highly stable, blue and green fluorescent, water-soluble materials by Balu et al. [29]. Those Pt-NMQCs were synthesized using H_2PtCl_6 as a precursor and Rec1-resilin as a reducing and stabilizing agent at a quantum yield of ~ 7.0%.

As was mentioned above, the properties depend on the applied metal atoms. Therefore also, a mixture of atoms might be used. Yellow light-emitting Au/Ag bimetallic nanoclusters were synthesized by Ungor et al. [10]. The obtained cluster emits λ_{em} = 560 nm with a quantum yield of 7.3%. This type of quantum material has high QY. Those yellow light-emitting bimetallic nanoclusters were used to determine folic acid in biological samples.

Copper quantum clusters in a protein matrix were tested as the sensor of Pb^{2+} ions [74]. In the same way, photoluminescent metal mixtures can be used. $Ag_{10}Cu_6$ Cluster stabilized by a PNNP ligand and phenylacetylene were investigated for selective and reversible sensing of ammonia in air and water [75].

The works described above have one thing in common. All these syntheses were carried out in a batch reactor. Those continuous microreactors have a number of advantages. For example, the production of highly monodispersed phosphine-stabilized gold nanoclusters at a rate of about 11.8 (mg s^{-1}) was achieved by Jin et al. [76] using a microreactor. This result is about 500 times over conventional batch syntheses based on the production rate per reactor volume. The bulk synthesis in bath reactors suffers from poorly controlled mixing as well as heat and mass transferring and a lack of control of nucleation and growth processes. Therefore, Wu et al. [77] used a droplet-based microreactor for Au nanocluster synthesis (AuNCs). For this purpose Au(III) chloride complex was taken as a precursor, ascorbic acid as a reducing agent, and ficin as a stabilizing agent for AuNCs. Perfluorodecalin was used as the continuous oil phase. It is well known that ascorbic acid is a slower reducing agent in comparison to sodium, the fast-reacting borohydride [44,78,79]. Therefore, to increase the reaction rate, the process was conducted at elevated temperatures (65 °C). Size-controlled preparation of gold nanoclusters using a microflow reactor was studied by Haesuwannakij et al. [80]. In their work, sodium borohydride was taken as a gold(III) ion reducer. The batch reactor obtained particles larger by about 0.5 nm in respect to the AuNCs obtained in the flow reactor at the same size distribution for both reactor types.

Sandeep et al. [12] presented a method of obtaining luminescent noble metal clusters using microdroplets [12]. Gold(III) chloride complex and silver(I) nitrate were used as a precursor. Bovine serum albumin and lysozyme proteins were used as stabilizing agents for NMQCs, and sodium borohydride as a reducing agent for precious metals ions.

The microdroplets were obtained by an electrospray system. The synthesis of the clusters in microdroplets leads to severalfold enhancement in the rate of the reaction. Moreover, clusters show severalfold enhancement in luminescence when compared to the same clusters prepared by the conventional solution-phase method. In this case, the NMQCs obtained using the droplets base method were used for in vitro imaging of retinoblastoma NCC-RbC-51 cells, which will be useful for diagnosis and for detecting associated brain abnormalities.

2. Non-metal-based nanoparticles and quantum materials

2.1. Carbon-based quantum materials

Carbon quantum dots (CDs) were discovered in 2006 [81]. The accidental discovery of this fluorescent carbon material during the separation and purification of single-walled carbon nanotubes was first described in 2004 [82]. The name carbon quantum dots were for the first time used in 2006 by Sun et al. [83]. Sun et al. produced CDs via laser ablation of a carbon target in the presence of water vapor with argon as carrier gas. However, this method is of limited use, mainly due to the narrow limits of particle size control. Moreover, the scalability of this process is strongly limited.

In the following years, further papers were published proposing various methods of obtaining CDs. This can be easily illustrated by the number of publications containing in the title, abstract, or keywords "carbon quantum dots" or "CQD" as an acronym and the word "synthesis". Using the SCOPUS database (August 21, 2021), results in Fig. 4 were obtained.

The number of publications in this area is growing exponentially.

CDs have widespread applications (see Fig. 5). First of all, CDs can be used in medicine as markers [84]. Thanks to low biotoxicity, CDs dots have gained considerable attention as potential rivals to semiconductor quantum dots [85-87]. The use of CDs in photocatalysis [88] or as light-emitting devices [89] has been documented multiple times [90], as well as corrosion inhibitors [91,92].

Currently, one of the most popular methods of CDs synthesis is to use a domestic microwave oven or dedicated microwave reactors as a heat source [93]. This method is very fast and efficient. Liu et al. were using this method for CDs synthesis [94]. The synthesis time was 3 min. CDs were prepared by a simple microwave heating method using citric acid,

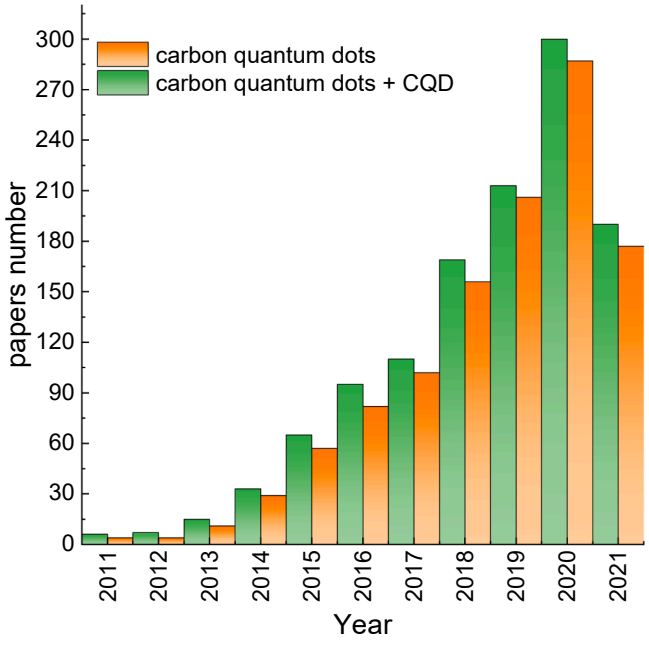

Fig. 4. Number of the paper about carbon quantum dots.

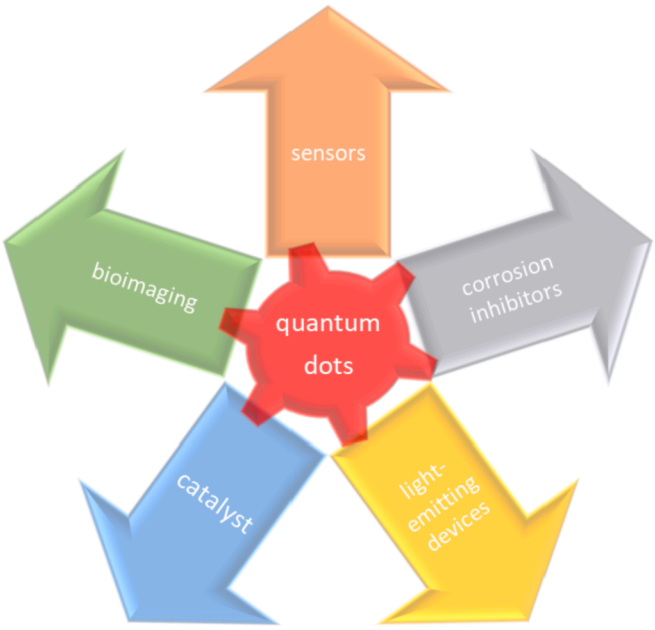

Fig. 5. CDs widespread applications.

L-cysteine, and dextrin as the precursors. Next, the solution was heated. After the reaction, the solution changes the color from transparent to brown. Most of the water is evaporated during the process. The obtained material exhibits a high QY equals 22%. The average diameter was 2.6 nm at a wide size exceeding 1.5 nm. The obtained QDs were tested as a potential sensor for the detection of metal ions (in particular Cu^{2+}).

Romero et al. [95] also use the domestic microwave to synthesize CDs. As a precursor, citric acid was used. The mean diameter of the CDs was equal 3.8 nm. The size is much larger than in the work Liu et al. [94]. This may be due to a different preparation. In this case, 100 g of citric acid was dissolved in 100 ml of water, which likely caused the reaction time to be much longer. Slow synthesis favors obtaining particles of larger size and large size distribution. AFM analyzes suggest that the size distribution is significant. The obtained quantum materials were tested towards antimicrobial photodynamic therapy applications.

An excellent example of the use of continuous flow microreactors with regard to process chemistry and engineering is the work of Lu et al. [96]. These authors conducted systematic research on the selection of the solvent, precursors, and conditions for the production of CDs. The first step of the screening was based on the solubility of precursors. After the first screening step, 15 combinations of carbon precursors and solvents were selected for further optimization. Next, more than 300 reaction conditions were screened to obtain desired PL properties of CDs. The reaction conditions have been screened quickly and effectively by using the microreactor system (ca. 15 min per condition). For this purpose, a simple system was used. The system consists of syringe pumps connected to a capillary of 1 mm internal diameter. The capillary was heated using an oil bath. Through analyzing the screened conditions, tunable PL emission maxima, from about 330 to 550 nm, with respectable PL quantum yields were achieved. Generally speaking, in the case of CDs synthesis, the compound is thermally decomposed in the flow-through microreactor. In the case of noble metals nanoparticles and semiconductors synthesis most useful model describing the evolution of size is Watzke and Finke (W - F). This model origin or modified form was successfully adopted to the process of nanosilver [97], gold [78], palladium [98], platinum [99] and transition-metal nanoclusters [100] formation. In the case of CDs, the nucleation mechanism is unclear. Therefore, numerous studies have been conducted in this area [101]. In the initial stage, individual free nucleus forms, which then forms clusters and finally forms nanoparticles/quantum dots (see Fig. 6). Due to the

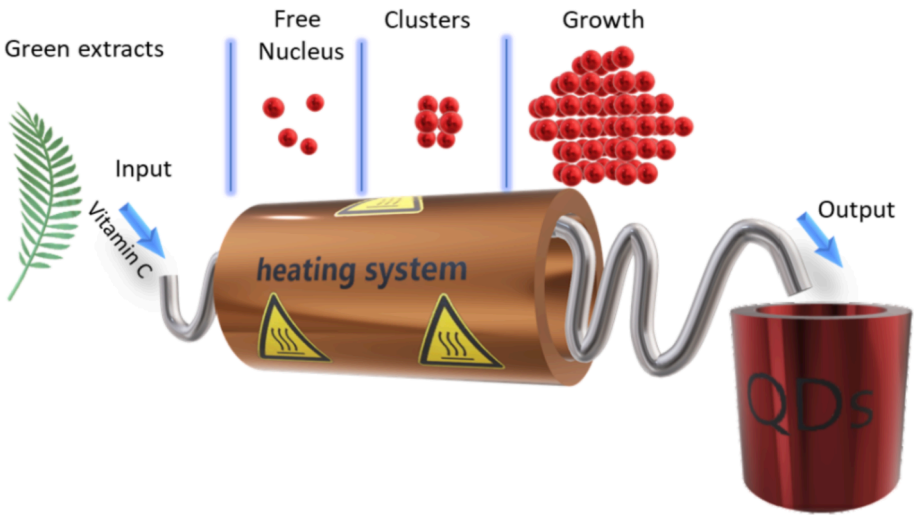

Fig. 6. Continuous microflow system for CDs synthesis.

use of a flow system, the individual steps of particle formation are kept separate from each other. This results in very narrow nanoparticle size distributions.

Ioan-Alexandru et al. developed continuous hydrothermal flow synthesis of S-functionalised carbon quantum dots for enhanced oil recovery [102]. In this case, supercritical water was used as a dispersant (temperature 450 °C and pressure 24.8 MPa. The concentration of CDs was high, 14 g/L. The size of obtained nanoparticles was 1.7 ± 0.7 nm. The use of supercritical water is costly and requires materials with high mechanical strength at high temperatures. The same reactor was previously used by Kellici et al. for the synthesis of quantum dots graphene [103,104].

Longshi et al. have used a microreactor for the efficient synthesis of highly fluorescent carbon dots at a synthesis time below 5 min and temperature in the range from 80 to 160 °C [105]. As a precursor, citric acid was used, and ethylenediamine was added. The obtained CDs exhibit a high quantum yield (c.a. 60.1%). Moreover, the influence of the microreactor shape on the carbon dots synthesis was investigated, and it was found that the size can be slightly tuned in this way. Nanoparticles were obtained with a size of 2.4 nm, 2.6 nm, 3.2 nm for the linear-like microreactor, double-snake microreactor, and snake-like microreactor, respectively.

Yong Tang et al. [106] presents a rapid synthesis of highly photoluminescent nitrogen-doped carbon quantum dots via a microreactor with foamy copper for the detection of Hg^{2+} ions. The influence of the porosity of foamy copper (porosities 50–98%) was investigated. Citric acid and ethylenediamine were used as a precursor. The synthesis time was c.a. 8 min. The foamy copper probably plays as a catalyst in the flow system. Thanks to this catalyst a high QY of 84.1% was achieved. It was shown that depending on the porosity of the copper foamy, synthesized CDs have different sizes and size distributions. For a foam with a porosity of 98% CDs size was equal to 2.4 nm, where for 50% the CDs the size was larger and equaled 3.2 nm. As already mentioned, the quantum yield and the PL wavelength depend on the particle size and composition. As was shown in this paper, the composition of the received CDs changes with the size, which further complicates the interpretation of the result.

Pedro S. et al. [107] synthesized CDs in a ceramic microreactor employing thermal decomposition of ascorbic acid in dimethyl sulfoxide. The system was programmed to work from 150 to 250 °C. A fluorescent sensor for pH was constructed using obtained CDs. The photoluminescence properties were studied in the pH range of 2–11. The results showed that the maximum fluorescence emission (420 nm) of the CDs at 325 nm excitation decreased linearly as the pH increased from 4.5 to 11.5. This property is very important. In typical pH sensors, the observed changes in the electrode potential are not linear, therefore these measurements may be affected by a significant error. The cytotoxicity of the CDs was also investigated. Cell viability was not affected in the presence of these concentrations of CDs, demonstrating that these non-toxic nanoparticles can act as suitable biosensors or bioimaging devices in living organisms.

Continuous hydrothermal flow synthesis of graphene quantum dots (GQDs) was performed using supercritical water by Baragau et al. [103]. The quantum yield of GQDs was 4.5%, and the emission maximum was $\lambda_{em} = 510$ nm.

Recently, the class of carbon QD nanomaterials was introduced, and so followed the microreactor investigations. Microreactors suit for the carbon QD nanomaterial synthesis even better than the metal QD because of the required high energy transfer. Typically, carbon QDs are obtained by the thermal decomposition of organic compounds to carbon and residues. In order for the reaction to take place quickly, very fast heat exchange is required in the entire volume of the reactor. This makes it possible to obtain monodisperse QDs. Only microreactors provide such a possibility. Moreover, very often, the temperatures used are significantly above the boiling point of the solvent. This means that high pressures are required. In the case of microreactors, high pressures above 10 bar are not a technical problem. Depending on the design, glass microreactors can withstand pressures above 15 bar. PTFE microreactors can operate at temperatures up to 300 °C and pressures up to 50 bar. The use of other construction materials broadens the application possibilities. The past investigations often focused on QY as well as light emitted color. If we make a simple comparison of metal QDs and carbon QDs, we can note that carbon QDs exhibit much higher QY. Unfortunately, the color of the emitted light is still weakly controlled. A number of investigations in microreactors show that the color of emitted light can be controlled by appropriate experimental conditions, for example, flow rate. This is a clear advantage of microflow reactors in respect to batch reactors.

2.2. *Semiconductor nanoparticles - quantum dots*

Semiconductor nanoparticles - quantum dots (QDs) are nanocrystals capable of transporting electrons. This allows addressing applications that need tunable emission spectra, high photostability, resistance to photobleaching, and controllable surface characteristics [108-110]. Semiconductor nanoparticles are used, i.a., for bio-labeling of DNA, proteins, and cells [108-110].

Microreactors have been successfully used for the efficient synthesis

of those QDs [111-113]. CdSe quantum dots are most commonly prepared [41]. The popularity of CdSe nanomaterials has a historical and practical background. At the end of the 1970 s, Russian physicist Alexei Ekimov for the first time, synthesized nanocrystals of copper chloride and then cadmium selenide in a molten glass matrix [114], giving fundaments for studying semiconductor-doped glasses and developing theories to explain their observed properties. The preparation of II-VI systems such as CdSe also has comparative ease of synthesis [115].

The history of quantum dots is long [116] and started with the well-known structures of the CdX type (where X = S, Se, Te) [117]. Unfortunately, the use of cadmium and other elements such as Se, Te, limits the use of these quantum dots in nanomedicine [118,119]. However, those materials may find application in other areas. The flow synthesis of CdS was studied by Edel et al. [120]. The micromixer chip (volume 12 nL), two inlet flows (containing respectively sodium sulfide and cadmium nitrate) are split into 16 partial trims before bringing contact. After mixing, the channels are then sequentially recombined in a reverse network until all partial flows are united in one broad outlet channel.

Lignos et al. developed a droplet-based microfluidic platform for the controlled and reproducible synthesis of PbS and PbSe QDs [121]. PbS nanocrystals with high photoluminescence quantum yields of 28% were obtained. The authors confirm that the capillary reactor can generate highly monodisperse particles with diameters of 3.8 ± 0.2 nm and 4.5 ± 0.3 nm, depending on the experimental conditions. No detailed error analysis was performed, but it can be presumed that the size distribution is close to the error resulting from image analysis. As it can be seen from this paper as well as it was shown in other quantum dots can be tuned with high resolution by flow conditions [122].

Based on our own experience, CdX and PbX based quantum dots with narrow size distribution are easier to obtain than metal-based nanoparticles. Albeit the reasoning is fully not evident, it is probably related to the mechanism of the formation of these materials. The more are the intermediate steps; the greater seems to be the chance of the formation of highly polydisperse materials. In such a situation, concentration gradients, temperature gradients, *etc*. will cause an increase in polydispersity.

After several years, this topic became popular. This can be easily illustrated by the number of publications containing in the title, abstract, or keywords "CdSe and synthesis and quantum" or "CdSe and microreactor". Using the SCOPUS database (September 21, 2021), results given in Fig. 7 were obtained. As can be seen, the subject of CdSe material synthesis has lost some popularity. Since 2012, the number of publications related to the synthesis of CdSe nanoparticles is decreasing every year. The number of publications containing the word "microreactor" comprise only a minor part of the overall number of CdSe publications and do not exceed the number of five per year; they follow the same trend a show declining popularity in the last decade. If we will look at Fig. 4 and Fig. 7, we can see decreasing attention towards quantum materials based on CdSe. The research focus has shifted towards carbon quantum materials and quantum materials based on noble metals. In our opinion, this is due to several factors. The number of scientists in the world is only slightly increasing every year [123]. Therefore, it is not possible to devote the same amount of time to research on both types of quantum materials. Thus, the "popularity" of one must decline in order for another to take his position. An additional important factor causing a change in the intensity of CdSe research is the fact that the technology is mature. It has already had numerous implementations. This causes a reduction in resources for research in this field. On the other hand, new research on new materials gains new funding.

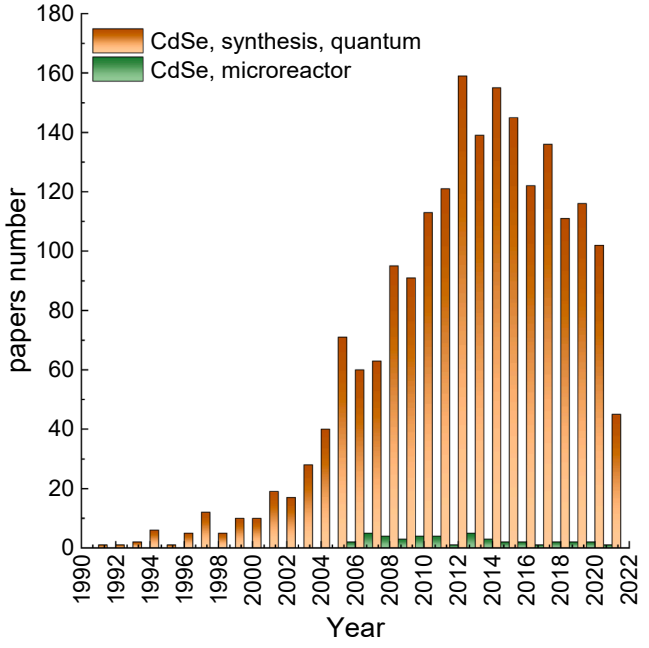

Fig. 7. Number of the paper about CdSe synthesis.

In respect to the CdSe quantum materials synthesis, continuous flow [124-126], supercritical processing [127], as well as droplet-based systems were used. Marre et al. [127] used, for the first time, supercritical conditions in a microflow system to synthesize CdSe QDs. The synthesis at supercritical conditions significantly narrows the size distribution of the CdSe QDs. Park et al. [125] synthesized core (CdSe) shell (ZnS) colloidal nanoparticles in a microreactor. They showed that, as to be expected, the particle size of the synthesized QDs is a function of the precursor flow rate. When the precursor flow rate increases, the size of the QDs decreases, and the bandgap energy increases. The photoluminescence properties were found to be strongly dependent on the flow rate of the CdSe precursor. In addition, this caused a gradual shift in the maximum luminescent wavelength (λ_{max}) to shorter wavelengths (blue shift). Mirhosseini et al. [128] synthesized CdSe in a continuous flow system and studied the influence of various parameters, such as temperature, residence time, and flow rate, on the CdSe QD optical properties and size. An increase in the synthesis temperature leads to a decrease in the QY. This dependence is linear in the temperature range from 240 to 270 °C. However, the correlation between emission wavelength and temperature of the synthesis turned out to be nonlinear. The QDs synthesized at temperatures of 240, 250, 260 and 270 °C emit light with the maximum wavelength of 500, 530, 560, and 560 nm, respectively. Marre et al. also synthesized CdSe QDs using high pressure, high-temperature microreactor and investigated the influence of temperature on optical properties and size [129]. The experiments were carried out in the temperature range of 180–350 °C. A nonlinear correlation was found between the reaction temperature and the particle size. The higher temperature allows for the synthesis of larger particles with a different emission maximum. Also, the influence of solvent type on photoemission maximum was shown. Generally, the PL curves from QDs synthesized in the different solvents show two main effects. The first one is related to the shift of the maximum emission going from viscous long carbon chain solvents to smaller molecule solvents. The second one is related to the narrowing of the PL curves as measured by a decrease in the full width half maximum. Yang et al. explored the scale-up of the CdSe QDs synthesis using a microreactor [130]. Based on the obtained results, the scaled-up synthesis of CdSe NCs was demonstrated, and a high quantity of 0.8 g dry CdSe NCs powder (3.5 nm, PSD 8.2%) was obtained within one h. This may open doors to a potential industrial application of microreactors in nanomaterial synthesis.

A more complex structure was obtained by Uehara et al. [124] using a continuous flow system. Core/shell/shell nanostructures were obtained consisting of ZnS/CdSe/ZnS multilayered composites. The core (ZnS) particles are spherical shaped and have a diameter 2.3 nm. The shell thickness was equal to 0.8 nm. This corresponds respectively 2–3

monolayers of CdSe and ZnS. The obtained composite material exhibits good PL QY equal to 50%. This work shows very well how precisely the production of nanomaterials/nanocomposites can be controlled when using flow microreactors. Similar core/shell/shell structures were described by Kikkeri et al. consisting of ZnS/SeTe/SeCd layers [131]. Depending on the experimental conditions (composition, solvent, and flow rate), the QY was varied from 8 to 23%. It can be predicted that the properties of core/shell or core/shell/shell composite materials strongly depend on the thickness and composition of each shell as well as on the size and composition of the core. Therefore it is very important to synthesize a core with a very narrow size distribution.

Hwan Kwak et al. have yielded monodispersive CdSe QDs using a droplet-base microfluidic reactor [132]. The size of CdSe QDs prepared using this system was from 1.6 to 2.6 nm, with an average size of 2.2 nm. The droplet-based microreactor made it possible to shorten the synthesis time below 30 s, which is much shorter than given for the batch reactor. Moreover, the residence times of the precursor solution in the oil bath were varied between 7, 15, and 30 s, to result in different optical properties of nanoparticles. The emission maximum depends on resident time and was equal to 500, 525, and 580 nm, respectively. A similar droplet-based system was used by Zeng et al. [133]. The fluorescence QY was greatly improved, with an increase from 0.15% to 2.91%, after a ZnS shell was coated outside the Ag_2S QDs. The average size of the QDs increased from 1.70 ± 0.4 nm to 1.85 ± 0.3 nm after covering Ag_2S by ZnS shell. The size precision setting is impressive, as the very narrow size distribution at the 0.3–0.4 nm level corresponds to no more than 1–2 monolayers of ZnS. Such precision of synthesis is close to the pinnacle of technical possibilities. The first works on the synthesis of CdS QDs were published in 2002 by Edel et al. [120,134]. Almost two decades later, using the same synthesis strategy, it is possible to obtain particles with a size distribution comparable to atomic layers [57,133]. Low-temperature synthesis of tetrapod CdSe/CdS quantum dots through a microfluidic reactor was reported by Weishuo Xing [135]. In this case, low temperature means 120 °C. Previous reports presented test results obtained at temperatures above 200 °C [128,129]. This is a significant change. The lower synthesis temperature means lower production cost as well as substantially simplifies the synthetic chemistry for the anisotropic growth of CdS on CdSe QDs.

The microflow reactors allow not only to obtain high precision but also to prepare different components of QDs. Hu et al. [136] realized $CuInS_2$/ZnS composites in a flow system consisting of 4 microchips.

In this particular case, the obtained composite was functionalized using BSA. The emission wavelength of dBSA-$CuInS_2$/ZnS QDs was found in the near-infrared range and can be tuned from 650 to 750 nm by varying the reaction parameters. The authors used simulation software (ComsolMultiphysics) to predict optical properties using reaction engineering, chemistry, transport of diluted species, and laminar flow built-in mathematics models. The obtained QDs were used for cell imaging and cell viability for HepG-2 and Panc-1 cells. The obtained QDs are suitable for direct usage in cell and tumor in vitro imaging work. It is worth emphasizing here that, in fact, the obtained composite does not contain toxic elements, unlike the popular CdSe.

The composite QDs $LiFePO_4$ and CdTe@$CePO_4$ were synthesized by Wang et al. [137] and Fang et al. [138], respectively. Wang et al. aimed at a material that could be used in batteries. Therefore, one of the ingredients is lithium. The QDs of CdTe@$CePO_4$ are uniform with a tunable size of the CdTe QDs, which gives rise to tunable emission from green to red color. It was underlined that for the CdTe-decorated $CePO_4$ nanorods, energy transfer from Ce^{3+} to CdTe is observed, which allows CdTe to be excited at shorter wavelengths.

Indium phosphide QDs are of significant interest for use in optoelectronic devices, specifically as a replacement for CdSe nanocrystals. The synthesis protocol of InP using a continuous flow microreactor was described by Baek et al. [139]. Their continuous flow three-stage silicon-based microfluidic system consisted of mixing, aging, and sequential injection stages operating at a pressure of 65 bar. Thanks to the application of high pressure, low-molecular-weight solvents can be utilized for QDs synthesis. Using this system, it was possible to synthesize InP QDs in 2 min.

The droplet-based microreactor was also used for the synthesis of water-soluble Ag_2S quantum dots [140] and CdTe [141]. The main advantage of using droplet-based microreactors is the lack of contact of the reactants with the walls (liquid / liquid droplets) [142]. This allows to eliminates the risk of the material slowly settling in the lumen of the channel, which may consequently lead to blockage.

From the biomedical point of view, ZnO QDs are a suited material matching the high safety aspects for human applicability. It is well-known from the literature and our daily life experiences that ZnO can be used in cosmetics and as a diet supplement. A significant number of scientific paper has been given for the ZnO synthesis, yet mostly in a batch reactor and only a few times in a microreactor. Schejn et al. [143] describe a simple method for PL tenability of ZnO QD. The temperature, flow condition as well as the capping ligand were varied. In the temperature range of 20 to 80 °C, the QD size changes from 3.6 to 5.2 nm. It was found that propionic acid as a stabilizing agent is favorable for the production of ZnO QDs with high photoluminescence quantum yields (up to 30%). It is worth noting that propionic acid is used in the food industry as a food preservative with the symbol E280. Thus, the obtained material is likely to be biocompatible; yet such studies are lacking. Yang et al. [144] studied ZnO synthesis with the aid of ultrasound in a microflow reactor. A high QY of 42.5% was obtained. This value is significantly higher as compared to Schejn et al. [143]. Unfortunately, the obtained material has a low potential for biomedical use because of application during the synthesis TMAH (Tetramethylammonium hydroxide). This chemical reagent is strongly toxic.

QDs with the general composition of MeS are often discussed and described in the literature, Me being a metal or semi-metal. Such QD is easy to synthesize. CdS and CdS/ZnS (core/shell) nanocrystals with in situ monitoring of the reaction progress were reported by Gomez-de Pedro et al. [145]. In this paper, a ceramic microreactor is controlled in real-time and with the integration of an optical detection system for absorbance and fluorescence measurements based on commercial miniaturized optical components. This type of microreactor not only can be fully automatized but also provides an efficient tool for QD synthesis. The QY reached 27%. PbS QD was synthesized by Pan et al. [146]. This work is particularly important as it emphasizes the possibility of full automation of QD production processes in continuous flow reactors. From this technology advancement, the door is open for applying artificial intelligence and/or machine learning to design and manufacture nanomaterials with tightly controlled properties [147]. As it was shown by Andrea Knauer and J. Michael Koehler [148] it is possible today to a screening of nanoparticle properties in microfluidic syntheses.

A new strategy for synthesizing $AgInS_2$ quantum dots emitting brightly in the near-infrared window for in vivo imaging was shown by LianjiangTan et al. [149]. This compound exhibit very interesting quantum properties, thanks to NIR fluorescent nanocrystals having huge potential for biomedical applications. The same QDs were synthesized in a microreactor several years later [150]. Thanks to the application of microreactor it was possible to obtain online fluorescence regulation through temperature control. The results showed that with the increase of reaction temperature, the obtained $AgInS_2$ QDs size increased and the fluorescence peak constantly red-shifted along with enhanced fluorescence intensity. The next step in the development of $AgInS_2$ QDs manufacturing technology was the use of microdroplets for syntheses. As is well known, microdroplets accelerate the mixing of the reagents. In order to accelerate the process of homogenization of the composition, ultrasounds have been additionally introduced [151]. Thanks to that, the mass transfer coefficient in the droplets microreactor was enhanced by 72.5 %.

3. Conclusions

The association of microreactors and quantum dot (QD) nanoparticles started more than a decade ago with semiconductor material synthesis, which was popular at that time. In fact, microreactor investigation always followed the temporary popularity of the QD nanomaterials; they hardly were used for the finding of new nanomaterial systems, e.g., as could have been done by high-throughput screening. Once a new class of nanomaterials became popular, microreactor studies switched to it. In the same way, the intensity of the microreactor studies followed the strength of the overall QD nanomaterial studies. Once the latter peaked and declined, the microreactor studies became less frequent as well, with some short time delay. This shows that nanomaterial researchers themselves governed largely the research innovation and interest; being interested in the "new tool" microreactor to test for the quality of the nanomaterials produced and their performance in various applications. In turn, this means that possibly opportunities in the nanomaterial synthesis invention itself might have been missed as well as a thorough engineering study to explore all opportunities, especially under new conditions, e.g. so-called novel process windows [152,153] The latter is, however, not completely true, as the nanomaterial synthesis has at least been done under supercritical conditions, and the results were promising. Thus, this review pledges to apply the engineering and particularly process engineering opportunities of microreactors more consequently.

The first investigations in microreactors focused on semiconductor QDs, as said. This is a high-temperature synthesis. While advanced thermal reaction guidance as such is 'homeplay' for microreactors, the speed of the temperature change is the crucial point for the semiconductor QD synthesis. Microreactors generally can offer fast temperature switches, yet the typical timescale of the nanomaterial synthesis is in the order of milliseconds. Such fast change can be better accomplished by mixing in microreactors. Therefore, the literature shows many reports using micromixer devices for nanomaterials, and those have been applied for metal QD synthesis, which is the second chapter in this review. The past investigations often focused on easily changeable parameters such as the flow rate (which promotes mixing) and the variation in adding reactants (e.g. reductants), either right from the start (all reactants together) or step by step (in consecutive microreactor synthesis). With the latter two approaches alone, a number of investigations in microreactors for creating diversity in the QD nanomaterials and their properties have been reported. This review pledges again to wide the scope of engineering and process engineering opportunities of microreactors more comprehensively and systematically.

To sum up, the potential of microreactors for QD nanomaterial synthesis has been largely explored in the last decade; yet there is nonetheless considerable room for further substantial improvement by more consequently using the engineering and process engineering space. More process engineers and microfluidic experts should approach the field of QD nanomaterial synthesis rather than in the opposite way. Still, the more relevant movement at this point of time seems that QD nanomaterials enter commercial applications, and there is a pull from industry and the market. That would motivate scale-up developments. The same happened with the application of microreactors for pharmaceutical manufacturing. Around 2007 an industrial roundtable of the pharmaceutical industry formed (at the American Chemical Society) happened and led to new momentum for the whole scientific field. Such closing of ranks is needed for the QD nanomaterials.

In order to emphasize how dynamically the world of quantum materials is, we should look at the number of review papers that are being created [154,155], which are showing the steep gradient in innovation and approaches with which the field develops after 2–3 years [156].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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