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Synthesis of novel core-shell structured dual-mesoporous silica nanospheres and their application for enhancing the dissolution rate of poorly water-soluble drugs

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ABSTRACT

Novel core-shell dual-mesoporous silica nanospheres (DMSS) with a tunable pore size were synthesized successfully using a styrene monomer as a channel template for the core and cetyltrimethyl ammonium bromide (CTAB) as a channel template for the shell in order to improve the dissolution rate of poorly water-soluble drugs. Simvastatin was used as a model drug and loaded into DMSS and the mesoporous core without the shell (MSC) by the solvent evaporation method. The drug loading efficiency of DMSS and MSC were determined by thermogravimetric analysis (TGA) and ultraviolet spectroscopy (UV). Characterization, using scanning electron microscopy (SEM), transmission electron microscopy (TEM), nitrogen adsorption, powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR) showed that simvastatin adsorbed in DMSS and MSC was in an amorphous state, and in vitro release test results demonstrated that both DMSS and MSC increased the water solubility and dissolution rate of simvastatin. The shell structure of DMSS was able to regulate the release of simvastatin compared with MSC. It is worth noting that DMSS has significant potential as a carrier for improving the dissolution of poorly water-soluble drugs and reducing the rapid release.

1. Introduction

With the development of nanotechnology, inorganic porous materials, due to their unique advantages, have been the subject of a great deal of scientific research involving pharmaceutical topics, such as biological compatibility, safety, structural versatility and achieving a high adsorption capacity [1–5]. In particular, the mesoporous structure plays a significant role in improving the solubility of poorly water-soluble drugs [6–9]. The mechanism for this involves the fact that the spatial confinement effect of the mesoporous structure can reduce the drug particle size, which is directly related to the drug's solubility and dissolution rate based on the Ostwald–Freundlich equation and the Noyes–Whitney equation. Moreover, the mesoporous structure with a large pore volume is appropriate for drug storage, and can prevent drug molecules from forming highly ordered crystals. Drug adsorbed in the mesoporous structure remains in an amorphous form, which helps increase the solubility of poorly water-soluble drugs. The high specific surface area increases the dispersed state of the drug, and that also improves drug stability. A large number of recent studies about increasing the dissolution rate of poorly water-soluble drugs have focused on mesoporous silica [10–12], mesoporous carbon [13–15] and mesoporous hydroxyapatite [16,17]. The pore size, pore shape, specific surface area, pore volume and material surface chemical groups are all important factors affecting the drug-release rate [18–20]. However, there is no structure that can regulate the release of the drug and avoid rapid release.

In this study, we examined a new method involving the use of a mesoporous shell structure for mesoporous nanospheres aimed at regulating drug release from mesoporous nanospheres. Both mesoporous shell structure and mesoporous core structure absorbed drug. The diffusional resistance of the mesoporous shell structure could delay and regulate drug release from the mesoporous core structure in order to ease the rapid release. Novel core-shell dual-mesoporous silica nanospheres (DMSS) were prepared using a two-step reaction. Firstly, solid silica nanospheres as a core were synthesized in an oil/water phase using styrene monomer as a template [21]. Secondly, the surface of the core was coated with CTAB-silica precursor solution in order to form a shell with a mesoporous structure [22]. Different reaction conditions produced different shell thicknesses, different core sizes and different pore sizes. After calcination, two kinds of structures, the mesoporous core (MSC) and core-shell dual-mesoporous silica nanospheres (DMSS) were obtained. Simvastatin was used for the treatment of hypercholesterolemia by inhibiting HMG-CoA reductase, a typical

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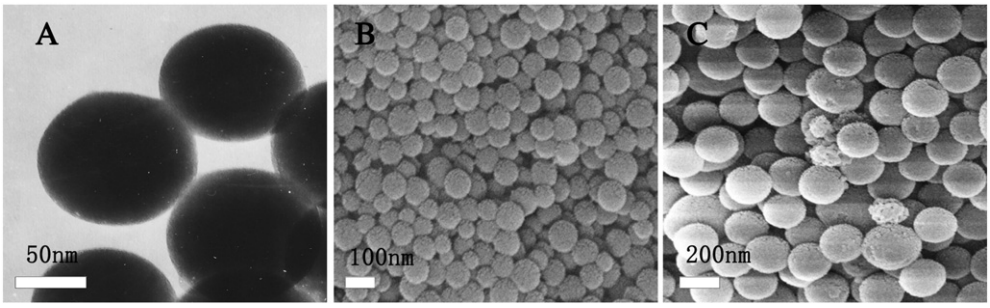

Fig. 1. TEM characterization of the core (A), SEM characterization of MSC (B) and DMSS (C).

Biopharmaceutic Classification System (BCS) class II drug, was chosen as a model drug and loaded into MSC and DMSS. Using their drug release behavior in vitro dissolution experiments, the relationship between carrier architecture and drug release was systematically studied by SEM, TEM, BET, TGA, DSC, XRD and FTIR. Finally, we discuss whether the shell structure of DMSS was superior to MSC in terms of drug release.

2. Materials and methods

2.1. Chemicals and materials

Tetraethylorthosilicate (TEOS), octane, hexadecyl trimethyl ammonium bromide (CTAB), styrene monomer, lauryl sodium sulfate (SDS) and anhydrous ethanol were purchased from the Jin Zhou Xing Bei reagent company. 2,2′-azobis [2-methylpropionamidine] dihydrochloride (AIBA) and L-lysine were purchased from Aldrich (USA). Simvastatin was supplied by the Wu Han Xin Jia Lin company with a purity of >99%.

2.2. Preparation of MSC and DMSS

Step 1. CTAB and water formed the water phase. Octane, used as the oil phase, was added to the water phase, and then styrene monomer, lysine, TEOS and AIBA were successively added to the oil-in-water emulsion at 60 °C under a N_2 atmosphere. The mass ratio of H_2O/TEOS/L-lysine/CTAB was 310:10:0.22:1. Styrene monomer (0.39–55 mg/ml) and AIBA (0.84 mg/ml) were able to control the pore size at 5–16 nm. After 3 h, the reaction was stopped and the suspension kept at room temperature for 12 h. Then, liquid was removed by filtration and the filtered particles from the core were dried at 50 °C [21].

Step 2. CTAB, water and anhydrous ethanol (0.15:30:13) were mixed and allowed to dissolve at room temperature. The core, ammonium hydroxide and TEOS were subsequently added to the solution under stirring. The reaction was allowed to continue for 6 h and then the particles were dried at 50 °C after centrifugation. The two kinds of particles obtained as described above were calcined at 500 °C to remove the templates completely. The obtained MSC and DMSS were then stored in a dryer.

2.3. Drug loading

Simvastatin, a BCS class II representative drug (solubility, 0.0004 mg/ml), was selected as a model drug. Absolute ethyl alcohol was chosen as the drug solvent because simvastatin was very soluble in it. Drug loading was carried out using the solvent evaporation method [23,24]. MSC and DMSS in an optimal mass ratio of 1/1, 1/2 and 1/3 were, respectively, mixed with simvastatin and stirred at room temperature until the absolute ethyl alcohol had volatilized completely. The dried composite samples were referred to as MSC-S (1/1, 1/2 and 1/3) and DMSS-S (1/1, 1/2 and 1/3). The loading capacity of MSC-S and DMSS-S was determined by TGA characterization and UV spectrophotometry.

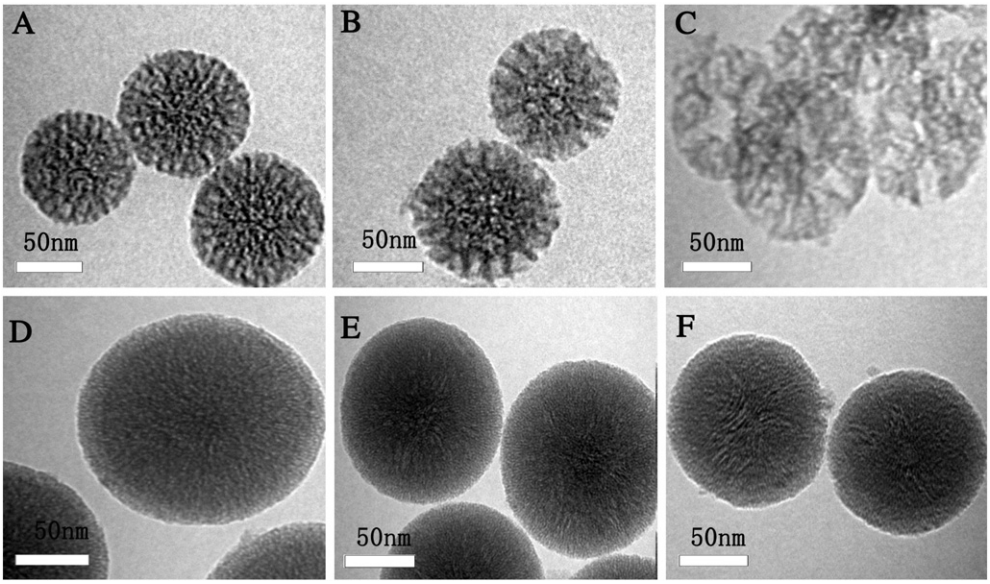

Fig. 2. TEM characterization of MSC with 5 nm pores (A), 10 nm pores (B), and 16 nm pores (C) and the corresponding DMSS (D, E, F) with a 20-nm-thick shell.