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Microfluidic Devices for the Synthesis of Nanoparticles and Biomaterials

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Abstract

This paper reviews the latest developments in microfluidic devices for synthesizing nanoparticles and biomaterials. Miniaturized reactor platforms provide more controlled fluid transport, rapid chemical reactions, and cost-saving advantages over conventional methods for chemical, biological, and medical applications. During the past five years microfluidic devices have been developed to synthesize particles with diameters of nanometers to micrometers and materials ranging from semiconductors, metals, to polymers. As many researchers have shown, nanoparticles have unique properties based on their sizes, shapes, and morphology. Therefore controlled synthesis processing methods and devices are highly desirable to achieve homogeneous nanoparticle sizes, shapes, and hence their properties. In this review paper nanoparticle synthesis in microfluidic systems was either carried out by continuous laminar flow or in multi-phase droplet reactors. Microfluidic devices offer various manipulation mechanisms and device fabrication materials. Reported nanoparticles obtained from microfluidic devices demonstrated less particle size distributions compared to those produced by conventional methods. Core-shell structures, colloidals, and bioconjugated nanoparticle syntheses have all been reported in microfluidic synthesis platforms.

Keywords: Microfluidics, Droplet, Nanoparticle, Biomaterial, Synthesis

Introduction

Microfluidic devices are designed to manipulate fluids in microchannels with greatly reduced consumption of reagents and demonstrate intrinsically efficient heat and mass transfer due to high surface-area-to-volume ratios. Efficient mixing and rapid chemical reaction at the nanoliter to picoliter scales allow microfluidic devices to better control the synthesis parameters and thus the nanoparticle sizes and properties. The miniaturization of synthesis systems provides new opportunities for advanced chemical synthesis, and also enables a broad range of biological and medical applications. The use of microfluidic devices for nanoparticle synthesis is advantageous in many aspects, including enhanced processing accuracy and efficiency; flexibility for multi-step platform design; rapid turnaround results for fine tuning properties of synthesized nanoparticles, cost savings from reduced consumption of source materials and reagents, and safer operation and environmental friendliness since the process consumes much reduced hazardous chemicals and reagents.

Microfluidic devices have the ability to generate homogeneous emulsions particles in a controllable manner [1-6]. To reach higher quality chemical, physical, optical, and biological properties for various applications, researchers have resorted to miniaturization of reaction platforms [7]. Micro and nanoparticles are of importance to biomedical science since their critical size dimensions are close to cells, tissues, microorganisms, and biological molecules [8-10]. Nanoparticles have applications in advanced drug delivery systems, biomolecular sensing, targeted imaging, and thin film coatings [11-13]. In the nano scale, the chemical, physical, and biological properties are strongly affected by size dimensions and shape morphologies. Recently, microfluidic devices are being developed to control the fine properties at the nano-scale. Besides the synthesis of pure nanoparticles, desirable features include double shell, composite materials, or functional surfaces. This paper intends to provide a research review and up-to-date information on microfluidic devices used for nanoparticle and biomaterial particle synthesis.

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Materials and Methods

Although conventional synthetic chemistry has produced micro/nano particles for many years, most methods and equipment have remained basically unchanged. Conventional methods for particle synthesis include nucleation followed by growth [14-15], emulsion [10,16], precipitation [17],

decomposition [18], and grinding [19], etc. Most processes are bench-top batch processes and designed for mass production. But these systems typically have severe limitations in the controlled generation of homogeneous and monodispersed particles and produce generally broad size distributions. For medical and biological applications, the particle quality requirement can supersede the need for large quantities, and the standards for particle synthesis methods and devices are consequently raised as well. Researchers with various backgrounds have been looking for alternative methods to improve and overcome the challenges of conventional synthesis methods based on nanotechnology's promising potentials [20-21].

Types of microfluidic devices

Fluid flow in microchannels is diffusion-based laminar flow due to low Reynolds numbers. The mixing from microchannels is by diffusion only but not necessarily slow, since it is 100 times faster when a system is 10-fold smaller [11]. The rapid mass and heat exchange enables higher throughput and faster reaction process [7].

Microfluidics devices can be made of various materials depending on the applications. Polymer, silicon, metal have all been used to fabricate microfluidic devices [22-24]. Typically syringe pumps or microfabricated pumps provide pressure-driven flow in the microchannels; electrokinetic devices provide other choices for pumping liquids [25]. Reagent solutions are manipulated inside microfluidic devices by either active or passive control [26]. Active control indicates applying external forces (electric field, magnetic field, optical force, heat, etc.) to control the flow movement in microchannels. Passive control indicates that the fluidic movement is controlled by channel geometries and/or liquid flow rates. In general, active control provides more flexibility and fine tuning of the flow patterns, on the other hand, passive control simplifies the experimental setup and prevents complications (e.g. heating, biodegradation) arising from external forces, and greatly reduces the channel design complexity and fabrication processes.

Based on the flow types in microfluidic devices, the nanoparticle synthesis methods can be primarily divided into two categories: single phase continuous flow synthesis and emulsion (2-phase) micro droplets/segmented flow synthesis. Continuous flow synthesis mix and react reagents in microchannels under diffusion-based laminar flow reaction conditions. Reaction times, temperatures, mixing efficiency, and reagent concentrations are parameters to control particle quality. The microfluidic generation of micro droplets has recently been explored extensively [21], and the reactions in micellar systems have been reviewed recently [27]. Nanoparticle synthesis taken place in micro droplet reactors to improve the mixing efficiency in microfluidic channels, and further reduces the particle size distributions.

The recent developments of particle synthesis in microfluidic devices are divided into four categories base on material types: metal, semiconductor, inorganic/polymer, and biomaterial.

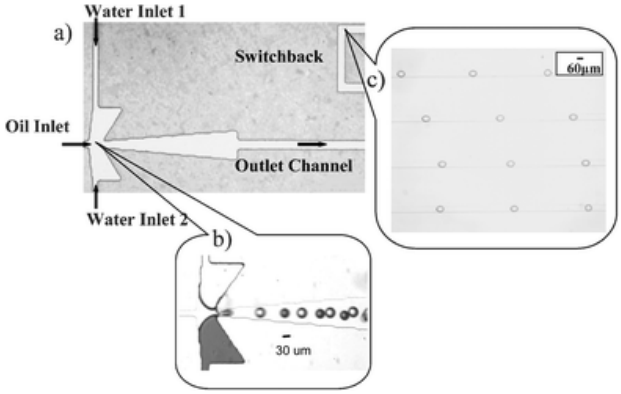

Figure 1. Double-T junction channels were designed to generate droplets alternatively and fuse two reagent droplets in tapered chamber. In long switchback channel, CdS nanoparticle synthesis was taken place in each droplet reactor. Reproduced by permission of The Royal Society of Chemistry.

Semiconductor nanoparticle synthesis

Semiconductor nanoparticles have unique optical and electronic properties, which are changeable based on their sizes or shapes and can be used for various applications including sensing, imaging, fiber optics, etc. [12]. Therefore semiconductor materials have gained the earliest interest for microfluidic synthesis. Conventional macroscale generation involves the atom-by-atom particle growth or precipitation, but the particle size distributions are usually large and need post treatment to extract the desired particle size [28]. Various semiconductor nanoparticles utilizing microfluidic devices have been studied in past few years. Using continuous flow microreactors and confine reagent mixing and reaction condition, cadmium sulfide (CdS) [29], cadmium selenide (CdSe) [30-33], titania [34] and CdSe-ZnS composite nanoparticles [35-36] synthesis have been reported.

Recent developments addressed on narrower particle size distribution using microfluidic droplet/segmented flow technique. In general, micrometer droplets are generated by two immiscible fluids and serve as miniaturized reactors where chemical synthesis takes place. Shestopalov et al. reported the multi-step synthesis of CdS and CdS/CdSe core-shell nanoparticles in micro droplets [37]. Hung et al. developed a microfluidic channel design which allows droplet fusion and synthesizes CdS nanoparticles within each droplet (Fig. 1) [38]. Chan et al. reported the high temperature synthesis of CdSe nanocrystals in nanoliter droplets [39]. Yen et al. used gas-liquid segmented flows for high-temperature synthesis of CdSe quantum dots. In gas-liquid segmented flow, the circulation of reagent is increased to facilitate the mixing and narrow the particle size distributions [40].

Metal nanoparticle synthesis

Metal nanoparticle formation includes the initial nucleation and subsequent particle growth. In most conventional methods both processes occur concurrently throughout the process, thus obtain particles with broad size distributions [41]. To prepare homogeneous nanoparticles, all nucleation processes should happen in short period of time, then supply materials slowly not to reach the concentration

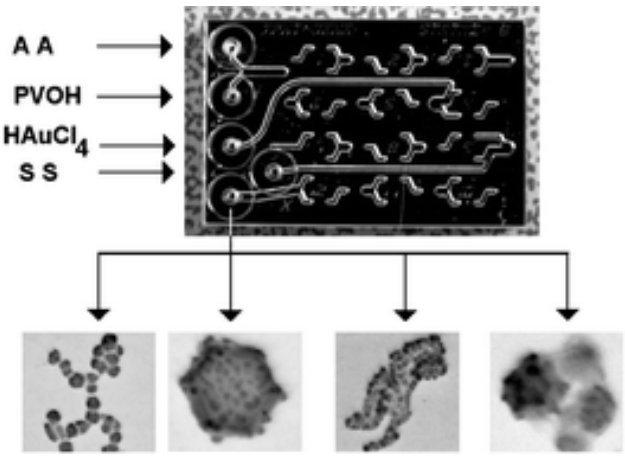

Figure .2 Microfluidic channel design for the mixing of reactant solutions with a three-step static micro-mixer. Isolated and clustered Au nanoparticles were synthesized. Reproduced by permission of The Royal Society of Chemistry.

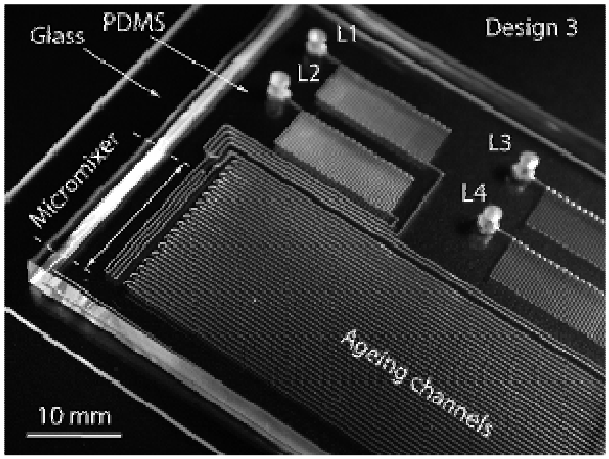

Figure 3. Segmented flow microreactor with micromixer and ageing channels for colloidal silica nanoparticle synthesis. Four liquid inlets lead reagents into micromixer , and gas is then injected to create gas-liquid plugs with recirculation and mixing in the ageing channels. (Reprinted with permission from *Langmuir* **2000**, 20, 8605. Copyright 2000 American Chemical Society)

level where new nucleation will occur again. After the success of semiconductor nanoparticle synthesis in microfluidic devices, metal materials were also taken into consideration. Because of the better control of the reaction kinetics parameter such as effective mixing and efficient heat and mass transfer, continuous-flow microfluidic reactors have been widely designed and used to generate homogeneous metal nanoparticles. For metal nanoparticle synthesis, the advantages of using microreactors over conventional methods hinge on the ability to control the temperature along the flow, efficient mixing in short periods of time, and allowing additional reagents to be added downstream.

J. M. Köhler and colleagues first reported on the synthesis of gold nanoparticles inside microchannel reactors. Their group demonstrated synthesized Au nanoparticles in glass/silicon microreators starting from Au seeds (2004) [42] and Au salt solution (2005) [43], respectively. Recently a new chip design featuring three mixing zones was reported (Fig. 2), and Au nanoparticles in single and cluster forms with different shapes and characters were observed [44]. Lin et al. described the synthesis of silver nanoparticles from silver pentafluoropropionate precursors in a continuous flow tubular microreactor [45]. He et al. further studied the interior wall effect of capillary tube on the synthesis of Ag nanoparticles. Results indicated that high affinity between the particles and interior wall resulted in broad size distribution and low production yield [46]. Another study focused on particle shapes has demonstrated the synthesis of rod-shaped Au and Ag nanocrystal in continuous flow microreactors by seed-mediated growth approach [47]. Song et al. used polymeric microfluidic devices for palladium nanoparticle synthesis. The device was fabricated by developing photoresist SU-8 on a PEEK (polyetheretherketone) substrate. Five parallel channels were fabricated to scale up the production yield and reduce the mixing volume and residue time [48]. The study and comparison of the copper nanoparticle formation between microfluidic and conventional batch process were also reported [49]. Compared with those produced by conventional batch process, Cu nanoparticles formed from microfluidic devices were smaller (8.9 nm vs. 22.5 nm) with narrower size distribution, as well as more stable to oxidation. Cobalt nanoparticles with three different crystal structures, face-centered cubic (FCC), hexagonal closed-packed (HCP), ε-cobalt, were generated from microfluidic devices as well [13].

Colloidal nanoparticle synthesis

Colloidal nanoparticles such as silica have potential applications in optical coatings, displays, chromatography, and catalyst [50]. The scaling down of reactors provides the flexibility of channel design and reagent manipulation, therefore multi-component channel design was possible for colloidal nanoparticle synthesis. Khan et al. reported and compared both laminar flow and segmented flow reactors for colloidal silica nanoparticles. The gas-liquid segmented flow microreactor enhanced better mixing in the liquid plugs and resulted in narrower silica nanoparticle size distribution (Fig. 3) [51-52]. Jorgen et al. used continuous segmented flow reactor combined with micromixer to generate homogenous inorganic composite nanoparticles including calcite, barium titanate, and nickel-manganese mixed oxalate [53].

Biomaterial particle synthesis

The miniaturization of biological and medical systems has attracted high interest because of the unique new applications and healthcare impact that can be realized. Micro-to-nano scale particles could serve as smart delivery systems, which can carry molecules to the target site directly. These particles can also be used as the critical components for artificial cells, biosensors, chromatography separation, and information storage. Drugs, hormones, proteins, nucleic acid, peptides, and antibodies can be carried by nanoparticles through various

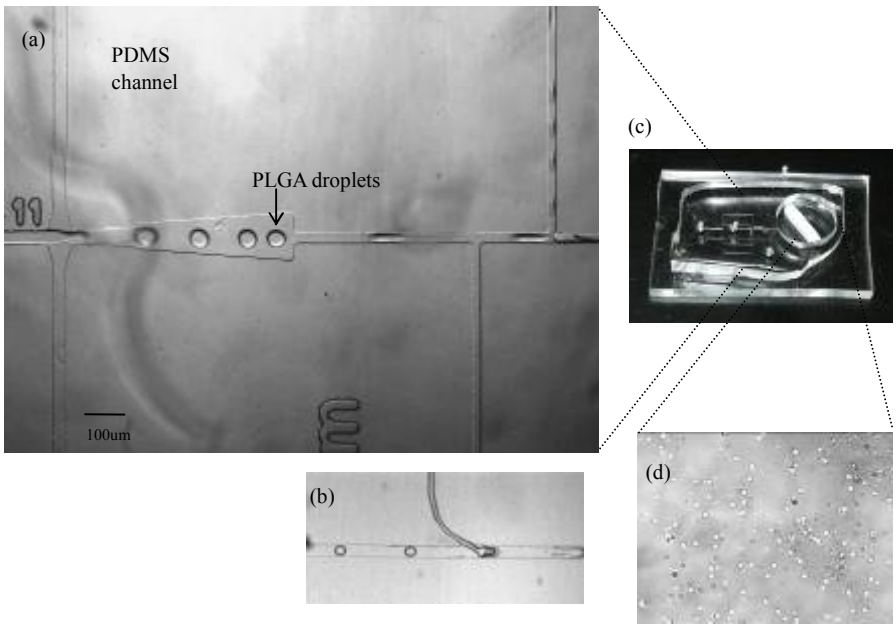

Figure 4. PDMS microfluidic devices for PLGA particle synthesis. (a) Channel design layout, including a pinch junction for PLGA droplet generation, and (b) merging junction where an extra reagent stream mix and react with droplets to form PLGA particles. (c) a mini-magnetic stirring bar to prevent particle aggregation. d) by adjusting flow rate and reagent concentration, PLGA micro- and nanoparticles can generated continuously.

routes of administration [9]. Those applications primarily depend on particle size, shape, morphology, and size distribution. It is worth noting that the useful size ranges of biomaterial particles can range from micrometers to nanometers. For example, the ideal sizes for cell encapsulation or certain drug delivery modalities would be in the microns range.

Biocompatible or biodegradable polymers have been extensively explored in recent years because of their potential biomedical applications. For examples, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-glycolic acid) (PLGA), polyethylene glycol (PEG), alginate, hydrogels are popular materials used either in the biomedical industries or in academic research labs. Our group has been studying the synthesis of monodispersed biomaterials using microfluidic devices. By miniaturizing conventional solvent evaporation/extraction process steps onto microfluidic chips, PLGA micro- and nanospheres were synthesized in microdroplet reactors (Fig. 4). With addition of extra reagents at the downstream, the device enables the coating of proteins on PLGA nanospheres [54]. Alginate is also suitable for microfluidic synthesis because of easiness of gel. Fisher et al. from our group reported the use of a flow-focusing channel for alginate bead generation and the application for cell encapsulation [55-56]. Sugiura et al. utilized the extrusion method to generate alginate and $CaCl_2$ beads from micro-nozzle arrays with gelation carried out afterwards. The living cells encapsulated into calcium alginate beads were shown viable [57]. Recently several alginate microsphere syntheses via micro droplet technique were published. Huang et al. utilized cross-junction channels to prepare chitosan [58] as well as alginate [59] emulsions, and form Ca-alginate microspheres at $CaCl_2$ outlet reservoir. Gold nanoparticles were encapsulated in alginate spheres to demonstrate the drug delivery capability. Liu et al. used similar flow-focusing channel to generate alginate and calcium droplets respectively, the channel design was allowed to merge two reagent droplets in the expansion chamber and form calcium alginate microspheres [60]. One additional advantage of alginate hydrogel bead generation through micro droplets is that droplets' size and shape are controllable continuously by adjusting the flow rates. Also the polymer gelation is achieved in situ by ionic cross-linking. Based on the idea, Zhang et al. reported another two biopolymer hydrogels synthesis (k-carrageenan and carboxymethylcellulose) by micro droplet generation in microfluidic devices [56].

Polymeric particles loaded with biomaterials are made through either encapsulation within the particle or assembly on the surface. Jeong et al. immobilized biocatalyst in hydrogel microparticles using photopolymerization and micro droplet systems [61]. Geest et al. synthesized dex-HEMA biodegradable microgels loaded with proteins [62]. Nie et al. reported the synthesis of Janus (two-phase) and ternary (three-phase) particles with narrow size distribution and controllable structure of different phases, as well as BSA bioconjugation [63]. Molecular imprinted polymer (MIP) beads can selectively target specific molecules and thus have been know as useful recognition materials. Molecular imprinting technique involves the polymerization of functional monomers with imprint molecules; subsequent removal of imprinted molecules leaves the polymer with specific "memory sites". Zourob et al. first design a spiral microfluidic device which allows the generation and polymerization of MIP beads, following by the template removal [64]. Kubo et al. came out the similar idea to generate atrazine-imprinted microspheres using a simple droplet generation channel design [65].

Conventional MIPs preparations are time-consuming with the batch processes while microfluidics provides continuous and rapidly adaptable methods for the synthesis and optimization of uniform MIPs beads.

As mentioned before, microfluidic devices have channel design flexibility and therefore allow droplet generation and manipulation, UV exposure, or polymer crosslink reservoir to be integrated together. Currently most of biomaterial particle sizes generated from microfluidic devices are in the micrometer range, but microfluidic system has shown promise in generating biomaterial nanoparticles [53]. Unlike metal and semiconductor nanoparticles that grow from precursor seeds, polymeric particles can form directly from emulsion and polymerization, and hence the aggregation of final products also will affect the sizes and the distributions.

Conclusion

Microfluidic devices have the ability to generate semiconductor, metal, and polymer nanoparticles in homogeneous and well controlled fashion. The nanoparticle size properties are improved compared to those obtained from conventional methods. However the synthesis of nanoparticles and biomaterial particles in microfluidic devices is still in the early stage, as the nanoparticles have extensive potentials on biological and medical applications. Still many materials could be explored using microfluidic synthesis methods, and the miniaturization of biomaterial particles is desired. With the rapid development of microfluidic device fabrication processes and microfluidic manipulation methods, new nanoparticle synthesis methods with better control and design of nanoparticle properties is expected to expedite in the coming years.

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