Microporous and Mesoporous Materials 219 (2016) 230–239

Contents lists available at ScienceDirect

Microporous and Mesoporous Materials

journal homepage: www.elsevier.com/locate/micromeso

High-yield hydrothermal synthesis of mesoporous silica hollow capsules

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ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form
12 August 2015
Accepted 13 August 2015
Available online 21 August 2015

Keywords:
Mesoporous silica
Hollow capsules
Templates
Hydrothermal treatment
Calcination

ABSTRACT

An improved method for the preparation of mesoporous silica hollow capsules (MSHCs) is reported. In the previous method, polystyrene (PS) particles and cylindrical assemblies of surfactants served as the templates for the hollow parts and mesopores of the capsules, respectively, which were thermally decomposed via calcination in ambient air at 550 °C. However, during calcination, the MSHCs aggregated and a considerable loss of the monodispersed capsules occurred. To reduce this loss, hydrothermal treatment was employed instead of calcination. As a result, the yield of the capsules (defined as the ratio of the numbers of the obtained capsules and PS particles) was increased from 35% for the calcination process to approximately 85% for the present method. Optimization of the conditions for hydrothermal synthesis of MSHCs to maximize the yield and minimize the fraction of unwanted products is also discussed in detail.

1. Introduction

Drug delivery systems are designed to deliver drugs safely and effectively to the sites where they are needed at concentrations required to minimize side effects and dosage, while maximizing the therapeutic efficacy. One of the promising strategies for realizing this concept is the utilization of drug carriers [1–5]. A drug carrier can protect the drug from degradation and prevent side effects, and the size and surface of the carrier can be tailored to achieve targeted delivery and controlled release. Mesoporous silica is one of the best candidates as a carrier material [4–10]; mesoporous silica nanoparticles with pore diameters of several nanometers are more resistant to mechanical and chemical stresses than polymer-based carriers and exhibit good biocompatibility [11–13]. The hydrolysis and condensation of silicon alkoxides (the so-called sol–gel reaction) extends the 3D network of ≡Si–O–Si≡ bonds, and bulk silica is formed [14]. When the sol–gel reaction is performed in the presence of surfactants, complexation between the silica and the surfactants occurs, with the cylindrical assemblies of surfactant aligned periodically. The mesoporous silica particles are formed following thermal decomposition of the surfactants via calcination [15–18] or dissolution of the surfactants using an appropriate solvent [18,19].

When the sol–gel reaction is performed in the presence of not only surfactants but also particles as templates for hollow structures, hollow capsules with mesoporous silica shells can be obtained as long as the particle templates can be removed after the reaction. The advantage of mesoporous silica hollow capsules (MSHCs) over mesoporous silica particles as drug carriers is the simultaneous reduction in the required dose and dosing frequency because of their higher capacity for drug loading [4]. Both loading and release properties of MSHCs, as well as their targeted delivery and controlled release performance, have been extensively studied [20–26].

To date, various types of templates have been used to generate the hollow structures of MSHCs, e.g., emulsions [27–32], gas bubbles [33–35], vesicles [36–39], polymers [40,41], latex particles [42–50], and inorganic particles [51–59]. Organic templates are removed with the surfactants via calcination, while inorganic templates are subjected to dissolution or selective etching [57]. However, because the monodispersity of the MSHCs is determined by the hollow structure template, the monodispersity of the template is important. Polystyrene latex is one of the best candidates because of its excellent monodispersity [42–48]. Previously we developed a method for the synthesis of monodispersed MSHCs using polystyrene (PS) particles and showed that the coefficients of variation (CV) of the diameters of the PS particles and resultant

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http://dx.doi.org/10.1016/j.micromeso.2015.08.015
1387-1811/

MSHCs (outer diameters of 145–400 nm) were nearly the same [49]. Furthermore, repetition of the sol–gel reaction prior to template removal provided control of the MSHC shell thickness between 30 and 120 nm. The loading and release properties of the MSHCs were also investigated [50]. However, as pointed out in Ref. [49], removal of the templates via calcination resulted in fusion of the MSHCs and the yield of the monodispersed capsules was limited to approximately 30%, where the yield is defined as the number of monodispersed capsules divided by the number of template particles. Because the silanol groups can be cross-linked via dehydration in the temperature range from 400 to 700 °C [60], calcination at 550 °C in ambient air causes the fusion of the capsules. Thus, to improve the capsule yield, their formation and removal of the templates must be performed under milder conditions.

It has been reported in the literature that after the sol–gel reaction, hydrothermal treatment at approximately 100 °C was applied to the dispersion of the generated silica/surfactant complexes prior to removal of the templates [41,61–65]. This hydrothermal treatment was performed to promote the gelation of the silica sol and extension of the 3D ≡Si–O–Si≡ network to fabricate a rigid silica framework [14]. On the other hand, hydrothermal treatment at a temperature higher than the melting point of PS was shown to remove the PS particles and form hollow titania capsules [66]. These reports inspired us to improve the capsule yield through the use of hydrothermal treatment, because the treatment temperature can be dramatically reduced from the calcination temperature of 550 °C. Herein, we report a revised method that provides an improved yield of the monodispersed MSHCs. A sol–gel reaction is performed in the presence of surfactants and PS particles to form silica/surfactant complexes on the particles, as previously described [49,50]. A first hydrothermal treatment (1st HT) is then performed to increase the rigidity of the silica framework of silica/surfactant complexes on the particles. A second hydrothermal treatment (2nd HT) is then performed using nitric acid to efficiently decompose the organic templates at a lower temperature. The conditions of the process have been optimized to maximize the capsule yield. Specifically, the heating and cooling rates during the 1st and 2nd HTs and the compositions of the dispersions in both HT steps were important parameters.

2. Experimental details

2.1. Materials

Aqueous dispersions of PS particles (5% w/v) with average diameters of 147 nm (standard deviation: 7 nm) were purchased from microParticles GmbH (Berlin Germany). Cetyltrimethylammonium bromide (CTAB, >99%) and tetraethoxysilane (TEOS, >99.9%) were purchased from Sigma–Aldrich Co. Limited Liability Company (Missouri, USA) and Alfa Aesar, A Johnson Matthey Company (Lancashire, UK), respectively. Ethanol (EtOH, >99.5%), aqueous ammonia (NH_3(aq), 25% w/w), and aqueous nitric acid (HNO_3(aq), 60% w/w) were obtained from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Pure water (>18 MΩ cm) was prepared using a Milli-Q system (Elix Advantage 3, Merck Millipore, Darmstadt, Germany).

2.2. Sample preparation

The proposed process using the hydrothermal treatments is summarized in Fig. 1. The process is divided into three major steps (Processes (a), (b), and (c)). Process (a) corresponds to the preparation of the particles coated by the silica/surfactant complexes. The PS particle dispersion was diluted 10 times to obtain a 0.5% w/v PS dispersion (PS(disp, 0.5)). The reaction solution for the sol–gel reaction was prepared by mixing CTAB (50 μmol), H_2O (11 mL), EtOH (4 mL), NH_3(aq) (0.1 mL), and PS(disp, 0.5) (1 mL), followed by stirring using a magnetic stirrer (500 rpm) for 10 min at 30 °C. The resultant concentration of CTAB and the volume fraction of EtOH for the mixture were 3.1 mM and 0.25, respectively [49]. Next, TEOS (50 μL) was added to the mixture to initiate the sol–gel reaction, and the reaction solution was stirred for an additional 2 h at 30 °C. Finally, the reaction solution was centrifuged and then washed with H_2O (Fig. 1) to separate the PS particles coated with silica/surfactant complexes from any excess reagents and by-products (small particles consisting of the silica/surfactant complex without the PS core).

In Process (b), the coated particles were redispersed in the dispersion medium (1 mL) in a Teflon-lined stainless steel autoclave (max. temperature: 150 °C; max. pressure: 5.0 MPa, Model F-1029, FLON INDUSTRY, Tokyo, Japan), and hydrothermal treatment at 100 °C was performed for 48 h (1st HT) to rigidify the silica framework of silica/surfactant complexes. Two different dispersion media (Fig. 1, with and without CTAB) and three different heating and cooling patterns (Fig. 1, Patterns A, B, and C) were investigated. The heating and cooling patterns applied using a constant temperature oven (DKM300, Yamato Scientific Co., Ltd., Tokyo, Japan) are indicated in Fig. 2. After the 1st HT, the dispersion was again centrifuged and washed with H_2O as shown in Fig. 1 to remove any remaining excess reagents and by-products to afford a 1 mL of dispersion of PS particles coated with silica/surfactant complexes.

The resultant dispersion of the coated particles (1 mL) was transferred again to the Teflon-lined stainless steel autoclave. After addition of HNO_3(aq) (0.3 mL), the 2nd HT was performed for 24 h (Process (c) in Fig. 1). Two different conditions were investigated for this step (Fig. 2): 100 °C with heating and cooling pattern B and 80 °C with pattern D. After HT, the dispersion was washed with H_2O to remove nitric acid and by-products. H_2O was then added to adjust the total volume of the aqueous dispersion of MSHCs to 1 mL.

After optimization of the above conditions, further refinement of the hydrothermal treatment steps was achieved using a thermostated oven equipped with a program controller (FP93, Shimaden Co., Ltd, Tokyo, Japan) to vary the temperature at constant heating and cooling rates (not stepwise as shown in Fig. 2).

To compare the capsule yields obtained with the new and previous methods, the MSHCs were also synthesized via the previous method using the same PS templates. Details of the procedure can be found in Fig. S1 in the Supplementary Information (SI). In brief, the sol–gel reaction was performed under the same conditions as described above. After washing with H_2O, the dispersion medium was replaced with EtOH, and the dispersion of the coated PS particles was transferred to a crucible. The EtOH was evaporated, and then the coated PS particles were calcined at 550 °C for 6 h in a muffle furnace (KDF S70, DENKEN-HIGHDENTAL Co., Ltd., Kyoto, Japan). The furnace was heated at a rate of 1 °C/min, and after calcination, it was cooled naturally. During calcination, further gelation of the silica framework and decomposition of the organic templates were achieved. The fused capsules were separated by washing with H_2O, and then 1 mL of an aqueous dispersion of the MSHCs was prepared.

2.3. Characterization

The reaction of Process (a) was made using the 1 mL of PS(disp, 0.5), and the particles or capsules obtained after each process were redispersed in 1 mL of water. The number densities in the resultant dispersions were the same to that of PS(disp, 0.5), if there were no loss of the particles during the processes. These dispersions of particles or capsules (2.5 μL) were placed at the center of a Cu grid