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High and Efficient Production of Nanomaterials by Microfluidic Reactor Approaches

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Abstract

This chapter overviews different approaches for the synthesis of nanostructured materials based on alternative methodologies to the most conventional and widespread colloidal wet chemical route and with a great potential applicability to large-scale and continuous production of nanomaterials. Their major outcomes, current progress in synthesis of micro and nanostructures by using microfluidics techniques and potential applications for the next future are reviewed throughout three different sections. Emphasis is placed on nanomaterials production basics, nanomaterials production techniques and microfluidic reactors (types, materials, designs). The integration of nanoparticle and microreactor technologies delivers enormous possibilities for the further development of novel materials and reactors. In this chapter, recent achievements in the synthesis of nanoparticles in microfluidic reactors are stated. A variety of strategies for synthesizing inorganic and polymeric nanoparticles are presented and compared, including continuous flow, gas-liquid segmented flow and droplet-based microreactors

Keywords: Microfluidics, inorganic nanomaterials, polymeric nanomaterials, microreactors, nanoengineering

1. Introduction

After more than twenty years of basic and applied research, nanotechnologies are gaining in commercial use due to their unprecedented potential. Nanomaterials are the heart of the nanotechnology, they are the key in the development of electronics, medical diagnostics and therapeutics, energy storage, cosmetics, catalysts, lubricants, pigments, healthcare. In fact, the latest update available from the inventory compiled by the Woodrow Wilson Center [1] indicates that the number of nanotechnology-based consumer products was above 1800 in 2014 and growing at a strong pace. These products are produced in more than 33 countries and can

be classified into different groups: Appliances, Automotive, Cross Cutting, Electronics and Computers, Food and Beverage, Goods for Children, Health and Fitness or Home and Garden. The composition of these products could contain up to more than 49 different types of nanomaterials, from gold to liposomes. Then, it is evident that during the past two or three decades there has been an explosive increase in our ability to nanoengineer and product nanostructures and nanosystems with an good degree of control. Therefore, given the expected economic and social impact of nanotechnology products and the fact that many areas of application are still scarcely explored, it seems reasonable to predict that industrial use of nanomaterials will continue to increase in the foreseeable future.

Nanomaterials can be defined as materials development at the atomic, molecular or macromolecular levels, in the length of scale of approximately 1- to 100-nm range in at least one dimension. Materials under these dimensions behave in a different mode that their bulk counterparts. The scale reduction provides special properties which are uniquely attributable to the nanoscale physical size. Consequently, it seems reasonable that the control in the synthesis procedure must be good enough to assure the properties of the nanomaterials produced. Otherwise, the quality of the products which contain those nanomaterials could be limited.

New materials properties are required as the Nanotechnology market is growing, which implies that highly sophisticated configurations at the nanoscale level need to be developed. These strict requirements on the characteristics of nanomaterials pose serious challenges to their mass production. In addition, many of the most sophisticated nanomaterials are nowadays prepared in lab scale by complex, multistep batch procedures that are not amenable to large-scale production [2]. This issue has been identified as one of the main barriers for the development of nanotechnology [3] and any potential technology able to overcome these drawbacks will enable the future development of Nanotechnology.

Microscale process engineering is the science of conducting chemical or physical processes inside small confined volumes, for instance inside channels with diameters of less than 1 mm (microchannels) or other structures with sub-millimeter dimensions [4]. These processes are usually carried out as continuous production with the potential to make microscale process a key for chemical production [4]. In fact, microscale process engineering enables an accurate control in the productivity of pharmaceutical and fine chemical industry. The small dimensions where the chemical reaction occurs lead to a relatively large surface area-to-volume ratios and promotes the heat and mass transport. In addition, the possibility of fast mixing of reactants and fast heating and cooling of reaction mixtures enables precise control of the reaction parameters. These advantages are well suited in the production of nanomaterials, where an exquisite control of synthesis conditions is required to assure an excellent quality.

This chapter overviews different approaches for the synthesis of nanostructured materials based on the application of microreactors derived from the microscale process engineering. The basics of nanomaterials production, the synthesis approaches to produce nanomaterials in continuous mode, present state-of-the-art and potential applications of microreactors for the next future are reviewed.

1.1. Overview of synthetic approaches to nanomaterials production

The fabrication of nanomaterials of tailored properties involves the control of size, shape, structure and composition. Fabrication techniques for nanostructures can be broadly divided into two categories: Top-down and Bottom-up approaches (Figure 1). Top-down approaches consist of the miniaturization or size reduction (for instance by etching or milling) of larger structures. On the other hand, bottom-up approaches are based on growth and self-assembly to build up nanostructures from atomic or molecular precursors. Lithographic patterning is usually the most common technique to structure bulk materials at the nanoscale. Optical lithography (also named Photolithography), has been the predominant patterning technique due to the fact that it enables the production of sub-100-nm patterns with the use of very short-wavelength light (currently 193 nm).

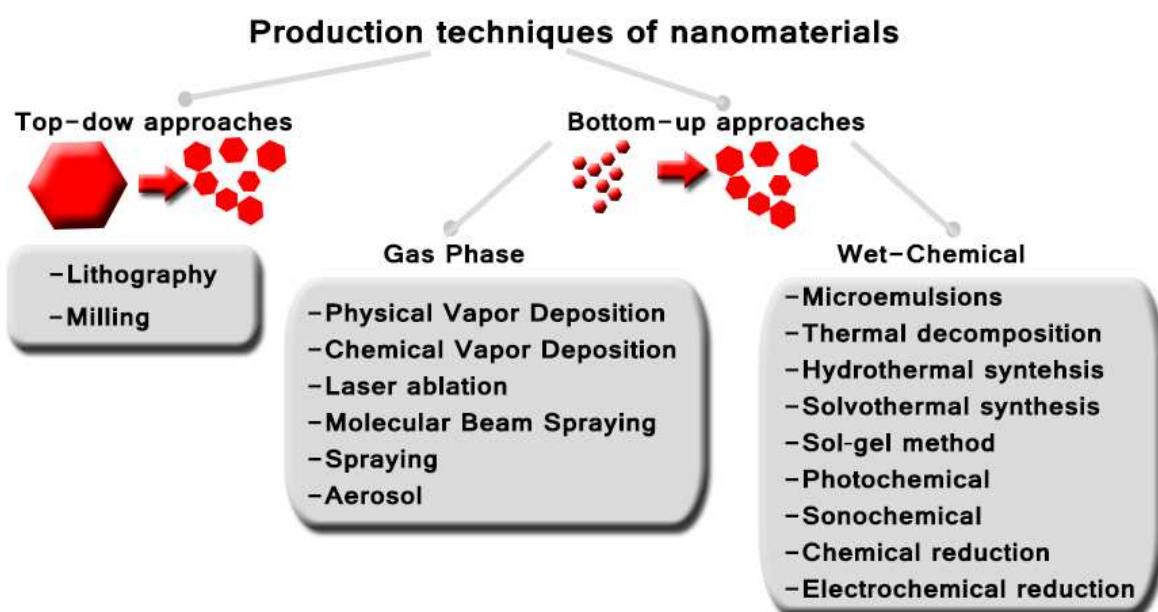


Figure 1. Scheme of the most relevant production techniques of nanomaterials

Regarding bottom-up approaches, they offers the most realistic solution toward the fabrication of complex and functional nanomaterials since the resolution and dimension control at the nanoscale level is better than in top-down approaches. Botton-up techniques can be classified into gas phase and wet-chemical methods, depending on the medium at which nanoparticles form (see Figure 1). The most important gas phase approaches comprise Physical Vapour Deposition, Chemical Vapour Deposition, Laser ablation, Molecular Beam Spraying, and Spraying-Aerosol. Physical vapor deposition (PVD) is a versatile method for preparing thin-film materials with structural control at the nanometer or even atomic scale by carefully monitoring the processing parameters. PVD involves the generation of vapour phase species via evaporation, sputtering, or laser ablation. Chemical vapor deposition (CVD) is a technique for thin film deposition which offers an excellent uniformity and it is amenable to large scale production. In CVD the substrate is exposed to one or more volatile precursor materials that

react and/or decompose on the substrate surface to produce the desired deposit. Molecular beam epitaxy (MBE) is a technique to produce ultrathin films as high quality epitaxial layers with very sharp interfaces and good control of thickness and chemical composition. To obtain epitaxial layers of high purity, the deposition takes place in very high vacuum. Spraying is a well-established method, which involves the atomization of chemical precursors into tiny droplets dispersed in a gas phase. Afterwards, the drops are combusted or evaporated to form nanoparticles or thin films. Pyrolysis is the chemical decomposition of organic materials by heating in the absence of oxygen or any other reagents. The use of a laser source induces a fast heating, in a solid target (ablation) either on the gas phase or in a liquid phase, which promotes the formation of nuclei and direct the growth of nanoparticles, for instance metal oxides.

Wet-Chemical techniques have been considered as one of the most important techniques for fabricating low-dimensional structures with an accurate control on the dimensions and composition. These techniques seem to be very attractive since they enable the production of a wide diversity of nanomaterials, at a low cost and with a high throughput to ease a high-volume production (see Figure 1). Nanomaterials can be tailored with sub-nanometer level accuracy by careful regulation of crystallization kinetics and thermodynamic parameters in liquid media under assistance of selected solvents, ligands and surfactants. Wet-Chemical techniques can be classified into: microemulsions, thermal decomposition, hydrothermal and solvothermal synthesis, sol-gel method, photochemical, sonochemical and electrochemical processes.

Microemulsions are ternary/quaternary systems of water, oil and amphiphilic surfactants forming micelles. Micelles form after the surfactant concentration is above the critical micellar concentration. Microemulsions can be generated after the solubilization of organic compounds in water (oil-in water, *o/w*), or hydrophilic compounds in the oil phase (water in oil, *w/o*). In addition, a high degree of complexity can be achieved producing multiple phase emulsions, such as *w/o/w* or *o/w/o*. Nanomaterials are usually produced by mixing two microemulsions, where each other contain a reactive chemical [5]. Once the microemulsions merge, new micelles are formed and the chemical reaction occurs. Then, micelles have the role of nano/micro reactor, confining the chemicals during the reaction. Consequently, microemulsions are a versatile preparation technique which enables an accurate control of nanoparticle properties such as size, geometry, morphology, homogeneity and surface area. Thermal decomposition is usually carried out with organometallic precursors compounds and metal complexes with the assistance of high boiling solvents. Hydrothermal and solvothermal synthesis are common methods to synthesize inorganic nanomaterials. These techniques take advantage of the high reactivity of metal precursors at elevated pressure and temperature. A good control on crystallization parameters such as pressure, temperature, time, pH and reactants concentration enable to tune the size and shape of nanomaterials. Sol-gel method it is generally used for the production of metal oxide nanomaterials and involves the hydrolysis, condensation and polymerization of metal precursors. A three-dimensional network is formed after the polymerization step, forming the gel, but a calcination treatment is usually required in order to drive off the structural water and transform the metal hydroxides into metal oxides. Photochemical techniques are based on the UV-irradiation of the chemical precursors to generate active

radicals which promote the NPs formation with a controlled kinetic rate. On the other hand, sonochemical approaches are associated with the absorption of ultrasound by water. Acoustic wavelengths range from 10 to 10^4 cm, which is far above the molecular or atomic range. Then, sonochemical reactions occur by the phenomena of acoustic cavitation, where the liquid is compressed or expanded according to the sound field. Hot spots are formed during the collapsing of bubbles generated during acoustic cavitation, achieving local temperatures of upto 4000K [6]. These conditions make water molecules dissociate into H and OH radicals and promote the reduction of metallic ions. Finally, chemical and electrochemical reduction approaches are one of the possible and powerful options for the fabrication of new types of nanomaterials. Chemical reduction relies in the presence of a substance, named reducing agent, with an oxidation potential high enough to easily donate electrons to an electron recipient compound, which is usually a metallic salt. If this electron transfer occur, metallic ions are reduced to atoms which form nuclei and later nanoparticles according to the nucleation-growth-ripening process [7]. However, this procedure is highly dependent from the presence of a proper reducing agent which enables the electron donation without potential interferences with the crystallization kinetics. On the other hand, electrochemical reduction processes, which involve electron transfer reactions at solid-liquid interfaces controlled by an externally applied voltage, are reliable tools for nanofabrication since the redox potential can be easily tuned according the redox potential required.

1.2. Nanomaterials production basics

Nanotechnology is a relatively new field; therefore applications of nanoparticles offer much promise to improve in future. However, most of applications based on nanoparticles are dealing only a few nanoparticle materials such as gold, silver, silica, alumina, carbon nanotubes, titanium oxide and zinc oxide. But, many other interesting nanomaterials that show unique and useful properties still remain on the laboratory bench due to slow progress in bridging laboratories with high-scale production factories [8]. The lack of development of large scale production is being considered as one of the main obstacles. For instance, carbon nanotubes (CNTs) was considered a remarkable nanomaterial due to their unique physical and chemical properties. However the number of applications of CNTs was limited at the Early 90's because the prize was too high (more than 1000\$/gram). Nowadays, Microreaction technology is expected to have a number of advantages for chemical production [2] as the high heat and mass transfer rates possible in microfluidic systems allow reactions to be performed under more aggressive conditions with higher yields that can be achieved with conventional reactors [10]. In addition, new reaction pathways considered too difficult to explore in conventional microscopic equipment could be pursued because if the microreactor fails, the small amount of chemicals released accidentally could be easily contained. Microreaction technology enables a continuous production, as well as allows the presence of integrated sensor and control units to follow the nanomaterials quality or even alert about any fails. A failed microreactor can be isolated and replaced while other parallel units continued production. Also these inherent safety characteristics could allow a production scale systems of multiple microreactors enabling a distributed point-of-use synthesis of chemicals with storage and shipping limitations, such as highly reactive and toxic intermediates [2,10]. Moreover, scale-

up to production by replication of microreactors units used in the laboratory would eliminate costly redesign and pilot plant experiments, thereby shortening the development time from laboratory to commercial-scale production.

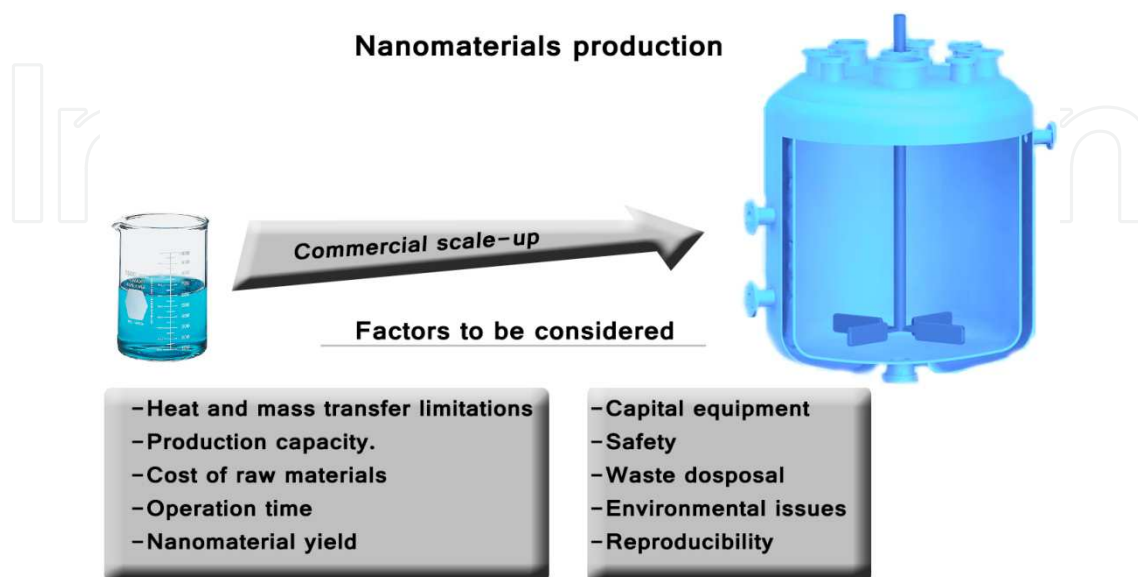


Figure 2. Factors to be considered in the commercial scale-up of nanomaterials production.

2. Microfluidic technology

Microreactors or Microfluidic reactors constitute perhaps the enabling technology of highest potential for liquid phase synthesis of nanomaterials since they have been proposed to overcome the inherent discontinuity and reproducibility of batch reactors, the inter and intra-batch dispersion regarding the physicochemical characteristics of the product nanomaterials and the difficulties regarding scale-up [2]. In addition to their well-known enhancement of heat and mass transfer, microfluidic reactors offer a flexible operation with modular design, with the possibility of increasing the number of modules to adapt to the specific process requirements. On the other hand, the scaling-up by arraying parallel microreactors allows capital investment and market growth to be coupled, reducing financial risk, which is especially important in emerging areas such as nanotechnology [2]. This section will deal with a summary of the most representative types of microreactors used in nanomaterials production, the synthesis approaches and few examples of nanomaterials production in continuous fashion.

2.1. Microreactors typology: From simple to complex

Considering that a microreactor is a micro vessel designed to contain chemical reactions, its design should maximize the reaction performance, which in nanomaterials typically means

achieving the highest yield to the desired particles shape, with a tunable size, as well as an homogenous size distribution. Considering the chemicals and the synthesis conditions, the function-relevant criteria, such as corrosion resistance, wettability, mechanical strength, and the temperature range in which the chemical reaction occurs and the material can be used, must be considered. In addition, some other aspects should be considered: price, availability, and workability. Nevertheless, no single material fulfils all these criteria to a completely ideal extent and it means that a compromise is usually required between the most important variables.

Microreactors have evolved from simple capillary tubing (Figure 3-a) to complex design integrating valves, control of operation parameters and in-situ characterization, appropriately named lab on a chip. Regarding capillary tubing microfluidic reactors, there are many choices in terms of materials (e.g., polytetrafluoroethylene (PTFE), glass, and fused silica) with an inner diameter of up to 25 μm . The most commonly used microfluidic reactors are made of polymers due to the fact that these microreactors are ease to fabricate at low cost and with an acceptable feature resolution (Figure 3). Polymer tubing made of transparent or semi-transparent material ease the optical access while the nanocrystallization reaction is carried out, which is convenient to follow the reaction advance (Figure 3-b). Among the polymer tubes, those made of PTFE are the most widely used since they can tolerate a broad range of chemicals and elevated temperatures up to 240 $^{\circ}\text{C}$. Considering the hydrophobic nature of PTFE, it naturally resists channel fouling and blockage when aqueous streams are injected in the reactor.

The straight tubing is a simple design that suffers from mixing limitations. Such mixing limitations (slow mixing) are undesirable for the synthesis of uniform nanocrystals, especially in the case when fast reduction or decomposition of a nanoparticle precursor is involved. Segmented flow is usually arranged to overcome this limitation (this flow approach will be discussed in section 2.2). Chaotic advection can effectively accelerate mixing in slug flow by using unsteady fluid flow to stretch and fold the slugs in a channel. Figure 3-c,d show that using a pinched tubing accelerate the mixing in comparison with a straight channel. However, it is not easy to create a homogenous distribution of pinched zones. Polymer tubing is usually used to fabricate coaxial flow microsystems (Figure 3-f)). These systems are used to produce microparticles by the drop-flow approach (this concept will be discussed in sections 2.2 and 2.4). For instance to produce o/w microparticles, an aqueous solution is pumped through the inner tubing. Oil stream is pumped through the outer tubing and it exerts shear on the aqueous phase at the annular junction, causing uniform microdroplets to break away and flow down the tubing.

An alternative to tubing microfluidic reactors is the use of microfluidic chips fabricated using the popular soft lithography technique. The most commonly fabricated microsystems are made of poly(dimethyl siloxane) (PDMS) and glass. The PDMS layer is peeled off and bonded to a glass slide to seal the channels (Figure 3 e, h, i, j). Figure 3-e depicts an elaborated PDMS-Glass microsystem, where an excellent control on fluid-dynamics is achieved. The channel dimensions (length and diameter) can be tuned according to the nano-crystallization reaction requirements, inserting meandering channels to improve the reagents mixing, as well as fabricating the proper micro-channels to control the pressure drop. However, these microsys-

tems have a limited operating temperature and pressures, as well as a poor chemical compatibility, since PDMS is swelled by most of the organic solvents. Some microreactors made of SU-8-PEEK have been reported to withstand temperatures and pressures up to 150°C and 2 MPa, respectively [11].

Sophisticated PDMS-glass microreactors can also be fabricated to produce microparticles by the before mentioned two-phase method using a co-flowing system. Differently from tubing co-flowing microsystems, lithography enables an accurate control on the nozzle zone where the non-miscible phases are put into contact, providing a superior control over fluid-dynamics. In addition, the microparticles production unit can be coupled to a polymerization unit by UV radiation, where a spiraling and gradually widening channel enables maximum absorption of radiated UV light for an inline photo-polymerization without coalescence and clogging issues (Figure 3-g) [16]. Figure 3-h depicts a PDMS glass microfluidic reactor also designed to receive a maximum absorption of LED radiation in order to promote a photochemical nucleation and shape selectivity towards certain Ag nanostructures. Figure 3-i shows another co-flowing system made in PDMS to produce PNIPAM polymeric nanoparticles with a tuneable size by the polymerization of NIPAM monomer. Monodisperse W/O/W double emulsions were prepared in glass microcapillary device, forming phospholipid vesicles using monodisperse double emulsions with a core-shell structure as templates (Figure 3-j). Finally, MPEG-PLGA nanoparticles can be produced with a high production speed by nanoprecipitation using a parallel flow focusing PDMS-Glass microfluidic reactor [19]. The microdevice contains 100 parallel outlets to improve the mixing of polymer-solvent-antisolvent system by diffusion and achieve a mixing time shorter than the nanoprecipitation time. An excellent mixing control was achieved and monodisperse nanoparticles was produced in a mixing time shorter than 60ms. The production speed can be further improved by several orders of magnitude just by increasing the number of outlet streams [19].

Metal based microreactors are especially advantageous for processes involving high heat load and toxic chemicals, except for strong acids, due to the good chemical compatibility and thermal resistance. Metal microreactors are usually fabricated using electrical discharge machining, laser ablation or etching techniques, which allow to achieve a precise shaping down to micrometer level. Highly precise microstructures can be also generated by the well-known lithographic structuring techniques (LIGA). Some of the difficulties in using metal microreactors arose from the leaks at the joints, but these days there are have been developed several welding, soldering and joining techniques that enable to create high-strength inter-metallic bonds. Metal microfluidic reactors withstand robust handling, which is quite convenient during cleaning operations. They have been also demonstrated in the synthesis of nanomaterials. Size-tunable methacrylic nanoparticles have been successfully produced by stainless-steel multilamination micromixer (Figure 4-a). The excellent mixing achieved in the micromixer promoted the nucleation step at a high extension and enabled to decrease the nanoparticle sizes under the ones obtained in batch reactors, saving also organic solvent. The same type of micromixer was also used to produce Au-SiO₂ nanoshells in a multi-step process (Figure 4-b). The micromixers enabled to improve the control over the optical properties of these nanoparticles, compared to the conventional batch process operation. A stainless steel

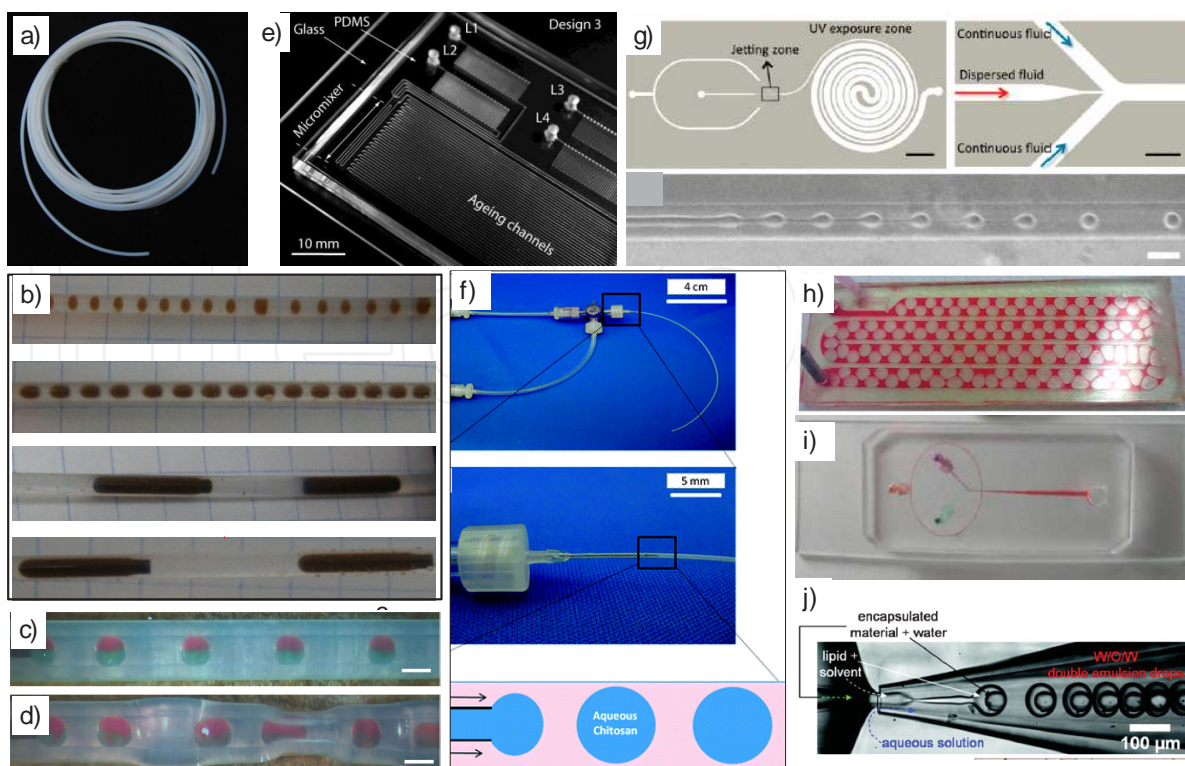


Figure 3. Examples of polymeric microreactors for nanomaterials synthesis. (a) PTFE tubing. (b) PTFE tubing microreactor, where the slug dimensions are modified to tune the crystallization kinetics of MOFs nanocrystals, (reprinted with permission from ref. [12], copyright 2013 American Chemical Society). (c-d) Straight and pinched PTFE microreactor to enhance the reactants mixing during the production of Au nanocrystals, (reprinted with permission from ref. [13], copyright 2014 John Wiley and Sons). (e) PDMS/Glass microreactor designed to produce SiO₂ nanocrystals (reprinted with permission from ref. [14], copyright 2004 American Chemical Society), (f) PTFE coaxial microreactor designed to produce chitosan microparticles (reprinted with permission from ref. [15], copyright 2013 The Royal Society of Chemistry) (g) PDMS-glass microsystem to produce uniform microbeads loaded with quantum dots. (reprinted with permission from ref. [16], copyright 2014 American Chemical Society). (h) PDMS-glass microsystem to produce Ag nanoparticles with a controlled size and shape by LED illumination. (reprinted with permission from ref. [17], copyright 2013 The Royal Society of Chemistry). (i) PDMS-glass microsystem to produce uniform PNIPAM nanoparticles by monomer polymerization. (reprinted with permission from ref. [18], copyright 2011 WILEY-VCH Verlag GmbH & Co.), (j) Glass parallel-flow focusing microsystem to produce uniform Phospholipid Vesicles. (reprinted with permission from ref. [26], copyright 2008 American Chemical Society).

spiral microreactor was used to control the production of Ag nanoparticles by gas and liquid segmented flow [22].

Silicon and glass-based microfluidic reactors are fabricated by the conventional lithographic techniques and have the advantage of high bond strengths which enable to work at high pressure. Differently from glass microreactors, silicon microreactors can be used in high temperature reactions because the high thermal conductivity of silicon. However, both materials are fragile, and these reactors do not withstand mechanical impacts. A spiral silicon-pyrex reactor was designed to have separated the mixing and reaction units and promote a homogeneous nucleation after a good mixing was achieved (Figure 4-c). This reactor could control the growth of Au nanoparticles, which is a pretty fast reaction and require from an excellent mixing control. The same design of spiral microreactor was applied in the synthesis of mesoporous nanomaterials (MCM-41), decreasing the synthesis time from days (batch reactor) to minutes

and improving the size and shape control [24]. Figure 4-d depicts a silicon-based microreactor where there are integrated two mixing units to control the growth and composition of Au/Ag hetero-structures. Glass microcapillary reactors can be fabricated with a higher resolution at micrometer scale than the polymer reactors ones, this fact enables to produce a better control in the production of emulsions and polymeric nanoparticles (Figure 3-j).

Finally, this section should highlight the existence of some other types of microreactors with a considered relevance in terms of functionality. Figure 4-e illustrates a continuous three-stage silicon-based microsystem consisting of mixing, aging and sequential growth stages, operating at 65 bar and temperatures as high as 340°C. This system is an example of complex fluid-dynamic control by the injection of different precursor flow-rates and pressure drop along the different microchannels. On the other hand, silicon and glass microreactors have the advantage of easy optical access, providing a mean for a wide range of in-situ characterization techniques. Figure 4-f depicts a microreactor where the size and shape of organic crystals can be determined by optical microscopy and the crystal phase determined by in-situ Raman spectroscopy. An advance microfluidic reactor for polymer particles production was designed using a sequence of microvalves which were digitally activated to control the composition of the polymer particles in a matter of seconds [29].

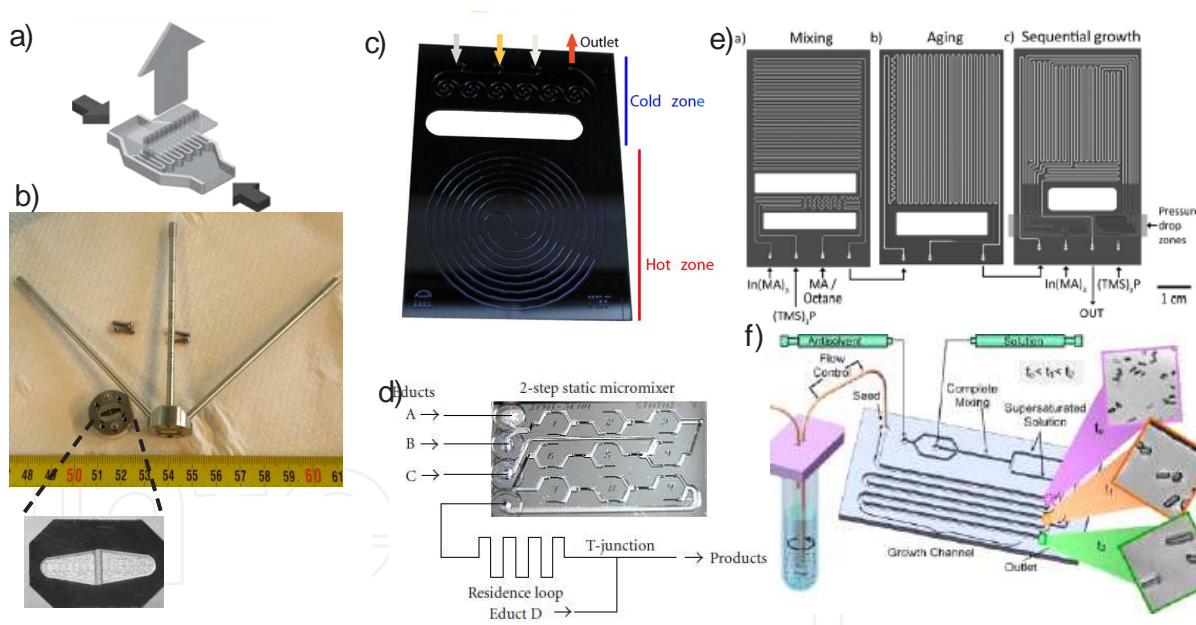


Figure 4. Examples of metal microreactors for nanomaterials synthesis. (a) Multilamination micromixer to produce polymer nanoparticles ref. [20]. (reprinted with permission from ref. [21], copyright 2012 Royal Society of Chemistry). (b) Multi-step multilamination micromixer to produce Au-SiO₂ nanoshells. (reprinted with permission from ref. [21], copyright 2012 Royal Society of Chemistry). (c) Spiral microreactor to produce Au NPs. (reprinted with permission from ref. [23], copyright 2012 American Chemical Society). (d) Two-stage micromixer to produce Au/Ag NPs. (reprinted with permission from ref. [25], copyright 2007 J. Michael Köhler et al). (e) Three-stage microfluidic system to produce quantum dots. (reprinted with permission from ref. [27], copyright 2011 WILEY-VCH Verlag GmbH & Co). (f) Microfluidic system with optical access for optical microscopy and Raman spectra coupling. (reprinted with permission from ref. [28], copyright 2012 American Chemical Society).

2.2. Synthesis strategies in microfluidics

Regarding synthesis strategies, microfluidic reactors can be mainly grouped into two categories related with their flow pattern: single-phase and multi-phase flow. Continuous flow (or single-phase flow) microreactors allow facile change of experimental conditions within microseconds and usually improve the homogeneity of solution during the synthesis process in comparison with batch reactors. The operability and stability of this type of flow pattern is quite good. However, liquid flow within microchannels is strictly a laminar flow due to the small Reynolds numbers, then, the mixing is achieved predominately by molecular diffusion since the absence of turbulence. The small cross section in combination with the no-slip boundary condition at the channel walls lead to a parabolic velocity profile. This velocity profile depends on the position within the cross section and can promote a wide residence time distribution depending on the flow conditions. This fact can be a serious problem in the production of those nanomaterials whose crystallization kinetics is sensitive to the residence time distribution in the early stages of growth. If this occurs, growing nanoparticles flowing near the walls will spend significantly a long time inside the reactor, as compared to those flowing near the center (Figure 5). This performance implies that the ones flowing near the walls will be bigger in size than the ones flowing by the center. To overcome nanoparticles polydispersity, continuous flow microreactors can include a micromixing stage, where a good mixing is achieved by reducing the diffusion lengths. Micromixers can be classified in passive and active according to the existence of mechanical agitation or external forces. Passive mixing simply creates lamination of multiple fluid streams, increasing the interfacial area for diffusion (Figure 5). A passive micromixer is illustrated in Figure 4 b, where the multi-lamination is achieved by splitting the streams and then recombining them again. Although micromixing by multi-lamination is effective, the narrow microchannels can lead to high pressure drops. This fact is even more important in high viscous fluids, which limit the operability in microsystems. Active mixing is directed by applying external forces such as ultrasonic waves, electric and magnetic fields. However, the fabrication of these microsystems require special fabrication techniques [30].

Multi-phase flow facilitates the passive mixing and reduces the propensity to foul after extended operation. Multiphase flow can be also classified into gas-liquid and liquid-liquid flow regimes. In gas-liquid flow systems, it is distinguished the slug and the annular flow patterns depending on the gas and liquids superficial velocities. Annular flow occurs when a continuous gas core flow in the channel center and a liquid film at the walls. On the other hand, in slug flow, gas bubbles are located between two liquid segments (Figure 5). Viscous drag at the channel wall induces convective mixing (recirculation) within each slug. As a result, it ensures an excellent chemical homogeneity. In addition, the slug move at the same speed, this implies that the residence time distribution is narrower than with continuous flow operations. Consequently, slug or segmented flow has the potential to improve size distributions in nanocrystallization process. Then, an inert gas can be introduced in a liquid system to improve mixing and residence time characteristics.

In liquid-liquid segmented flow, the surface tension differences between immiscible streams enables to achieve a steady fluid segmentation (Figure 5). Considering the surface wettability

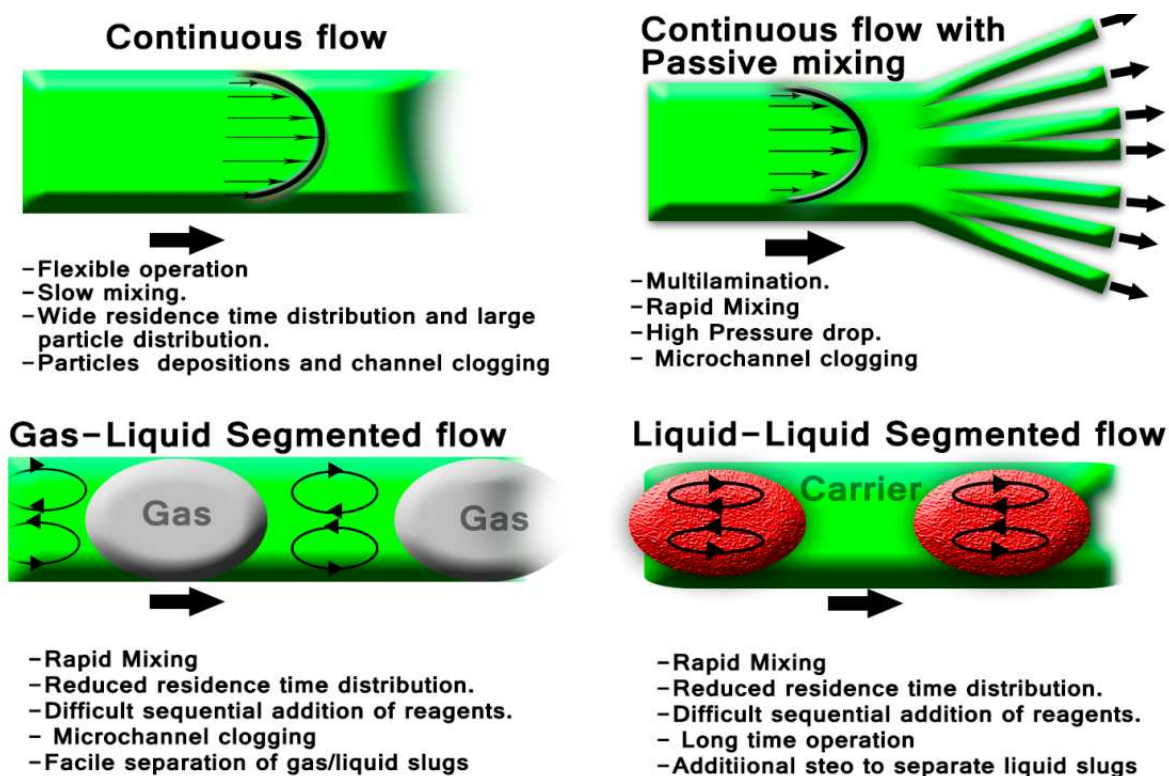


Figure 5. Comparison of the synthesis strategies in continuous microflows to produce nanomaterials: Continuous flow (with and without multilamination) and segmented flow (gas-liquid and liquid-liquid).

of the microchannel, the reactor clogging occurs usually with a high frequency in the gas-liquid slug flow since the liquid segments are flowing in contact with the microchannel wall. However, the liquid entities where the chemical reaction occurs are easier to separate in gas-liquid segmented flow. On the other hand the single-phase systems enable the subsequent addition of reagents in order to operate in a multi-stage system. A sequential addition of reagents in a multi-phase system is challenging because the formation of multiple liquid entities without connectivity. This issue can be addressed by the use of a merge drop flow, but, at the end, the segments merging could affect negatively to the residence time distribution.

2.3. Microfluidic synthesis of inorganic nanomaterials

Inorganic nanoparticles have been widely used in diverse areas such as electronics, energy, textiles, biotechnology and medicine, bio-imaging and bio-sensing. There have been tremendous interests in the development of microfluidic methods for producing inorganic nanoparticles because microfluidics provide an excellent control on the nanocrystallization process. There are numerous examples of synthesis of inorganic nanomaterials in microfluidic devices [31, 32], but some of them will be discussed in the present section due their relevance and novelty.

Gold nanoparticles production has been extensively studied due to their wide variety of properties and the challenge in controlling the shape and size. Typical microfluidics recipes

involve the reduction of a gold precursor in the presence of different types of ligands and stabilizers. The presence of a strong reducing agent, such as sodium borohydride, promotes fast nucleation and the production of small nanoparticles. The reduction of Au ions occurs in a time scale of seconds, following a fast kinetic nanocrystallization. However, fast kinetic reactions should be carried out if the mixing time is shorter than the reaction time, otherwise a wide distribution of nanoparticles can be achieved. As it was considered in section 2.2, flow segmentation promotes a rapid mixing and an efficient heat/mass transfer by internal recirculation. But, it is required to operate with the proper segmented flow pattern and conditions in order to achieve the expected results. Consequently, the particle size distribution in fast kinetic reactions, such as Au nanoparticles production, is strongly dominated by the mixing conditions induced by internal recirculation and not only by the type of flow [33]. Figure 6 a-d illustrates the effect of the residence time on the Au nanoparticle size distribution. The length of the slugs is influenced by the residence time, obtaining small slugs at smaller residence times (Figure 6-c). The slug recirculation is higher in small slug than in the long ones, promoting a fast mass transfer. So the control of the slug length is a strict requirement to decrease the particle polydispersity (Figure 6-d). On the other hand, liquid-liquid and gas-liquid improve the micromixing but the grade of mixing achieved is not comparable, even if the residence time is the same. Figure 6 e-g shows that the particle size distribution of nanoparticles produced at the same residence time is sensitive to the fluid of segmentation. Air segmentation provides a better internal mixing than silicone oil (Figure 6-h) [33]. Silicone oil presents a higher viscosity than air, reducing both the slip velocity and the circulation rates.

Microfluidic reactors are able to produce complex hybrid nanostructures in a simple process that reduces the synthesis time and provide an additional level of reaction control that it is not attainable in bulk stirred reactors. Silica gold nanourchin particles with hyper-branched Au nanowires were produced in batch reactors after the sequential addition of reagents (at least 10 times) (Figure 6-m). Gold was anisotropically grown on the surface of silica nanoparticles decorated with Au seeds by maintaining a good control on the kinetics in a batch reactor (Figure 6-j). After several cycles of reagents addition, the length of the nanowires was long enough to use these hybrid nanostructures in SERS. However the exquisite control required during the sequential addition of reagents unable a reproducible production of these interesting nanostructures. The continuous production of gold nanourchin structures was achieved successfully in a PTFE microreactor using a single addition of reagents (Figure 6-i). The microreactor showed perfect performance for manipulating the reagent concentrations and promote a kinetic control of the reaction during the anisotropically growth of Au. Finally, those nanostructures showed a remarkable SERS performance, which evidences the quality of the produced nanostructures.

Gold nanorods have been widely used in biomedical application due to their interesting optical properties. The growth comprises a two-stage process: 1) Gold seeds formation and 2) Gold addition by the secondary growth of gold seeds. The optical properties of the resulted nanorods are sensitive to synthesis variables such as seed size, temperature, mixing, reagents concentration, reducing rate and so. In addition, the synthesis of Au nanorods is usually achieved in the presence of cetyltrimethyl ammonium bromide (CTABr), a high cytotoxic

ligand which requires several purification treatments after synthesis. Although there are several microfluidic approaches to produce Au nanorods and circumvent the limited reproducibility of Au nanorods production, they are based in the use of seeds and CTAB [36]. A new microfluidic approach enables the continuous production of Au nanorods in a single step (without seeds) and using a biocompatible ligand (Lysine) instead of CTAB [35]. Optical properties of the produced Au nanorods are tunable with the Lysine/Au precursor ration, obtaining nanorods with an aspect ratio of 5 and a Surface Plasmon Resonance Peak centered in 780nm. Moreover, microfluidics facilitate the manipulation of separate reagent streams, which enabled the fast screening and optimization of the synthesis conditions on demand. The Au nanorods produced by this approach were successfully applied as contrast agents in Photothermal Optical Coherence Tomography (OCT) of human breast tissue. The simplicity of this approach will made feasible that unskilled staff could in future produce this type of contrast agent on demand and out from the laboratory.

Magnetic nanoparticles (MNPs) are of significant interest due to their unique properties in terms of chemical stability, size-dependent magnetic response, biocompatibility, and low price, which make them ideal candidates in a wide-range of applications in biomedicine-related fields: drug delivery, hyperthermia, magnetic resonance imaging (MRI), tissue engineering and repair, biosensing, and biochemical separations [37]. High quality crystalline MNPs were obtained with a narrow size distribution of mean diameter 3.6 nm and standard deviation 0.8 nm in a passively-driven capillary-based droplet reactor [38]. Reagents were fully compartmentalised within the droplets, preventing the fouling of the channel walls. In contrast, when the reaction was allowed to proceed in a single-phase mode of operation, a dark brown deposit formed on the inner surface of the main channel within minutes. Then, as it was before mentioned, segmented flow is a useful tool to prevent microfluidic reactor from clogging and promote a narrow size distribution of nanoparticles during the growth process. However the flow segmentation can provide a new function, controlling the crystal phase. That is, by controlling the atmosphere in the gas segments, the crystalline phase and size of the resulting nanoparticles can be accurately tuned [37]. Pure magnetite nanocrystals with their characteristic octahedral shape were obtained when N_2 and H_2 were used to segmentate the liquid stream of reagents (Figure 7-a). In fact, the reducing properties of H_2 accelerates the production of high crystalline magnetite NPs in 1 minutes residence time at $100^\circ C$.; whereas flow segmentation with N_2 required 6 minutes. If O_2 was used instead of N_2 or H_2 , oxidant conditions direct the synthesis to the production of an orange colloid (Figure 7-a). The nanoparticles formed were nanoflakes with a mean size (along the longest axis) of about 30 ± 8 and 3 nm thickness which was identified as feroxyhyte (δ -FeOOH). Finally, carbon monoxide is generally considered as a poisoning agent in many catalytic studies but is also considered as a reducing agent or even a capping agent to direct the shape control in nanoparticle synthesis. When a CO-liquid segmented flow was created, it was observed that feroxyhyte was obtained at temperatures lower than $80^\circ C$ (see Figure 7-a). But these nanostructures were bigger in size than the ones produced with O_2 , (70 ± 12 nm and thickness of 3 nm). Then, at low temperatures CO does not act as a reducing agent, as H_2 does, and instead directs the oxidation of iron hydroxides to feroxyhyte. With a further increase of temperature to $100^\circ C$, crystalline and pure magnetite nanoparticles were obtained at 1 min of residence time,

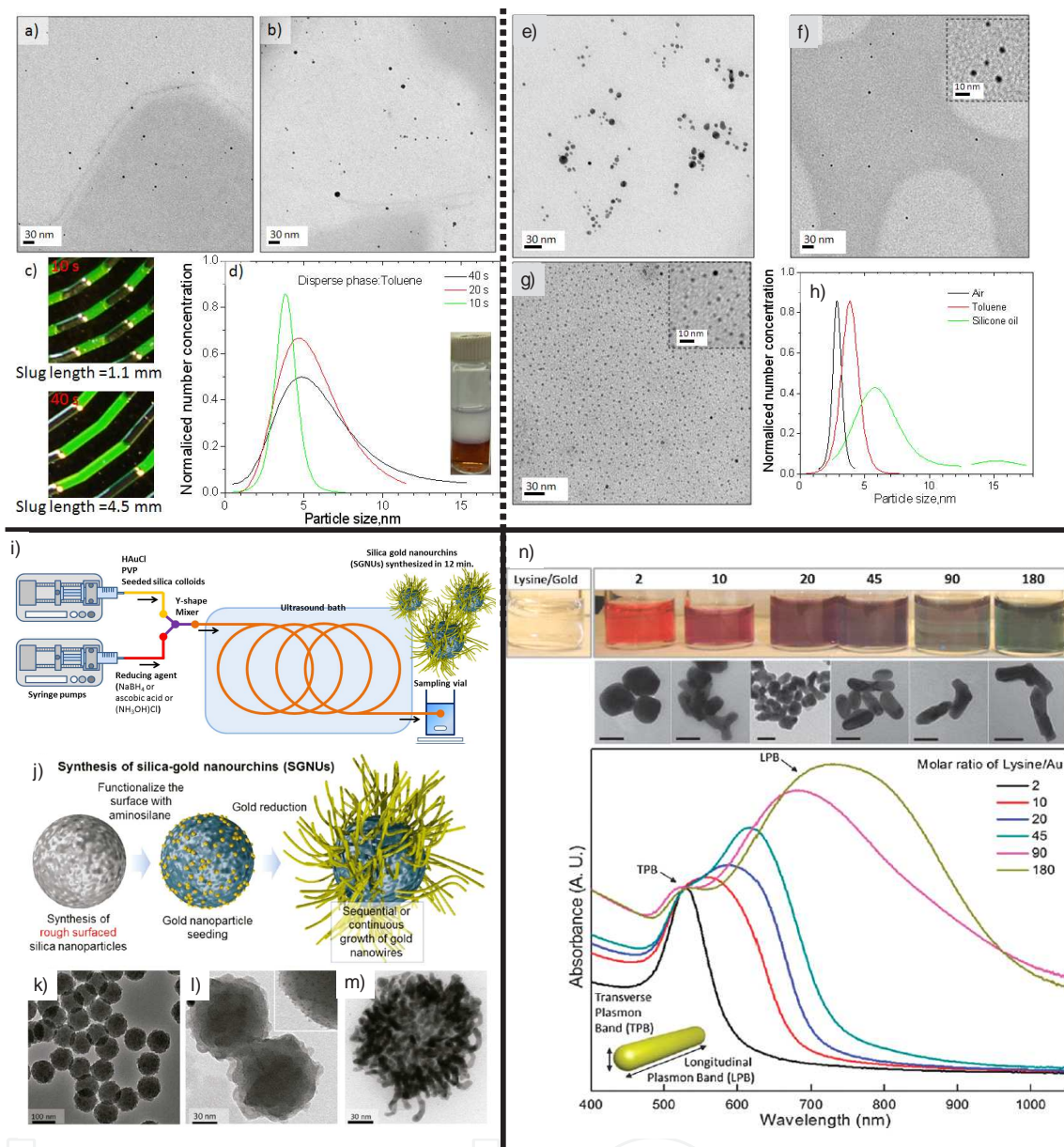


Figure 6. Gold nanoparticles produced in microfluidic reactors. TEM image of gold NPs synthesized in toluene-aqueous segmented flow: a) Residence time (Rt) = 10 s, b) Rt = 40 s, c) segmented slugs generated at Rt = 10 and 40 s d) Particle size distribution diagram from AuNPs obtained in toluene - aqueous segmented flow at Rt = 40, 20, and 10 s. TEM image of gold NPs synthesized at Rt = 10 s in a : (e) silicone oil-aqueous segmented flow, (f) toluene-aqueous segmented flow, (g) air - aqueous segmented flow. (h) Particle size distribution diagram from AuNPs obtained in silicone oil/toluene/air-aqueous segmented flow at Rt = 10 s.(reprinted with permission from ref. [33], copyright 2012 American Chemical Society).i) Microfluidic system to produce Au nanourchin particles :j) Scheme for the synthesis of silica-gold nanourchins formation with representative images from: k) silica NP, (l) silica decorated with Au NPs (m) Au nanourchin (reprinted with permission from ref. [34], copyright 2014 Royal Society of Chemistry). n) Absorption spectra and TEM images of the gold nanorods produced with microfluidic reactors. (reprinted with permission from ref. [35], copyright 2012 Royal Society of Chemistry).

confirming the reduction potential of CO at these conditions. Consequently the gas slug microfluidics provide a flexible, easy option to implement a process to produce customized iron oxide nanostructures.

Laboratory syntheses tend to be complex, based in multistep batch processes with yields that are typically well below the gram range. These batch processes often suffer from irreproducibility of the morphology, size, size distribution and quality. Then, implementing the continuous, or at least automated, production of nanomaterials is clearly desirable in terms of improving the product homogeneity and facilitating scale-up production. The continuous production of nanomaterials is challenging because of the difficulties involved in translating the complexity of nanomaterial synthesis into on-line operations. The production of hollow gold nanoparticles constitute a clear example of the strict requirements in the dimensional control, since their optical properties are sensitive to the nanoparticle dimensions and shell thickness. The synthesis of hollow Au nanoparticles comprises a multi-stage process: 1) Synthesis of a Co NP as a template, 2) Galvanic replacement of Co by Au⁺³ ions. The conventional lab scale production of hollow gold NPs deals with a reaction volume of 120 mL [39]. But if the production scale was increased 10 folds, the quality and consequently the optical properties, are not reproducible. The poor quality of the NPs in the scaled-up batch syntheses was probably caused by insufficient mixing as the reaction volume increased. This problem is even more serious if the nano-crystallization reaction is directed by a fast kinetic. A microfluidic system was proposed to overcome the production limitations of hollow gold nanoparticles, but incorporating two additional stages to yield nanostructures suitable for biomedical applications: 1) PEG functionalization to improve the biocompatibility and 2) Sterilization (see Figure 7-b). Considering the 4 implemented stages, high quality nanoparticles were produced in only 22 minutes, being the sterilization process the slowest stage (15 min). The galvanic replacement reaction is a fast process, and then it is required to get an excellent mixing of reagents to promote an even distribution of Au⁺³ ions over the Co templates. As can be observed in Figure 7-b, the galvanic replacement of Co by Au⁺³ ions was properly directed since there is no trace of Co in the NP volume, releasing the hollow structure. Consequently, the application of microfluidic systems on multi-stage reactions is highly convenient to preserve the quality of materials and reduce irreproducibility.

A continuous three-stage microfluidic system that separates the mixing, aging, and subsequent injection stages of InP nanocrystal synthesis was designed to optimize the synthesis conditions (Figure 4-d). The microfluidic system operates at high temperature and high pressure enabling the use of solvents such as octane operating in the supercritical regime for high diffusivity resulting in the production of high-quality InP nanocrystals in as little as 2 minutes (Figure 7-c). To control the size of InP nanocrystals, six sequential injections of chemical precursors were injected. This procedure ease the production protocol of these nanocrystals, since the sequential addition of reagents in a batch reactor requires at high temperature of an exquisite control and accuracy.

2.4. Microfluidic synthesis of polymeric nanomaterials

Microfluidic devices have emerged as promising tools for the synthesis of polymer particles. Over conventional processes, microfluidic-assisted processes allow the production of polymer particles with an improved control over their sizes, size distributions, morphologies, and compositions. This is particularly important since the synthesis of polymeric nanoparticles by

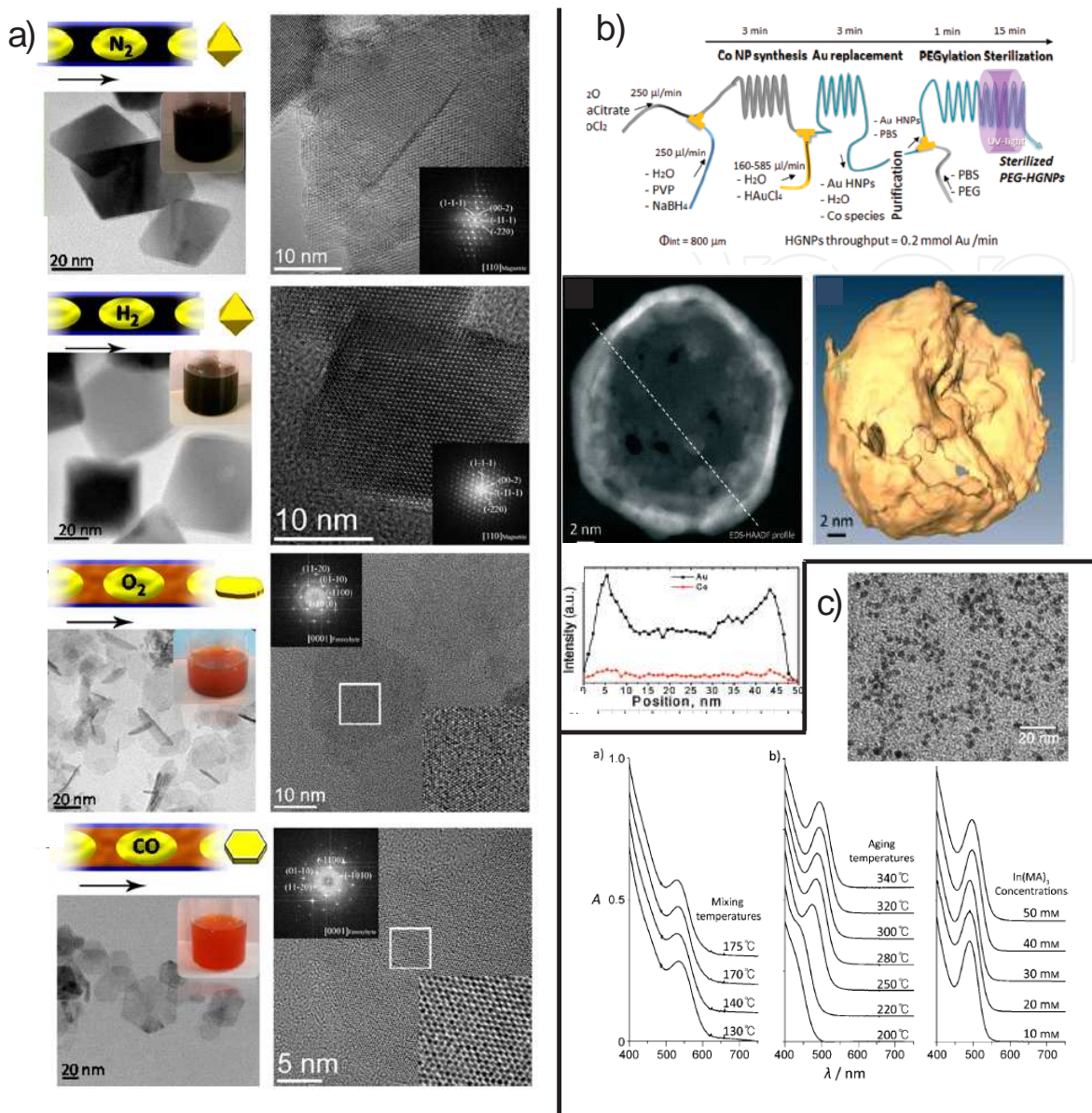


Figure 7. Synthesis of inorganic nanomaterials in microfluidic systems: a) Gas selective crystallization of iron oxides nanocrystals in segmented flow reactors(reprinted with permission from ref. [37], copyright 2015 American Chemical Society). b) Multi-stage production of hollow gold nanoparticles (reprinted with permission from ref. [39], copyright 2013 Royal Society of Chemistry). c) Production of InP nanocrystals in pressure and temperature condition (reprinted with permission from ref. [27], copyright 2010 WILEY-VCH Verlag GmbH & Co).

bulk methods typically lacks control over the mixing processes, which may compromise the properties of the resulting nanoparticles. Nanoparticles dimensions can be tuned by varying microfluidic parameters such as flow rates, precursor composition, and mixing time. The available techniques to produce polymer nanoparticles can be classified depending on the starting state of the polymers: From dispersion of preformed polymers and from polymerization of monomers. The most common techniques which use a preformed polymer can be stated as: solvent evaporation method, nanoprecipitation, emulsification, salting out, dialysis and supercritical fluids. On the other hand, the current techniques available for monomer poly-

merization can be divided into: emulsion, mini emulsion, micro emulsion, interfacial polymerization and radical polymerization.

This section will deal some of the most interesting examples of polymer nanoparticles production by the most relevant techniques for the production of polymer particles within microfluidic devices: (a) the direct polymerization through continuous flow projection photolithography [40], (b) nanoprecipitation and (c) the emulsification of liquid monomers, followed by the polymerization of the subsequent monomer droplets.

Polymerization through continuous flow projection photolithography consists in the UV irradiation, through the objective of an optical microscope, of a polymer solution flowing within a microchannel (See Figure 8-a). A mask placed in the field-stop plane of the microscope allows polymerizing and the desired particle shape to the flowing monomer solution. Then, the polymerized microparticles are formed when flow was stopped in the microfluidic device. Then, particles were pushed out of the polymerization area with flow of the monomer solutions. This approach is very powerful because it allows for nearly unlimited designs, including the production of barcodes and multifunctional particles [41].

Two-dimensional hydrodynamic focusing was commonly used to produce polymer nanoparticles (ca. PLGA) by nanoprecipitation. Three-dimensional flow-focusing prevent the formation of aggregates and microreactor fouling. While these approaches have provided significant advantages, there still remain challenges. First, these microfluidic approaches using slow diffusive mixing at a low flow rate, limiting the productivity. Second, diffusive mixing does not allow the development of particles that require the assembly of precursors dispersed in different phases, (e.g., lipid) in the aqueous phase with precursors (e.g., polymer) in the organic phase such as lipid-polymer hybrid nanoparticles [42]. To overcome those limitations and develop a high-throughput and reproducible nanoparticle synthesis technology, new advances have been performed in improving the mixing. The application of a microvortex considerable improves the mixing and enable a controlled nanoprecipitation [42]. The use of microvortices results in a rapid mixing between phases, enabling up to 1000 times higher productivity (3 g /hour) and better size control (30-170nm) than previous methods (See Figure 8-b).

A simple and versatile coaxial turbulent jet mixer consisting of coaxial cylindrical tubes where NP precursors and non-solvent are injected through the inner and outer tubes, respectively, was fabricated to produced PLGA-PEG, Lipid vesicles and polystyrene, obtaining production rates up to 3 kg/d (see Figure 8-c) [43]. This versatile mixer provides an inherently high NP production throughput due to operation in the turbulent regime (Re 500-3500) with device dimensions in the millimeter scale. The production rates achieved are suitable for in vivo studies, clinical trials, and industrial-scale production, while retaining the advantages of homogeneity, reproducibility, and control over NP properties (size and morphology). A strong point in using this type of microfluidic devices is the potential use in biomedical research laboratories, where it is not required specialized microfabrication facilities since this is a robust and simple device, as well as a microfluidic know-how to operate in the optimum conditions.

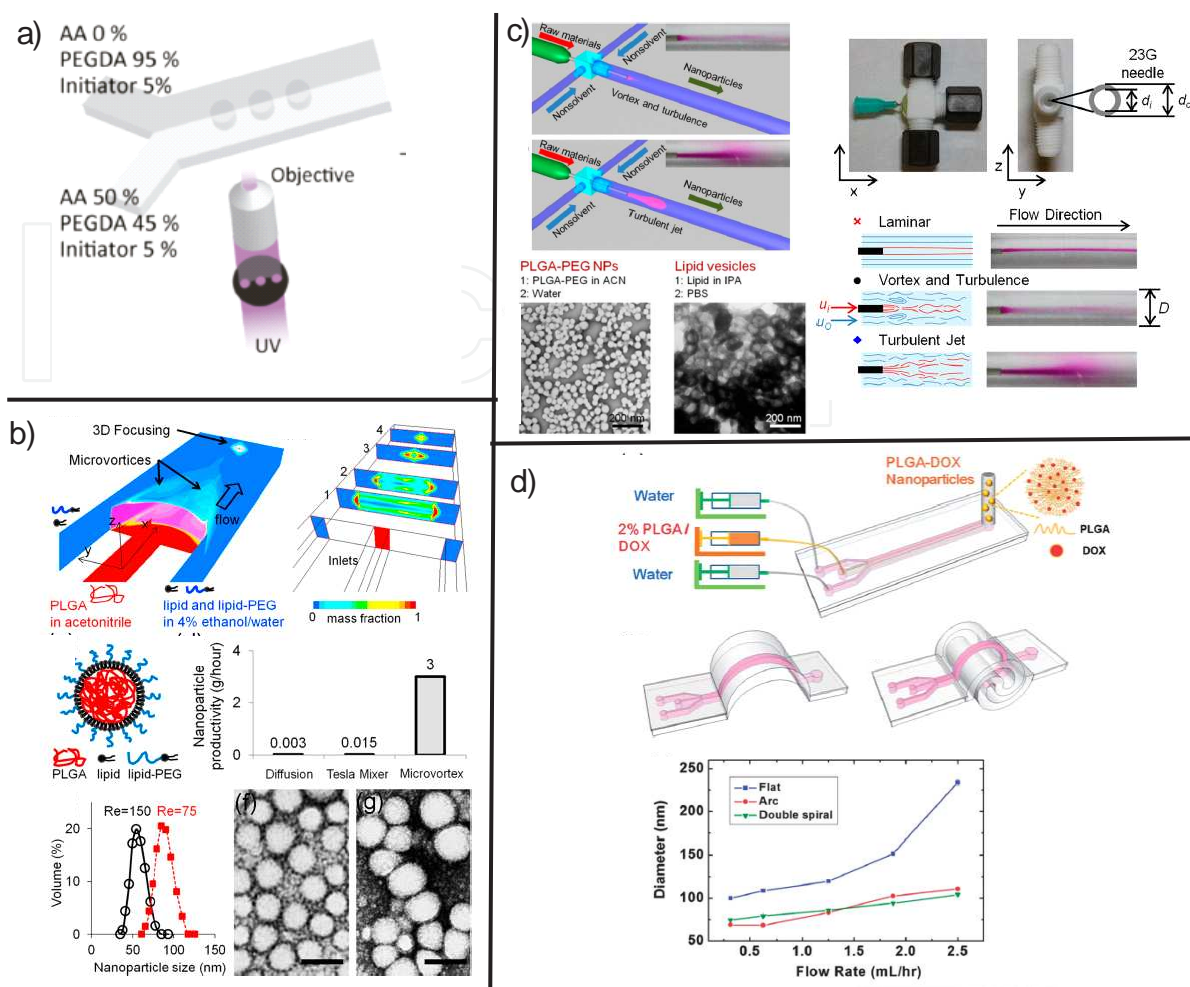


Figure 8. Synthesis of polymeric nanomaterials in microfluidic systems: a) Direct polymerization through continuous flow projection photolithography. Schematic diagram of dot-coded particle synthesis showing polymerization across two adjacent laminar (reprinted with permission from ref. [46], copyright 2012 American Chemical Society). b) Schematic and cross section views of a three-inlet microfluidic platform generating lipid-polymer hybrid nanoparticles through controlled microvortices by nanoprecipitation. Scale bars indicate 100 nm (reprinted with permission from ref. [42], copyright 2012 American Chemical Society). c) Schematic illustration of the coaxial turbulent jet mixer for high-throughput synthesis of NPs with turbulence induced by jetting. Photograph of coaxial turbulent jet mixer fabricated from PTFE tee union tube fittings and schematic illustrations and top views of fluid flow at laminar, vortex and turbulence and turbulent jet regimes (reprinted with permission from ref. [43], copyright 2014 American Chemical Society). d) Schematics of a microfluidic origami chip for synthesizing monodisperse DOX-loaded PLGA nanoparticles. Different 3D geometries (arc and double spiral) obtained by manually folding the origami chip. (reprinted with permission from ref. [44], copyright 2011 WILEY-VCH Verlag GmbH & Co).

A microfluidic origami chip with different geometries that enables the production of PLGA nanoparticles loaded with doxorubicin (DOX) by rapid mixing was designed to tune the nanoparticle size from 70 to 230 nm in a single nanoprecipitation step. The origami chip can be set in a two-dimensional flat geometry or can be folded in a three-dimensional geometry such as an arc or a double spiral. The combination of hydrodynamic focusing and 3D curved microchannels can significantly shorten the mixing distance and reduce the mixing time, which can reduce the mean nanoparticle size and size distribution (see Figure 8-d). The mixing time

in the 3D double spiral configuration was approximately 46% faster than the 2D flat configuration. This improvement was due to the formation of two counter-rotating vortices perpendicular to the flow direction that could efficiently increase the mixing after curved turns [44].

Multiple emulsion drops are useful in the production of complex microcapsules for encapsulation and sequential release of multi-component active materials while avoiding cross-contamination. Most approaches utilize sequential emulsification using a series of single drop microfluidics units, but the device fabrication requires complex procedures and a good control to synchronize the frequencies of drop generations in all drop units [45]. Figure 9-a shows a flow focusing microdevice to produce monodisperse multiple emulsion drops of high order using stable biphasic flows in confining channels. Four immiscible fluids are simultaneously introduced into the orifice in the form of a coaxial flow. This results in the formation of triple emulsion drops with the simplicity of a single emulsification process. The interesting novelty of this system is that the breakup of the interfaces is achieved in dripping or jetting modes, determined by the flow rates. The jetting breakup mode promotes the injection of different numbers of drops in the core of a multiple emulsion (see Figure 9-a). On the other hand, the dripping mode facilitates the production of monodisperse triple or quadruple emulsion drops with an onion-like configuration (Figure 9-b).

Loading inorganic nanomaterials in polymer particles entails the formation of multifunctional entities. Batch synthesis has been the method of choice for preparing inorganic-doped microparticles due to practical advantages in productivity and accessibility, despite limitations such as poor loading, low throughput, and material loss. In addition, a significant portion of loading materials is wasted during the multistep process of synthesis, purification, loading, and washing. These shortcomings are especially problematic when expensive inorganic nanomaterials are used [16]. Figure 3-g illustrates a microfluidic reactor designed to produce uniform emulsions loaded with quantum dots using high-throughput harmonic breakup of a jet in a high shear coflowing system with a well-designed nozzle. Uniform fluorescent microbeads containing about 10 wt % CdSe/ZnSe QD nanocrystals were produced with a tuned size ranging from 13 μm to 100 μm through in-line photopolymerization of biocompatible prepolymer resin. Unlike the batch synthesis, there are no additional washing steps required for the removal of unreacted residues causing dissipation of materials. Then, it is clear the advantages of microfluidics in producing complex nanostructures.

3. Conclusions and outlook

The characteristics of micro- and nanoparticle formulations produced by continuous flow microfluidic systems have remarkable advantages over traditional bulk methods that motivate their adoption. The exquisite control of flow and mixing conditions in microfluidics led to improved homogeneity of particle size distributions and the control of particle size in a reproducible and continuous fashion. Microfluidic systems often integrate real-time analysis of the generated particles in order to tune the properties of the produced materials according to specifications. From the reported examples in this chapter, there is no doubt that microfluidic

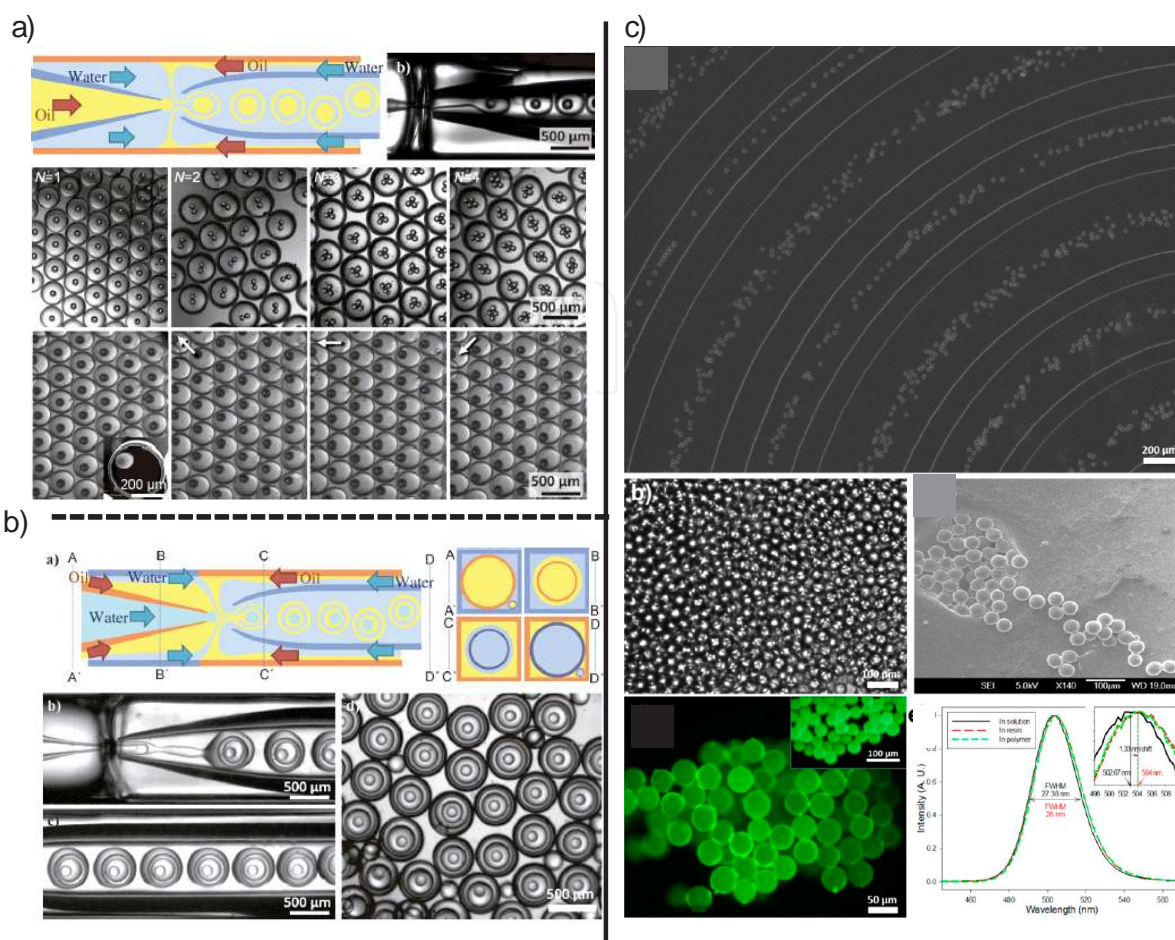


Figure 9. Synthesis of polymeric nanomaterials in microfluidic systems. a) Microfluidic capillary device for preparation of O/W/O/W triple emulsion drops. Microcapsules containing single-, two-, three-, and four-core particles. Microcapsules containing a magneto-responsive core particle which align upon application of an external magnetic field. (reprinted with permission from ref. [45], copyright 2011 WILEY-VCH Verlag GmbH & Co.) b) Quadruple emulsion drops generation and downstream motion (reprinted with permission from ref. [45], copyright 2011 WILEY-VCH Verlag GmbH & Co.) c) Images and characteristics of the polymerized PEGDA microparticles produced by jet mode in a flow focusing microreactor and a spiral channel section for photo-polymerization. Pseudocolor fluorescent image of highly monodisperse PEGDA polymer beads with 9.9 wt % of highly loaded CdSe/ZnS core-shell nanocrystals. (reprinted with permission from ref. [16], copyright 2014 American Chemical Society)

devices will represent new promising tools for the production of size and shape-controlled inorganic, polymer and hybrid nanomaterials.

It is clear that microfluidics can reproduce the nanostructures synthesised in batch reactors, improving their properties and reducing the synthesis time. Furthermore, particles with new morphologies and multicomponent compositions, like janus or multicore emulsions colloid can be prepared only in such systems. However, microfluidics reactors will need to overcome some shortcomings such as fouling and low throughput production. Along with chemical stability, surface properties, and ease of fabrication, other important considerations should be taken in account. Although several nanomaterials have been produced in a high-throughput mode, the majority of the procedures reported suffer from this lack, which limits the implementation of this technology in companies and medical centres. Then, for future microfluidic

systems to become high-throughput platforms to produce high-value particulate materials beyond the lab bench, they will need to become robust, well-integrated, scalable, modular, computer controlled. Another avenue of future research will be the integration of a quality evaluation unit together with feedback control through a combination of microfluidics, robotics and automation. Consequently, continuous flow microfluidic systems will have the potential to become a standard technology to produce nano/micro-particle formulations with unprecedented homogeneity and fine control, which on the other hand are not feasible to achieve in bulk techniques

Meanwhile, the search for applications which require the use of relatively small amounts of high quality nanomaterials will be vital for the development of the field. Considering the good reproducibility and quality on nanomaterials produced using microfluidics, it is believed that microsystems will push forward new applications in promising fields such as nanomedicine, drug delivery, electronic displays, and photonics.

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References

- [1] Wilson Center| Virginia Techstr. The project on Emerging Nanotechnologies [Internet]. Available from: HeaHPPT URL}http://www.nanotechproject.org/cpi/search-products/ [Accessed: August-2015]
- [2] Victor Sebastian, Manuel Arruebo, and Jesus Santamaria. Reaction Engineering Strategies for the Production.. ;10:835-853. DOI: 10.1002/sml.201301641

- [3] Willems & van den Wildenberg (W&W). Roadmap Report on Nanoparticles [Internet]. November 2005. Available from: <http://nanoparticles.org/pdf/PerezBaxEscalano.pdf> [Accessed: August-2015]
- [4] Chih-Hung Chang, Brian K. Paul, Vincent T. Remcho, Sundar Atre and James E. Hutchison. Synthesis and post-processing of nanomaterials. *Journal of Nanoparticle Research*. 2008;10:965-980. DOI: 10.1007/s11051-007-9355-y
- [5] Christophe Petit, Patricia Lixon, Marie Paule Pileni. In situ synthesis of silver nanocluster in AOT reverse micelles. *The Journal of Physical Chemistry*. 1993;97:12974-12983. DOI: DOI: 10.1021/j100151a054
- [6] KS SUSLICK. THE CHEMICAL EFFECTS OF ULTRASOUND. *SCI AMERICAN INC*. 1989;:80. DOI: WOS:A1989R736400006
- [7] J. A. Marqusee and John Ross. Kinetics of phase transitions: Theory of Ostwald ripening. *The Journal of Chemical Physics*. 1983;79:373. DOI: 10.1063/1.445532
- [8] Takuya Tsuzuki. Commercial scale production of inorganic. *International Journal of Nanotechnology*. 2009;6:567-578. DOI: 10.1504/IJNT.2009.024647
- [9] Research And Markets. The Global Market for Carbon Nanotubes to 2024 [Internet]. Available from: <http://www.researchandmarkets.com/reports/2908187/the-global-market-for-carbon-nanotubes-to-2024> [Accessed: August 2015]
- [10] Jean-Claude Charpentier. Four main objectives for the future of chemical and process engineering mainly concerned by the science and technologies of new materials production. *Chemical Engineering Journal*. 2005;107:3-17. DOI: 10.1016/j.cej.2004.12.004
- [11] Yujun Song, Challa S S R Kumar and Josef Hormes. Fabrication of an SU-8 based microfluidic reactor on a PEEK substrate sealed by a 'flexible semi-solid transfer' (FST) process. *JOURNAL OF MICROMECHANICS AND MICROENGINEERING*. 2004;14:932-940. DOI: 10.1088/0960-1317/14/7/013
- [12] Lorena Paseta, Beatriz Seoane, Daniel Julve, Víctor Sebastián, Carlos Tellez, and Joaquín Coronas. Accelerating the Controlled Synthesis of Metal-Organic Frameworks by a Microfluidic Approach: A Nanoliter Continuous Reactor. *ACS Applied Materials & Interfaces*. 2013;5:9405-9410. DOI: 10.1021/am4029872
- [13] Lei Zhang and Younan Xia. Scaling up the Production of Colloidal Nanocrystals: Should We Increase or Decrease the Reaction Volume?. *Advanced materials*. ; 26:2600-2606. DOI: 10.1002/adma.201304897
- [14] Saif A. Khan, Axel Günther, Martin A. Schmidt, and Klavs F. Jensen. Microfluidic Synthesis of Colloidal Silica. *Langmuir*. 2004;:8604-8611. DOI: 10.1021/la0499012
- [15] Chandamany Arya, Jason G. Kralj, Kunqiang Jiang, Matthew S. Munson, Thomas P. Forbes, Don L. DeVoe, Srinivasa R. Raghavana and Samuel P. Forry. Capturing rare

- cells from blood using a packed bed of custom-synthesized chitosan microparticles. *Journal of Material Chemistry B*. 2013;1:4313-4319. DOI: 10.1039/c3tb20818d
- [16] Seung-Kon Lee, Jinyoung Baek, and Klavs F. Jensen High Throughput Synthesis of Uniform Biocompatible Polymer Beads with High Quantum Dot Loading Using Microfluidic Jet-Mode Breakup. *Langmuir*. ;30:2216-2222. DOI: 10.1021/la4041198
- [17] Simone Silvestrini, Tommaso Carofiglio and Michele Magg Shape-selective growth of silver nanoparticles under continuous flow photochemical conditions. *Chemical Communication*. 2012;49:84-86. DOI: 10.1039/c2cc35652j
- [18] Shuqiang Huang, Bingcheng Lin, Jianhua Qin Microfluidic synthesis of tunable poly-(N-isopropylacrylamide) microparticles via PEG adjustment. *Electrophoresis*. 2011;32:3364-3370. DOI: 10.1002/elps.201100340
- [19] Xianjie Kang, Chunxiong Luo, Qiong Wei, Chunyang Xiong, Qian Chen, Ying Chen, Qi Ouyang Mass production of highly monodisperse polymeric nanoparticles by parallel flow focusing system. *Microfluidics and Nanofluidics*. 2013;15:337-345. DOI: 10.1007/s10404-013-1152-6
- [20] Florence Bally, Dhiraj Kumar Garg, Christophe A. Serra, Yannick Hoarau, Nicolas Anton, Cyril Brochon, Dambarudhar Parida, Thierry Vandamme, Georges Hadziioannou Improved size-tunable preparation of polymeric nanoparticles by microfluidic nanoprecipitation. *Polymer*. 2012;53:5045-5051. DOI: 10.1016/j.polymer.2012.08.039
- [21] Leyre Gomez, Manuel Arruebo, Victor Sebastian, Laura Gutierrez and Jesus Santamaria Facile synthesis of SiO₂-Au nanoshells in a three-stage microfluidic system. *Journal of Materials Chemistry*. 2012;22:21420-21425. DOI: 10.1039/c2jm34206e
- [22] D.V. Ravi Kumar, B.L.V. Prasad, A.A. Kulkarni Segmented flow synthesis of Ag nanoparticles in spiral microreactor: Role of continuous and dispersed phase. *Chemical Engineering Journal*. 2012;192:357-368. DOI: 10.1016/j.cej.2012.02.084
- [23] Victor Sebastian Cabeza, Simon Kuhn, Amol A. Kulkarni, and Klavs F. Jensen Size-Controlled Flow Synthesis of Gold Nanoparticles Using a Segmented Flow Microfluidic Platform. *Langmuir*. 2012;28:7007-7013. DOI: 10.1021/la205131e
- [24] Xinqing Chen, Manuel Arruebo, King Lun Yeung Flow-synthesis of mesoporous silicas and their use in the preparation of magnetic catalysts for Knoevenagel condensation reactions. *Catalysis Today*. 2013;204:140-147. DOI: 10.1016/j.cattod.2012.07.017
- [25] J. Michael Kohler, H. Romanus, U. Hubner, and J. Wagner Formation of Star-Like and Core-Shell AuAg Nanoparticles during Two- and Three-Step Preparation in Batch and in Microfluidic Systems. *Journal of Nanomaterials*. 20017;:98134. DOI: 10.1155/2007/98134

- [26] Ho Cheung Shum, Daeyeon Lee, Insun Yoon, Tom Kodger, and David A. Weitz Double Emulsion Templated Monodisperse Phospholipid Vesicles. *Langmuir*. 2008;24:7651-7653. DOI: 10.1021/la801833a
- [27] Jinyoung Baek, Peter M. Allen, Mounqi G. Bawendi, and Klavs F. Jensen Investigation of Indium Phosphide Nanocrystal Synthesis Using a High-Temperature and High-Pressure Continuous Flow Microreactor. *Angewandte Chemie International Edition*. 2010;49:1-5. DOI: 10.1002/anie.201006412.
- [28] Mahmooda Sultana and Klavs F. Jensen Microfluidic Continuous Seeded Crystallization: Extraction of Growth. *Crystal Growth and Design*. 2012;12:6260-6266. DOI: 10.1021/cg301538y
- [29] Kan Liu, Hao Wang, Kuan-Ju Chen, Feng Guo, Wei-Yu Lin, Yi-Chun Chen, Duy Linh Phung, Hsian-Rong Tseng and Clifton K-F Shen A digital microfluidic droplet generator produces self-assembled supramolecular nanoparticles for targeted cell imaging. *Nanotechnology*. 2010;21:445603. DOI: 10.1088/0957-4484/21/44/445603
- [30] Ryan L. Hartman and Klavs F. Jensen Microchemical systems for continuous-flow synthesis. *Lab on a Chip*. 2009;9:2495-2507. DOI: 10.1039/b906343a
- [31] Samuel Marre and Klavs F. Jensen Synthesis of micro and nanostructures in microfluidic systems. *Chemical Society Reviews*. 2010;39:1183-1202. DOI: 10.1039/b821324k
- [32] Katla Sai Krishna, Yuehao Li, Shuning Li, Challa S.S.R. Kumar Lab-on-a-chip synthesis of inorganic nanomaterials and quantum dots for biomedical applications. *Advanced Drug Delivery Reviews*. 2013; DOI: /dx.doi.org/10.1016/j.addr.2013.05.006
- [33] Victor Sebastian Cabeza, Simon Kuhn, Amol A. Kulkarni and Klavs F. Jensen Size-Controlled Flow Synthesis of Gold Nanoparticles Using a Segmented Flow Microfluidic Platform. *Langmuir*. 2012; DOI: 10.1021/la205131e
- [34] Victor Sebastian, Seung-Kon Lee and Klavs F. Jensen Engineering the synthesis of silica-gold nano-urchin particles using continuous synthesis. *Nanoscale*. ; DOI: DOI: 10.1039/c4nr04021j
- [35] Victor Sebastian, Seung-Kon Lee, Chao Zhou, Martin F. Kraus, James G. Fujimoto and Klavs F. Jensen One-step continuous synthesis of biocompatible gold nanorods for optical coherence tomography. *Chemical Communications*. 2012;48:6654-6656. DOI: 10.1039/c2cc32969g
- [36] Suhanya Duraiswamy and Saif A. Khan Droplet-Based Microfluidic Synthesis of Anisotropic Metal Nanocrystals. 2009;24:2828-2834. DOI: 10.1002/smll.200901453
- [37] Ane Larrea, Victor Sebastian, Alfonso Ibarra, Manuel Arruebo and Jesus Santamaria-Gas Slug Microfluidics: A Unique Tool for Ultrafast, Highly Controlled Growth of Iron Oxide Nanostructures. *Chemistry of Materials*. 2015;27:4254-4260. DOI: 10.1021/acs.chemmater.5b00284

- [38] Kritika Kumar, Adrian M. Nightingale, Siva H. Krishnadasan, Nazila Kamaly, Marzena Wylenzinska, Arridge, Katharina Zeissler, Will R. Branford, Ecaterina Ware, Andrew J. deMello and John C. deMello Direct synthesis of dextran-coated superparamagnetic iron oxide nanoparticles in a capillary-based droplet reactor. *Journal of Material Chemistry*. 2012;22:4704-4708. DOI: 10.1039/c2jm30257h
- [39] Leyre Gomez, Victor Sebastian, Silvia Irusta, Alfonso Ibarra, Manuel Arruebo and Jesus Santamaria Scaled-up production of plasmonic nanoparticles using microfluidics: from metal precursors to functionalized and sterilized nanoparticles. *Lab on a Chip*. ; 14:325-332. DOI: 10.1039/c3lc50999k
- [40] Christophe A. Serra, Zhenqi Chang Microfluidic-Assisted Synthesis of Polymer. *Chem. Eng. Technol.*. 2008;31(8):1099-1115. DOI: 10.1002/ceat.200800219
- [41] Daniel C. Pregibon, Mehmet Toner, Patrick S. Doyle Multifunctional Encoded Particles for High-Throughput Biomolecule Analysis. *Science*. 2007;315:1393-1396. DOI: 10.1126/science.1134929
- [42] YongTae Kim, Bomy Lee Chung, Mingming Ma, Willem J. M. Mulder, Zahi A. Fayad, Omid C. Farokhzad, and Robert Langer, Mass Production and Size Control of Lipid-Polymer Hybrid Nanoparticles through Controlled Microvortices. *Nano Letters*. 2012;12:3587-3591. DOI: 10.1021/nl301253v
- [43] Jong-Min Lim, Archana Swami, Laura M. Gilson, Sunandini Chopra, Sungyoung Choi, Jun Wu, Robert Langer, Ultra-High Throughput Synthesis of Nanoparticles with Homogeneous Size Distribution Using a Coaxial, Turbulent Jet Mixer. *ACS nano*. ; 8:6056-6065. DOI: 10.1021/nn501371n
- [44] Jiashu Sun, Yunlei Xianyu, Mengmeng Li, Wenwen Liu, Lu Zhang, Dingbin Liu, Chao Liu, Guoqing Hub and Xingyu Jiang* A microfluidic origami chip for synthesis of functionalized polymeric nanoparticles. *Nanoscale*. 2013;(5):5262-5265. DOI: 10.1039/c3nr01289a
- [45] Shin-Hyun Kim and David A. Weitz One-Step Emulsification of Multiple Concentric Shells with Capillary Microfluidic Devices. *Angewandte Chemie International Edition*. 2011;50:8731-8734. DOI: 10.1002/anie.201102946.
- [46] Su Kyung Suh, Kai Yuet, Dae Kun Hwang, Ki Wan Bong, Patrick S. Doyle, and T. Alan Hatton Synthesis of Nonspherical Superparamagnetic Particles: In Situ Coprecipitation of Magnetic Nanoparticles in Microgels Prepared by Stop-Flow Lithography. *Journal of the American Chemical Society*. 2012;134:7337-7343. DOI: 10.1021/ja209245v