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

Chao Wu a, Xiaohu Sun b, Zongzhe Zhao a, Ying Zhao a, Yanna Hao a, Ying Liu a, Yu Gao c,⁎

a Department of Pharmaceutics, Liaoning Medical University, 40 Songpo Road, Linghe District, Jinzhou, Liaoning Province 121001, China
b Management Center for Experiments, Bohai University, 19 Keji Road, Songshan District, Jinhua, Liaoning Province 121000, China
c Department of Medical Oncology, First Affiliated Hospital of Liaoning Medical University, 40 Songpo Road, Linghe District, Jinzhou, Liaoning Province 121001, China

ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 30 July 2014
Accepted 13 August 2014
Available online 21 August 2004

Keywords:
Core-shell dual-mesoporous silica nanosphere (DMSS)
Simvastatin
Poorly water-soluble drugs

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.

© 2014 Elsevier B.V. All rights reserved.

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 remains in an amorphous form, which helps increase the solubility of poorly water-soluble drugs. 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 diffusion 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

http://dx.doi.org/10.1016/j.msec.2014.08.040
0928-4931/© 2014 Elsevier B.V. All rights reserved.
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 N2 atmosphere. The mass ratio of H2O/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. 1. TEM characterization of the core (A), SEM characterization of MSC (B) and DMSS (C).

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.
2.4. SEM and TEM characterization

The morphology of MSC and DMSS were examined by using a field emission scanning electron microscope at an accelerating voltage of 20 kV (JEOL JSM-7001 F). Prior to examination, a thin layer of gold was sputtered under vacuum onto the samples. TEM (Tecnai G2F30, FEI, USA) was used to characterize the structural features of MSC and DMSS.

2.5. Particle size analysis

Particle size analysis of the MSC and DMSS was performed by laser diffraction using a Coulter LS 230 instrument (Beckmann-Coulter Electronics, Krefeld, USA). The determination of volume-weighted particle size distribution was over the size range 0.040 to 2000 μm particle size distribution.

2.6. Nitrogen adsorption/desorption analysis

The pore characteristics of MSC and DMSS were determined by nitrogen adsorption using a surface area and pore size analyzer (Beckman Coulter, USA). Using the nitrogen adsorption data, the Brunauer–Emmet–Teller (BET-SSA) and the Barrett–Joiner–Halenda (BJH) method was used to calculate the specific surface area and pore diameter distribution of MSC and DMSS.

2.7. Thermal characterization

DSC analysis of the samples was carried out using a DSC-60 differential scanning calorimeter (Shimadzu, Japan) with a scanning speed of 10 °C/min. TGA analyses were performed using a TGA-50 instrument (Shimadzu, Japan) with a heating rate of 10 °C/min under a nitrogen stream (40 ml/min).

2.8. XRD characterization

XRD was performed using a Rigaku Geigerflex XRD with Cu-Kα radiation (λ = 1.54 Å). The angular range was recorded from 5° (2θ) to 60° with a scan speed of 0.5°/min and a step size of 0.02°.

2.9. FTIR characterization

FTIR characterization of the samples was carried out using an FTIR spectrometer (Bruker IFS 55, Switzerland). The KBr pressed-disk technique was used and the spectra were recorded from 400 to 4000 cm⁻¹.

2.10. In vitro dissolution studies

Dissolution studies were conducted using a method involving USP dissolution apparatus type II (RC-8D, Tianjin Guoming Medical Equipment Co., Ltd.). The dissolution medium was 900 ml phosphate buffer (pH 6.8) containing 0.2% SDS maintained at a temperature of 37 ± 0.5 °C and stirred at 100 rpm. SDS can improve the solubility of poorly water-soluble drugs in the dissolution medium in order to meet the sink conditions. Samples equivalent to 10 mg of simvastatin were placed in dissolution vessels and 5 ml of dissolution medium was removed at specified times (5, 10, 15, 20, 30 and 45 min). This was replaced by the addition of an equal volume of fresh release medium to the dissolution cup. Ultraviolet spectrophotometry (UV-2000, USA) was used to determine the simvastatin content at 238 nm [25].

3. Results and discussion

3.1. Preparation and characterization of DMSS

In this study, the solid core (Fig. 1A, TEM image) was synthesized in an O/W phase with styrene monomer as a template. MSC was obtained after calcination. The SEM images in Fig. 1B,C showed that the particle size of MSC and DMSS was 100 and 200 nm, respectively. One major advantage of this preparation method was that the pore size (5–16 nm) of the core in DMSS could be easily controlled by adding different amounts (0.4–0.6 mg/ml) of styrene monomer [21]. The pore size change of MSC reflected the pore size change in the DMSS core. As seen in Fig. 2A, B and C, the TEM images clearly showed that MSC had a nanometer-sized porous structure with a pore size of 5, 10 and 16 nm, respectively. The mesoporous diameter (2 nm–50 nm) effectively limited the drug crystallinity [26,27]. A change in pore size in the mesoporous range would not be able to improve the solubility of poorly water-soluble drugs, but a smaller pore size and longer channels could delay drug release. Therefore, the core with a pore size of 5 nm was selected as a carrier model. DMSS with a uniform particle size was constructed by coating the CTAB–silica precursor solution onto the core surface. As shown in Figs. 3A, B, C and 4, the thickness of the shell could be adjusted by the
reaction time, although a maximum thickness of 50 nm was achieved at 6 h and this did not increase after an extended reaction time. After 6 h, adding TEOS made the reaction continue for 1 h under the constant reaction condition. It was found that the particle size of the product was not uniform and a large number of small particles arose as by-products. The particle size of DMSS did not increase. This meant that the change of the amount of TEOS did not affect the thickness of the shell. In Fig. 2D, E and F, a 20 nm shell with a porous connected structure was added to the surface of MSC (Fig. 2A, B and C). The greater the mesoporous shell thickness, the stronger the regulating effect on the release of drug absorbed in the mesoporous core structure. DMSS with maximum shell thickness was selected as a carrier model. Due to the low diffusional resistance of the shell structure, it promoted the dissolution of drug absorbed in the shell. The release of drug absorbed in the core was delayed on account of the channel resistance effect of the shell. This was able to overcome the rapid release.

3.2. \(N_2\) adsorption/desorption studies

As shown in Fig. 5A, the \(N_2\) adsorption–desorption isotherms of MSC and DMSS resembled a type IV isotherm [28]. Compared with MSC in Fig. 5B, it indicated DMSS with a dual-mesoporous distribution had a core-shell structure. The BET-specific surface area (\(S_{\text{BET}}\)), the total pore volume (\(V_t\)) and the BJH pore diameter (\(W_{\text{BET}}\)) of the core, MSC, MSC-S, DMSS and DMSS-S, before and after drug loading, are presented in Table 1. It was confirmed that the core with a small \(S_{\text{BET}}\) (40 m\(^2\)/g) was solid. MSC and DMSS possessed a higher \(S_{\text{BET}}\) and \(V_t\), \(W_{\text{BET}}\) (943 m\(^2\)/g and \(V_t\) (1.325 ml/g) of DMSS were greater than that of MSC (\(S_{\text{BET}}, 521 \text{ m}^2/\text{g}; V_t, 0.907 \text{ ml/g}\)). DMSS had a promising potential as a reservoir for storing more drug and regulating drug release. Furthermore, the \(S_{\text{BET}}\) and \(V_t\) of MSC and DMSS appeared to be reduced after loading simvastatin, confirming that simvastatin was incorporated into the pore channels.

3.3. Estimation of simvastatin adsorption efficiency from UV and TGA analysis

The amount of simvastatin absorbed in MSC and DMSS could be quantified by TGA. As shown in Fig. 6, the loading efficiency was estimated from the ratio of the weight loss. The weight loss of MSC-S (1/2) and DMSS-S (1/2) was 33.52% and 37.18%, respectively (Table 1). Moreover, the loading efficiency obtained by UV was consistent with that obtained by TGA after conversion of the drug amount. As seen in Table 1, the entrapment efficiency of MSC and DMSS was 34.26% and 35.39%, respectively. Because the drug-loading ratio was the same, MSC and DMSS had a similar loading efficiency. However, because DMSS had a larger specific surface area, it had a better dispersion than MSC. These results suggest that MSC and DMSS have a good drug adsorption capacity.

3.4. XRPD and DSC characterization

The XRPD patterns of the samples were able to show whether a crystalline simvastatin phase was present. As shown in Fig. 7, the characteristic peak of raw simvastatin was 8.4° and, for the physical mixture, the peak at 8.4° was attributed to raw simvastatin. In contrast, no crystalline simvastatin was detected in MSC-S (1/2, 1/3) and DMSS-S (1/1, 1/2 and 1/3) compared with the physical mixture with the same ratio. It is well known that the absence of distinctive peaks indicates that the simvastatin loaded into MSC and DMSS is in an amorphous state and this is the critical factor for improved dissolution [29]. MSC-S (1/1) had a lower intensity than the physical mixture with the same ratio. This showed that the crystallization of simvastatin was reduced by the adsorption of MSC, although simvastatin was not completely absorbed. The remaining simvastatin was still in a crystalline state.

The DSC results further confirmed the conclusions of the XRPD characterization. As shown in Fig. 8, the DSC curve of simvastatin exhibited a single endothermic peak at 178 °C (intrinsic melting point). However, no simvastatin melting peak was identified in the DSC curves of MSC-S (1/2, 1/3) and DMSS-S (1/1, 1/2 and 1/3). In contrast, the melting peak of the physical mixture with the same ratio was observed at 178 °C. The absence of phase transitions confirmed that simvastatin absorbed in MSC and DMSS was in an amorphous state. This result

Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>(S_{\text{BET}}) (m(^2)/g)</th>
<th>(W_{\text{BET}}) (nm)</th>
<th>(V_t) (ml/g)</th>
<th>TG (%)</th>
<th>LE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The core</td>
<td>39.8</td>
<td></td>
<td>0.221</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MSC</td>
<td>521.5</td>
<td>5</td>
<td>0.907</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DMSS</td>
<td>942.7</td>
<td>2-8</td>
<td>1.325</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MSC-S</td>
<td>121.4</td>
<td>2</td>
<td>0.132</td>
<td>33.52</td>
<td>34.26</td>
</tr>
<tr>
<td>DMSS-S</td>
<td>237.8</td>
<td>2-3</td>
<td>0.249</td>
<td>37.18</td>
<td>35.39</td>
</tr>
</tbody>
</table>

\(S_{\text{BET}}\), Brunauer–Emmet–Teller specific surface area.
\(W_{\text{BET}}\), Barrett–Joiner–Halenda pore diameter.
\(V_t\), total pore volume.
TG, the weight loss of simvastatin inside MCS-S and DMSS-S.
LE, load efficiency of MCS and DMSS.

Fig. 6. TGA of MSC, DMSS, MSC-S and DMSS-S.
indicated a change in the crystallinity of simvastatin absorbed in MSC and DMSS. The spatial confinement of the mesoporous structure in MSC and DMSS effectively inhibited simvastatin crystallinity allowing simvastatin to remain in an amorphous form to increase the solubility of simvastatin. MSC-S (1/1) had a lower intensity, which further confirmed that part of the simvastatin remained in a crystalline state. DMSS (1/1) had stronger dispersive capacity in comparison with MSC (1/1).

3.5. Fourier-transform infrared spectroscopy characterization

FTIR could provide some information about possible intermolecular interactions between simvastatin and the carrier. The IR spectra of pure simvastatin, MSC-S, DMSS-S and the corresponding physical mixtures were presented in Fig. 9. The carbonyl peak of simvastatin was at 1725 cm$^{-1}$. The typical features of MSC-S and DMSS-S in comparison with those of the corresponding physical mixtures indicated no migration of the characteristic peak position. This demonstrated that the absorption of simvastatin in MSC and DMSS was physical. Moreover, the MSC and DMSS FTIR spectra had $\text{−OH}$ stretching peaks at 3000–3700 cm$^{-1}$, which showed that MSC and DMSS had a hydrophilic surface. This hydrophilic surface could be quickly wetted with water so that the simvastatin molecules surrounded with water accelerated the drug dissolution.

3.6. In vitro dissolution

In the present work, the dissolution profile of MSC-S and DMSS-S formulations with different simvastatin/carrier ratios was determined and compared with that of raw simvastatin. The results obtained showed that the use of hydrophilic MSC and DMSS as a vehicle improved the dissolution of simvastatin. As shown in Fig. 10A, for raw simvastatin, 48% of simvastatin dissolved within 45 min, indicating the poor dissolution of raw simvastatin. MSC-S and DMSS-S exhibited a rapid release of 80% within 20 min. However, the dissolution for MSC-S within 5 min was 60% in comparison with 30% for DMSS-S. Clearly, MSC-S had a rapid-release effect. DMSS-S effectively reduced the dissolution rate in the initial stages of dissolution and prevented the rapid release. In addition, the dissolution profiles for MSC-S and DMSS-S formulations with different drug/carrier ratios were compared to investigate the effect of the amount of carrier on the dissolution behavior of simvastatin and to optimize the drug/carrier ratios for dosage. As seen in Fig. 10B and C, upon increasing the amount of MSC and DMSS, the dissolution rate of simvastatin increased. For MSC-S and DMSS-S, the formulation with the highest carrier content (drug/carrier = 1:3) exhibited the fastest dissolution rate (more than 90% dissolution within 20 min). This suggested that both MSC and DMSS could improve the drug dispersibility. Some other factors might contribute to the improved dissolution. Firstly, MSC and DMSS typically possessed nanometer-sized pores and a large specific surface area. Due to the spatial confinement effect, simvastatin molecules do not normally form highly ordered crystals, and remain in an amorphous form. Amorphous simvastatin has a good solubility [29]. Secondly, the hydrophilic surface and interconnected pore networks of MSC and DMSS could promote the wettability and transport of simvastatin, resulting in a fast dissolution. In addition, a large
specific surface area could increase the drug dispersibility and stability, which was also a reason for the increased dissolution. Mesoporous silica (2 nm < pore size < 50 nm) is a carrier for poorly water-soluble drugs and it has been widely used for obtaining fast drug release, such as SBA15 and MCM41 [30]. The pore size range of MSC is 5–16 nm, which allows the drug to remain in an amorphous state and improve the drug dissolution rate. However, the rapid-release effect is an unavoidable problem. In contrast, both the mesoporous core and the mesoporous shell in DMSS were filled with simvastatin. The simvastatin in the mesoporous shell was released at first, followed by the simvastatin in the mesoporous core. Due to the delaying effect of the mesoporous shell in the drug dissolution process, DMSS markedly slowed down the drug dissolution in the initial stage of drug release in contrast with MSC. This suggested that DMSS had the ability to overcome the rapid release.

4. Conclusions

In this study, both MSC and DMSS possessed a high specific surface area, porous structure and high pore volume for improving the dissolution rate of poorly water-soluble drugs. According to the TEM, BET, XRD, DSC and FTIR characterization, simvastatin adsorbed in MSC and DMSS was in an amorphous state and the in vitro drug dissolution results showed that both MSC and DMSS accelerated the release of simvastatin in comparison with pure simvastatin. The findings obtained in this study demonstrate the significant potential of MSC and DMSS for use as a novel delivery system for poorly water-soluble drugs. Moreover, DMSS can effectively regulate drug dissolution and overcome the rapid release. The core-shell structured DMSS has a number of obvious advantages as an alternative to other carriers currently used to improve the solubility of poorly water-soluble drugs in BCS (class 2).

Acknowledgments

This work was supported by the National Natural Science Foundation of China (no. 81302707), Natural Science Foundation of Liaoning Province (no. 2013022052) and the Construction of Clinical Cardiovascular System Drug Evaluation Research Technology platform (no. 2012ZX09303016-002).

References