Synthesis of Uniform-Size Hollow Silica Microspheres through Interfacial Polymerization in Monodisperse Water-in-Oil Droplets

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ABSTRACT We have developed a microfluidic method to produce monodisperse, size-controllable silica microspheres via hydrolysis and polymerization of TEOS at the interface of water-in-oil droplets. By altering the concentration of TEOS in oil phase and CTAB in aqueous phase, we achieved control over morphology of the microspheres from hollow, to partly hollow, to solid. The hollow silica microsphere can be used for rapid waste removal and detoxification extraction with a very simple procedure.

KEYWORDS: silica microspheres • morphology • microfluidic • interfacial reaction • detoxification

Hollow microspheres have attracted broad interests because of their potential applications in drug delivery, adsorption, and microreactors (1−17). The conventional techniques for fabricating hollow microspheres include hard-template (18−21), layer-by-layer (LBL) (22, 23), and emulsion methods (24−27). The first two methods require multistep processes and are time-consuming. By comparison, the emulsion method is a simpler and more direct route for preparing hollow microspheres. However, the resulting microspheres have a wide size distribution and tend to form aggregates. Therefore, methods for single-step, reproducible synthesis of uniform-sized hollow microspheres are in great demand. Microfluidic technology is an ideal method for obtaining uniform-size microspheres and has the advantages of continuous, reproducible, and scalable production. Studies on using microfluidic technology to fabricate monodisperse hollow microspheres by means of interfacial polymerization, photopolymerization or removal of the solvent from droplets have been reported. For example, recently Yang et al. (13) have reported a method to fabricate monodisperse hollow TiO_2 spheres with embedded nanoparticles in a coflow microfluidic device. Zhang et al. (28) and McQuade et al. (29) have reported the synthesis of monodisperse hollow microspheres with controllable morphology using a droplet microfluidic technique. However, hollow spheres produced using microfluidic devices are limited to polymers (7, 12, 14, 15, 28, 30), organosilicon (29), or inorganic materials like TiO_2 (13). Synthesis and fabrication of monodisperse inorganic hollow silica microspheres with controlled size and morphology using microfluidic emulsion technique have not been demonstrated yet. Because silica is chemically inert, biocompatible, and has a rich chemistry for conjugating with other ligands, hollow silica spheres have great potential in a variety of applications. It is thus important to develop a simple method to synthesize uniform size silica hollow microspheres with different morphology.

In this study, we developed a facile one-step approach to synthesize size and morphology controllable monodisperse silica hollow microspheres using a cross-flow microfluidic device. This approach is based on interfacial polymerization in monodisperse water-in-oil droplets generated from a cross-channel microfluidic device with a flow-focusing geometry. Dispersed aqueous phase ($V_{water}/V_{ethanol} = 1:1$) containing catalyst ammonia and cationic surfactant cetyltrimethylammonium bromide (CTAB) is slowly injected into the inlet of the cross-flow microfluidic device, and the immiscible fluid, the hydrophobic continuous oil phase (31) containing precursor tetraethyl orthosilicate (TEOS), is injected into the other two inlets in a direction perpendicular to the dispersed phase. Monodisperse water-in-oil droplets are continuously generated based on the mechanism of shear force-driven break-off. Hollow spheres can be produced when the hydrolyzation and subsequent condensation of TEOS take place at the water−oil interface. When the TEOS in the oil phase diffuses to the interface, it will interact with basic catalyst in the aqueous phase. As a result, the hydrolysis of TEOS occurs. The hydrolyzed TEOS monomers will then condensate at the interface. The resultant negatively charged silicates can be steadily fixed by ammonium cation of CTAB at the W/O interface because of electrostatic interaction (25, 32), and gradually form the hollow shell structure (see Scheme 1).

To demonstrate this strategy, we first fabricated a cross-channel glass microfluidic chip with 250 μm × 200 μm (width × depth) for the flow-focusing section (see the Sup-

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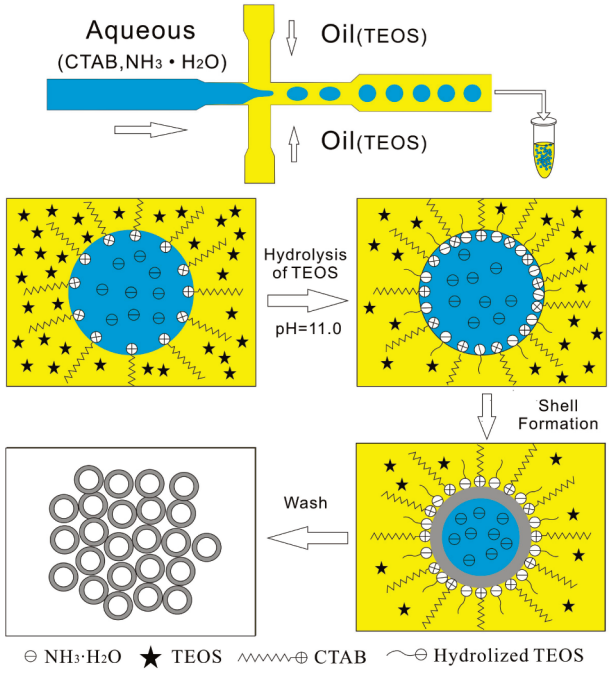
Scheme 1. Schematic Illustration of the Droplet Microfluidic Approach for Preparing Monodisperse Hollow Silia Microspheres



porting Information). As shown in Figure 1A, the W/O droplets generated at the condition of 1 mL/h of oil flow rate and 0.18 mL/h of aqueous flow rate have a highly uniform diameter of 131.4 ± 3.0 μm. Figure 1B shows scanning electron microscopy (SEM, Hitachi S-4800, Japan) image of monodisperse hollow silica particles (mean diameter = 137.0 μm, σ = 3.2 μm) with rough surface. The broken microsphere caused by high vacuum clearly illustrates the hollow structure. The thickness of the shell is about 500 nm according to SEM measurement (see Figure S1 in the Supporting Information). Furthermore, to verify the hollow structure, we fabricated luminescent shell by adding 5% (v/v) 100 μmol/L 5(6)- TAMRA solution to the oil phase. As

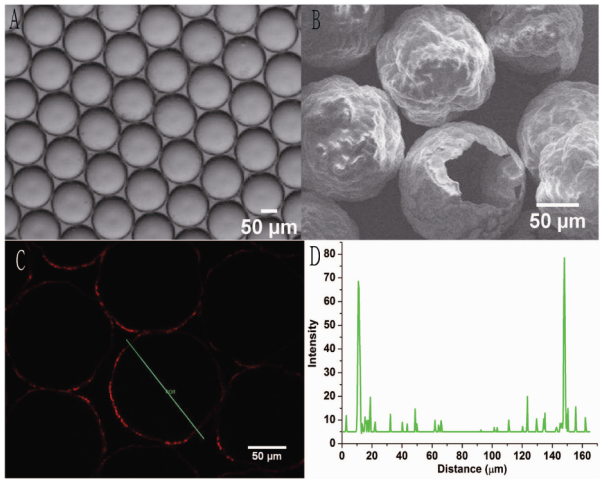


FIGURE 1. (A) Uniform droplets generated by microfluidic device. (B) SEM image of the as-synthesized hollow microspheres. (C) Confocal microscopy image of silica shells with embedded TAMRA. (D) Profile of luminescence intensity in a single microsphere.

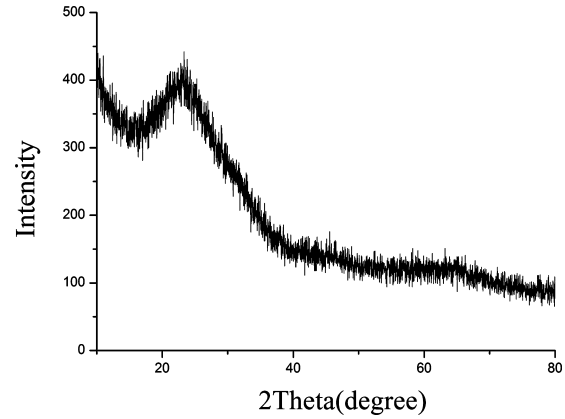


FIGURE 2. XRD pattern of SiO_2 hollow microspheres.

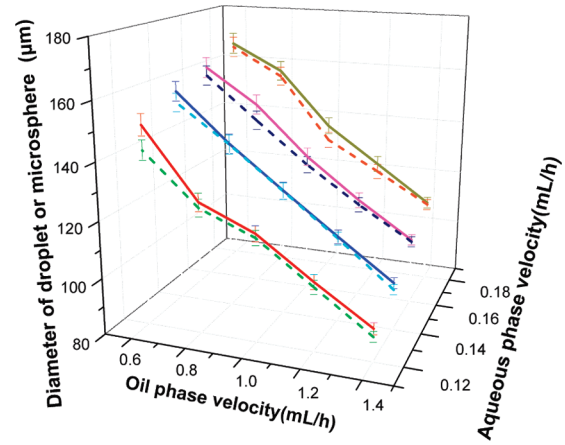


FIGURE 3. Relationship between flow rate (oil/aqueous phase) and diameter of microsphere (solid line) and droplet (dashed line).

shown in Figure 1C, the luminescent shells synthesized were observed through Laser Scanning Confocal Microscope (Leica TCS SP5, Germany). Fluorescence intensity profile over a cross-section of the silica shell in Figure 1D indicates the diameter of the hollow spheres is about 137 μm, consisting with the size of the microsphere observed by SEM. Figure 2 is the XRD pattern of SiO_2 hollow microspheres, the bread peak at 20−26° is the characteristic diffraction peak of SiO_2 with amorphous structure. By BET nitrogen absorption experiment, specific surface area of the microspheres is measured to be 196.6 m^2/g, and pore size is concentrated at about 2 nm.

One advantage of the droplet microfluidic approach for hollow sphere synthesis is that we can easily control the diameter of droplets by varying flow rate of oil and aqueous phase, and then regulate the diameter of spheres. Figure 3 shows the relationship between the flow rate of two phases and the diameter of microsphere and droplet, At a fixed oil flow rate, the diameter of microsphere and droplet both increase as the velocity of the aqueous flow increases. On the other hand, when the aqueous flow rate is fixed, the diameter of microsphere and droplet both decrease as the velocity of the oil flow increases. The diameter of as-synthesized microspheres are slightly larger than droplets because silica at the interface grows out slowly via interfacial polymerization. Uniform-size hollow microspheres at the range of 91 to 167 μm can be easily obtained when the oil

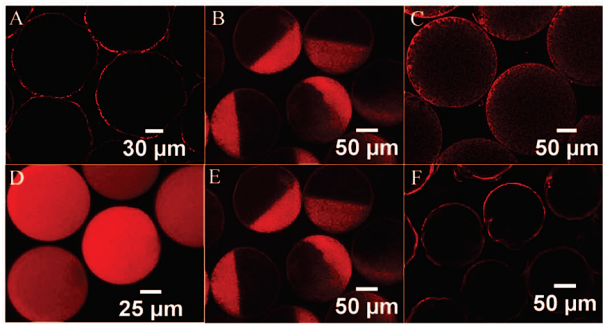


FIGURE 4. Confocal microscopy images of silica microspheres with embedded TAMRA under different conditions. (A−C) Fixed amount of CTAB (0.03 g), changing the concentration of TEOS (v:v) from 0.08 to 0.2 then to 1.0; (D−F) fixed concentration of TEOS = 0.2 (v:v), changing the amount of CTAB from 0 g to 0.03 g and then to 0.06 g.

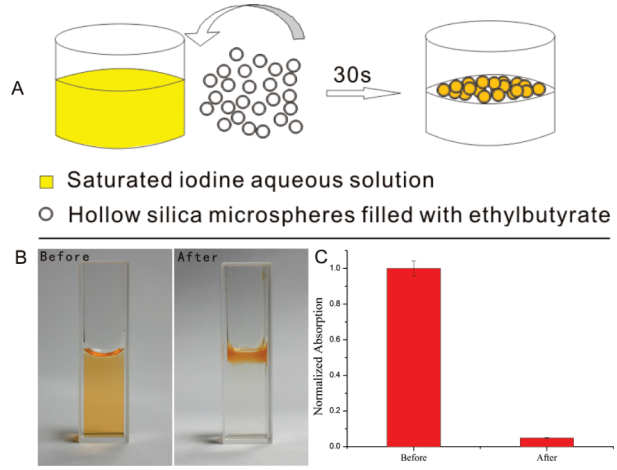


FIGURE 5. (A) Schematic drawing of extraction process of iodine in hollow microspheres. (B) photos of iodine solution in a quarz cuvette taken before and after extraction with hollow microspheres. (C) Normalized UV absorption of iodine aqueous solution collected at 365 nm before and after adding microspheres.

flow rate varies from 0.6 to 1.4 mL/h and the aqueous flow rate varies from 0.12 to 0.18 mL/h.

With the microfluidic droplet synthesis approach, not only the size of the sphere can be flexibly controlled but the morphology of the silica microspheres (ratio of solid part to hollow part) can also be regulated by altering the concentration of TEOS and CTAB. For a given amount of CTAB (0.03 g in 4 mL aqueous phase), the increasing of concentration of TEOS (v:v) from 0.08 to 1.0 resulted in the microspheres morphology varying from totally hollow (Figure 4A), partly hollow and partly solid (Figure 4B) to completely solid (Figure 4C). On the other hand, when the concentration of TEOS (v:v) was fixed at 0.2, increasing the amount of CTAB from 0 g to 0.06 g resulted in the change of sphere morphology from totally solid (Figure 4D), to partly solid and partly hollow (Figure 4E), to totally hollow ((Figure 4F). At a certain concentration of CTAB, the negatively charged silicates stabilized at the W/O interface were limited, which led to the formation of hollow microspheres as shown in Figure 4A. However, when the concentration of TEOS increased, the surplus of silicates condensated and precipitated to the bottom of W/O droplets because of gravity, producing the solid part of microspheres (Figure 4B,C) with a loosened structure. To fabricate a hollow structure at an increased concentration of TEOS, the concentration of CTAB needs to be increased accordingly (Figure 4F).

Compared to conventional hollow nanospheres, the as-synthesized hollow silica microspheres offer a much higher storage capacity, making them suitable material for applications in waste removal and drug detoxification. Herein, iodine was used as a toxic drug analogue to illustrate the detoxification capability of our hollow microspheres. The assay was carried out by adding 0.6 mg of hollow silica microspheres pre-filled with ethyl butyrate (incubated in ethyl butyrate and then filtered) to 2 mL of saturated iodine aqueous solution. Because iodine has a very low affinity to the silica shell and is therefore expected to partition strictly between the oil core and the aqueous solution (3). After a brief intense shaking, the aqueous solution turned from yellow to colorless; simultaneously, the microspheres turned from colorless to deep yellow, indicating that iodine in the saturated aqueous solution was uptaken by the hollow spheres filled with ethyl butyrate (Figure 5A). Figure 5B are photos of iodine solution taken before and after extraction with hollow microspheres. Figure 5C shows the normalized UV absorption of iodine aqueous solution collected at 365 nm before and after adding microspheres. The UV absorption intensity of iodine decreased over 95% within 30 seconds after adding microspheres, clearly illustrating the speed and efficiency of the microsphere for detoxication. Compared with traditional liquid−liquid extraction technique, it's much quicker (30 s) and simpler to use the as-synthesized hollow microspheres for extraction, as the sample solution and microspheres can be easily separated by filteration. Furthermore, the microspheres can be repeatedly used. These advantages make the microspheres a suitable material for applications such as waste removal or drug detoxification.

In summary, we have reported a microfluidic route to produce monodisperse, size controllable silica microspheres via hydrolysis and polymerization of TEOS at the interface of water-in-oil droplets. By altering the concentration of TEOS and CTAB, we achieved control over morphology of the microspheres from hollow, to partly hollow, to solid. The hollow silica microsphere can be used for rapid waste removal and detoxification with a very simple procedure.

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Supporting Information Available: Details in fabrication of microfluidic chip, synthesis of hollow silica microspheres and measurement of shell's thicknss, and SEM images of hollow silica microspheres before and after calcination (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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