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Hierarchical mesoporous silica microspheres prepared by partitioned cooperative self-assembly process using sodium silicate as precursor and their drug release performance

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ABSTRACT

This work demonstrates that using sodium silicate as precursor, hierarchical mesoporous silica (HMS) microspheres with ordered mesochannels and large intra-particulate mesopores can be prepared by partitioned cooperative self-assembly process based on a P123 templated system. The influence of various experimental parameters on mesostructures and particle morphology was investigated, including the ethanol, addition combinations, interval times, synthesis temperatures and hydrothermal treatment temperatures. Importantly, the crucial role of ethanol in shaping the particle morphology and hierarchical mesostructures was identified. The resultant micro-sized HMS microspheres reveal clew-like feature: the 'yarns' comprise bundles of ordered mesochannels (1st mode mesopores, *ca.* 10–15 nm in sizes), while the 2nd mode intra-particulate pores (*ca.* 20–45 nm in sizes) exist between the intertwined 'yarns'. For example, a representative HMS microsphere prepared under optimized conditions (6-6 h-4Et5@36H140) shows two modes of mesopores, 12.3 nm and 27.7 nm for the 1st and 2nd mode mesopores, respectively. The spherical particle size is around 1.5 μm. Both the regularity of the 1st mode mesostructure templated by the P123 and well-defined 2nd mode mesostructures can be secured when the hydrothermal treatment (HTT) temperature is controlled at 140 °C, while higher HTT temperature at 160 °C disintegrates the 1st mode mesostructures and thus destroy the meso-orderings. In the release performance tests of indomethacin (IMC) in simulated intestinal fluid (SIF), HMS microspheres with high 2nd mode mesoporosity show higher drug release rate than that with low 2nd mode mesoporosity, while two of them both show higher drug release rate than conventional SBA-15 fibers. This work, as we believe, also represents a new strategy to regulate drug releasing performance by simply tuning the hierarchical mesostructures of HMS and can allow flexible design of IMC/meso-silica formulations.

1. Introduction

Mesoporous silica microspheres (MSMs), with high surface area, high pore volumes and spherical particle morphology, have found important applications in adsorption [1–3], chromatographic separations [4–6], controlled delivery [7,8] and catalysis [9,10]. In order to meet the versatile demands on mesostructural and morphological properties, the controllable preparations of MSMs have attracted a great deal of attention [11,12]. Sol-gel processes assisted by different templates have been extensively studied, including some hard-templates or surfactants or both. Nearly all commonly commercial available surfactants, such as Cetyltrimethylammonium bromide (CTAB) [13–15], polyalkoxylene-based nonionic surfactants (P123, F127) [5,6,13–20] and polymer nano/particles [1,21] can serve as template for the preparation of MSMs, allowing the facile tuning of porous structures. For example, based on the self-assembly process, CTAB surfactant can induce the formation of small mesopores less than 5 nm, while the P123 template alone can produce MSMs with larger mesopores than up to 10 nm or even larger. Polymer particles, as hard template, can further enlarge the pore size even beyond the mesoscopic regime [1].

With respect to the silica precursor, tetraethoxysilane (TEOS) [1,4–6,13–20] and sodium silicate (SS) [2,3,21], or its equivalents (derived from other sources like plant bottom ashes [22] and rice husks [23]), are two dominant categories, while the SS received much attention due to its low-cost and has been used to prepare MSMs. Based on SS, some hard-templates [24] and surfactants like CTAB [25,26],

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nonionic surfactants [22,23,27–29] or combined ones [30] have been used to prepare MSMs. For example, Kosuge et al. reported that MSMs can be prepared using SS as precursor from various nonionic surfactants [29]. However, the mesopores are smaller than 5 nm [29]. In particular, P123, a famous nonionic surfactant used for the preparation of SBA-15s with large mesopores, is demonstrated to be NOT suitable for the preparation of MSMs [29]. In fact, in the literature, the preparations of SBA-15 microspheres are still very limited up to now. It is believed that both the strong tendency to form elongated P123 micelles and high acidic synthesis conditions (rapid condensation reaction and thus fast macroscopic phase separation process) employed in the syntheses favor the formation of hexagonally aligned mesochannels, complying with the formation of either platelet or rod or fibrous particles. Only a few works succeeded to prepare spherical SBA-15s using silicon alkoxides as precursors, *e.g.*, *via* sophisticated templating systems [15] or high-pressure CO_2 treatment [13]. And so far, using SS as silica precursor there is still no work on the successful preparation of MSMs with large mesopores using P123 as sole template. On the other hand, the MSMs reported so far, no matter what surfactants used, in most cases show to be monomodal, and the preparation of hierarchical mesoporous silica (HMS) microspheres is still challenging, although the latter ones have shown fast mass transport properties that are important for adsorption [31], catalysis [32–35] and so on [3,36]. There are only very limited reports on the preparation of hierarchical mesoporous silica microspheres based on SS, which resorted to the employment of multi-templates, *e.g.*, CTAB + P123 [37] or specially designed CTAB-templated sol-gel process [3,25]. Therefore, using SS as precursor to prepare either MSMs or even further HMS microspheres is still challenging and yet highly desirable.

Recently, a simple ternary nonionic surfactant templating system (TEOS/P123/HCl(aq.)) was reported to prepare HMS clew-like particles [38] based on the partitioned cooperative self-assembly (PCSA) process [39]. The hierarchical mesoporous structures, with the 1st and 2nd mode intra-particulate mesopores of 7–10 nm and 16–32 nm, respectively, can be facilely obtained without using any additives or complicated procedures. Moreover, the morphologies of resultant HMS silicas particles can be tuned by selecting suitable partition and synthesis conditions (temperature and acidity) [40–42].

In this work, based on the SS as precursor, facile and controllable preparation of HMS microspheres is attempted. It is found that ethanol, though in small amounts, plays a crucial role in inducing the formation of both well-defined spherical particle morphology and hierarchical mesoporous structure. This is the first work showing that the hierarchical mesoporous silica microspheres can be prepared from SS using P123 as sole template. The influence of various synthesis conditions on porous structure and particle morphology was also investigated.

Indomethacin (IMC) is one of the most widely used non-steroidal anti-inflammatory drugs whilst being poorly soluble in water [43]. Interestingly, IMC, once loaded into porous silica, including the mesoporous ones with different pore geometries and pore sizes [44–49], shows improved chemical stability and dissolution property (*in vitro*) [44–54] and oral delivery performance (*in vivo*) [53]. In this work, the influence of hierarchical mesoporous structure on IMC release properties was studied and the possibility of manipulating the IMC release behaviour by tuning hierarchical mesostructures will be unveiled.

2. Experimental

2.1. Chemicals

Concentrated hydrochloric acid (37 wt %, *c*-HCl), absolute ethanol, sodium silicate (SS, AR) was purchased from the Sinopharm Chemical Reagent Co., Ltd. Pluronic $PEO_{20}PPO_{70}PEO_{20}$ (P123 with Mn = 5800) was purchased from Aldrich.

2.2. Preparation of HMS microspheres

Typically, 2.0 g P123 was dissolved in 78.0 g de-ionized (DI) water, 5.0 g ethanol and 13.5 g c-HCl under stirring at 36 °C, to which 6.3 g SS aqueous solution (50 wt%, 1st addition) was added. After 4.0 h, another 4.2 g SS solution (50 wt%, 2nd addition) was added. The synthesis mixture was stirred for 24 h at 36 °C and then transferred to an autoclave for hydrothermal treatment (HTT) at 140 °C for 24 h statically. The product was collected by filtration, washing, drying and final calcination at 550 °C in air for 4 h with heating ramp of 1.5 °C/min. The calcined sample was designated as 6-4 h-4Et5@36H140, where, '6', '4' and '4 h' stand for the mass percentage of SS added in the 1st (60%) and 2nd addition (40%) and the interval time between them, respectively; '@36' denotes the synthesis temperature; 'H140' denotes HTT temperature for a fixed period of 24 h. Other naming can be deduced by analogy.

2.3. Characterization

Small-angle and wide-angle X-ray Diffraction (XRD) patterns were recorded on a Bruker D8 diffractometer using Cu K-alpha radiation. Transmission electron microscopy (TEM) test was performed using a JEOL 2100 F instrument instrument operated at 200 kV. The samples were prepared by dispersing a small amount of powders in ethanol and placing drops of the solution on a carbon-coated copper grid, followed by evaporation. Field emission scanning electron microscopy (FE-SEM) images were recorded using Hitachi Scanning Electron Microscope (S4800). Low operation voltage (2 kV) and low height between detector and sample were used to guarantee quality imaging. Nitrogen adsorption isotherms were measured at −196 °C using Tristar 3020 volumetric adsorption analyzers. The samples were out-gassed for over 2 h at 200 °C before test. The specific surface areas of the samples were calculated using the BET method within the relative pressure (P/P_0) range of 0.04–0.2. The pore size distributions were determined using the BJH method. The calculation of pore volumes from different modes can be found in Ref. [38].

2.4. In vitro drug release study

The mixture of the IMC solution in acetone and silica support with the weight ratio of IMC to support of 1:3 was stirred for 12 h. The silica supported IMC was collected by centrifugation after evaporation and washing with HCl (pH = 1.2) and fully dried in vacuum to remove any solvent. In order to test the IMC loaded into the matrix, the specific amounts of IMC loaded silicas were re-dispersed in 20 ml methanol by sonication for 5 min. The concentration of IMC was measured by UV absorption at wavelength of 320 nm.

Dissolution tests were carried out in buffer solution under stirring. The dissolution medium phosphate buffer (pH ~ 6.8, simulated intestinal fluid, SIF) was prepared by using KH_2PO_4 and NaOH (mixed solution 250 ml 0.2 M KH_2PO_4 and 118 ml 0.2 M NaOH being diluted to 1 L). Dissolution studies were carried out at 37 °C with a paddle speed of 100 rpm. A sample corresponding to 10 mg IMC was introduced to the dissolution medium at zero time. Aliquots (5 ml) of the dissolution medium were withdrawn at interval of 10 min. The drawn out medium was replaced with the same amount of fresh phosphate buffer. All measurements were carried out for three times.

3. Results and discussion

3.1. SS as precursor without using additive

In previous works based on the TEOS, various synthesis parameters associated with the PCSA process have been demonstrated to have great influence on hierarchical mesoporous structures and particle morphologies as well, including the partition conditions (addition