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Exploitation of 3D face-centered cubic mesoporous silica as a carrier for a poorly water soluble drug: Influence of pore size on release rate

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ABSTRACT

The purposes of the present work were to explore the potential application of 3D face-centered cubic mesoporous silica (FMS) with pore size of 16.0 nm as a delivery system for poorly soluble drugs and investigate the effect of pore size on the dissolution rate. FMS with different pore sizes (16.0, 6.9 and 3.7 nm) was successfully synthesized by using Pluronic block co-polymer F127 as a template and adjusting the reaction temperatures. Celecoxib (CEL), which is a BCS class II drug, was used as a model drug and loaded into FMS with different pore sizes by the solvent deposition method at a drug–silica ratio of 1:4. Characterization using scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transformation infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), nitrogen adsorption, X-ray diffraction (XRD), and differential scanning calorimetry (DSC) was used to systematically investigate the drug loading process.
The results obtained showed that CEL was in a non-crystalline state after incorporation of CEL into the pores of FMS-15 with pore size of 16.0 nm. In vitro dissolution was carried out to demonstrate the effects of FMS with different pore sizes on the release of CEL. The results obtained indicated that the dissolution rate of CEL from FMS-15 was significantly enhanced compared with pure CEL. This could be explained by supposing that CEL encountered less diffusion resistance and its crystallinity decreased due to the large pore size of 16.0 nm and the nanopore channels of FMS-15. Moreover, drug loading and pore size both play an important role in enhancing the dissolution properties for the poorly water-soluble drugs. As the pore size between 3.7 and 16.0 nm increased, the dissolution rate of CEL from FMS gradually increased.

1. Introduction

In recent years, the emergence of inorganic porous materials (such as porous silica, porous carbon, and composites) has opened up a new path for the development of drug delivery systems [1–5]. Compared with traditional pharmaceutical carriers, such as liposomes and polymer nanoparticles, inorganic carriers offer considerable advantages because of their pore structure, particle size, shape control, stability and surface functionalization [6–8]. Among these mesoporous materials, mesoporous silica offering different pore structures, a large pore size and pore volume, and high thermal and hydrothermal stability has been shown to be suitable for use as a drug delivery system [9,10]. There have been several studies of delivery systems involving mesoporous silica with 3D cubic, 2D hexagonal and 1D pore channel structures [11–13]. The 3D cubic mesoporous silica has several interesting features: including a large pore volume, interconnected pore channels, accessibility of pores from any direction, and a regular pore shape [14,15]. It has been reported that the potential advantages of 3D cubic mesoporous silica in the control of drug release are superior to those of 2D hexagonal and 1D mesoporous silica [16]. The above-mentioned advantages suggest that 3D cubic mesoporous silica is a very promising material for use as drug delivery system.

Among the many factors that will play a role, the pore size is especially important for 3D cubic mesoporous silica together with its pore structure [17–19]. As far as we know, only two papers have been published using 3D cubic mesoporous silica as a drug delivery system for carbamazepine, oxcarbazepine, and carvedilol [16,20]. However, we were surprised that the pore sizes of the 3D cubic mesoporous silica reported in these studies were all lower than 10 nm. So, there were no studies of 3D cubic mesoporous silica with pore size (>10 nm). To address this problem, we need a systematic study to explore the ability of 3D cubic mesoporous silica with pore size (>10 nm) to improve the dissolution rate of poorly water-soluble drugs.

In recent years, 3D cubic mesoporous silica with different pore morphologies has been synthesized, such as face-centered cubic mesoporous silica and body-centered cubic mesoporous silica [21,22]. However, although face-centered cubic mesoporous silica had recently been synthesized, it had not been studied as a drug delivery system. Face-centered cubic mesoporous silica possesses a highly ordered face-centered cubic (space group Fm3m) mesostructure, which has a cubic unit cell with atoms located at each of the corners and the centers

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of all the cube faces [23]. In view of its advantages, we carried out a systematic study of face-centered cubic mesoporous silica as a drug delivery system. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is mainly used for the treatment of rheumatoid arthritis and acute pain [24,25]. Several studies have explored its application in the prophylactic treatment of tumors [26,27] and CEL is now seen as a promising drug for the treatment cancer diseases due to its potential application and, so, it was used as a model drug because of its poor water solubility. Mesoporous silica has been used in pharmaceutical applications as a drug carrier and its safety after oral administration is well known [28,29].

In the light of the above considerations, the purposes of our study were to evaluate the suitability of face-centered cubic (Fm3m) mesoporous silica (FMS) with pore size (>10 nm) as a carrier for CEL (a poorly water-soluble drug) and investigate the effect of its pore size on drug release. Face-centered cubic (Fm3m) mesoporous silica with pore size (16 nm) was successfully synthesized using a low temperature method with Pluronic block co-polymer F127 as a template, TEOS as a silica source and TMB as a pore enlargement agent. Notably, the synthetic process was simplified because the method involved modification of only one factor (temperature). The pore size of FMS was successfully enlarged to 16.0 nm by lowering the temperature and it could be easily regulated by controlling the synthesis temperature of the new method. This not only helped to explore its applications involving large pores, but also helped to investigate the effect of the pore size on the release properties of FMS. CEL was incorporated into FMS with different pore sizes by the solvent deposition method at a selected drug–silica ratio (1:4). The corresponding samples were characterized by TEM, FT-IR, TGA, BET, DSC and XRD investigations. The release behavior of CEL from FMS with different pore sizes was compared.

2. Materials and methods

2.1. Materials

Pluronic block co-polymer F127 was kindly donated by BASF. Tetraethyl orthosilicate (TEOS), hydrochloric acid and potassium chloride were purchased from Yu Wang Reagent Company (Shandong, China). 1,3,5-trimethylbenzene (TMB) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Celecoxib (purity >99.0%) was kindly supplied from Shenyang Funing Pharmaceutical Co., Ltd. All other chemicals were used in accordance with the requirements of analytical/spectroscopic/HPLC grade. Deionized water in all experiments was prepared by ion exchange.

2.2. Synthesis of FMS

For the synthesis of 3D face-centered cubic mesoporous silica (FMS) with different pore sizes, 1.25 g of KCl and 0.5 g of F127 were mixed under gently stirring in 30.0 mL of HCl (2.0 M) at three different reaction temperatures (15, 18 and 20 °C), followed by the addition of 0.5 g of TMB under stirring. After 1 h of stirring, 2.0 g of TEOS was added drop by drop to the obtained solution under vigorous stirring. After another 24 h of stirring, the obtained suspension was homogenized by an ATS AH110D homogenizer (ATS Engineer Inc., Shanghai, China). Then, the mixture was placed into a Teflon-lined autoclave and carried out by hydrothermal reaction for 24 h at 130 °C which corresponds to the reaction temperature. The obtained mixture was filtered and dried at 60 °C in the air. The as-synthesized mesoporous silica was filtered and burn out at 600 °C for 5 h to remove surfactant completely. Finally, face-centered cubic mesoporous silica (FMS-15, FMS-18 and FMS-20) by controlling the different action temperatures (15, 18 and 20 °C), was obtained until the powers were dried at 60 °C for 48 h.

2.3. Drug loading procedure

CEL was respectively loaded into FMS samples (FMS-15, FMS-18 and FMS-20) by a solvent deposition method, which involved soaking equilibrium and solvent evaporation. In detail, CEL was dissolved in methanol to get a homogeneous solution (10 mg/mL), and then obtained solution was mixed with a selected amount of FMS samples to obtain a mixture at a certain proportion (1:4) (note: safer solvent such as ethanol can be used instead of methanol). Then, the mixture was brought to adsorption equilibrium under gently stirring for 24 h at room temperature in a closed container. Finally, the solvent was allowed to evaporate under gently stirring and then the precipitated powder was washed with ethanol to remove the drugs on the surface of carrier. The obtained powder was dried at 40 °C in air until no organic solvent residue was left. The drug-loaded samples were labeled FMSC-15, FMSC-18 and FMSC-20, respectively.

2.4. Analysis of drug content

Thermogravimetric analysis (TGA) was performed by a TGA-50 instrument (Shimadzu, Japan) at a heating rate of 10 °C/min under a nitrogen purge of 40 mL/min. The following equation was used to calculate the drug-loading rate. Drug-loading rate = weight of CEL in sample / weight of carrier in sample. All the drug content of samples was within 20 ± 5% of the theoretical value.

2.5. Characterization techniques

2.5.1. SEM study

The morphology of the samples was characterized using a field emission scanning electron microscope (JEOL-6700, Japan).

2.5.2. TEM study

The mesoporous structure of the samples was characterized using TEM (Tecnai G2 20, FEI, USA).

2.5.3. FT-IR study

The functional groups and chemical bonding of samples were characterized using an FT-IR spectrometer (Bruker IFS 55, Switzerland). The scanning range of FT-IR spectroscopy was in the range of 400–4000 cm^{-1}.

2.5.4. Nitrogen adsorption analysis

Adsorption–desorption measurements were conducted on a surface area analyzer (SA3100, Beckman Coulter, USA). The carriers were degassed at 120 °C for 12 h, and the CEL-loaded samples were degassed at 50 °C for 24 h to remove physically adsorbed water before analysis. The BET (Brunauer–Emmett–Teller) method and BJH (Barrett–Joyner–Halenda) method were used to investigate the pore characteristics.

2.5.5. XRD and DSC analysis

The crystalline characteristics of samples were described using X-ray diffractometer (PW3040/60 PANALYII CALB.V Netherlands). XRD patterns were obtained from 5° to 50° with a scan rate of 5°/min and a step size of 0.02°. DSC profiles of the samples were recorded from a DSC instrument (TA Instruments, Q1000, USA). The temperature range was 50–200 °C at a heating rate of 10 °C/min.

2.6. In vitro release profile study

Dissolution studies were carried out using a USP II paddle method with a KC-8D dissolution instrument (KC-8D, Tianjin Guoming Medical Equipment Co., Ltd.). The dissolution media was phosphate buffer (pH 6.9). The dissolution procedure was as follows, dissolution media (900 mL) in basket was kept at 37 °C. The 200 mg samples (equivalent to 50 mg of CEL) were added with a stirring rate of 100 rpm and