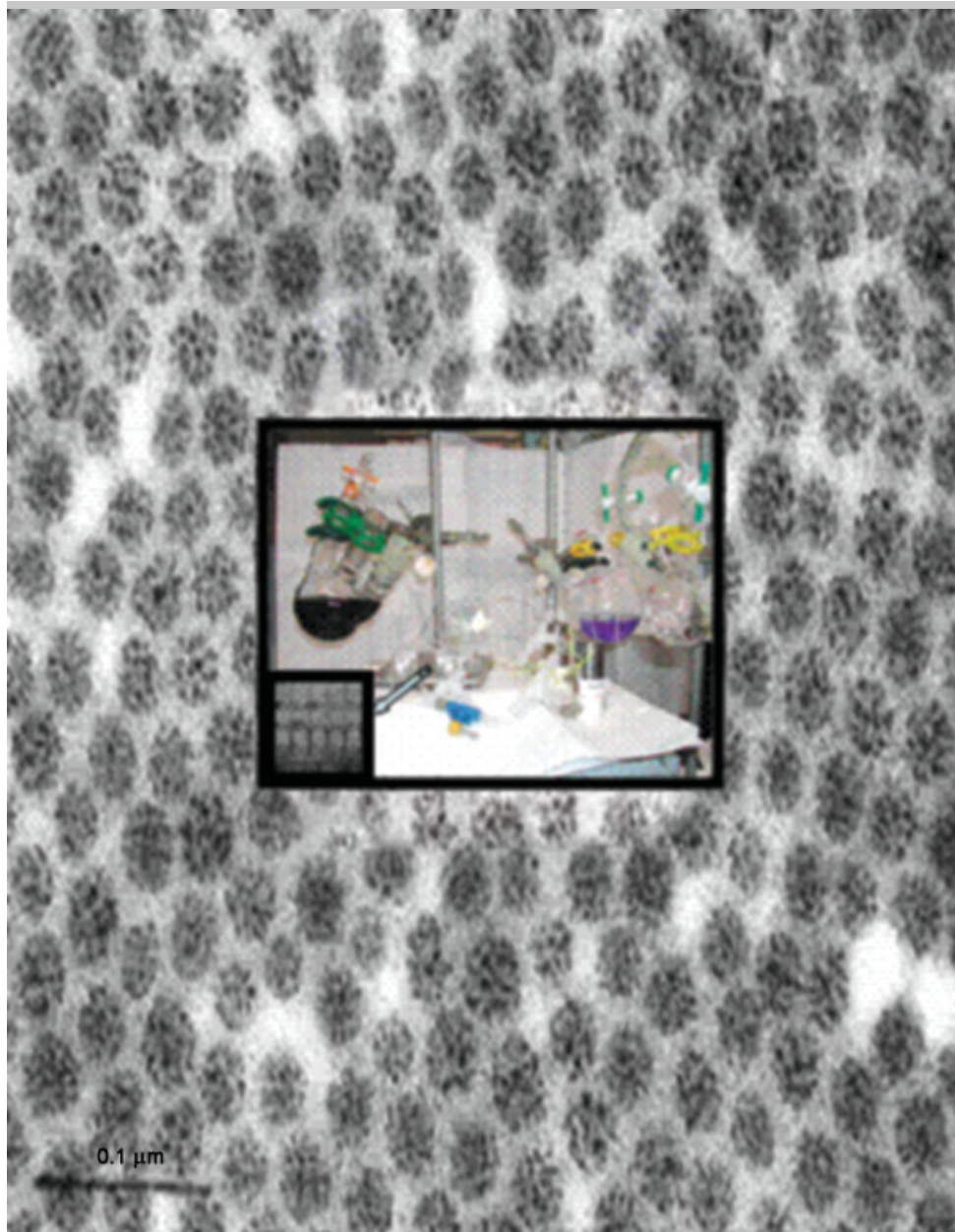


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Microfluidic Synthesis of Nanomaterials

*Yujun Song, Josef Hormes, and Challa S. S. R. Kumar**



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An overview of the current information and analyses on the microfluidic synthesis of different types of nanomaterial, including metallic and silica nanoparticles and quantum dots, is presented. Control of particle size, size distribution, and crystal structure of nanomaterials are examined in terms of the special features of microfluidic reactors.

1. Introduction

Microfluidic reactors, a part of the vast field of micro-fabrication, deal with the flow of minute amounts of liquid within micrometer-size channels. Although microfluidic reactors were first developed in the early 1990s, state-of-the-art developments in recent years in the design, fabrication, and utilization of microfluidic devices have found many applications in pharmaceutical, biotechnology, and chemical industries for applications such as fine chemical synthesis, diagnosis, crystallization, combinatorial synthesis, rapid chemical analyses, and high-throughput screening.^[1–3] In addition, several possibilities to fabricate three-dimensional (3D) networks of nanoscale flow paths and the ability to focus nanoparticles within microfluidic systems are beginning to open up^[4,5] and are likely to lead to unique microfluidic, even nanofluidic,^[6] designs and reactors for a newer variety of applications. Therefore, it is not surprising that these developments in microfluidic devices coupled with nanotechnology are beginning to pave the way for growing numbers of investigations to replace, in the future, conventional synthesis of nanomaterials by lab-on-a-chip systems.

Microfluidic reactors offer many potential advantages in the chemical industry due to superior reaction control, high throughput and safer operational environment.^[1,2] Complications in traditional batch processes associated with large-scale transport and storage as well as safety and health issues (such as explosion and leakage of toxic and flammable solvents) are minimized.^[7,8] Process scale-up, based on the concept of parallel processing, with a precise control of the synthetic aspects of the final product to produce chemicals with well-defined and pre-determined properties in higher yields, has been well demonstrated.^[1,2,7–9] The option of manipulating and controlling additional reaction parameters, compared to traditional batch processes, such as flow rates and the ability to cease the reaction as soon as the product is formed in a microliter or even nanoliter volume, offers even more possibilities for product control.^[9]

Fundamentally, it is pertinent to understand the various forces and interactions within the microfluidic environment that impact the outcome of a reaction. In addition to producing diffusive mixing, an inherently high surface-to-volume ratio enables heat generated by exothermic reactions to be dissipated rapidly, thereby creating more “active sites” for reactions.^[10] The impact of surface forces (e.g., surface tension), electrical effects, van der Waals interactions and surface roughness of the channel side walls become more significant and often dominate the particle motion, particularly for nanometer-sized materials (such as proteins, DNA,

nanocrystals, etc.).^[11] The possibility to create complicated 3D fluidic geometries^[4,5] offers unique opportunities to manipulate these surface forces as their effects on nanometer-sized materials are significant. In addition to the “laminar flow-dominant” microfluidic reactors, “segmented flow” microfluidic reactors are providing alternate approaches to chemical syntheses.^[3c,12] Through the possibility of introducing time-control parameters (flow rates and sequence of reagent addition), reactions can be controlled at different stages, resulting in a flexible kinetic control and reactor design according to the reaction mechanism. The main advantage, as well as a challenge, in using microfluidic approaches is the possibility to creatively use these different effects and reaction parameters to produce tailor-made nanomaterials.

While the recent publications clearly demonstrate the potential of microfluidic reactor technology in chemical syntheses, we believe that microfluidic reactors are likely to play an extremely important role in nanomaterials synthesis. Nanomaterials are finding a number of unique applications in a broad range of fields such as catalysis, biomedical, electronics, and the environment.^[13] As they exhibit a variety of size-, shape-, and crystal-structure-dependent physical and chemical properties, their synthesis requires superior control of reactions, both kinetic and thermodynamic, in order to produce materials of required features and properties.^[14] The role of microreactors in nanomaterials synthesis is therefore primarily in three areas: 1) size-, shape-, and structure-controlled syntheses, 2) scale-up through continuous flow processes, and 3) high-throughput tools in process development. The Review presented here provides up-to-date information and analysis on microfluidic synthesis of nanomaterials. It also compares the efficiency of microfluidic reactor processes with the conventional batch processes. Syntheses of different types of nanomaterial (nanoparticles, nanowires, nanotubes, etc.) using microfluidic reactors are also reviewed and attempts to find explanations for the claimed control over particle size, size distribution, and crystal structure of nanomaterials, vis a vis special features of microfluidic reactors, have also been made. As results reported in the majority of the publications are more qualitative than quantitative, it is rather difficult to obtain a complete and clear picture about the potential of microfluidic reactors for nanomaterial synthesis. Nevertheless, we can draw

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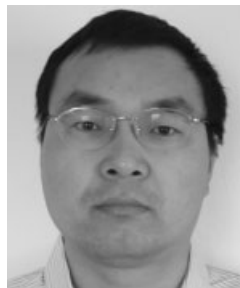
some valuable conclusions and lessons. In addition, we anticipate that the topic is of interest to a large group of scientists and this Review will serve as a guide, generate enthusiasm, and spark new developments in the field of “microfluidic synthesis of nanomaterials”. The Review is divided into three major sections. In the first section, an overview of microfluidic reactors is provided for those who are not familiar with microfluidic reactor technology. The second section contains an analysis of controlled synthesis of nanomaterials using some of the unique features that microfluidic reactors offer. Finally, the last section presents some important conclusions on the status, trends, and a future perspective of this new technology.

2. Microfluidic Reactors: An Overview

The fabrication of microfluidic reactors can be divided into four major stages: in the first stage, microstructuring of wafers and polymer substrates to form microchannels is carried out by various microfabrication processes. The microstructures, which may be endowed with functional surfaces, are designed to function as catalytic reaction channels or micromixers, microensors, microseparators, and so on. In the second stage, microstructures are sealed and then bonded to a substrate by welding, gluing, or by using any other suitable bonding process. In the third stage, integration of various components such as microparts (mixers, actuators, pumps, separators, and heat exchanger) is carried out to form a microfluidic device. In the final stage, the microfluidic device is connected to the macroscale world to provide the microparts with energy and the chemicals necessary to carry out chemical synthesis, to collect the products and to analyze product/process development data, if necessary. More specific details on several types of microfabrication processes can be found in several review articles.^[15]

A microfluidic device, in general, needs to be integrated with various components such as micromixers, microscale heat exchanger, micropumps, microensors such as pressure and flow sensors, microextractors, and microactuators depending on the nature of the reaction being carried out and the type of application. To date, fabricating a single microscale reactor chip with all the microcomponents integrated is still a challenge. Also, providing flexible connections with macroscale feed and detector is still not a trivial task. Usually, screws or orifice holes are designed in the substrate (e.g., glass, polymers) itself and the tubing from the external devices (such as syringe pumps, product collectors) is connected by direct gluing to the opening parts of the microfluidic reactor through fittings and nuts.^[10b,16–18] The microreactors used for nanoparticle synthesis usually have micromixers, microchannels, and microheaters in a single reactor chip.^[19,20–26]

While the majority of studies on nanomaterial synthesis reports using microfluidic reactors are based on conventional laminar flow, other reactor designs such as tubular reactors, segmented-flow reactors, microstructured mixers, and microfluidic droplet reactors are also beginning to show promise.^[27–29] Inherent problems associated with laminar-flow-based microfluidic reactors such as velocity and residence



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time distributions are to a certain extent addressed in segmented-flow microfluidic reactors, leading to better control over nanoparticle size distribution. However, the problem of physical contact of the particles with the walls of the reactor channels, resulting in cross contamination and significant volume changes due to gases utilized, still exists. One possible solution for these problems is to use microfluidic droplet reactors, where the precursor solutions can be encapsulated within nanoliter-scale droplets of the carrier fluid. Two microfluidic devices based on the concept of droplet reactors have been reported for the synthesis of nanoparticles. In the first device, as shown in Figure 1, a polydimethylsiloxane (PDMS)-based reactor was fabricated with microfluidic channels approximately 50 μm high, 50 μm wide, and 24.5 mm long based on rapid prototyping in PDMS.^[27,30,31] In the second device, as shown in Figure 2, a glass-based microfluidic reactor with a droplet jet injector was specifically fabricated for the high-temperature synthesis of quantum dots (Q dots).^[29,32] In addition to the droplet generator, the microfluidic reactor was designed to include 200- μm -wide heated serpentine channels, with semicircular turns intended for mixing, thermocouple wells, and inlets.^[33a] An out-of-plane expansion with sharp increase in channel height at the beginning of the nozzle was designed for producing monodisperse emulsions.^[32] The microfluidic droplet reactor can be used to manipulate droplets over a wide range of flow rates with the ability to form droplets at a low viscosity ratio of the two immiscible liquids at high capillary numbers and temperatures.

Though the techniques for microfluidic device fabrication have seen some rapid developments, especially for fabrication of microstructures that serve as pipes, valves, mixers, pumps,

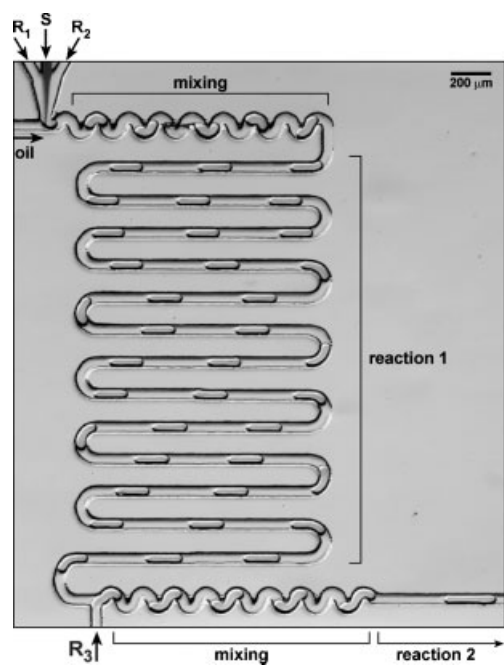


Figure 1. Micrograph of a PDMS microfluidic device for performing droplet based synthesis of nanoparticles. Reproduced with permission from Reference [27].

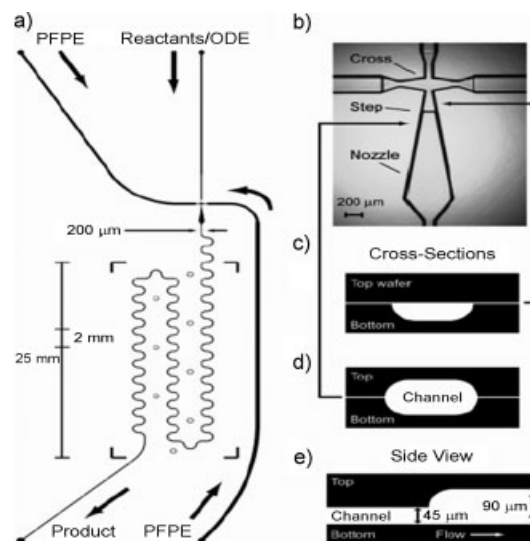


Figure 2. Microreactor with droplet jet injector. a) Channel schematic showing dimensions, inlets (b), thermocouple wells (O), and boundaries of Kapton heater (square brackets). b) Optical micrograph of droplet-injection cross section. Octadecene is injected in the top channel, while the PFPE is injected in the side channels. The narrowest point is 160 μm wide. c) Lateral “D”-shaped cross section of channel etched on the bottom wafer only. d) Cross section of ellipsoidal channel etched on both top and bottom wafers. e) Axial cross section showing the 45- μm step up in channel height. Reproduced with permission from Reference [29].

and so on, there is a need for further investigation into further improving the fabrication processes, utilization of appropriate materials, and, most importantly, in integrating microprocessing components related to the microfluidic reactor system (such as micropumps or electro-osmosis parts, microheaters, microseparators). The interested reader can refer to the text by O. Levenspiel for more information on designing continuous-flow reactors.^[33b]

3. Unique Features of Microfluidic Reactors for Controlled Synthesis of Nanomaterials

Nanoparticles exhibit a variety of size-, shape-, and crystal-structure-dependent physical and chemical properties.^[8,9,34–37] Synthesis of nanoparticles, therefore, requires superior control of reactions, both kinetic and thermodynamic, in order to produce materials of required features and properties.^[9,34,35,37–40] Some of the challenges, particularly in the control of particle size, have been overcome using traditional wet-chemical methods.^[41] For example, reactions using inverse micelles,^[42–44] polymer templates,^[45–47] mesoporous ceramic hosts,^[48,49] and high-temperature hydrolysis^[36,50–55] have been employed to obtain nearly monodisperse nanoparticles. However, most of the traditional approaches usually require multipurification steps in order to obtain stable monodisperse nanoparticles.^[55] Nanoparticles made by using physical techniques such as laser vaporization,^[56,57] sputtering,^[58a] metal evaporation,^[59b] and grinding (ball milling)^[60] usually produce “naked” nanoparticles.^[46] These are easily

oxidized and agglomerate intensively, thereby decreasing the post-synthesis processing ability for their practical applications.^[60] Small production rates and expensive equipment also limit the commercialization of these “physical” methods.^[9,34,35,37,61,62] Unlike the physical methods, most wet-chemical methods, involving liquid-phase synthesis, can provide larger amounts of nanoparticles conveniently coated with organic stabilizers to protect them from aggregation and, possibly, oxidation from air, in some cases, using relatively simple equipment, which is crucial for commercialization.^[42] A majority of the liquid-phase reactions are usually performed at high temperature ($\approx 200^\circ\text{C}$), limiting the choice of solvents and reagents. Metal-salt reduction to obtain nanoparticles is widely used in liquid-phase synthesis. However, chemical contamination of the final product from reducing agents, solvents, and other reagents utilized in wet-chemical synthesis is unavoidable.^[36,50–61] Since it is difficult to control the reaction conditions precisely on a large scale in a liquid-phase synthesis, there is a need for using microfluidic-reactor-based synthetic methods where a better control over reaction conditions is expected to provide monodisperse nanoparticles of a defined size, shape, and crystal structure without recourse to multipurification steps.^[36,45,50,63]

The six key challenges in the wet-chemical synthesis of nanomaterials are: 1) Can we synthesize monodisperse nanoparticles of a desired size? 2) Can we obtain nanomaterials with satisfactory crystallinity and the desired crystal structure and composition, particularly for alloy nanoparticles? 3) Can we synthesize nonspherical, that is, anisotropic nanomaterials? 4) Can we fine tune interactions between the stabilizing ligands and the nanoparticle surface, not only for better compatibility in the required application system but also for controlling the properties? 5) Can we ensure self-assembly of the nanoparticles on a desired substrate with desired geometrical patterns? 6) Can we produce nanomaterials with desired properties on a large scale?

Over the past couple of years, preliminary experiments using microfluidic reactors demonstrated that physical properties of a variety of nanomaterials, such as quantum dots, nanoparticles, nanotubes, nanowires, and nanocomposites can be fine tuned through control of nanocrystal growth parameters and kinetics.^[19–21,23–25,64–66] In addition to the majority of laminar-flow-based microfluidic approaches, microfluidic droplet techniques for nanoparticle synthesis have also been found to be promising.^[27–29] Based on these results from initial investigations, one can anticipate that microreactors are likely to provide cost-effective and environmental friendly technologies for the rational design and synthesis of nanoparticles. Also, process scale-up either by utilizing several thousands of microreactors in parallel or using continuous-flow reaction protocols can provide several advantages in large-scale production of nanoparticles.^[8,10,11,61] Some of the unique features of microfluidic reactors are the ability to:

- efficiently mix reagents, using appropriate mixers, on a short time scale, resulting in an homogeneous reaction environment throughout
- investigate the fundamentals of nanoparticle formation through spatial resolution
- operate within continuous flow regimes allowing additional reagents to be added downstream as required
- control properties of nanomaterials by controlling their formation at the desired nucleation or growth stage
- continuously vary the composition of a reaction mixture by varying differential injection rates of the inlet channels
- scale up the synthesis with controlled kinetic parameters

These features endow microfluidic devices with the significant potential to resolve many of the current issues in the wet-chemical synthesis of nanomaterials.

The development of microfluidic devices for the synthesis of nanomaterials is still in its infancy. There is yet to be a clear demonstration of their superiority over “flask” reactions. However, the available information from the literature (as described briefly in the following examples) indicates that there is a potential for obtaining better control in size, size distribution, crystal structure, and shape of nanomaterials on both small- and large-scale processes.^[9,18,34,64] Given below are some examples from the literature that illustrate how the above-mentioned critical features of microfluidic reactors are being utilized for the controlled synthesis of nanomaterials.

3.1. Micromixing

Several approaches to offset the negative impact of laminar flow and the absence of turbulence in the microchannels have been undertaken in order to increase the efficiency of mixing and thereby improve the monodispersity of synthesized nanoparticles. For example, Edel et al. demonstrated the synthesis of CdS nanoparticles in a continuous-flow microfluidic reactor with a micromixer based on the principle of distributive mixing (Figure 3a).^[19] In contrast to the nanoparticles synthesized in traditional flask reactions (inset curve in Figure 3), nanoparticles synthesized in the microfluidic reactor showed a sharper decline in

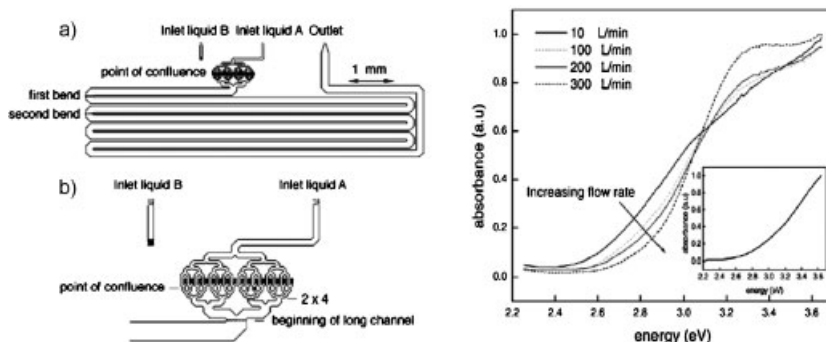


Figure 3. a) Typical micromixer fabricated in a glass/silicon/glass sandwich for CdS nanoparticles; b) absorption spectra of fluid streams exiting the micromixer chip subsequent to mixing of cadmium nitrate and sodium sulfide solution as a function of volumetric flow rate. Graph: absorption spectrum of nanoparticles produced by mixing bulk solutions (750 μL). Reproduced with permission from References [19] and [26].

polydispersity tending towards monodispersity rather than a gradual increase in polydispersity. Over all, it appears that, just downsizing the reaction vessel from bulk to microliter volume is sufficient to improve monodispersity of the nanocrystallites. The nanoparticle aggregation on channel surfaces is a common occurrence within microreactors having simple T-mixer geometries. In order to overcome this, an innovative microreactor system with a radial interdigitated mixer, as shown in Figure 4, was utilized for the synthesis of nanoparticles of gold stabilized by an adsorbed monolayer of a thiol (monolayer-protected clusters).^[67] Efficient mixing in the microfluidic syntheses produced particles with improved monodispersity with the standard deviations of particle size range between 0.6 and 0.9 nm in comparison with those obtained from the bulk syntheses, which vary between 1.3 and 2.1 nm.

Size-controlled Pd nanoparticles were also demonstrated using a polymer-based microfluidic reactor with mixing elements.^[9] The completely polymeric microreactor used in this study is shown in Figure 5a. The microfluidic reactor, fabricated using SU-8 on a polyetheretherketone (PEEK) substrate, was found to be tolerant of a variety of organic solvents. It has five parallel reaction channels on a single $10 \times 10\text{-cm}^2$ chip and the flow rate in the channels can be varied from $120\text{ }\mu\text{L min}^{-1}$ to $2400\text{ }\mu\text{L min}^{-1}$. In order to ensure that the reagents mix rapidly (fast on the time scale of the reaction),^[68,69] two four-way mixers (Figure 5b) are incorporated into the reactor. Two additional four-way mixers were included to enhance the mixing efficiency and to prevent back flow. Pd nanoparticles obtained from the microreactor have a

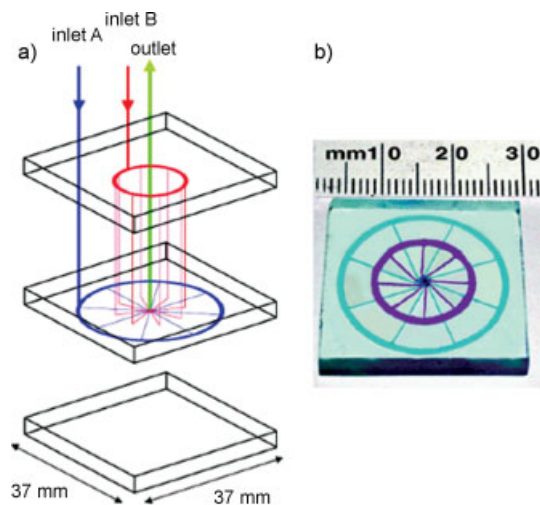


Figure 4. a) Three-dimensional schematic of a radial interdigitated mixer. Each mixer is fabricated in three layers. In the first two layers, input flows are directed to two circular bus channels which, in turn, split the flow into eight identical fluid laminae and deliver reagent streams towards a central mixing chamber. The final layer acts as a cap to enclose channels and as a guide for input and output capillaries. The output is from the centre of the uppermost layer. b) Photograph of the fabricated mixer. Microchannels are filled with dye solutions to show different shadings for the different channels. Reproduced with permission from Reference [67].

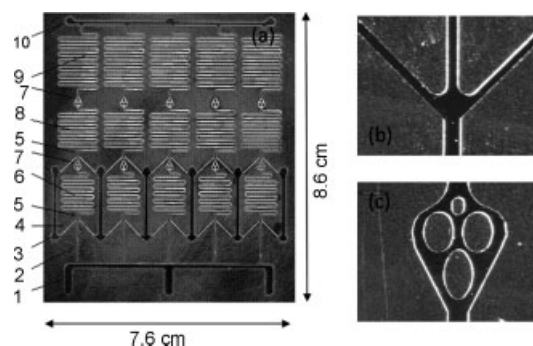


Figure 5. a) Schematic of the microreactor: 1) Orifices to Feed A reservoir, \varnothing 1.6 mm; 2) Feed A (metal salt THF solution) inlet channels, $150\text{ }\mu\text{m}$ wide and 9.5 mm long; 3) orifices to Feed B ($\text{LiBH}(\text{C}_2\text{H}_5)_3$ THF solution) reservoir, \varnothing 1.6 mm; 4) Feed B inlet channels, $100\text{ }\mu\text{m}$ wide and 5.5 mm long; 5), Four-way mixers; 6, 8, 9) reaction channels, $300\text{ }\mu\text{m}$ wide and 70 mm long for (6), $400\text{ }\mu\text{m}$ wide and 120 mm long for (7), $400\text{ }\mu\text{m}$ wide and 160 mm long for (8); 7) four-pole mixers, smallest poles, $100\text{ }\mu\text{m}$ wide; 10) orifices to product collector, \varnothing 1.6 mm. b) Four-way mixer. c) Multipole mixer. Reproduced with permission from Reference [16].

smaller mean particle diameter of 3.0 nm, with a narrower size distribution, in comparison to those obtained from the flask process.^[9]

Apart from the examples given above, recent investigations have also focused on alternate ways to improving mixing efficiency and control of the concentration of reagents through microfluidic droplet fusion techniques, both at room and higher temperatures.^[27–29]

3.2. Spatial Resolution of Kinetics

In addition to the possibility to provide opportunities to control the properties of the nanomaterials produced within the microreactor, the microfluidic system provides a unique platform for investigating the fundamental reaction processes through spatially resolved analysis of nanoparticle formation within the channels. This was recently demonstrated in our laboratory. Using a PMMA microreactor, cobalt nanoparticle formation was probed at three different positions using synchrotron-radiation-based X-ray absorption spectroscopy.^[70] CoK-edge XANES spectra recorded at three different positions of the microchannel together with reference spectra of the precursor and the final product collected at the end of microfluidic system show that time resolution of the reaction (in the order of milliseconds) is obtained by spatial resolution within the microreactor. Similarly, Sounart et al. have recently reported spatially resolved photoluminescence imaging and spectroscopy of Q dot formation within a microfluidic reactor.^[71b] The results from their investigation have provided direct insight into the kinetics and mechanistic data on the Q dot formation (Figure 6). The study also shows how a diffusion-controlled reaction environment forces the nanoparticles to nucleate under uniform conditions of negligible precursor concentration in a narrow region at the centre of the channel.

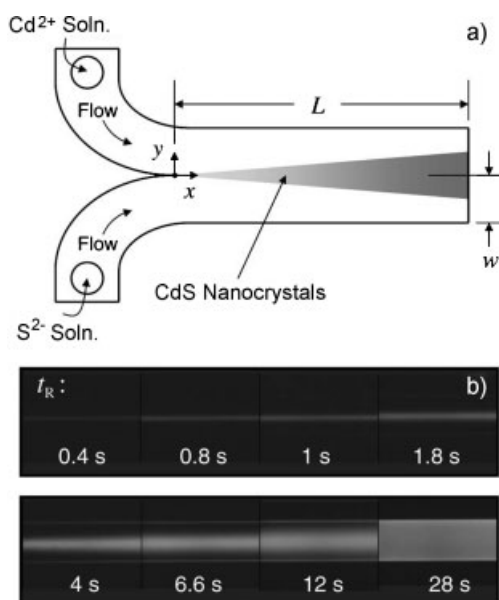


Figure 6. Continuous flow microfluidic reactor used for observation of CdS-Cys NC synthesis at the boundary between two laminar flowing streams. a) Sketch of microfluidic device (channel width exaggerated); $w = 100 \mu\text{m}$, $L = 2 \text{ cm}$, depth $2h = 20 \mu\text{m}$. b) Fluorescent plume of CdS NPs, 25 mM CdSO_4 , $\text{Cd:S} = 1:1$, $\text{Cys:Cd} = 4:1$. Reproduced with permission from Reference [71].

3.3. Online Variation of Reactant Composition

Wet-chemical synthesis of nanomaterials using microfluidic reactors can also take advantage of yet another unique ability of the microfluidic reactor to operate within continuous-flow regimes allowing additional reagents to be added downstream as required. Such a feature allows for pre and post treatment and multistep synthesis in a single continuous-flow regime. Shestopalov et al.^[27] carried out a multistep synthesis of Q dots at room temperature using the microfluidic droplet reactor shown in Figure 1. The advantage of using such a reactor is that the reaction can be controlled on a millisecond time scale. Such a segmented-flow microfluidic approach temporarily isolates the reactants from the channel walls minimizing or eliminating cross contamination. As can be seen from the figure, aqueous streams of a mixture of CdCl_2 , mercaptopropionic acid (MPA), and Na_2S are injected into the reactor through the left and right inlets, with NaOH solution infused through the middle aqueous inlet. Droplets are formed when the aqueous streams flow into the flow of oil within 5 ms (Figure 7). The reaction is allowed to take place for 75 ms and then quenched using MPA to improve the monodispersity of the particles obtained. A comparison of the reactions, with and without the use of a microreactor indicates better control over particle size distribution when the microreactor was used. The ratio of CdCl_2/MPA to Na_2S had an effect on the particle size. A twenty fold increase in the ratio resulted in obtaining smaller CdS particles. A more startling finding is that when the reaction was quenched using Na_2S instead of MPA, larger CdS particles with Na_2S -rich shells were obtained. These observations logically led to the development of a microfluidic droplet reactor for synthesis

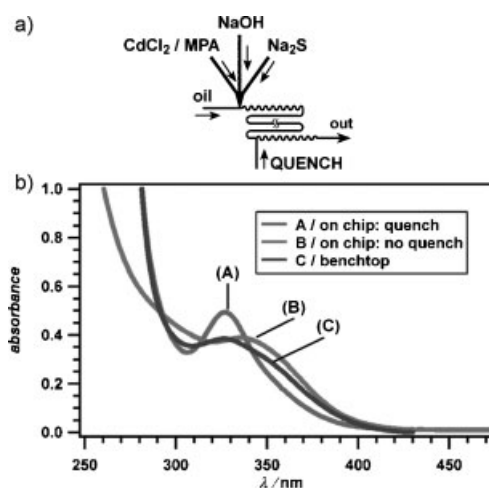


Figure 7. Two-step synthesis on chip with millisecond quenching yields CdS colloidal nanoparticles that are less disperse than those synthesized without millisecond quenching. a) A schematic diagram of the microfluidic network. b) UV/Vis spectra of nanoparticles synthesized on chip with millisecond quench (A), on chip without quench (B), and on the bench top (C). Reproduced with permission from Reference [27].

of core/shell nanoparticles. When the reaction was quenched using Na_2Se instead of Na_2S , CdS core/CdSe shell Q dots were obtained (Figure 8). Findings such as these illustrate yet another unique feature of the microfluidic device for synthesis of nanoparticles where, in a single step, core/shell nanoparticles can be obtained. The core/shell nanoparticle synthesis using microreactors therefore has advantages such as the ability to control overcoat thickness, avoid secondary

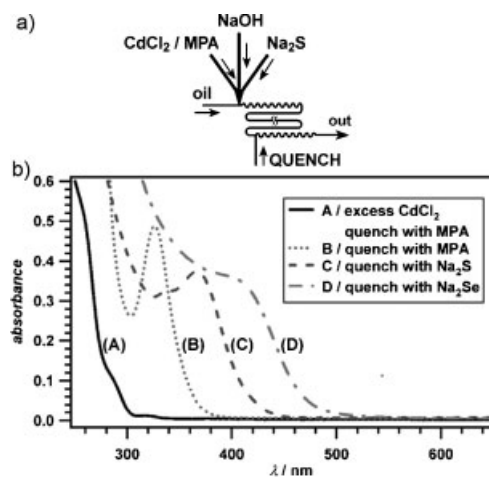


Figure 8. Two-step synthesis of nanoparticles with various sizes and composition. a) A schematic diagram of the microfluidic network. b) UV/Vis spectra of four different types of nanoparticle. A) CdS nanoparticles synthesized using a 20:1 ratio of CdCl_2 to Na_2S with thiol quench. B) CdS nanoparticles synthesized using a 1:1 ratio of CdCl_2 to Na_2S with thiol quench. C) CdS nanoparticles synthesized using a 1:1 ratio of CdCl_2 to Na_2S with Na_2S quench. D) CdS/CdSe core/shell nanoparticles synthesized using a 1:1 ratio of CdCl_2 to Na_2S with Na_2Se quench. Reproduced with permission from Reference [27].

nucleation and aggregation, and maintain a narrow particle size distribution. This was also recently demonstrated by coating colloidal silica core particles with titania layers of tunable thickness in a one-step, continuous-flow process through controlled hydrolysis of titanium tetraethoxide (TEOT).^[71a]

3.4. Separation of Nucleation and Growth Stages

According to the generally accepted mechanism of nanoparticle formation in a wet-chemical synthetic reaction, as proposed by LaMer and Dinegar,^[66] there are four distinct stages involved: supersaturated solute formation, nucleation, growth, and aggregation. The solutes (or the dissolved atoms or molecules forming the particles) are formed by chemical reactions (e.g., metal-salt reduction, decomposition of organometallic compounds, etc.). As the solute concentration increases above the super saturation limit, eventually reaching a critical concentration, the result is nucleation and formation of many nuclei in a short burst. This nucleation stage is followed by the growth of particles. At this stage, the solute concentration is reduced to a value that is below the critical nucleation concentration and thereby halts further nucleation and hence freezes the number of nuclei formed. The growth of the particles continues until all of the solute has been consumed, thus lowering the overall free energy of the system (particles and solutes). Since aggregation of individual nanoparticles also lowers the free energy of the system, the particles tend to coagulate and precipitate out of the solution.^[61,66] Therefore, nanoparticles of desired size and size distribution can only be obtained if: i) growth stops at the right time, for example, due to the reagent depletion, when the particles are still in the desired nanometer size range and ii) an absence of particle aggregation. Clearly, in order to obtain a narrow particle size distribution, the reaction should be controlled to ensure that the nucleation takes place in as short a time as possible and no further nucleation and coagulation of individual particles takes place during the growth of nanoparticles.^[37,61] Investigations by T. L. Sounart et al. suggest that the homogeneous reaction and particle nucleation are diffusion limited and occur only at the boundary between the two laminar streams, while a slower activation process occurs on a longer (seconds) time scale, thereby clearly demarcating the nucleation and growth stages (Figure 6).^[71b] This offers the possibility to control particle size and size distribution. This was demonstrated by several investigators, for example, in the case of gold nanoparticles synthesized by J. Wagner et al. in a glass-silicon microreactor under continuous-flow conditions,^[34b-d] where a standard deviation (σ) of about 13%, which is two times smaller than the mean σ achieved in syntheses conducted using conventional lab equipment, is obtained. Similarly, silica nanoparticles with better size distributions were reported by S. A. Khan et al.^[72]

3.5. Kinetic Control of Nanoparticle Formation

It was recently demonstrated, in the case of Pt nanoparticles, that the growth kinetics of nanoparticles may depend on space confinement.^[73] In microfluidic-reactor processes, an

extra variable (i.e., retention time), in addition to concentrations and ratios of reactants and the reaction temperature, is introduced in comparison with a standard flask process. Therefore, microfluidic processes offer the possibility of controlling the kinetics. This was recently demonstrated through kinetically controlled synthesis of cobalt nanoparticles of three different crystal structures. Control of the crystal structure of nanoparticles is one of the key issues in nanoparticle synthesis; for example, in the case of Co nanoparticles, at least three different types of crystal structure are known. Conventional techniques such as thermal-annealing process, pressure-induced phase transition, ball milling, surfactant-induced phase transition, and size-dependent phase transition have been explored in order to prepare Co nanoparticles of a desired crystal structure. Recent investigations in our laboratory indicate the possibility of controlling the crystal structure of nanoparticles through the control of flow rates and quenching procedures in microfluidic reactors.^[35] This was illustrated by preparing cobalt nanoparticles in a microreactor by the reduction of CoCl_2 in tetrahydrofuran (THF) using lithium hydrotriethylborate ($\text{LiBH}(\text{C}_2\text{H}_5)_3$) as a reducing agent and 3-(*N,N*-dimethyldodecylammonia)-propanesulfonate (SB12) as a stabilizer. When the reaction was carried out using a higher flow rate ($>0.9 \text{ mL min}^{-1}$) and quenching the reaction immediately, spherical cobalt nanoparticles of a face-centered cubic (fcc) crystal structure with an average size of $3.9 \pm 0.9 \text{ nm}$ were obtained. When the flow rate was reduced to $84 \mu\text{L min}^{-1}$, keeping the rest of the reaction conditions the same, cobalt nanoparticles (average size of $3.5 \pm 0.7 \text{ nm}$) of a mainly hexagonal close-packed (hcp) crystal structure were obtained. Additionally, when this product was left undisturbed in the receiver flask for a long period ($\approx 8 \text{ h}$) without quenching, formation of larger cobalt nanoparticles (average size of $4.7 \pm 1.3 \text{ nm}$) having a mainly epsilon crystal structure was observed. It is important to keep in mind that continuous-flow, pressure-driven microreactors, such as those in this example, are unlikely to lead to narrower size distributions because of velocity and residence time distributions. However, the possibility of controlling crystal structure using microfluidic reactors opens up avenues for the utilization of droplet-based microfluidic reactors (Figures 1 and 2) for producing both size- and crystal-structure-controlled nanoparticles.

3.6. Microfluidic Reactor Design

One of the goals of the microfluidic reactor design is to optimize the reactor structure to improve the efficiency of mass and heat transfer based on the kinetic features of a specified reaction.^[33b] Microfluidic reactors offer an opportunity to fine tune the reactor design for kinetic control at different reaction stages during the nanoparticle formation. It has been recently demonstrated that such control at different stages is essential to control the properties of nanoparticles obtained.^[74] Synthesis of silica nanoparticles illustrates this effect of microreactor design on particle size and size distribution.^[72] Two reactor designs, the single-phase laminar-flow reactor (LFR) and the two-phase (gas-liquid) segmented-flow reactor (SFR), depicted schematically in Figure 9, were

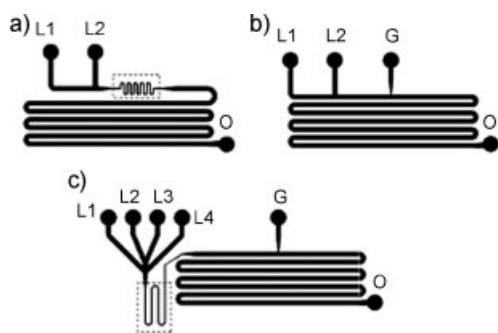


Figure 9. Schematic images of microfluidic reactor channels: a) design 1 (LFR), b) design 2 (SFR), c) design 3 (SFR). Reproduced with permission from Reference [90].

utilized.^[72,75] The LFR was designed to have two liquid inlets (L1 and L2) and one outlet (O) in the micromixing section (150 mm long; Design 1). Two designs for the SFR were explored: Design 2) Two liquid inlets (L1 and L2), a gas inlet (G), and an outlet (O); Design 3) Four liquid inlets (L1–L4), a gas inlet (G), and an outlet (O) in the micromixing section (2.3 m).

The microreactor synthesis was carried out by pumping stock solutions of tetraethoxy silane (TEOS) in ethanol and NH_4OH in ethanol through two inlets. In addition to these two liquid streams, the segmented-flow reactor had an air stream into the reactor. The particles obtained from the two microreactor processes were compared with those obtained in a flask using the well known Stober process. The sizes of the particles obtained in LFR (Design 1) were found to be directly proportional to the residence times. However, the size

distribution was found to be inversely proportional to the residence times, which is not surprising due to the axial dispersion of the growing particles as they flow through the reactor. In the case of the SFR (Design 2), the size distributions were much narrower ($\approx 8\%$) at low residence time and though similar to those obtained from LFR were still wider compared to batch processes ($\approx 5\%$). This deviation from the results obtained in the batch process was mainly attributed to nonuniform distribution of reagents between the two adjacent inlet channels. Therefore, a micromixing section was introduced into the design of SFR (Design 3) and a better size distribution ($\approx 4.5\%$) was obtained with this modification. It is obvious from this study that the use of SFR eliminates axial dispersion effects, unlike in LFR, and results in obtaining a narrower size distribution of nanoparticles. LFRs are affected by axial dispersions at high linear velocities, and a narrow size distribution using LFR is only feasible if one could minimize or eliminate axial dispersion.

4. Discussion and Analysis

The application of microfluidics to wet-chemical synthesis of nanomaterials is gaining momentum and one can clearly see a synergy between the two fields. Leveraging the strengths from both fields is likely to bring about a paradigm shift that can have profound influence on chemical, biological, biotechnological, electronic, and mechanical industries. More specifically, based on the limited research investigations carried out, it is clear that the on-chip synthesis of nanomaterials will be positively influenced by advances in microfluidics.

As can be seen from the examples outlined above, microfluidic approaches have the potential to produce monodisperse nanoparticles of desired size, size distribution,

Table 1. A summary of nanomaterials synthesized using microfluidic reactors. RT: room temperature.

Sl. No	Type of microfluidic device	Type of nanomaterial	Type of flow/flow rate	Channel dimensions	Micromixer	Reaction conditions	Ref.
1	glass microchip	Q dots	laminar flow/ $1.5\text{--}3.0\ \mu\text{L min}^{-1}$	$150 \times 47\ \mu\text{m}^2$; 65 cm long	no	organic solvents/ 180–210 °C	[21]
2	glass/ silica microchip	Q dots	laminar flow/ $10\text{--}300\ \mu\text{L min}^{-1}$	$49\text{--}58 \times 20\ \mu\text{m}^2$; 50 mm long	yes	aqueous	[18,19]
3	glass microchip	Q dots	laminar flow/ $0.5\text{--}10\ \mu\text{L min}^{-1}$	$170 \times 80\ \mu\text{m}$; 40 cm long	no	organic/220–270 °C	[89]
4	PDMS microchip	Q dots	segmented flow/ residence time 1–5 ms	$50 \times 50\ \mu\text{m}^2$; 24.5 mm long	no	two-phase (organic–water)/RT	[27]
5	glass microchip	Q dots	segmented flow/ $2\ \mu\text{L min}^{-1}$	$45\text{--}90 \times 45\ \mu\text{m}^2$; 2.4 mm long	no	two phase (organic–perfluoro)/ 240–300 °C	[29]
6	glass microchip	Au NPs	laminar flow	$178 \times 700 \times 160\ \mu\text{m}^3$	no	aqueous	[34b–d]
7	SU-8 microchip	Pd NPs	laminar flow/ $120\text{--}2400\ \mu\text{L min}^{-1}$	$300 \times 150\ \mu\text{m}^2$; 70 cm long	yes	organic/RT	[9,16]
8	ceramic microchip	TiO_2 NPs	laminar flow	$200 \times 300\ \mu\text{m}^2$; 9 cm long	no	two-phase/RT	[33]
9	PDMS microchip	silica NPs	LFR & SFR	$400 \times 150\ \mu\text{m}^2$; 15 cm long and $300 \times 200\ \mu\text{m}^2$; 2.3 m long	yes	organic/RT	[72]
10	SU-8 microchip	Cu NPs	laminar flow/ $120\text{--}2400\ \mu\text{L min}^{-1}$	$300 \times 150\ \mu\text{m}^2$; 70 cm long	yes	organic/RT	[34]
11	SU-8 microchip	Co NPs	laminar flow/ $120\text{--}2400\ \mu\text{L min}^{-1}$	$300 \times 150\ \mu\text{m}^2$; 70 cm long	yes	organic/RT	[35]
12	PDMS microreactor	Si@titania	continuous flow/ segmented flow	$300\ \mu\text{m}$, wide, $250\ \mu\text{m}$, deep and 2.1 m long	yes	organic/RT	[71a]

and crystal structure without the need for additional size-selection steps. However, it is obvious that more intensive investigations need to be carried out in order to meet future demands for automated nanoparticle synthesizers. A careful analysis of available information from these investigations, in conjunction with future market trends, needs to be carried out in order to determine future directions and opportunities. A summary of the microfluidic devices utilized for on-chip synthesis of nanomaterials is presented in Table 1. Analysis of the information provided in the table leads to some very interesting observations, which, in turn, point to future directions in this new field. Such an analysis also reveals that there are several issues that need to be addressed before microfluidic processes are acceptable for commercial production of nanoparticles. Some of these issues are outlined below.

5. Conclusion

The field of microfluidic synthesis of nanomaterials has already demonstrated a great deal of potential. If all the breathtaking advances that are being made in the field of microfluidics^[76,77] are utilized in conjunction with growing applications of nanomaterials, this new field will bring about a paradigm shift in miniaturization. All that is required is one “major” application, which can bring the field of microfluidic synthesis of nanomaterials to the level of microelectronics.

5.1. Design of Microfluidic Device

The type of microfluidic device utilized for synthesis of nanomaterials is an important issue. Basically, four types of microfluidic reactor have been utilized for the synthesis of nanomaterials. They are microcapillaries, microchips, micro-tubular coils, and segmented-flow tubular reactors. Simplicity in microfluidic design and fabrication (for example, micro-capillaries) leads to easy scalability of the process, albeit compromising on the quality of the nanomaterials produced. On the other hand, microfluidic reactors with more complicated designs (for example, segmented-flow microreactors) offer better control over properties of nanomaterials. Overall, segmented-flow microreactors are likely to be useful for the synthesis of a broad spectrum of nanomaterials, both at room temperature and elevated temperatures. However, if the scale-up of the process is an issue then microcapillaries operating in a continuous mode are preferred, especially for nanomaterials that are relatively less sensitive to changes in the reaction conditions.

5.2. Material of Construction

The material of construction of microfluidic devices is important as it is likely to affect the properties of the nanomaterials being synthesized.^[75,76] Microfluidic reactors fabricated so far for synthesis of nanomaterials have been constructed from glass, silicon, PDMS, stainless steel (SS), ceramic, and SU-8. Each material has its own advantages and disadvantages, depending on the final use and application. The

glass-based microreactors are preferred if high-temperature reactions ($>200^{\circ}\text{C}$) are carried out. The polymer-based microreactors are useful for applications at room temperature or temperatures lower than 200°C . They are also useful for large-scale production. With the recent trend moving toward soft-lithography techniques, primarily based on printing and molding of organic materials, organic/polymer-based microfluidic reactors are likely to be the preferred choice for on-chip synthesis of nanomaterials.^[79]

5.3. Control of Critical Features of Nanomaterials

It remains a challenge to control all the critical features such as size, size distribution, shape, and crystal structure of nanoparticles simultaneously in a single experiment. While the investigations, so far, clearly demonstrate that crystal structure can be controlled, as is the case with Co nanoparticles, the size and the size distribution remain challenging issues.^[35] This is not very surprising as the microreactor utilized for the crystal-structure-controlled synthesis was operated under laminar-flow conditions where broader velocity and residence-time distributions are unavoidable. Combining this knowledge with the understanding of the reasons for superior control of size and size distribution of particles obtained in segmented-flow microreactors is likely to lead to the development of newer designs of microreactors; which will provide, in a single experiment, both size as well as crystal-structure control of nanoparticles.

Attempts to improve the yield of Ag nanoparticles by increasing the flow rate resulted in a broader particle size distribution.^[24] The effect of flow rate on the size and size distribution of nanoparticles cannot be generalized and it varies from one type of nanoparticle to another. Low flow rates lead to a narrower size distribution in the case of Ag nanoparticles but a broader size distribution in the case of CdSe nanoparticles. It is very likely that one needs to optimize the design of the microfluidic device and process parameters keeping in mind the physical and chemical characteristics of nanomaterial to be synthesized. However, by taking advantage of the chip-based technologies for real-time sizing of nanoparticles,^[5] in addition to utilizing segmented-flow microreactors, some of these problems are likely to be addressed in the near future. By using recent techniques, such as holographic optical tweezers,^[80] one can independently suspend and manipulate tiny particles for size-dependent transportation, the so-called “optical fractionation”, faster progress can be made in controlling size and size distribution of nanoparticles obtained. As there are only a few types of nanoparticles synthesized using microfluidic approaches (Table 1), we foresee more investigations in this direction leading to the development of innovative on-chip synthetic methods for the preparation of a variety of metallic, polymeric, and other types of nanomaterial. Of the different types of nanoparticle investigated to date, quantum dots have been studied in most detail. A majority of nanoparticles synthesized, utilizing microfluidic reactors, are those of spherical shape; we anticipate synthesis of anisotropic nanomaterials in the near future.

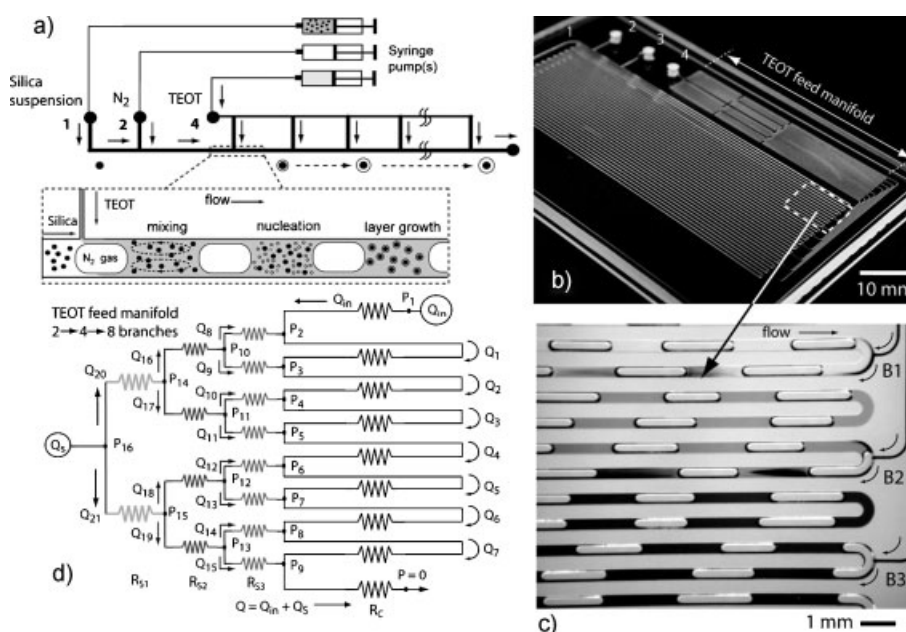


Figure 10. a) Design concept for continuous-flow coating reactor. b) Photograph of fabricated reactor. c) Stereomicroscope image of flow-visualization experiment: ethanol dyed with black ink was introduced into a primary air–ethanol feed. The first three manifold branches (B1, B2, and B3) are seen feeding ethanol (dyed with black ink) into the gas–liquid flow (air–ethanol) in the main channel. d) Circuit model for microfluidic coating reactor showing hydraulic resistances R , flows Q , and pressures P . R_{Si} ($i = 1–3$) and R_C are the hydraulic resistances for the various manifold branches and the main reaction channel, respectively. Reproduced with permission from Reference [71a].

5.4. Blockage or Fouling of Channels

The blockage of microfluidic channels caused either by nanoparticle agglomeration or by a reaction with the surfaces of the channels is a major concern.^[75] Therefore, direct translation of normal batch process into a microfluidic reactor process is not trivial.^[34a] One needs to evaluate and optimize the design of microfluidic-reactor processes based on each type of nanoparticle being synthesized, type of reagents being used, reaction conditions, and the mechanism of formation of the nanoparticles. For example, a successful microfluidic process for Cu nanoparticles required the use of stable and soluble Cu^+ complex in order to overcome the blocking of the channels by the $CuCl_2$ salt in THF.^[34a] An effective approach to prevent microreactor fouling through deposition of solid materials within the microchannels was recently reported by J. Wagner et al.^[34b–d] They successfully prevented or minimized blockages by carrying out reactions at elevated pH and by making the internal channel surfaces hydrophobic through silanization. We anticipate the development of more suitable construction materials for microfluidic reactors to prevent clogging of channels, the optimization of channel structures according to the fluid dynamics, and also the use of newer kinds of surfactants and stabilizers to prevent agglomeration.

5.5. Scale-Up of Microfluidic Processes

Even though a scale-up of nanoparticle synthesis using microfluidic process has several advantages, especially when using a continuous mode, the need for utilization of thousands of microreactors stacked together, in order to produce nanoparticles on an industrial scale, creates at least three

major challenges. The first is the fabrication of thousands of microreactors with identical features in a cost-effective manner, which is not trivial. Technologies such as LIGA and hot embossing have the potential to meet this challenge using fabrication of polymeric microreactors; very few investigations of this nature have been reported so far. The second is the flow-rate control in each individual microfluidic reactor within a stack of microreactors. The design of appropriate stack of microreactors in itself is not trivial. The distribution of flow rate uniformly in each channel from a single source is a concern and not many investigators have been conducted on this subject so far. The utilization of micropumps for each individual microfluidic reactor unit is not practical. We anticipate more practical approaches and significant improvements either through modeling or properly designed experiments. The use of novel concepts, such as multilayer soft lithography (MSL), could offer a possible solution by enabling the formation of pumps, valves, and channels integrated within the microfluidic chip.^[81]

The third is that very little research has been conducted on process systems engineering for the design and operation of a stacked microreactor system or “micro chemical plants,” in general, for chemical synthesis and, in particular, for synthesis of nanomaterials.^[82]

It is pertinent to mention that investigations are currently ongoing in several laboratories to address scale-up issues related to microfluidic reactors in general and for chemical synthesis and nanoparticles in particular. Several companies, such as Cellular Process Chemistry, mgt mikrogilas, FZK, IMM, and Ehrfeld Microtechnik, are developing modular microreaction platforms consisting of functional elements for reactions, unit operations, transport, measurement, and

control.^[83] Recently, the American Center for Process Analytical Chemistry (CPAC) and the German consortium of microprocess engineering have developed a compact microreactor system for chemical syntheses.^[84] There are also reports of the development of automated microreactor systems capable of carrying out repeated injections, mixing, and reactions.^[85] While the modular systems mentioned above have been only tested for chemical syntheses, they haven't been utilized for the synthesis of nanoparticles. In order to fill this gap, we have recently started investigations into developing an integrated stacked microreactor system for synthesis of metallic nanoparticles.^[86] This user-friendly system consists of three basic functional blocks for controlled flow from the chemical container (inlet), a custom made temperature-controlled microreactor stack, and an outlet control unit to optimize all critical reaction parameters. The system operation is controlled by a computer. Based on the experimental conditions developed for the synthesis of Pd nanoparticles using a single polymeric microreactor chip in our laboratory,^[9] we have now utilized the integrated stack of microreactor and demonstrated its utility for scale-up of nanoparticle synthesis and for generating process developmental data. In a recent publication, a manifold PDMS microreactor with controlled multipoint addition and mixing of a reactant to a primary feed was successfully utilized for controlled synthesis of silica-coated titania nanoparticles.^[71a] Figure 10 shows the design concept and the reactor design has the inherent advantage of scalability through parallel operation of multiple reactors.

5.6. Mechanism of Nanoparticle Formation

The process design for the microfluidic synthesis of nanoparticles requires an understanding of the mechanistic principles in the formation of each type of nanoparticle. Such information obtained, using either microfluidic reactor based on spatial resolution of the reaction^[70] or using even the traditional wet chemical process,^[74] is still incomplete and continues to be a challenge. The practical use of microfluidic reactor synthesis requires investigations in this direction and we anticipate more serious investigations into unraveling the mechanistic principles.

5.7. Microfabrication Processes

Finally, the fabrication of microfluidic reactors itself is in its developmental stage. There is need for investigation into improving the fabrication processes, identification, and utilization of appropriate material of construction, and most importantly, in integrating microprocessing components related to the microfluidic reactor system (such as micropumps or electro-osmosis parts, microheaters, microseparators). Innovative approaches to flow the fluids, such as the use of light, within microchannels without the need for pumps or external aids or advances in soft lithography could significantly aid development of microfluidic devices, which in turn will have the effect of transforming the burgeoning field of microfluidic devices in nanotechnology into a revolutionary technology.^[87] Increased efforts to develop nanoscale biomo-

lecular motors, such as kinesins, which can be integrated into microfluidic devices to power them, will significantly enhance scale-up of nanomaterial synthesis using parallel arrays of microreactors.^[88]

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