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Facile large-scale preparation of mesoporous silica microspheres with the assistance of sucrose and their drug loading and releasing properties

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ABSTRACT

Mesoporous silica microspheres (MSMs) with a pore-size larger than 10 nm and a large pore-volume have attracted considerable attention for their application in delivering poorly water-soluble drugs. Here we developed a simple method for large-scale synthesis of MSMs using sodium silicate as silica precursor. The novelty of this approach lies in the use of sucrose solution to achieve large size and volume of nanopores. The highest values of pore size and pore volume are 13.2 nm and 1.97 cm^3/g, respectively. Importantly, the method is reliable and easily upscalable. The blank and drug-loaded MSMs were characterized by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). Ibuprofen and resveratrol were successfully loaded into the nanopores of MSMs in amorphous and nanocrystalline form and showed high drug-loadings and enhanced dissolution rates. This kind of MSMs appears to be a promising candidate as a new oral drug delivery vehicle providing a rapid drug release.

1. Introduction

Encapsulation of drug molecules inside mesoporous carriers is an excellent approach to improve the release rate of poorly soluble drugs. The nanopores in mesoporous materials can inhibit drug crystallization and confine the nanoparticles' growth in a rigid manner and afford a large dissolution area, hence the dissolution velocity, saturation solubility and storage stability of the drug are improved. Mesoporous silicon, silica, Al_2O_3, TiO_2, carbon and hydroxycarbonate apatite have been developed for that purpose (Xu et al., 2013), among which, mesoporous silica such as MCM 41 (Charnay et al., 2004) and SBA-15 (Letchmanan et al., 2015; Li et al., 2015) attracted much attentions.

Large nanopores exhibit superiority over smaller ones with regard to the storage, diffusivity, and penetration ability of drugs, especially for large drug molecules or proteins. Unfortunately, the pore diameter of mesoporous silica prepared from silicon alkoxide is usually smaller than 6 nm, unless micelle-clusters (Zhang et al., 2013) or surfactants with longer chains (Niu et al., 2014; Letchmanan et al., 2015; Deng et al., 2013) are used as template or an etching process is attached (Chen et al., 2015). In an effort to replace the costly silicon alkoxides with sodium silicate (water glass, abbreviated as WG), researchers reported the preparation of large pore size mesoporous silica from sodium silicate solutions in the presence of surfactant template (Wang et al., 2015; Kim et al., 2000). However, it is still a challenge to seek out a low-cost and simple route for large scale preparation of mesoporous silica with pore size larger than 10 nm.

In this paper, a template-free emulsification–solidification method was developed to prepare mesoporous silica microspheres (MSMs) using WG as silica precursor. The pore size and pore volume can be enlarged by diluting WG with aqueous sucrose solution (ASS). Furthermore, the drug loading and releasing properties of MSMs were investigated using resveratrol (RESV) and ibuprofen (IBP) as model drugs.

2. Materials and methods

2.1. Materials

WG (with a modulus of 3.3; Na_2O, 8.3%; SiO_2, 26.5%), Span-80 and Tween-80 were purchased from Qingdao Usolf Chemtech

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Co., Ltd. (Qingdao, China). Ibuprofen (98%) was supplied by Wuhan Biocause Pharmaceutiacl Co., Ltd. (Wuhan, China). The commercial trans-RESV (98.9%) was purchased from Tianjin Jianfeng Nature Product R&D Co., Ltd. (Tianjin, China). Other Chemicals such as petroleum ether (boiling range 60–90 °C), sucrose (AR) and ammonium bicarbonate (NH_4HCO_3, AR) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

2.2. Preparation of MSMs

A typical reaction procedure for the preparation of MSMs is described using the following three solutions: water phase-1 (WP-1, 50 g); oil phase (OP, 100 mL), a petroleum ether solution of Span-80 (5%, w/v); water phase-2 (WP-2, 500 mL), an aqueous solution containing NH_4HCO_3 (15.8%, w/v) and Tween-80 (1%, w/v). OP and WP-1 was mixed and emulsified for 2 min using the homogenizer Heidolph DIAX 900 with 26,000 rpm to obtain an emulsion (W/O). The emulsion was then poured into WP-2 and further stirred for 1 h for the formation and aging of MSMs. The precipitate was centrifuged (4000 rpm for 1 min) and rinsed with distilled water and ethanol alternately. Finally, the solid was dried at 100 °C for 12 h. The microspheres' porosity was modified by adding ASS (25%, w/w) into WG. When WG, WG-water (4:6, w/w) and WG-ASS (4:6, w/w) were used as WP-1, respectively, the prepared microspehres were labeled as M_0, M_1 and M_2.

Optical microscopy was used to observe the morphology of MSMs. The hollow structure of some microspheres in sample M_0 was studied by a field emission scanning electron microscope (SEM, Nova Nano SEM 250, FEI Company). Prior to imaging, the micospheres of M_0 were placed between two pieces of cover glass and grinded to small fragments.

2.3. Nitrogen adsorption

The surface area and pore volume of MSMs were studied by determining the nitrogen adsorption and desorption using a Micromeritics 3Flex Surface Characterization Analyzer from Micromeritics Instrument (Shanghai) Ltd. (Shanghai, China). The samples were degassed at 120 °C for 15 min before analysis to remove adsorbed water. The specific surface areas (S_{BET}) were determined according to the Brunauer–Emmett–Teller (BET) method, and the pore size distributions were determined from adsorption branches of isotherms using the BJH method. The total pore volume (V_{pore}) was determined from the amount adsorbed at a relative pressure of 0.99.

2.4. Drug-loading

2.4.1. IBP-loaded MSMs

IBP was dissolved in ethanol to obtain a high concentrated solution (50%, w/w). Then 1 g of MSMs (M_2) was mixed thoroughly with 2.5 mL of IBP solution to obtain a white paste. The paste was transferred into a crystallizing dish, dried at room temperature for 12 h and milled into powder.

2.4.2. RESV-loaded MSMs

RESV-loaded MSMs were prepared by the same procedure as that of IBP. Typically, 2.5 mL solution of RESV in ethanol was mixed thoroughly with 1 g of MSMs (M_2) to obtain a white paste. Respectively, 2% (w/v), 4% (w/v) and 6% (w/v) solutions of RESV were used and the products were labelled as F_1, F_2 and F_3. To improve drug loading of MSMs, 2 mL of 6% solution of RESV was mixed with 1 g of dried F_3 to obtain F_4, 1.5 mL of the same RESV solution was mixed with dried F_4 to obtain F_5 and another 1.5 mL of the RESV solution was mixed with dried F_5 to obtain F_6. The morphological examination of drug-loaded MSMs was performed using polarizing microscope.

2.5. X-ray powder diffraction (XRPD)

The XRPD patterns were recorded on a D8 Advance X-Ray Diffractometer (Bruker-AXS, USA) using CuKα monochromatized radiation at 40 kV, 40 mA. The step scan mode was performed with a step size of 0.02° at a rate of 4°/min.

2.6. Thermal analysis using differential scanning calorimetry (DSC)

DSC experiments were performed on a TA Instruments Q-2000 DSC apparatus over a temperature range of 20–300 °C at a heating rate of 10 °C/min. Measurements were performed under a dry nitrogen atmosphere and an empty pan was used as reference.

2.7. Determination of loading efficiency

The drug loading efficiency of MSMs was determined by adding 50 mg of loaded MSMs in 100 ml ethanol and stirred for 2 h in the dark. The samples were centrifuged at 4000 rpm for 30 min. The supernatant was collected and determined by HPLC-UV method.

The HPLC system was composed of two P230II pumps and a UV-230II detector (Dalian Elite Analytical Instruments Co., Ltd., Dalian, China). A Baseline-C18 (200 × 4.6 mm) analytical column (BaseLine Chromtech Research Centre, Tianjin, China) was used with the mobile phase of 0.1% (v/v) aqueous phosphoric acid-acetonitrile (60:40, for RESV) and of 0.3% (v/v) aqueous phosphoric acid–methanol (20:80, for IBP) at the detection wavelength of 306 nm (for RESV) and of 220 nm (for IBP). The flow rate was 1.0 mL/min at room temperature.

2.8. Dissolution rate study

The dissolution rate experiment was performed according to the Ch.P.2010 Edition Apparatus II (paddle) method (ZRS-8G, Tianda Tianfa Technology Co., Ltd., Tianjin, China). Accurately weighed samples (90 mg) were dispersed in 900 mL dissolution medium (0.5% aqueous solution of Tween 80). The temperature was set to 37 °C, and the stirring rate was kept at 150 rpm. At predetermined times, 5 mL samples were withdrawn and passed through a 0.22 μm syringe filter. The drug concentration was determined by HPLC-UV method (2.7).

3. Results and discussion

3.1. Preparation and characterization of MSMs

MSMs were obtained after drops of WP-1 were transferred from OP to WP-2 (Fujiwara et al., 2004). The optical microscope images reveal the effect of composition of WP-1 on MSMs structure. When undiluted WG were used as WP-1, some hollow MSMs can be distinguished from solid ones due to a clear outline of the sphere (Fig. 1a, indicated by arrows). The coexistence of hollow and solid MSMs was also confirmed by the TEM images (Fig. 2) of partially broken MSMs. However, when WG were diluted with ASS, the optical microscopic images of prepared MSMs (Fig. 1b, c) showed homogeneous structure without macroscopic holes.

The silica particles are spherical in shape before heat drying even when the ratio of WG to ASS decreased to 1:9. However, after heat drying, even the ratio of 3:7 (WG: ASS) could lead to irregular shape (Fig. 1d) of silica. A possible reason is that the solidification of WG in WP-2 is not complete because of excessive ASS, but a further solidification is triggered by heating when sucrose has been removed. The bulk density of MSMs is decreased with the dilution