

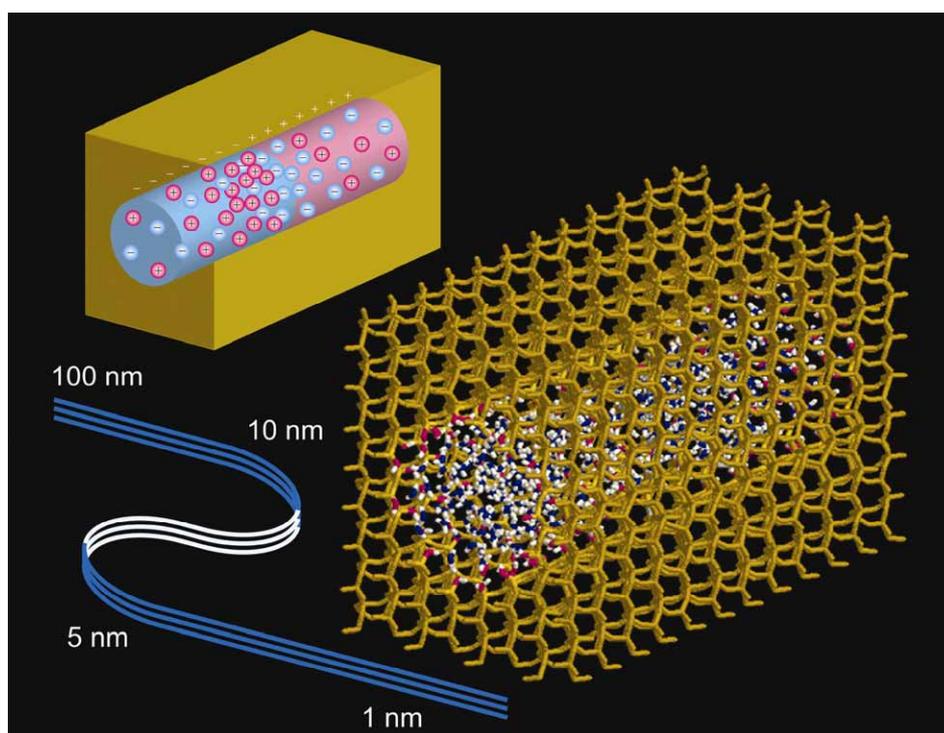
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**From microfluidic application to
nanofluidic phenomena issue**

Reviewing the latest advances in microfluidic and nanofluidic
research

Guest Editors Professors Albert van den Berg, Harold Craighead and Peidong Yang

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Synthesis of micro and nanostructures in microfluidic systems†

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In this *critical review*, we present an overview of the current progress in synthesis of micro and nanostructures by using microfluidics techniques. Emphasis is placed on processes that can be realized on chip, such as polymerization, precipitation, sol–gel, thermolysis and multistep processes. Continuous flow, microfluidic systems show particular promise in controlling size, shape and size distribution of synthesized micro and nanoparticles. Moreover, the use of microfluidics expands the synthesis space (*e.g.*, temperature, pressure, reagents) to conditions not easily accessed in conventional batch procedures and thus, opens new methods for the realization of complex engineered nanostructures and new materials systems. (187 references)

I. Introduction

Microfluidics have advanced biological and chemical research, in particular through the integration of analytic techniques with cell handling, biochemical assays, and chemical synthesis.^{1–5} More recently, microfluidic systems have also been used to produce micro- and nanoparticles with excellent control of size, composition, and morphology, as well size distribution. We review this progress with particular emphasis on results realized in microfluidic chips and capillaries.

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Chemically synthesized nanomaterials are being considered as the active elements in many applications, including photovoltaic, energy, displays,⁶ catalysis, and bio-chem sensing.^{7,8} In order to realize the promise of these devices, it will be critical to have an efficient, reproducible synthesis technique of the nanostructures. Currently, nanoparticles are synthesized in a batch mode in small volumes, which is appropriate for studying the fundamental properties of nano-sized structures and for developing proof of principle device structures. However, batch synthesis tends to suffer from irreproducibility of size, size distribution, and quality of the nanomaterials from batch to batch. It is also difficult to implement fast screening and optimization of the synthesis conditions in batch, and there are challenges in scaling batch procedures up to quantities needed for device development and optimization.

Continuous flow reactors based on microfluidics (micro-reactors), integrated with heaters and fluid control elements, offer a solution to these challenges, as well as additional



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advantages, including enhancement of mass and heat transfer, feedback control of temperature and feed streams, reproducibility, potential for sensor integration for *in situ* reaction monitoring, rapid screening of parameters, and low reagent consumption during optimization. The small reaction volumes combined with the high heat and mass transfer rates enable reactions to be performed under more aggressive conditions with higher yields than can typically be achieved with conventional batch reactors. Moreover, the ability to work at elevated temperatures and pressures while confining potentially toxic, high reactive starting materials could become important for the synthesis of novel nanostructured materials.

In this critical review, we present, through selected examples, recent developments in microfluidic synthesis of micro and nanostructures, starting with current microfabrication techniques and materials for microreactors, followed by synthesis of organic and inorganic nanomaterials. Next, we address the use of microfluidic systems for engineering complex heterogeneous and multifunctional micro and nanostructures, such as core-shell nanoparticles or microcapsules containing functional nanomaterials. Finally, we discuss the opportunity to synthesize novel materials and structures by using microfluidics to realize conditions difficult to achieve in standard batch mode methods.

II. Microfluidic systems for materials synthesis

A “microreactor” can be considered as a micro vessel designed to contain a chemical reaction. Its design aims to maximize the reaction performance, which typically means achieving the highest efficiency towards the desired output product. From these considerations, blood vessel, cells or micro and nanoporous structures such as zeolites could be regarded as microreactors. The main challenge in applying microfluidics to materials synthesis is to design microsystems capable of producing the desired solid materials at the desired conditions (pressure, temperature, chemical compatibility, concentration...) without the products clog the system.

Along with the development of microscale processes for nanomaterials synthesis, microreactors have evolved from simple tubing to more complex systems integrating control of operating parameters and *in situ* characterization techniques.^{3,9} Capillary tubings (stainless steel, silica, polymers) were used from the very beginning to access small scale flows within the simplest feature. They provide cheap and simple approaches for continuous flow experiments with well known hydrodynamics¹⁰ and easy manipulation of operating parameters (residence time, *etc.*).¹¹ Silica tubing-based microfluidic systems have been combined to achieve specific co-flow structures for mixing reagents and/or generating hydrodynamic microstructures, which can be used as templates for materials synthesis, such as droplets, jets^{12,13} (Fig. 1a), and double emulsions (Fig. 1b).^{14–16} Considerable fundamental understanding of the transitions from dripping to jetting regimes has already been developed.^{17,18}

Although relatively simple to implement, capillary-based microfluidic systems often lack flexibility in design and face challenges in integration of actuation and monitoring components. “On-chip” microfabricated systems address

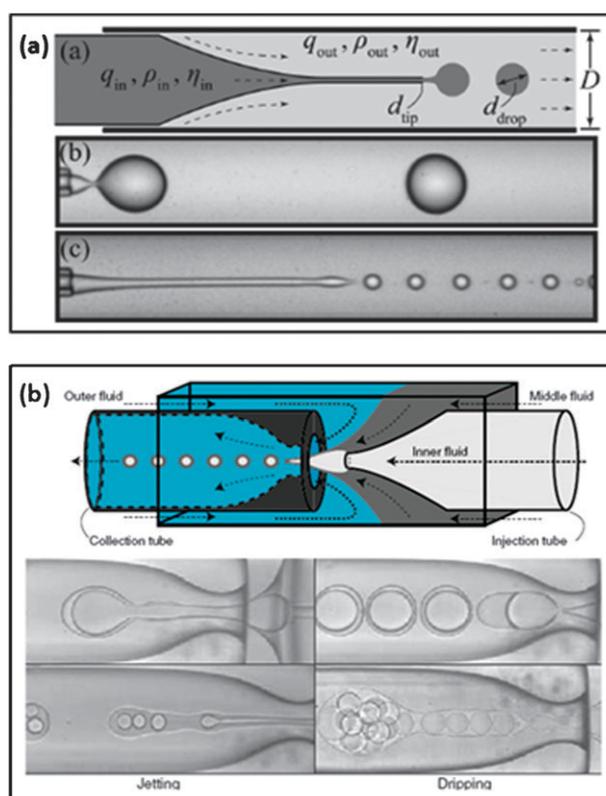


Fig. 1 Capillaries-based microsystems assemblies for (a) droplets/emulsions and jets formation (reprinted from ref. 13, with permission from the American Physical Society), and (b) multiple emulsions (reprinted from ref. 16, with permission from the Materials Research Society).

these limitations, providing for a wide range of designs, from two dimensional layouts extruded in the third dimension (*e.g.*, lithography followed by etching) to fully three dimensional structures. This design flexibility imparted by microfabrication allows for precise manipulation of hydrodynamics for fast mixing^{19,20} and controlled addition of reagents^{21,22}—two process features typically needed in synthesis. As a result of advances in microfabrication processes, several materials can now be chosen among for building microreactors, depending on the constraints imposed by the materials synthesis processes.

II.1 Microreactor fabrication

Perhaps the most commonly used microfluidic systems are made of polymers, in particular poly(dimethyl siloxane) (PDMS) and glass (Fig. 2a). Their fabrication by the popular soft lithography technique^{23,24} involves photolithography steps with negative photoresist, followed by the silicon elastomer casting onto this mold and further curing. The PDMS layer is peeled off and bonded to a glass slide to seal the channels.^{24,25} These microreactors are easy to fabricate at low cost and often make excellent prototypes, but they have limited operating pressure and temperature ranges as well as poor chemical compatibility, since most of the organic solvent tends to swell PDMS and interrupt the bonding to glass.²⁶ Surface modification techniques, such as glass coating of PDMS microchannels, alleviate some these problems (Fig. 2b),²⁷ enabling

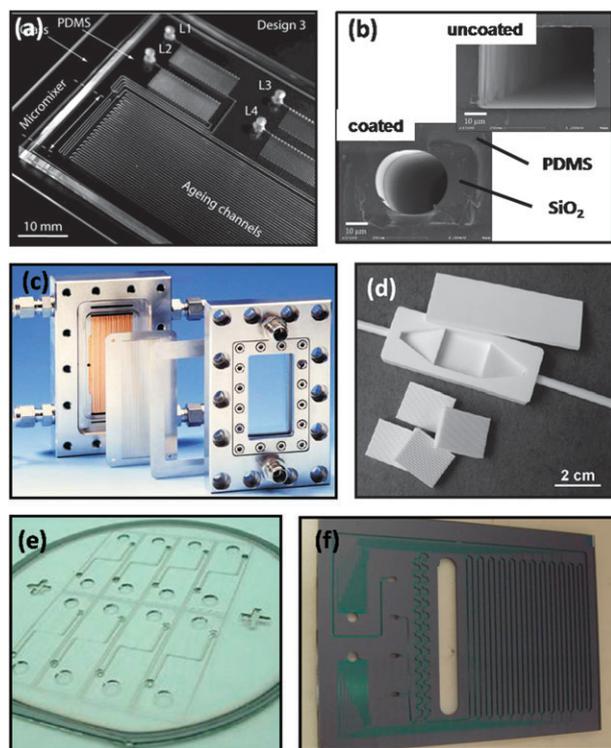


Fig. 2 Examples of microreactors for nanomaterials synthesis. (a) PDMS/Glass (reprinted with permission from ref. 34, copyright 2004 American Chemical Society), (b) PDMS/Glass microchannel with additional coating with silica (reproduced by permission of the Royal Society of Chemistry),²⁷ (c) metal (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 35), (d) ceramics (reproduced by permission of the Royal Society of Chemistry),³⁶ (e) Glass/Glass (reprinted from ref. 37 with permission from Elsevier), (f) Silicon/Pyrex.^{38,39}

the use of more aggressive chemicals while providing opportunity to modify wettability properties of the channels, thanks to the wide range of silane chemistry for surface modifications.^{28–30}

Fluoropolymer integrated devices have excellent chemical compatibility,^{31,32} but the weak bond strength between fluoropolymers and glass, or other polymers, limits operation at elevated pressures. Fluoropolymer capillaries could also be used but they have temperature limitations, too. Finally, SU-8-PEEK microreactors have been developed for room temperature nanomaterials synthesis based processes, although temperatures up to 150 °C and pressure up to 2 MPa have been reported.³³

Metal based microreactors are especially advantageous for processes involving high heat load and toxic chemicals thanks to good chemical compatibility and thermal resistance of these materials, except for strong acids. Metal microreactors (Fig. 2c) are typically fabricated using conventional machining, electroforming, electro-discharge machining (EDM), or laser ablation.⁴⁰ They have been demonstrated in chemical synthesis applications,³⁵ including fluorination reactions,^{41,42} and in materials synthesis.⁴³ Ceramics microreactors (Fig. 2d) are fabricated by molding techniques^{44,45} and commonly used for extremely high temperature processes (*e.g.* $T > 800$ °C) such as hydrogen production from continuous reforming of propane,^{36,44,46} catalyzed gas phase reactions³⁶ or nanomaterials

synthesis.⁴⁷ Microreactors can be realized in metals or ceramics without clean room facilities, but current micromachining tools limit feature sizes to few tenths of micrometres.

Glass/glass microreactors (Fig. 2e) are typically fabricated through HF/BOE (Buffered Oxide Etchant) etching or sand-blasting of either borosilicate^{37,48} or soda-lime glasses^{49,50} with further thermal bonding. They have the advantage of easy optical access, providing a mean for a wide range of *in situ* characterization techniques. Although high pressures can be reached using these microreactors,⁵¹ the low thermal conductivity of glass limits applications requiring good heat transfer. Reactors microfabricated in silicon and Pyrex⁵² (Fig. 2f) by silicon etching followed by anodic bonding provide good thermal, chemical and pressure characteristics, while maintaining optical access through the Pyrex side. The good thermal conductivity of silicon devices make them excellent candidates for HT processes, such as fuel conversion.^{52–55}

II.2 Packaging techniques

Fluidic connections between the microreactors and macroscopic fluid handling systems, *e.g.* pumps, so-called “packaging”, raises additional materials engineering challenges. Conventional connection methods are divided in two main families. First, the permanent integrated connections (Fig. 3a–c), including epoxy glueing,^{51,56} glass brazing,^{57,58} metal soldering,^{59,60} or anodic bonding of Kovar tubes to glass.⁶¹ These fluidic connections are reported to stand up to 17 MPa or more with particular designs. However, these techniques generally require complicated micro-fabrication procedures to optimize the connection strength and

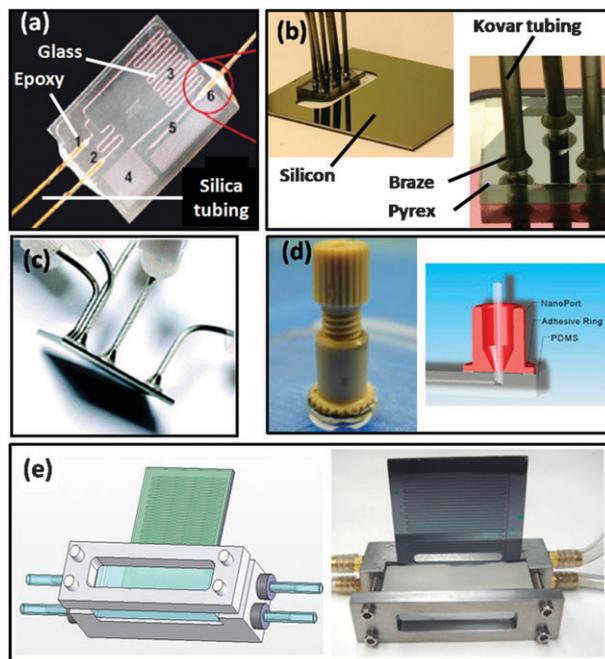


Fig. 3 Examples of packaging techniques. (a) epoxy glueing of silica capillary tubings to a glass–glass microreactor (reprinted from ref. 51 with permission from Elsevier), (b) glass brazing⁷⁷ (c) solder-based approach (reproduced by permission of the Royal Society of Chemistry),⁵⁹ (d) commercially available nanoport connectors (reproduced by permission of the Royal Society of Chemistry),⁶² and (e) modular compression fittings.³⁹

are not versatile in term of chemical compatibility. The second family constitutes non-permanent modular connections such as commercial microfluidic interfaces assembly that can stand up to 10 MPa^{62–64} (Fig. 3d) or modular fluidic connections through compression sealing with rubber O-rings (Fig. 3e).^{38,39} This latter method provides an efficient way to access high pressure (up to 50 MPa) with the ability to easily interchange the microreactors.

The packaging schemes can be combined with heater and temperature controllers to realize a single or multiple temperature zones on the microreactors. Multiple zones heating allows decoupling of nucleation and growth processes for nanomaterials. Finally, the incorporation of optical fibers directly into a channel, enable spectroscopic information of chemical transformations by optical spectroscopy techniques.³

III. Organic materials processing in microfluidic devices

III.1 Polymerization reactions

Organic materials processing, from polymer-based micro- and nanostructures to crystallization of organic molecules or proteins has attracted increasing interest in the field of microfluidics.^{65–70} Polymerization reaction in droplets^{71,72} or at interfaces⁷³ combined with the ability of microfluidic systems to create precise microsized droplets with narrow size distribution have led to the synthesis of polymer microbeads.^{74–76} Similarly, thermoresponsive microcapsules for drug released applications have been realized through formation of multiple emulsions, as exemplified with poly(*N*-isopropylacrylamide) (PNIPAm) gels microcapsules that release internal droplets depending on the temperature (Fig. 4a).⁷²

Photopolymerization offers a flexible way to form particles in microfluidic devices, taking advantages of the transparency of glass–glass or PDMS–glass microreactors. Droplets containing monomers and an activator are exposed to near ultra violet (UV) light to initiate the formation of the final polymer particle shape.⁷⁸ Complex polymer particle structures can be realized, taking advantages of complex flow fields enabled by microfluidics devices. For example, micrometre size polyacrylate microcapsules (Fig. 4b) have been synthesized starting from double emulsions (water in acrylate monomer in silicon oil).⁷⁹ Janus hydrophilic–hydrophobic microparticles have also been obtained starting from double emulsions generated from an inner oil core drop containing an hydrophobic methacrylate precursor solution and an outer aqueous shell containing an acrylamide precursor solution. UV irradiation induced polymerization and subsequent phase separation led to the formation of micrometres size Janus particles (Fig. 4d).⁸⁰ Combining multiple laminar co-flowing liquids of two monomer solutions containing a photo initiator, with photopolymerization elegantly exploits microfluidics in the synthesis of Janus and more complex particle structures (Fig. 4c).⁸¹

Doyle *et al.* have developed a particular, useful combination of photo-polymerization and stop flow microfluidics for synthesizing particles with controlled shape and functionality,

such as encoded, non spherical shapes (Fig. 5).^{82–84} UV exposure through a mask and focused with microscope objective on the flowing fluid produces controlled non spherical microstructures. Use of co-flow and multi-phase fluids further enables fast, continuous synthesis of advanced particle structures, including 2-D multi-shaped microparticles (Fig. 5-b),⁸⁵ amphiphilic microparticles—which can further auto-assemble⁸⁶—and multifunctional microparticles combining an encoding scheme and molecular identification, which can be used for high throughput screening applications in genetic analysis, among other applications (Fig. 5a).⁸⁴

III.2 Precipitation of polymers

Other microfluidic techniques for producing polymer particles are based on precipitation created *via* solvent removal (*e.g.*, by evaporation) or antisolvent addition. These synthesis methods present the advantage of being chemical reaction-free, since only physical processes occur during the precipitation of the solute. Therefore, the starting material can directly be a polymer dissolved in a solvent. The main limitation of these processes is finding a suitable [solute–solvent] system to address evaporation and solubility requirements. Again, microfluidic systems facilitate control the shape of the polymer–solvent phase, before its precipitation. With these techniques, polymersomes and gel shells have been obtained from double emulsions (Fig. 6a).^{87–89} However, defects often appear on the surface of the polymersomes from non-uniform drying of the intermediate phase or dewetting instabilities.⁸⁷ Nevertheless, complex structures, such as toroidal microparticles, have been produced from a single emulsion⁹⁰ through the transfer of the solvent phase, containing the polymer, into a non solvent phase. The resulting slow dissolution process leads to the formation of non spherical particles (Fig. 6b).

Slow addition of an antisolvent phase leads primarily to rearrangement of the polymer chains and agglomeration depending on the structure of the flow field. On the other hand, fast mixing with an antisolvent produces high supersaturation, leading to nucleation and generation of polymer nanoparticles. For instance, PLGA–PEG copolymer nanoparticles have been achieved by flow focusing of a acetonitrile solution in a water flow (Fig. 6c).⁹¹ Thanks to fast micromixing effects enabled by microfluidics, microscale liquid/liquid antisolvent process shows promise as a technique for achieving polymer nanoparticles with well controlled sized distribution.

III.3 Crystallization of organic materials and proteins

Crystallization of organic materials,^{66,92} such as small active pharmaceutical ingredients (APIs)^{93,94} and proteins,^{95–101} constitutes yet another application that could benefit from microfluidics. The optical access and tight control of supersaturation offer the potential for detailed studies of fundamental crystallization processes, as well as fast screening of crystallization conditions.^{101,102} Droplets-based microsystems can be used as ideal nanolitre reactor volumes for studying temperature or mixing effects, as demonstrated in Fig. 7a. In this case, the authors studied the crystallization of protein in liquid segments and measured the influence of the flow

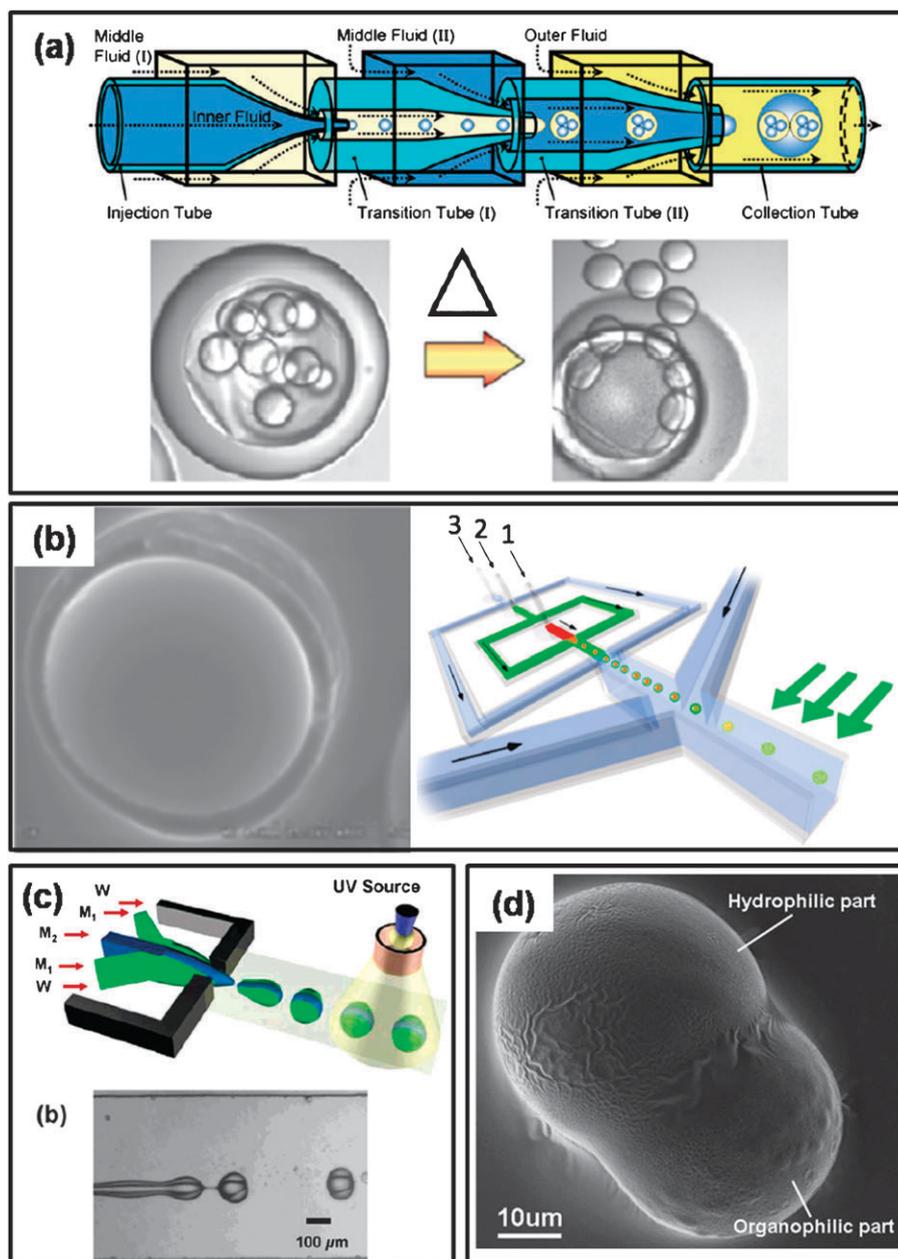


Fig. 4 Microfluidics processes for the preparation of microparticles: (a) microgels from the polymerization of multi emulsions of thermosensitive PNIPAm (reproduced by permission of the Royal Society of Chemistry),⁷² (b), (c) and (d) microcapsules, ternary microparticles and Janus microparticles obtained from UV photo-induced polymerization, respectively. (reprinted with permission from ref. 79–81, copyright 2006–2009 American Chemical Society).

velocity, and related recirculation in the segments, over the size of the obtained crystals, demonstrating precipitation of microcrystals at low flow rates and large crystals growth at high flow rates.⁹⁸ Several crystallization conditions and proteins (Fig. 7b) can therefore be screened with nanolitres of volumes.⁹⁹ Controlled evaporation and fluid transfer among fluid wells allows for screening of nucleation feasibility and measurement of crystallization kinetics when crystals form. These methods are providing new approaches to work with challenging membrane protein systems, which have typically been difficult to crystallize by conventional means. Microfluidic techniques also offer opportunity for realizing

nanosized crystals of APIs which have the advantage of improving bioavailability.^{94,103,104}

IV. Inorganic micro and nanostructures synthesis in microsystems

There have been tremendous interests in the development of microfluidic methods for synthesizing inorganic nanoparticles. As for organic materials processing, microfluidics provide opportunities for synthesizing inorganic materials in a continuous manner, with uniform and tunable size distribution, and controlled shapes (spheres, rods, etc.). Batch synthesis

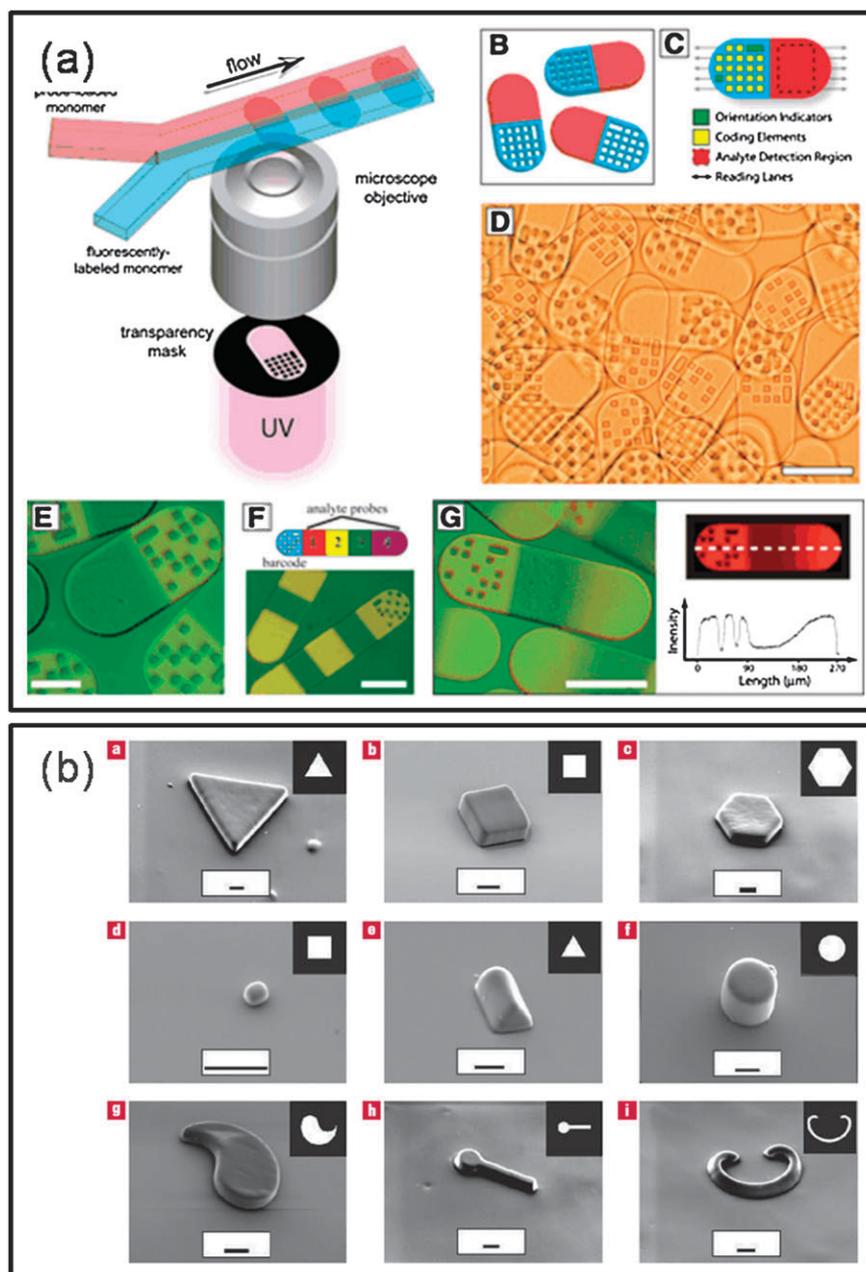


Fig. 5 Non spherical multifunctional encoded microparticles obtained from the UV-photo induced polymerization of multiphase laminar flows within a microchannel (scale bar is 100 μm in (D), (F) and (G) and 50 μm in (E)), (from ref. 84, reprinted with permission from AAAS), and (b) shape controlled polymer microparticles obtained from the same techniques (scale bar is 10 μm), reprinted by permission from Macmillan Publishers Ltd: *Nature Materials* ref. 85, copyright (2006).

often suffers from irreproducibility of size, size distribution, and quality of the nano-material from batch to batch. A microfluidic approach allows for fast screening and optimization of the synthesis conditions. In the following section, we review works on synthesis of metal, oxides or semiconductors nanoparticles and expand upon previous reviews of the topic.^{105,106}

IV.1 Synthesis of metal nanoparticles

Room temperature processes for the synthesis of metal nanoparticles have often been developed in batch mode, initially, and then adapted to microfluidics.¹⁰⁷ Typical microfluidics

recipes involve reducing metal salts with reducing reagents, such as sodium borohydride (NaBH_4),¹⁰⁸ citrate^{109,110} or a mixture of lithium hydrotriethyl borate ($\text{Li}[\text{Bet}_3\text{H}]$) with 3-(*N,N*-dimethyldodecylammonia) propane sulfonate (SB12).^{111–114} Metal nanoparticles synthesis in microfluidic systems has been performed with glass capillaries, PDMS–glass, or Silicon–Pyrex microreactors at room to mild temperature conditions by mixing an aqueous stream containing the metal salt with the reducing agent. A number of ligands and surfactants systems have been used to stabilize the synthesized particles and minimize agglomeration and deposition on the walls of the channel. These systems include thiols, polymers (polyvinyl

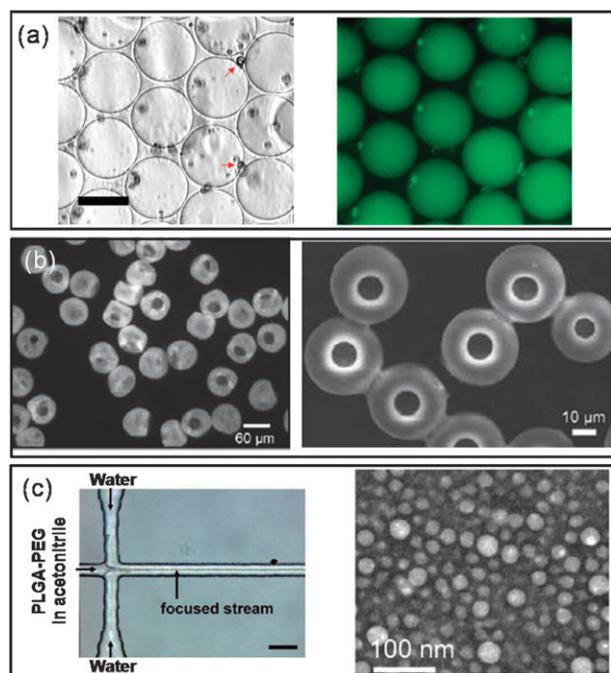


Fig. 6 Microstructures obtained using precipitation of polymer in microfluidic systems. (a) polymersomes from evaporation of the intermediate phase of a water/oil/water double emulsion (*reprinted with permission from ref. 88 copyright 2008 American Chemical Society*), (b) toroidal microparticles from the solvent removal by dissolution of a single emulsion in a PDMS/Glass microreactor (*Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 90*), (c) liquid/liquid micro antisolvent process for the synthesis of PLGA-PEG nanoparticles from acetonitrile-water flow focusing microreactor (*reprinted with permission from ref. 91 copyright 2008 American Chemical Society*).

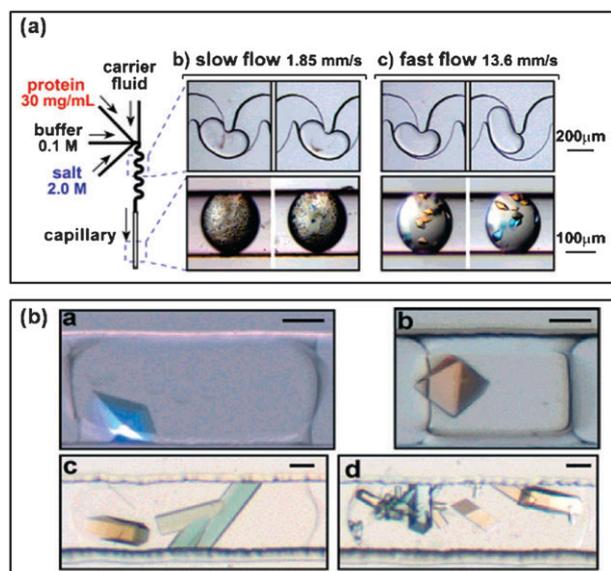


Fig. 7 (a) Example of proteins crystallization droplets-based microfluidic platform, for studying the effect of mixing. (b) Different proteins crystallized within slugs—Thaumatococcus, bovine liver catalase and glucose isomerase (*reprinted with permission from ref. 98 and 99, respectively. Copyright 2003 and 2005 American Chemical Society*).

pyrrolidone-PVP), alcohol (polyvinyl alcohol-PVOH), and dendrimers (poly(benzyl ether dendrons-PBED).

Two main approaches are employed. The homogeneous synthesis approach is illustrated with the growth of silver nanoparticles (Fig. 8a) in which the authors used three microreactors in series.^{108,115} The process starts with the generation of an aqueous concentration-tunable solution of silver nitrate in a first microreactor. This step is followed by the addition in the second microreactor of the reductant, NaBH₄. An ageing loop allows the particles to grow to a certain size. In the final step, ligands are added to the reaction medium to stabilize the synthesized nanoparticles. The main advantage of this approach is the possible continuous addition of reagent within the reacting media and the easy implementation of the

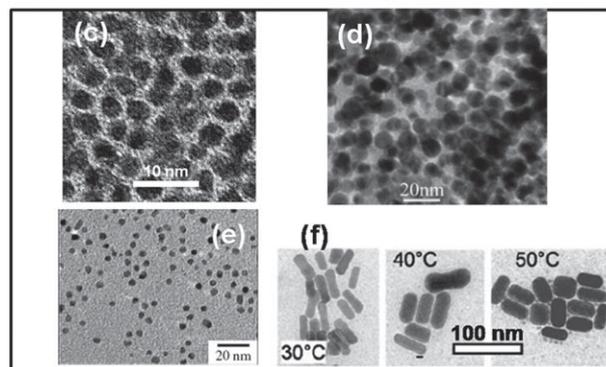
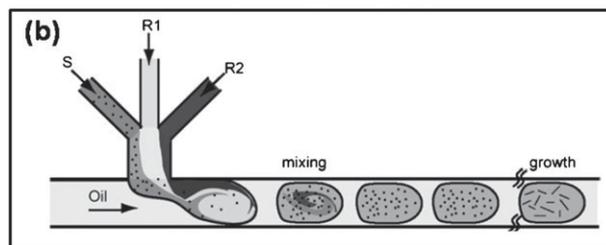
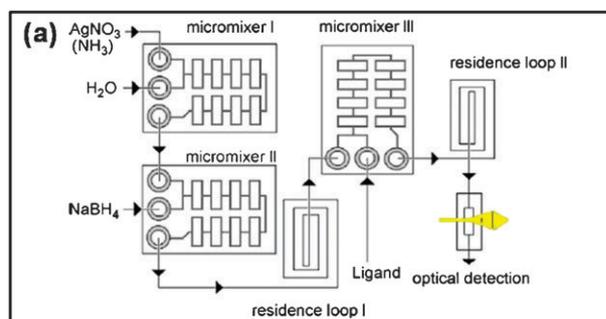


Fig. 8 General strategies for (a) the homogeneous synthesis of metal nanoparticles (*reprinted from ref. 108 with permission from Elsevier*) and (b) the droplet-based synthesis of nanorods (*Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 123*). Examples of metal nanoparticles generated in microreactors. (c) gold nanoparticles (*reprinted from ref. 121 with permission from Elsevier*), (d) copper nanoparticles (*reprinted with permission from ref. 111. Copyright 2005 American Chemical Society*), (e) palladium nanoparticles (*with kind permission from Springer Science + Business Media ref. 126*), and (f) gold nanorods synthesized at different temperatures (*reproduced by permission of the PCCP Owner Societies*).¹²⁴

microreactors, each of them being able to achieve one single step of the synthesis. However, large residence time distributions through axial dispersion are generally obtained with these continuous single phase approach, leading to broad size distribution for the nanomaterials. In addition, nanoparticle deposition on the walls of the channel during the synthesis could lead to further clogging of the device or to a loss of the optical access.

The second family of synthesis procedures is droplet-based processes. Reagents in aqueous solutions are delivered separately through different inlets before being contacted in the microreactor (Fig. 8b). The aqueous phase is thereafter contacted with an organic phase to generate aqueous droplets suspended in the organic phase, *e.g.* a segmented flow. Nucleation and growth of the nanostructures take place inside the droplets and benefit from the mixing characteristics of the two-phase flow.^{116,117} For this second approach, a narrow residence time distribution can be obtained, enhancing the quality of the produced nanomaterials. However, limitations arise from the requirement to find a suitable [reacting fluid/carrying fluid] couple, since they should be non-miscible over all the range of experimental conditions (*p*, *T*, pH, *etc.*). The choice often goes towards a potentially toxic solvent for the carrying phase (fluorous solvent, silicon oil). Note also that further phase separation downstream is needed, which can be addressed through the use of an in-line phase separator.^{118,119}

A wide range of metal nanoparticles have been realized with the aid of microfluidic devices and these processes (Table 1), including gold (Fig. 8c),^{107,109,110,120–123} silver,^{108,115,124} cobalt,^{112–114} palladium,³³ and copper¹¹¹ (Fig. 8d). Moreover, the addition of surfactants¹¹⁰ and the initial introduction of seeds¹²³ have enabled control of particle shape. For example, gold and silver nanorods form from their respective salt solutions in the presence of gold or silver seeds, which serve as initial growth support for the reduction of the metal salts (Fig. 8f).^{123–125} Finally, a recent example presents yet another synthesis process based on the thermal decomposition in a microchannel of a metal organic precursor dissolved in a high boiling point solvent to form palladium nanoparticles (Fig. 8e).¹²⁶

IV.2 Oxides

Oxide particles are typically synthesized in microfluidic devices using either sol-gel^{34,129} or redox reactions.¹³⁰ To date, only temperature conditions close to ambient have been reported. Two main strategies are pursued: (i) generating nanoparticles using microchannels or droplets as nanolitre well-stirred reactors, targeting nanosized particles but without advanced control over their shape, and (ii) synthesizing microstructures from the size and shape of droplets, taking advantage of the complex flow fields enabled by microfluidics

Table 1 Metal nanoparticles synthesized in microfluidics devices

Metal	Microreactors	Conditions	Reactants	Ref.
Gold nanoparticles	Glass–Glass	Room temperature (RT)	HAuCl ₄ + NaBH ₄ + dodecanethiol	121
Gold nanoparticles	PDMS–Glass	115 °C	HAuCl ₄ + Trisodium citrate	110
Gold nanorods	PVC and PEEK tubing	RT	Seeds + HAuCl ₄ + NaBH ₄ + CTAB	124
Gold nanoparticles	Silicon–Pyrex	RT	HAuCl ₄ + Ascorbic acid + PVP	122
Gold nanoparticles	Silicon–Pyrex	RT	HAuCl ₄ + Ascorbic acid + Fe(II) + PVOH + Na ₂ SiO ₃	127
Gold NCs and nanorods	PDMS–Glass	RT	(Au seeds) + HAuCl ₄ + Ascorbic Acid + CTAB	123
Copper nanoparticles	SU-8-PEEK	RT	CuCl ₂ + Li[Bet ₃ H] + SB12	111
Cobalt nanoparticles	SU-8-PEEK	RT	CoCl ₂ + Li[Bet ₃ H] + SB12	112
Cobalt nanoparticles	SU-8-PEEK	20–50 °C	CoCl ₂ + Li[Bet ₃ H] + SB12	113,114
Palladium	SU-8-PEEK	RT	PdCl ₂ + Li[Bet ₃ H] + SB12	128
Palladium nanoparticles	Glass capillary	140–200 °C	Pd(OAc) ₂ + PBED	126
Silver nanorods	PVC and PEEK tubing	RT	Seeds + AgNO ₃ + NaBH ₄ + CTAB	124
Silver nanoparticles	Silicon–Pyrex	RT	AgNO ₃ + NaBH ₄	115
Silver nanoparticles	Silicon–Pyrex	RT	AgNO ₃ + NaBH ₄	108

Table 2 Examples of oxide structures synthesized in microfluidic devices

Metal	Microreactors	Conditions	Reactants	Ref.
Fe ₃ O ₄	PDMS–Glass	RT	FeCl ₂ + FeCl ₃ + NH ₄ OH	133
Fe ₃ O ₄	PDMS–Glass	RT	FeCl ₂ + FeCl ₃ + NaOH	135
γ-Fe ₂ O ₃	PDMS–Glass + capillary injection	RT	FeCl ₂ + FeCl ₃ + NH ₄ OH	130
α-FeOOH	PDMS–Glass + capillary injection	RT (ageing at <i>T</i> = 60 °C)	FeCl ₃ + TMAOH	134
SiO ₂ nanoparticles	PDMS–Glass	RT	TEOS + NH ₄ OH + H ₂ O + EtOH	34
Silicalite	SS capillary	115 °C and 1 MPa	TEOS + TPAOH + H ₂ O	136
SiO ₂ microspheres	PDMS–Glass	RT	TEOS + HCl + H ₂ O + EtOH	137,138
SiO ₂ microspheres and slugs	Silica capillary	RT	TEOS + HCl + H ₂ O	129
TiO ₂ hollow spheres	PDMS–Glass	RT	Ti(oBu) ₄ + H ₂ O + Butanol + hexadecane	139
TiO ₂ nanorods	PDMS–Glass	90 °C	TTIP + Oleic acid + TMAO	140

devices, but limiting, so far, the size of the synthesized particle to the micrometre scale or just below.¹³¹ Table 2 summarizes examples of oxide particles synthesized in microfluidic systems.

The first family of methods uses compartmented reacting media (segmented flows^{34,132,133} or coflowing fluids¹³⁴) for the realization of homogeneous chemical transformations of precursors, which lead to the nucleation and growth of particles. The microfluidic technique has the advantage of narrowing the residence time distribution, which directly correlates with the final size distribution of the nanoparticles.¹¹⁶ However, preventing the synthesized nanoparticles from

adhering to the microchannel walls and clogging the reactor is a challenge. 3D injection^{130,134} or droplets-based chemistry¹³³ have been developed as effective means to reduce, or even eliminate, channel clogging by the synthesized nanoparticles.

Microfluidic methods have been applied to the synthesis of iron oxide nanoparticles, from magnetic maghemite nanoparticles (Fe_3O_4 or $\gamma\text{-Fe}_2\text{O}_3$) to Goethite Nanoparticles ($\alpha\text{-FeOOH}$). Iron oxide nanoparticles were obtained from the reaction of an aqueous solution of iron chloride with a basic solution of NaOH , NH_4OH or tetramethyl ammonium hydroxide (TMAOH). To contact the two solutions, the iron

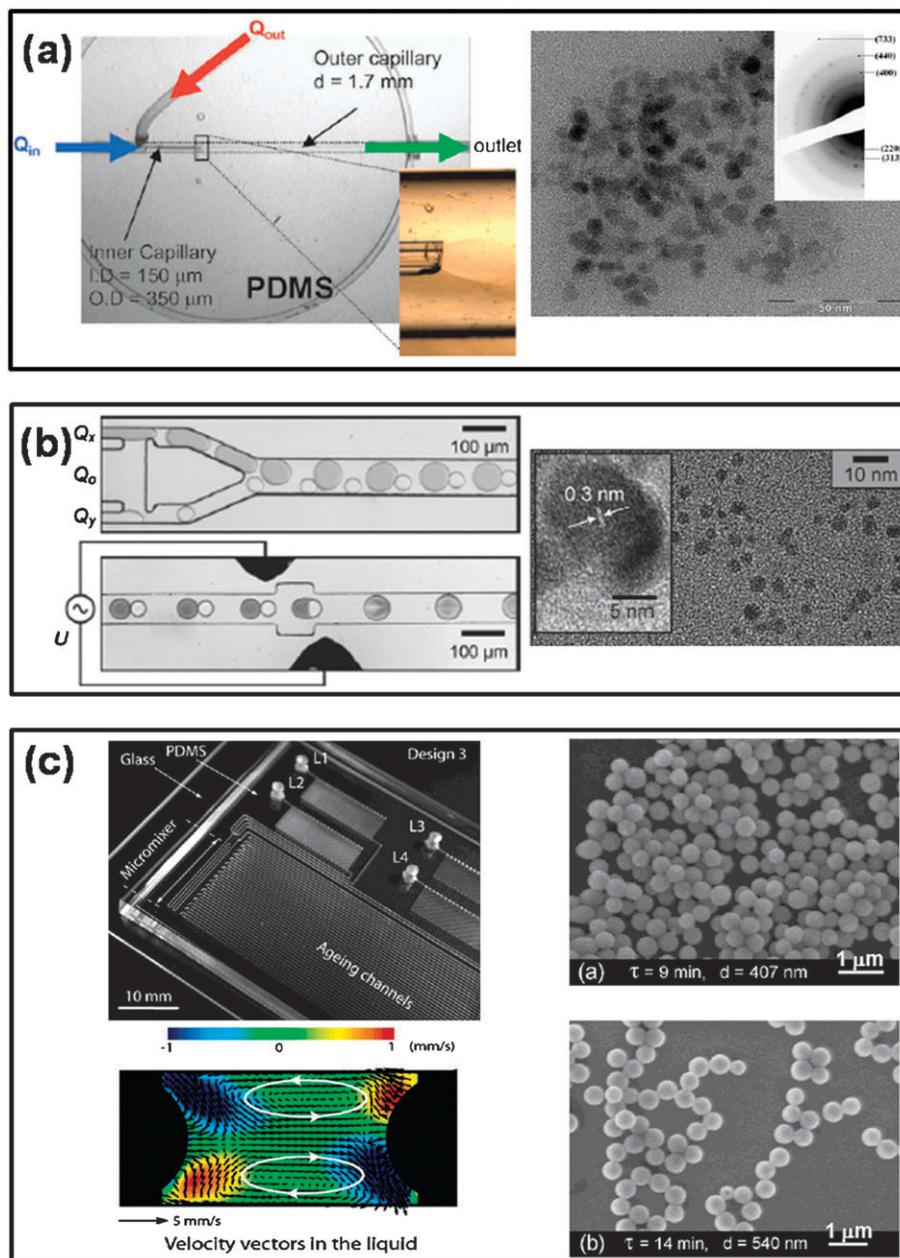


Fig. 9 Examples of oxides nanoparticles generated in microreactors. (a) iron oxide from the 3D coaxial injection of iron chloride and NH_4OH (reproduced by permission of the Royal Society of Chemistry),¹³⁰ (b) iron oxide from electrocoalescence of droplets containing iron chloride and NH_4OH (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 133), (c) silica nanoparticles from the Stober process developed in a gas-liquid segmented microflow (reprinted with permission from ref. 34. Copyright 2004 American Chemical Society).

chloride solution was injected 3D coaxially through a silica capillary tubing introduced inside a millifluidic channel in which the basic solution is flowing. This approach produced a well defined jet, centered in the channel, at the border of which the two fluids diffused in each other and iron oxide nucleated far from the channel walls (Fig. 9a).^{130,134} The pH mapping of this device was further studied with fluorescence confocal laser scanning microscopy.¹⁴¹

An alternative approach exploits the coalescence of two flowing droplets, each of them containing the reactant, e.g. iron chloride and base solution. In a refinement of this method, the drops are brought together by electrocoalescence. After the creation of droplets of both reacting media, the flowing droplets enter a fusion module equipped with electrodes, allowing merging the droplets by applying current (Fig. 9b).¹³³ This approach produces faster mixing (in few milliseconds) of the two phases compared to laminar co-flowing fluids, and the synthesized nanoparticles have no contacts with the reactor walls.

As discussed earlier, the dispersion inherent in laminar flow presents challenges to achieve narrow particle size distributions with homogeneous flows in microfluidic channels. Introduction of an inert second phase to create a segmented flow, generates segments of the synthesis medium that move through the channel as nearly independent, well stirred reactors.¹¹⁷ As a result, dispersion effects are eliminated and a sharp size distribution is achieved. With a stable droplet flow, there is virtually no communication between the isolated drops and a very narrow size distribution results if the synthesis occurs in the droplets. On the other hand, if the reaction takes place in the continuous phase, material can be interchanged among segments through the thin menisci around the droplets. The net result is a broadening of the size distribution relative to the ideal case.¹⁴² As an example of the latter case, segmentation of a reacting phase with gas¹³² was used to synthesize silica nanoparticles through the Stöber process.³⁴ Gas has the advantage that it can be inert and easily added or removed from the system.¹⁴³ In the example, a solution of tetraethyl *ortho* silicate (TEOS) in ethanol was contacted and premixed with an ammonium hydroxide solution. This flowing reacting medium was then segmented by the injection of an inert gas, nitrogen. Recirculation inside each liquid segments meant that they acted as nearly independent nanolitre reactors producing narrow size distributed silica nanoparticles (200–500 nm) (Fig. 9c). Although the reacting medium wetting the walls broadens the size distribution slightly,¹⁴² it has the advantage of enabling easy addition of reagents to the reacting phase, which becomes important in synthesizing core-shell structures (see section V).

Titania nanorods have also been synthesized in segmented flows. However, in this case, the reaction occurred at the interface between two liquids segments, one containing oleic acid and titanium tetraisopropoxide (TTIP), the other one containing trimethylamine *n*-oxide dihydrate (TMAO).¹⁴⁰ More recently, siliclike nanoparticles (50–100 nm) have been synthesized in solvothermal conditions (150 °C, 1 MPa) in a stainless steel capillary by the reaction of TEOS with tetrapropyl ammonium hydrate (TPAOH) in water.¹³⁶

The second family of methods takes advantages of the size and shape of micro droplets that can be generated inside microfluidic devices to form microparticles, similarly to what is done for organic materials processing (synthesis of polymeric materials or polymer-based hollow spheres, cf. sections III-1 and III-2). The size of the synthesized objects is directly dependent on the size of the hydrodynamic structures (e.g. micrometre scale). Microporous silica microspheres are synthesized in a water/oil segmented flow by combining pre-hydrolyzed TEOS–HCl–ethanol mixtures with an oily phase (generally hexadecane). The transfer of the ethanol into the oily phase then produces mesoporous silica microspheres through condensation (Fig. 10a and b).^{137,138} Another method consists in hydrolyzing the TEOS directly in the microfluidic device, dissolving the TEOS in silicone oil, used as the continuous phase, while creating droplets of the hydrolyzing medium (HCl + water). The diffusion and further hydrolysis of the TEOS in the droplets forms the particles. Controlling the shape of the dispersed phase leads to segment-like mesoporous silica particles (Fig. 10c).¹²⁹ Combining sol-gel chemistry with microfluidic droplets-based techniques can also

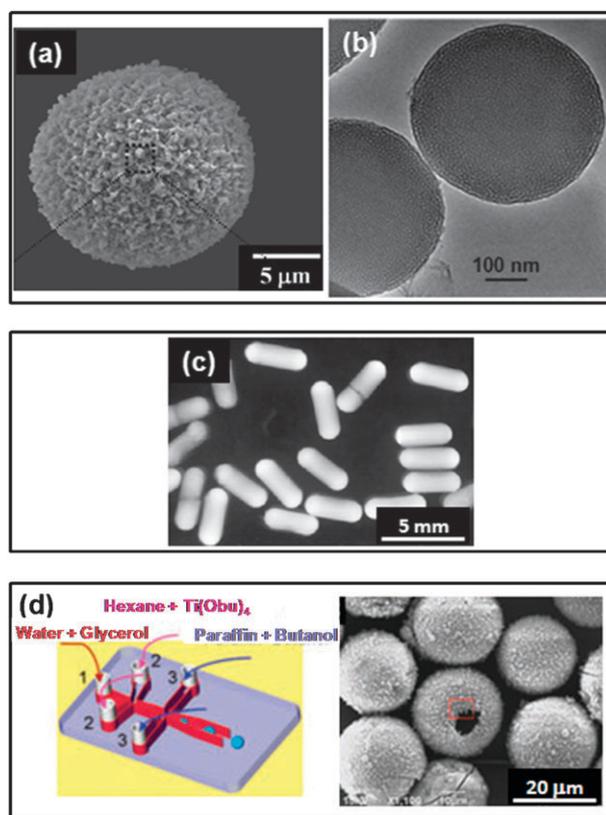


Fig. 10 Examples of oxides microstructures generated with the microfluidics technology, taking advantages of the hydrodynamic structures (droplets, slugs). (a) and (b) silica microporous particles (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 138 and reprinted with permission from ref. 137, copyright 2008 American Chemical Society). (c) silica slug-like particles obtain with millifluidic reactor (reprinted from ref. 129 with permission from Elsevier), (d) Titania hollow spheres with additional experimental procedure (reproduced by permission of the Royal Society of Chemistry).¹³⁹

lead to more complex microstructures such as hollow spheres (Fig. 10d). Titania hollow spheres were obtained from the hydrolysis of titanium tetrabutoxide (TTB) at the interface between a water dispersed phase and a TTB oily phase.¹³⁹

IV.3 Synthesis of crystalline semiconductor nanoparticles

Over the last decade, the synthesis of crystalline semiconductor nanoparticles, quantum dots (QD), in microfluidics has been widely studied because of the potential advantages of the technique over conventional batch approaches. The batch mode-based process have inherent shortcomings in the control of QD size and size distribution, leading to limited control of the optical properties of the synthesized nanomaterials, *e.g.*, broad emission line width. On the other hand, synthesis of QDs in microfluidic devices offers several advantages over conventional macroscale chemical processes¹⁴⁴ including enhancement of mass and heat transfer,^{52,145} reproducibility,¹¹ and low reagent consumption during optimization. Table 3 summarizes examples of QDs synthesis by microfluidic techniques.

Low temperature QDs syntheses are mainly dedicated to cadmium sulfide (CdS) nanocrystals synthesis. Redox reactions of cadmium salts (generally hydrate Cd(NO₃)₂) with Na₂S, leads to the formation of CdS QDs, at room temperature.^{146–149} Sodium polyphosphates is used in some cases to stabilize the as-synthesized QDs.^{148,149} Analogous to oxides nanoparticles synthesis, the sulfate and cadmium solutions can be contacted in several different ways. Droplets coalescence has been achieved by a reduction of the continuous phase velocity with an enlargement of the microchannel inducing droplets to contact and fuse (Fig. 11a).¹⁴⁹ Similarly, compartmentalization of the reacting aqueous phase in droplets or slugs with an oily continuous phase¹⁴⁷ (Fig. 11b) or reaction by diffusion between two laminar flow¹⁴⁶ (Fig. 11c) reduce the contact of the reacting medium with the microchannel walls and allows for measurement of the nucleation and growth kinetics. Changing the reagent from Na₂S to Na₂Se produces CdSe QDs.¹⁴⁷ However, large full width at half maximum (FWHM) in the photoluminescence spectra are typically obtained for the synthesized QDs (typically around

50 nm or above), reflecting a wide particle size distribution (PSD). Going to elevated synthesis temperatures (200 °C < *T* < 350 °C) improves luminescence quality and narrows particle size distribution.

Several microscale processes have been adapted from well known batch mode synthesis recipes.^{150–153} One difficulty of the high temperature synthesis is the requirement for solvents that can both dissolve the precursors at ambient conditions and also remain liquid over the entire operating temperature range (25 °C to 350 °C), significantly limiting the set of solvents, ligands, and precursors that are compatible with continuous flow systems. High boiling point solvents, such as squalane, octadecene (ODE) or trioctylphosphine oxide (TOPO) are commonly used. The cadmium source was initially the highly reactive and pyrophoric trimethyl cadmium (Cd(CH₃)₂), but now tends to be cadmium carboxylates such as cadmium oleate (Cd(Ole)₂) or cadmium stearate (Cd(st)₂), obtained from the pre-reaction of cadmium acetate or acetylacetonate with carboxylic acids at medium temperature (*T* ~ 130 °C). The selenium source is almost always trioctyl phosphine selenide (TOPSe) or tributyl phosphine selenide (TBPSe), both obtained from the dissolution of selenium shot in TOP or TBP. Carboxylic acids such as oleic acid (OA) and long carbon chain amines such as oleylamine (OLA) or dodecylamine typically serve as ligands.

Initial studies realized continuous synthesis of CdSe QDs at atmospheric pressure using a single phase laminar flow capillary reactors.^{3,6,11,154–157} These devices have the advantage of not requiring any microfabrication procedure and commercially available silica tubing can easily be immersed in oil bath for a good temperature control (Fig. 12a). This single phase laminar synthesis process has been extended to glass microchip reactors to gain flexibility in term of space, design of the microfluidic devices, and facile access for online characterization.¹⁵⁸ The main limitations of the single phase reacting mixtures is the high viscosity (0.5 mPa s < η < 1.5 mPa s) leading to slow mixing, broad residence time distributions (RTD), and as a consequence, broad QDs size distributions (FWHM of typically 35–50 nm).¹⁵⁴

Flow segmentation of the reacting phase with an immiscible phase overcomes these shortcomings by narrowing the RTD

Table 3 QDs and other materials nanocrystals synthesized in microfluidics devices

Metal	Microreactors	Conditions	Reactants	Ref.
CdS	PDMS–Glass	Room T	Na ₂ S + Cd(NO ₃) ₂ + sodium polyphate	148,149
CdS	PDMS–Glass	Room T	Na ₂ S + CdCl ₂	147
CdS	PDMS–Glass	Room T	Na ₂ S + CdSO ₄	146
CdSe	PDMS–Glass	Room T	Na ₂ Se + CdCl ₂	147
CdSe	Glass–Glass	220–270 °C	TOPSe + Cd(Ac) ₂ + TOPO	158
CdSe	Silica capillary	210–330 °C	TOPSe + Cd(St) ₂ + TOPO	155,156
CdSe	Glass–Glass	180–210 °C	TBPSe + Cd(CH ₃) ₂ + Dodecylamine + ODE	162
CdSe	Silica capillary	240–300 °C	Cd(Ole) ₂ + TOPSe + OLA + TOPO	157
CdSe	Silica capillary	160–255 °C	Cd(Ole) ₂ + TOPSe + ODE	9
CdSe	Silica capillary	230–300 °C	Cd(st) ₂ + TOPSe + TOPO	11
CdSe	Silica capillary	240–320 °C	Cd(Ole) ₂ + TOPSe + OLA + TOP + Squalane	154
CdSe	Silicon–Pyrex	260–280 °C	Cd(Ole) ₂ + TOPSe + OLA + Squalane	57
CdSe	Glass–Glass	240–300 °C	Cd(Ole) ₂ + TOPSe + TOP + ODE + Fomblin	159
CdSe	Silicon–Pyrex	210–270 °C and 5 MPa	Cd(Ole) ₂ + TOPSe + OLA + TOP + Hexane	38
InP	Silica capillary	225 °C	InCl ₃ + (TMS) ₃ P + OA + OLA + ODE	161
Si ₃ N ₄	Ceramic	1300–1400 °C	SiO + NH ₃	47

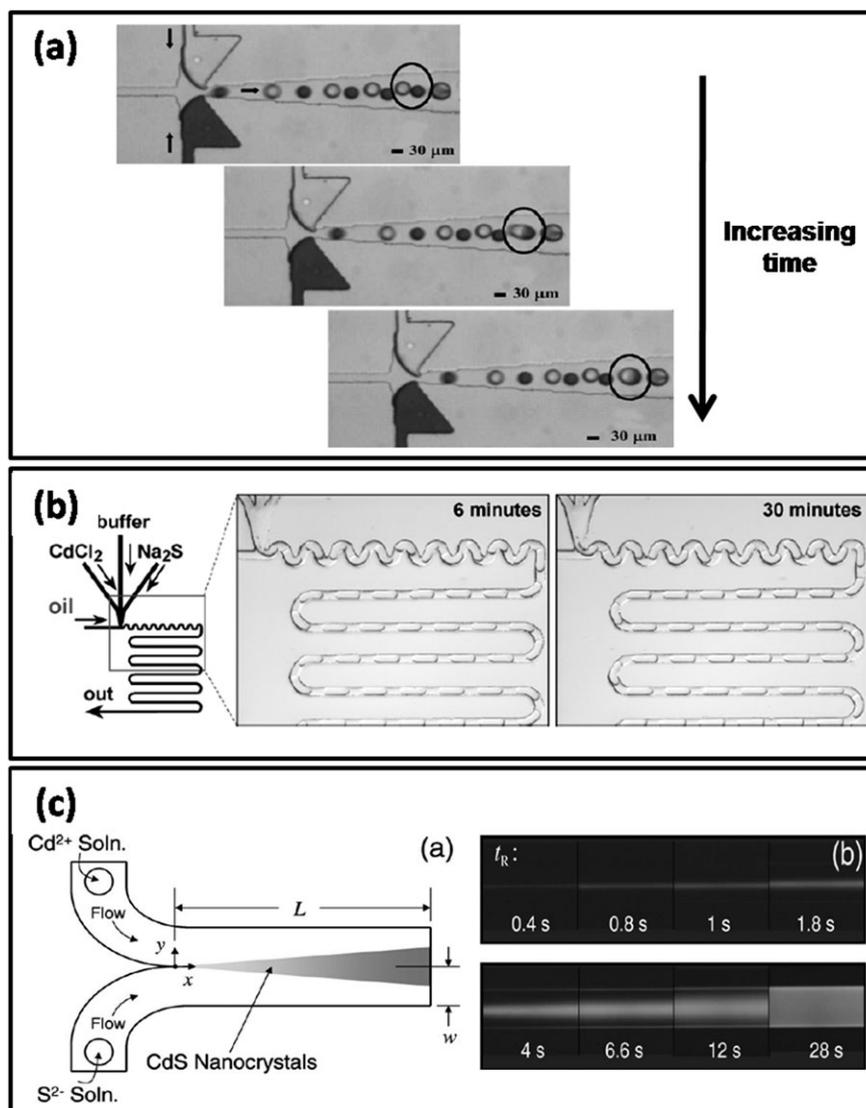


Fig. 11 Examples of microfluidic processes for generating QDs (CdS or CdSe) at room temperature. (a) droplets fusion method by generating a velocity gradient to force droplets of both reacting media (Na₂S from the top and Cd(NO₃)₂ from the bottom) to contact and fuse (reproduced by permission of the Royal Society of Chemistry),¹⁴⁹ (b) CdS or CdSe QDs synthesis in water in oil segmented microflows. Note the good stability over time from 6 to 30 min (reproduced by permission of the Royal Society of Chemistry),¹⁴⁷ (c) CdS QDs synthesis from interface diffusion of species in a coflowing laminar system leading to a spatially resolved analysis of both nucleation and growth (reproduced by permission of the Royal Society of Chemistry).¹⁴⁶

and improving reactant mixing.^{57,132} Application of segmented flows for continuous synthesis of narrowly distributed CdSe QDs has been demonstrated for liquid–gas,⁵⁷ and liquid–liquid segmented flows.¹⁵⁹ In the first case, the procedure was similar to that employed for silica nanoparticles synthesis discussed above. Solutions of cadmium and selenium in high boiling point squalane were introduced separately through two inlets inside a heated silicon–Pyrex microreactor, mixed and then segmented with argon gas, generating well mixed nanoliter reactors in series.^{132,160} The QDs were allowed to grow along an ageing channel before the reacting medium was cooled down to quench the reaction and recover the sample (Fig. 12b).⁵⁷

In the second case, octadecene (ODE) was used as the reacting media. Cadmium and selenium precursors were mixed

at room temperature before being injected into a continuous immiscible Fomblin phase (perfluorinated polyether), resulting in the reagents-containing phase being segmented into liquid droplets. In order to ensure that the fluorine phase wetted the walls of the glass–glass microreactor, the surface was modified with perfluorosilane. Cross flow focusing generated a jet that broke into droplets whose size could be controlled down to few microns. The resulting reacting droplets further flowed along the microchannel, allowing the QDs to grow (Fig. 12c).¹⁵⁹

The two segmented flow methods dramatically improved the FWHM of the synthesized QDs—down to 30 nm.

Replacing high boiling point viscous solvent systems by supercritical fluids (SCFs) allows for narrowing the CdSe QDs size distribution, without flows segmentation (FWHM can go

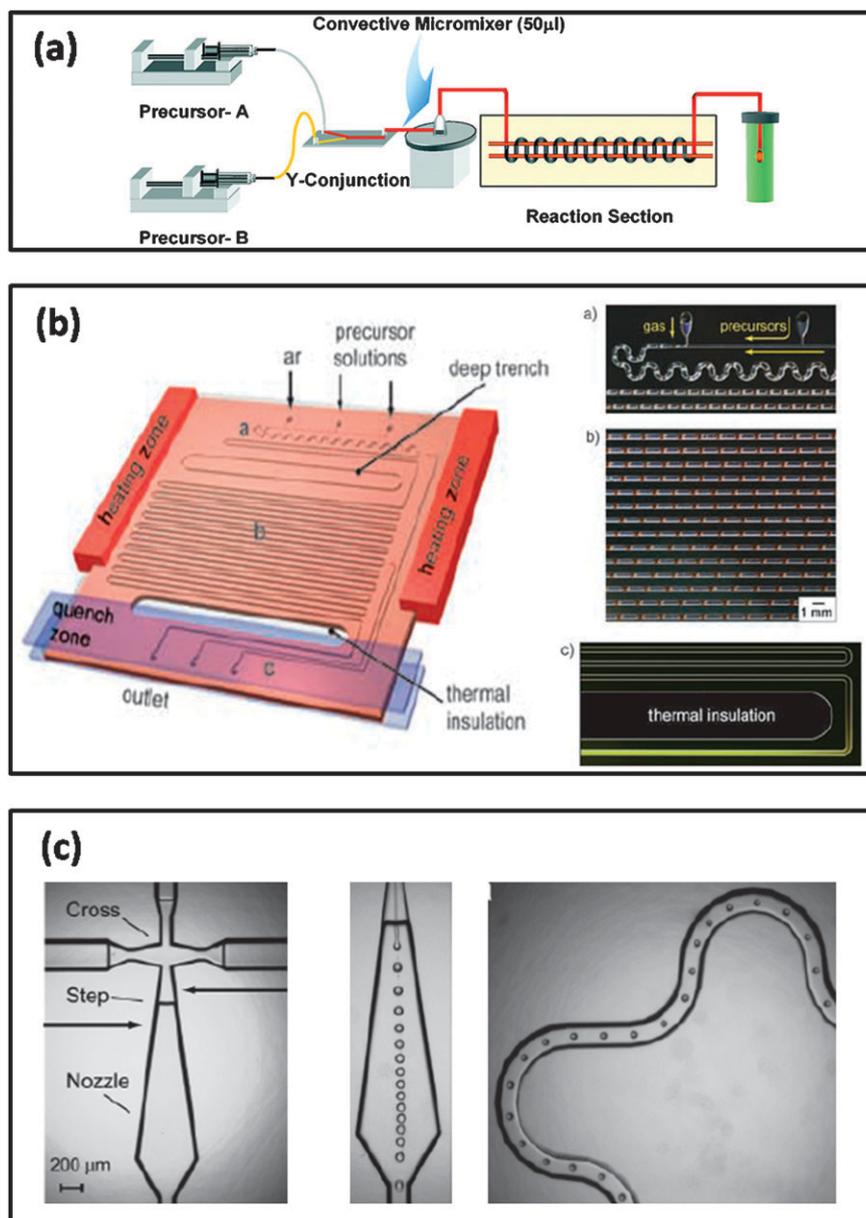


Fig. 12 Examples of microfluidic high temperature processes for generating QDs. (a) Simple silica capillary tubing set-up based on an oil bath heating system to grow QDs (reprinted with permission from ref. 157, copyright 2009 American Chemical Society). (b) Silicon–Pyrex microreactor for the segmented gas–liquid synthesis of CdSe QDs with on chip mixing, ageing and quenching zone.⁵⁷ (c) Droplet-based liquid–liquid (ODE–Fomblin) microsystem for the synthesis of CdSe QDs (reprinted with permission from ref. 159, copyright 2005 American Chemical Society).

down to 25 nm).³⁸ Further developments of these synthesis techniques will be discussed in section VI.

Another QDs material, indium phosphide (InP), was recently synthesized in a microsystems.¹⁶¹ The process was adapted from batch mode synthesis by reacting indium chloride (InCl_3) with tris(trimethylsilyl)phosphine ($(\text{TMS})_3\text{P}$) in a mixture of OA, OLA and ODE. This is to date one of the few applications of microfluidic systems to the synthesis of QDs materials besides CdS and CdSe.

Finally, silicon nitride (Si_3N_4) constitutes an interesting example of high temperature synthesis of nanoparticles in microreactors. This material was synthesized from reaction of SiO nanoparticles with gaseous ammonia (NH_3) in a

ceramic microsystem at temperatures ranging from 1300 °C to 1400 °C.⁴⁷

V. Synthesis of heterogeneous and hybrid micro and nanostructures

V.1 QD core shell structures

The flexible design and association of microreactors in series provide a simple way to continuously add reagents to a reacting phase and hence to generate heterogeneous nanostructures such as core–shell QDs. A first example is ZnS overcoated CdSe (CdSe@ZnS) QDs, where the higher band

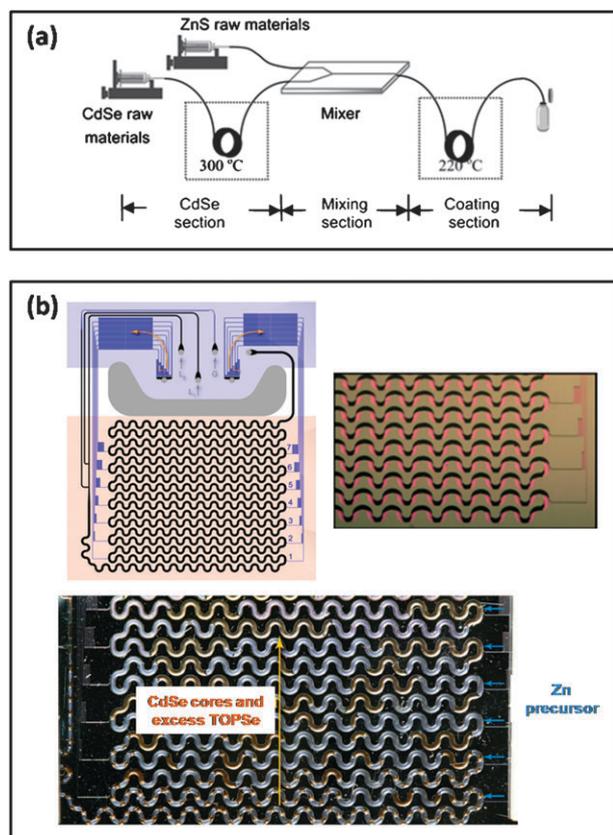


Fig. 13 Examples of microfluidic processes for generating core-shell QDs. (a) Multisteps process based on silica capillary tubing with a first section for CdSe cores synthesis, a mixing section to add Zn and S precursor and a coating section to grow the ZnS shell (*reproduced by permission of the Royal Society of Chemistry*).¹⁶⁵ (b) Silicon-Pyrex microreactor equipped with two temperature zones with a main reaction channel in which flows a segmented gas-liquid colloidal solution of CdSe cores with excess TOPSe. This channel is continuously fed by Zn precursor through shallow side channels for growing a ZnSe shell.⁷⁷

gap ZnS shell confines the excitons and passivates the surface to produce a higher quantum yield for the core shell structure than the bare CdSe QD. Their synthesis has been achieved in silica capillary and in silicon-Pyrex microreactors starting from a colloidal suspension of CdSe nanoparticles (Fig. 13).^{77,163–166} Growth of the ZnS shell generally requires lower synthesis temperature than for CdSe cores (typically 100–250 °C). Among the precursors used for the ZnS shell is the highly reactive diethyl zinc ($\text{Zn}(\text{Et})_2$), which tends to decompose quickly, therefore potentiality creating second nucleation and deposition of the channel walls. Less reactive precursors such as long carbon chain zinc carboxylates (oleate, stearate) reduce this complication. Bis(trimethylsilyl)sulfide ($(\text{TMS})_2\text{S}$) is the most common sulfur source, however, zinc diethyldithiocarbamate (ZDC) has a relatively low decomposition temperature and has attracted much interest as a single source precursor for ZnS shell synthesis.^{163,164}

Direct introduction of the coating solution at a single point generates a region of high concentration, creating the possibility of secondary nucleation of ZnS particles instead of the desired overcoat. Continuous feeding of the zinc and sulfur

precursors through small side channels ensures low, controlled concentration levels, eliminating the risk of secondary nucleation. This latter option was used to overcoat CdSe cores by ZnS or ZnSe shells in a silicon-Pyrex microreactor equipped with two different temperature zones (Fig. 13b).⁷⁷ TOPSe was added in excess to a CdSe colloidal solution and allowed to flow through a main reaction channel (black channel, Fig. 13b). The Zn precursor ($\text{Zn}(\text{Et})_2$) was continuously added to the flowing reaction medium through several shallow side channels at different points (blue channels, Fig. 13b). These side channels were designed to have the same pressure drop to ensure equal flow rates at each addition point. This microfluidic control of the core shell material provides flexibility and promises synthesis of more complex nanostructures requiring precise control over concentrations, such as concentration graded overcoats, dumbbells, and tetrapods.¹⁶⁷

V.2 Overcoating nanoparticles with oxides

In addition to controlling optical properties of nanoparticles by overcoating, there is considerable interest in adding materials that have specific properties, *e.g.*, biocompatibility and ease of surface modification. In this context, silica and titania are often materials of choice. Taking advantages of the studies detailed in sections IV-2 and V-1, microfluidics-based synthesis of nanoparticles can be combined with continuous addition of sol-gel reagents to grow oxides shells. As an example, overcoating of silica nanoparticles by a titania shell has been demonstrated in a PDMS-glass microreactor (Fig. 14a)²¹ using a procedure similar to that described above for overcoating of CdSe by ZnS.⁷⁷ Silica nanoparticles were flown through the main channel with multipoint side channel addition of the titania shell precursor, titanium tetra ethoxide (TEOT) in an ethanol-water/hydroxypropyl cellulose solution. The shell thickness could be tuned from 20 to 30 nm depending on the flow and concentration of the titania precursor solution.

Another example is the recently reported multistep synthesis of fluorescent $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$ nanoparticles.¹⁶⁸ Overcoating magnetic iron oxide nanoparticles with silica shells, subsequently grafted with biomolecules, is of particular interest for biological applications, such as cancer diagnosis and treatment. In this case, the procedure involved several coaxial silica-capillary-in-PDMS-Glass microreactors for the different steps: synthesis of the $\gamma\text{-Fe}_2\text{O}_3$ cores, coating with silica shell, mixing and grafting (Fig. 14b).

V.3 Engineering multifunctional microparticles

Combining organic and inorganic materials synthesis strategies in microfluidics opens opportunities for realizing hybrid microparticles made of organic materials (microgels, microcapsules) and incorporating inorganic nanoparticles such as magnetic iron oxide or QDs. Such structures are of particular interest for bio imaging. This sub section aims to give a brief overview of structures recently realized using microfluidics. Table 4 summarizes examples of heterogeneous nanoparticles and hybrid microparticles synthesized within microreactors.

Encapsulation of QDs or magnetic particles such as iron oxide has been realized through procedures similar to those described in sections III-1 and III-2. Thermosensitive

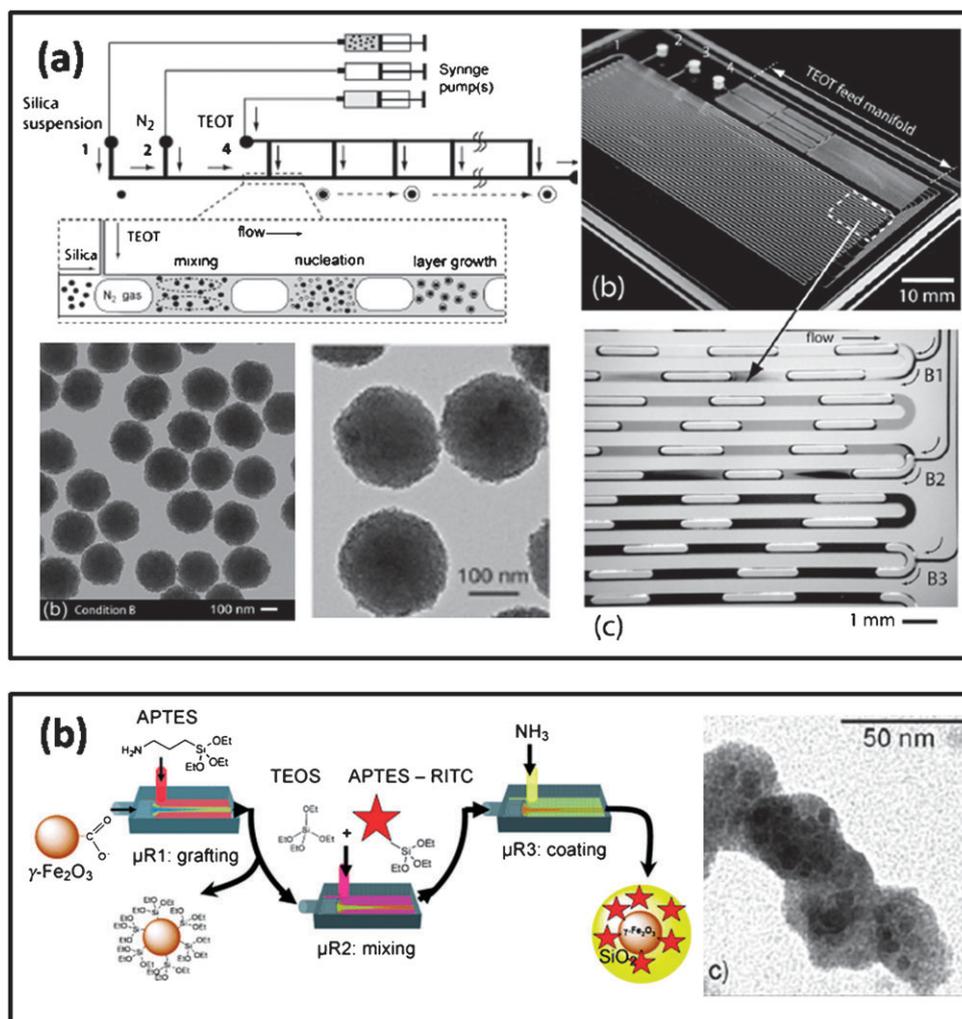


Fig. 14 Microfluidic processes for the synthesis of silica@titania core-shell Nanoparticles (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 21), (b) Multisteps synthesis procedure for fluorescent $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ Nanoparticles (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 168).

Table 4 Examples of heterogeneous Nanoparticles and hybrid microparticles synthesized within microreactors

Material	Microreactors	Conditions	Reactants	Ref.
CdSe@ZnS	Silica capillary	80–160 °C	CdSe QDs + OLA + TOP + ZDC	163
CdSe@ZnS	Silica capillary	140–250 °C	CdSe QDs + TOP + TOPO + ZDC	164
CdSe@ZnS	Silica capillary	220 °C	Online synthesized CdSe QDs + TOP + TOPO + Zn(Et) ₂ + (TMS) ₂ S	165
CdSe@ZnS	Silicon–Pyrex	140 °C	CdSe QDs + Squalane + TOP + Zn(Et) ₂ + (TMS) ₂ S	77
CdSe@ZnSe	Silicon–Pyrex	240 °C	CdSe QDs + TOP + ODE + Zn(Ole) ₂ + TOPSe	77
SiO ₂ @TiO ₂	PDMS–Glass	Room T	SiO ₂ Nanoparticles + TEOT + HPC + EtOH + H ₂ O	21
$\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$	Silica capillary + PDMS–Glass	Room T	$\gamma\text{-Fe}_2\text{O}_3$ + APTES then addition of TEOS + fluorescent APTES	168
[CdSe@ZnS] in PLGA microgels and microcapsules	Silica capillary + PDMS–PDMS	Room T	CdSe@ZnS QDs + PLGA + PVOH + CS	169
$\gamma\text{-Fe}_2\text{O}_3$ in micro hydrogels	PDMS–Glass + aluminium reflectors	Room T	$\gamma\text{-Fe}_2\text{O}_3$ + PEGDA + photo initiators	170
$\gamma\text{-Fe}_2\text{O}_3$ or QDs in PNIPAm micro capsules	Capillary-based microsystem	Room T	$\gamma\text{-Fe}_2\text{O}_3$ or QDs aqueous solution + NIPAm + APS	89
Superparamagnetic Janus particles	PDMS–Glass + aluminium reflectors	Room T	$\gamma\text{-Fe}_2\text{O}_3$ + PEGDA + photo initiators	171

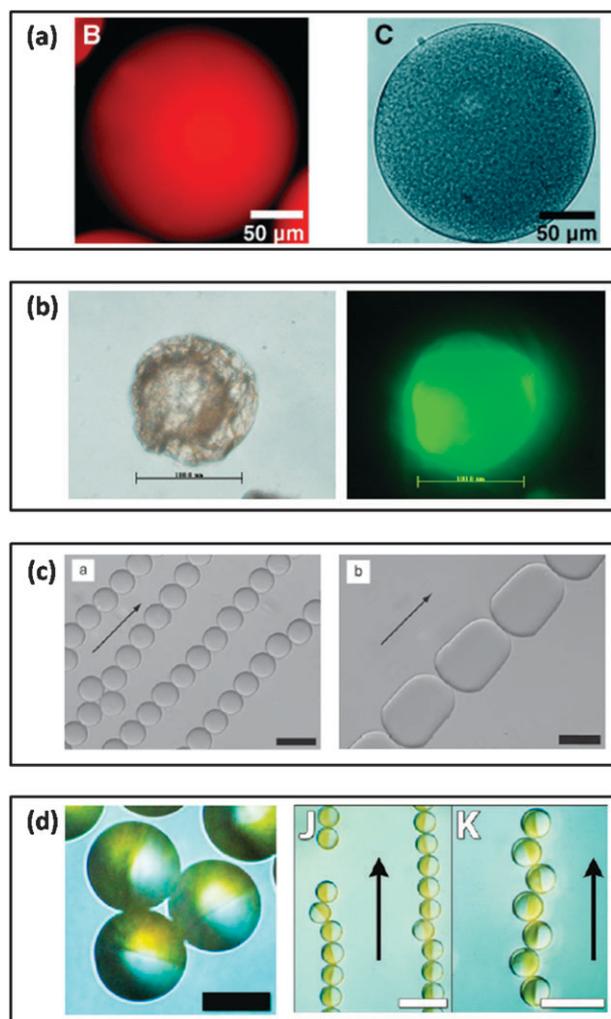


Fig. 15 Examples of microfluidics engineered multifunctional micro-particles. (a) Thermosensitive PNIPAm microgels containing QDs (left) or magnetic iron oxide particles (right) (*Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 89*), (b) Multiple emulsions preparation of PLGA microparticles containing CdSe@ZnS QDs,¹⁶⁹ (c) PEG microparticles containing magnetic nanoparticles, obtained from photo-induced polymerization (*reproduced by permission of the Royal Society of Chemistry*),¹⁷⁰ (d) superparamagnetic janus particles obtained from multiple laminar co-flowing fluids combine to UV exposure (*reprinted with permission from ref. 171, copyright 2009 American Chemical Society*).

poly(*n*-isopropylacrylamide) hydrogels (PNIPAm) containing either QDs or iron oxide nanoparticles were prepared from the polymerization in double emulsions of NIPAm with ammonium persulfate (APS) in the presence of a cross linker *N,N* methylene bis acrylamide (BIS). The preparation of the microgels was achieved through the use of an inner fluid containing a colloidal solution of QDs or magnetic nanoparticles (Fig. 15a).⁸⁹

Another method based on solvent evaporation, generally employed for polymersomes synthesis,^{87–89} was used to prepare core shell CdSe@ZnS QDs in PLGA microcapsules. An emulsion was generated from of a colloidal CdSe@ZnS QDs chloroform solution containing dissolved PLGA with polyvinyl alcohol and chitosan as stabilizers. Evaporation of

the chloroform produced PLGA microspheres containing QDs (Fig. 15b).¹⁶⁹

UV photoinduced polymerization through a mask is yet another means for incorporating magnetic nanoparticles into PEG microparticles.⁶⁷ In this case, the mask design provides control of the particle morphology (Fig. 15c),¹⁷⁰ while the microfluidic approach allows for multiple laminar co-flowing fluids for the generation of superparamagnetic spherical Janus particles. Both streams contains UV curable poly(ethylene glycol) diacrylate, except magnetic Fe₃O₄ NPs are suspended in one of the two (Fig. 15d).¹⁷¹ Using their magnetic characteristics, these microparticles can be aligned under a magnetic field to create different particle assemblies (Fig. 15c and d).

From these first few examples, one can envision multi steps synthesis of much more complex microstructures, by engineering their shape, composition or surface properties by coupling microreactor systems, similarly to what has been demonstrated for chemical applications.¹¹⁹

VI. HP/HT microfluidics and supercritical microfluidics: towards new processes and new materials

The development of high temperature microfluidic reactors for nanoparticles synthesis has been demonstrated in several studies with the continuous synthesis of nanocrystals (NCs) at atmospheric pressure using either a single laminar phase or segmented flows, as reported above (see section IV). However, the need for using high boiling point solvents has limited synthesis conditions and choice of precursors. The use of elevated pressures is one avenue to address this limitation and expand solvent choices and synthesis conditions in micro-reactors. At sufficiently high pressure, virtually any common solvent, precursor, and ligand will remain either liquid or become supercritical (sc) at the temperatures required for nanomaterials synthesis. Additionally, the ability to work at elevated temperatures and pressures while confining potentially toxic, highly reactive starting materials could become important for the synthesis of novel nanostructured materials or chemical reactions. In particular, it would be possible to develop HP/HT solvothermal and hydrothermal processes on chip.

The particular case of supercritical conditions offers additional advantages. Potential useful characteristics of supercritical fluids (SCFs) include high diffusivity (typically one order of magnitude higher than in liquid phases), gas-like viscosity (in the order of few tens of μPa), while being able to dissolve a wide range of reagents due to the liquid-like density (typically 200–1000 kg m^{-3}). These advantages lead to narrowing of the residence time distribution (RTD) in channel flows, thanks to low viscosity and high diffusivity, reducing the dispersion along the channel, and therefore providing a useful option for efficiently narrowing the size distributions of nanomaterials during synthesis. These advantages have recently been demonstrated in a study of CdSe QD synthesis in a HP/HT microreactor comparing the high boiling point squalane solvent with supercritical hexane. The supercritical fluid synthesis produced a narrower FWHM and particles size

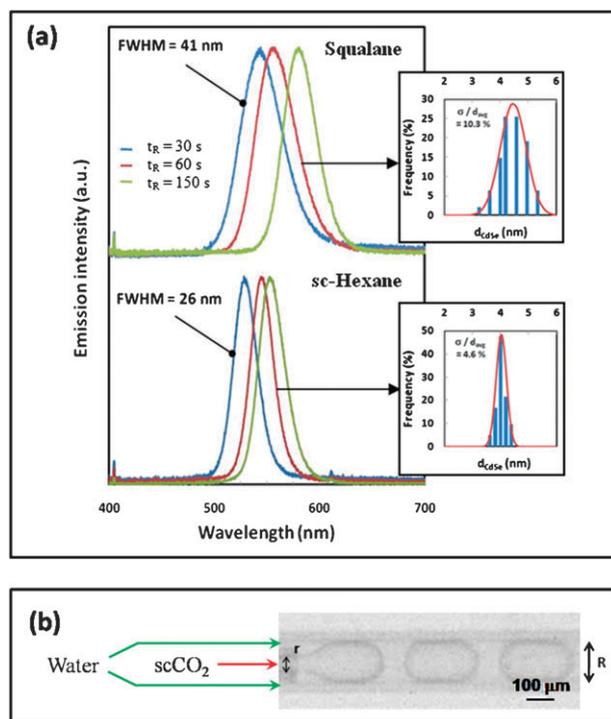


Fig. 16 (a) Comparison of the photoluminescence and FWHM obtained for CdSe QDs synthesis in liquid high boiling point squalane and in supercritical hexane (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 38), (b) Supercritical CO₂ in liquid water droplet microflows observed in capillary microreactor at high pressure (reprinted with permission from ref. 183. Copyright 2009, American Institute of Physics).

distribution than liquid phase synthesis at the same conditions (Fig. 16a).³⁸

Nanomaterials synthesis at supercritical conditions has been reported using stainless steel capillary tubing. For example, nanoparticles of ZnO¹⁷² and Fe₃O₄¹⁷³ were synthesized at supercritical water conditions through an ultra fast process by mixing aqueous solutions of zinc and iron salt, respectively, with KOH. Although stainless steel capillary tubings can be considered as microreactors, the lack of optical access and difficulty of integration fluid distribution/mixing elements limits their use relative to silicon–glass microfluidic systems.

Most other applications of SCFs in microfluidics devices have been focused to chemical transformations.¹⁷⁴ Several examples demonstrated the improvement of chemical yield and reaction time, replacing conventional liquid solvents by supercritical CO₂.^{51,175,176} From these first demonstration case studies, one can envisage to adapt several SCFs-based processes for organic,^{177,178} inorganic^{179–182} and hybrid nanomaterials synthesis¹⁸⁷ to microreactors, enlarging the synthesis capability of microfluidic systems.

The characteristics of SCFs could also improve mixing in microchannels through the enhanced diffusivities and ability to reach larger Reynolds numbers than generally accessible in conventional microfluidics. Moreover, SCFs properties (density, viscosity, diffusivity, dielectric constant) can be tuned continuously by simple variations of temperature and pressure, unlike for liquids. Additionally, SCFs such as sc-Water or

sc-CO₂ could potentially replace more harmful solvent systems for droplet-based processes, as recently demonstrated with the generation of scCO₂ in liquid water segmented microflow at $T = 50\text{ }^{\circ}\text{C}$ and $8 < p < 18\text{ MPa}$ (Fig. 16-b).¹⁸³ The reverse system could also be employed meaning that, for instance, sc-CO₂ could be employed as a continuous phase to replace oily phases such as fluorosilicone oil, to stabilize water droplets in microfluidics applications, such as synthesis of microcapsules. After depressurization, the gaseous nature of CO₂ in the normal conditions of pressure and temperature would simplify phase separation and avoid additional purification steps.

Conclusions

Continuous flow, microfluidic systems have already been demonstrated to be useful platforms for synthesizing micro- and nanoparticles with controlled size, shape and size distribution. They have yielded particles of organic polymers, oxides, semiconductors, and metals as well as hybrid structures combining multiple materials and functionalities. Further integration of measurement techniques will provide additional control of synthesis processes. Moreover, integration of multiple microfluidic systems show promise for the realization of engineered nanoparticles with unique optical, electronic, and catalytic properties. Clogging of channels during materials synthesis remains challenging for some systems, in particular oxides. However, advances are being made in identifying and understanding the clogging mechanisms, such as constriction by deposition and accumulation on the walls or particle agglomeration creating plugs by hydrodynamic bridging between particles.^{184–186} Therefore, these shortcomings can be minimized by reducing agglomeration by microfluidic design, surface modifications, flow modulation, and/or external forcing (e.g., ultrasonic). Finally, the expanded synthesis space with high pressure and high temperature conditions not easily accessed in conventional batch procedure opens new methods for the realization of complex engineered nanostructures and additional materials systems.

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