Powder Technology 240 (2013) 48–53

Contents lists available at SciVerse ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Hollow mesoporous silicas as a drug solution delivery system for insoluble drugs

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ARTICLE INFO

Available online 6 July 2012

Keywords:
Hollow mesoporous silica spheres
Carbamazepine
Poorly water-soluble drug
Delivery system
Dissolution

ABSTRACT

Hollow mesoporous silica spheres (HMSS) as a novel drug solution delivery system were developed for oral administration, intending to improve the drug loading capacity and dissolution rate of poorly water-soluble drugs. HMSS with an average diameter of 900 nm and shell thickness of 100 nm were synthesized in a facile route using a soft template. The morphological, structural, and textural properties of HMSS were characterized by scanning electron microscopy, transmission electron microscopy, nitrogen adsorption–desorption measurements, Fourier transform infrared spectroscopy, and X-ray powder diffraction. Carbamazepine, a model drug, was dissolved in PEG 400 and subsequently loaded on HMSS to investigate the release behaviors in vitro. The significant improvement of drug loading and dissolution rate demonstrated that HMSS could provide good reservoirs for drug solutions to enhance the dissolution of poorly water-soluble drugs, and have high potential in future applications for oral delivery of therapeutic drugs.

1. Introduction

Oral route represents the most convenient and usually the safest and least expensive administration for drugs. However, for a poorly water-soluble drug, an oral administration has obvious limitation because the drug must dissolve in gastrointestinal fluids in order to be absorbed into systemic circulation. Namely, dissolution in gastrointestinal fluids is the rate-limiting step for the absorption of poorly water-soluble drugs. It is known nearly 40% of new chemical entities are poorly water-soluble or insoluble. So, developing strategies to improve the water solubility and dissolution rate of drugs is one of the crucial tasks for pharmaceutical scientists worldwide.

Various formulation strategies have been developed to increase dissolution rate, and among them preparation of drug solutions in non-toxic and non-volatile hydrophilic fluids was a relatively simple formulation. However, compared with solid dosage forms, the liquid dosage forms are not conventional to handle and additionally not suitable for controlled release through film coating [1]. An alternative has been well studied by adsorbing drug solutions onto carriers with a large surface area, such as silica or cross-linked polyvinylpyrrolidone, to produce solid solutions or liquisolids [2–6]. These solid dosage forms displayed enhancement in drug release properties and bioavailability because the wetting properties and the surface of drug available for dissolution were significantly improved with the aid of adsorbent carriers [7–11]. Indeed, this technique was especially successful for low dose poorly water-soluble drugs [12–14]. However, high drug loading is still a challenge, and few research reported novel materials as adsorbent carriers to improve drug loading. In the present study, hollow mesoporous silica spheres (HMSS) were synthesized as a novel adsorbent carrier for drug solution to achieve a substantial increase of drug loading. The drug loading process was schematically shown in Fig. 1.

Hollow mesoporous silica, which has a hollow core and a shell with mesopores, combines the characteristics of both macroporous and mesoporous structures in one single unit. The hollow core can act as a storage reservoir or a micro-reactor, whereas the mesoporous shell provides pathways for encapsulated substances or substantial surface area for reactions. Hollow mesoporous silica has shown great potential in many fields, for example, as drug carrier, sorbent, or sensor in biotechnology, catalysis, and separation. A variety of methods have been reported to synthesize hollow mesoporous silicas [15–21]. On the basis of the templates for the formation of hollow interiors, these methods can be generally divided into two categories: hard template method and soft template method. However, these reported synthesis processes were complicated and the pore size of hollow mesoporous silica (<4 nm) was too small for adsorption of drug molecules.

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doi:10.1016/j.powtec.2012.07.008

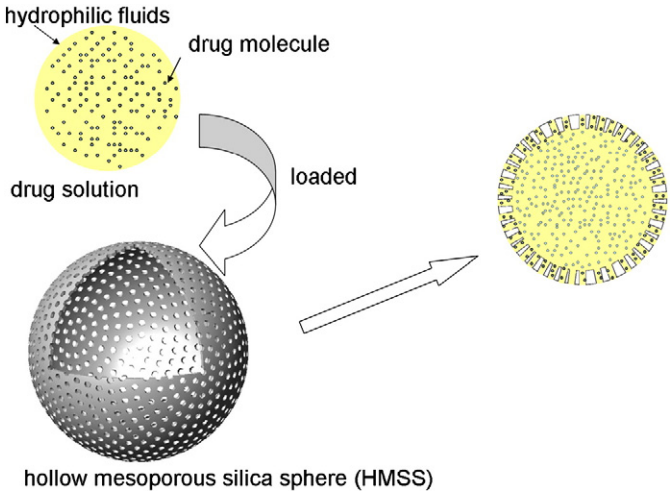

Fig. 1. Schematic representation for loading drug solution onto HMSS.

In the present study, a simple synthesizing process using a soft template method was firstly reported to produce hollow mesoporous silica spheres in monodisperse and uniform size with mesoporous shells and large pore size of 4–8 nm.

Usually poorly water-soluble drugs are dissolved in hydrophilic fluids for adsorption into solid carriers, so the drug loading on carrier materials is dependent on the adsorbing amount of hydrophilic fluids. In this study, PEG 400 was used as a model hydrophilic fluid, and the drug loading capacity of carrier materials could be determined by the adsorbing amount of PEG 400.

Carbamazepine (CBZ), 5H-dibenzazepine-5-carboxamide, was chosen as a model drug due to its poor water solubility, high solubility in PEG 400 and small molecular size. The size of CBZ molecule was less than 1 nm, which was calculated from the density functional theory (DFT) and shown in Fig. 2. According to previous studies [22,23], such small molecules can be loaded into HMSS which have pore size greater than 4 nm.

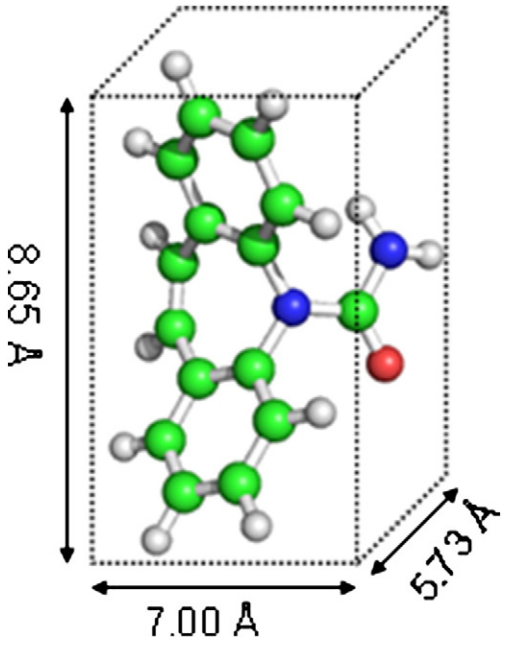

Fig. 2. DFT optimized molecular geometry (B3LYP/6-31G* in GAUSSIAN03) of carbamazepine.

2. Materials and methods

2.1. Materials

Carbamazepine was purchased from Suzhou Hengyi Pharmaceuticals Co. Ltd. (Jiangsu, China). Commercially available fast-release carbamazepine 100 mg tablets were purchased from Guangdong Huanan Pharmacy Ltd. (Guangdong, China). Microsilica was purchased from Huzhou Zhanwang Pharmaceutical Co. Ltd. (Zhejiang, China). HDK®N20P silica (Wacker, Munich, Germany) was kindly donated by Jiefu Trade Co. Ltd. (Guangzhou, China). Standard silica (99.999%) was purchased from Shanghai Reagent Factory (Shanghai, China). PEG 400 was purchased from Sigma-Aldrich (Shanghai, China). Cetyltrimethyl ammonium bromide (CTAB), tetraethoxysilane (TEOS), 1,3,5-trimethylbenzene (TMB), n-heptane and triethanolamine were obtained from Fuchen Chemicals Reagent Factory (Tianjin, China). HPLC grade methanol was obtained from Fisher Scientific (Shanghai, China). Other chemicals were of reagent grade and used without further purification.

2.2. Synthesis of HMSS

HMSS were synthesized by using a soft template method in an oil/water phase. Briefly, 2 g of CTAB was added to 500 mL of deionized water at 60 °C under constant stirring. After the solution became clear, 40 mL of triethanolamine, 20 mL of TMB and 90 mL of n-heptane were added to the solution, and the mixture was stirred at 400 rpm for 1 h. Subsequently, 20 mL of TEOS was added dropwise into the mixture solution under continuous stirring for 2 h. After aging in a sealed container at 60 °C for 24 h without stirring, the mixture solution was filtered to recover the solid. The solid product was washed with water till the filtrate was neutral and then rinsed with ethanol twice before dried overnight at 80 °C. Calcination of the solid product was carried out by slowly increasing temperature from room temperature to 550 °C in 4 h and then maintaining at 550 °C for 6 h. Finally, a pure white and feathery powder, HMSS, was obtained.

2.3. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

A small amount of synthesized HMSS was ultrasonically dispersed in dehydrated ethanol for 5 min. One drop of the HMSS dispersed solution was placed on the surface of a silicon wafer, and after the sample was dry, the coverslip was mounted onto the metal stubs and coated with gold in a sputter coater. The morphology of HMSS was examined by a JSM-6330F model field emission scanning electron microscope (JEOL, Tokyo, Japan).

One drop of the above HMSS dispersed solution was deposited on a carbon-coated copper grid and dried at room temperature for characterizing the porous structure of HMSS using JEM-1400TEM (JEOL, Tokyo, Japan).

2.4. Nitrogen adsorption–desorption measurements

Brunauer–Emmett–Teller (BET) surface area, pore volume and pore diameter distribution of HMSS were measured at −196 °C by ASAP 2020C (Micromeritics, Georgia, USA). Before analysis, the samples were degassed at 300 °C for 3 h. Pore volume was determined from the adsorption branch of nitrogen adsorption–desorption isotherm curve at a relative nitrogen pressure $P/P_0 = 0.97$ signal point. Pore diameter was calculated from the adsorption branch of the isotherms using the Barrett–Joyner–Halenda (BJH) method, and the specific surface area was calculated using the multiple-point Brunauer–Emmett–Teller (BET) method.