Journal of Pharmaceutical and Biomedical Analysis 118 (2016) 267–275

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Preparation of a novel starch-derived three-dimensional ordered macroporous carbon for improving the dissolution rate and oral bioavailability of water-insoluble drugs

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ARTICLE INFO

Article history:
Received 13 June 2015
Received in revised form 31 October 2015
Accepted 3 November 2015
Available online 10 November 2015

Keywords:
Starch
Three-dimensional ordered macroporous carbon
Felodipine
Insoluble drug
Dissolution rate
Relative oral bioavailability

ABSTRACT

In our study, soluble starch was applied as a novel carbon source for preparing three-dimensional ordered macroporous carbon (3DOMC) using monodisperse silica nanospheres as the hard template. The 3DOMC was used as an insoluble drug carrier when it was found that it could markedly improve the water solubility of felodipine (FDP). The structural features of 3DOMC were characterized by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The 3DOMC structure was found to have a higher drug loading than microporous and mesoporous structures, and the interconnected nanostructure effectively inhibited the formation of drug crystals. FDP, belonging to the Biopharmaceutics Classification System II (BCSII), was chosen as the model drug and was loaded into the 3DOMC structure by solvent evaporation. The state of FDP in the 3DOMC structure was characterized by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). The results obtained showed that FDP was present in the pores in an amorphous or microcrystalline state. In vivo and in vitro experiments indicated that 3DOMC could significantly improve the drug dissolution rate, but the FDP-3DOMC self-made common tablets had the disadvantage of a burst effect. For this reason, osmotic pump technology was used to control the drug release rate. We developed a potentially useful insoluble drug carrier for pharmaceutical applications.

1. Introduction

It is a well-known problem that many newly discovered compounds have good biological activity, but their poor water solubility limits their clinical application [1–3]. Improving the water solubility of such poorly soluble drugs poses a great challenge for researchers. Recently, many porous carbon-based materials have been used to improve the water solubility of poorly soluble drugs, such as mesoporous carbon [4–10] and macroporous carbon [11–13]. These materials are mostly synthesized by the template method, but the most critical step is the choice of a suitable carbon source.

Sui et al. used a resorcinol sucrose-derived polymer as a carbon source and prepared ordered and three dimensionally interconnected macroporous carbon with mesoporosity [14] while Lu et al. used furfuryl alcohol as a carbon source [15] and Kim et al. applied a resorcinol formaldehyde-derived polymer as a carbon source [16]. Huang et al. used the dual-template method to synthesize porous carbon where the carbon source was phenol-formaldehyde resins [17], while Xiangjie Bo used sucrose as the carbon source [18] and Hongqiang Wang used resol and phenolic resol containing phosphoric acid (PA) as the carbon source [19,20]. Indeed, after these studies were published, the number of successful procedures for synthesizing porous carbon materials from different templates using a variety of carbon sources, such as CMK-2 (from SBA-1), CMK-3 (from SBA-15) or SNU-2 (from HMS), has rapidly increased [21,22]. However, the carbon source has always been a problem, and the preparation process is both complex and time-consuming.

The template carbonization method has been shown to be useful for the preparation of macroporous carbon materials [23–29] because it can effectively control and maintain the pore structure. Some researchers have prepared three-dimensional ordered mesoporous/macroporous carbon using the template method. For example, Qinfu Zhao used polystyrene (PS) spheres as templates and sucrose as a carbon precursor [30], while Yanzhuo Zhang used mesoporous silica as a template and sucrose as a carbon source [9].

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http://dx.doi.org/10.1016/j.jpba.2015.11.003
0731-7085/

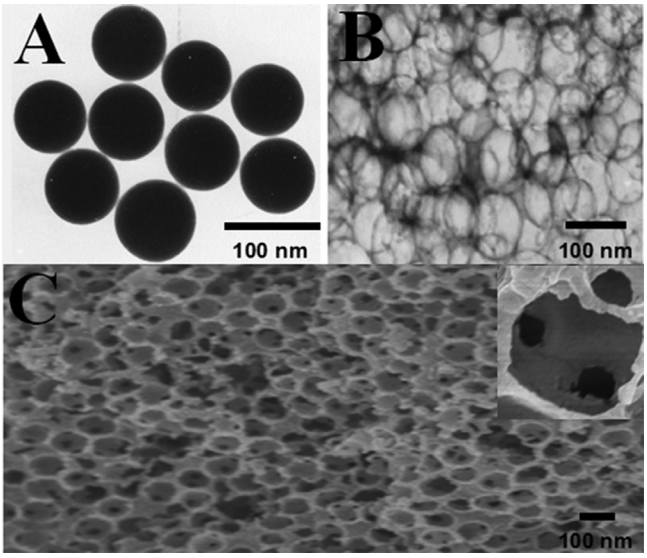

Fig. 1. TEM micrographs (A) of silica nanospheres; TEM micrographs (B) and SEM micrographs (C) of 3DOMC (100 nm).

In this study, soluble starch was used as a carbon source to prepare 3DOMC. This is a novel process that has many outstanding advantages: lack of toxicity, cheapness, good biodegradability and biocompatibility. Furthermore, the production process is simpler and less expensive.

Monodisperse silica nanospheres are closely packed, and the starch solution, as the carbon source, can be used to fill the voids between the silica nanospheres. After carbonization, 3DOMC can be obtained by removing the silica nanospheres and the pore size of the 3DOMC can be regulated. Importantly, 3DOMC displays excellent three-dimensional interconnected ordered channels, and this markedly reduces the resistance of drugs passing through the channels and allows a higher drug loading level than the mesoporous structure. Furthermore, the spatial confinement effect of the macroporous structure (3DOMC) can reduce the drug particle size, which is directly related to the dissolution rate and relative oral bioavailability of the drug, making them promising candidates for solving the solubility problem of poorly water-soluble drugs [31]. FDP, a BCS II drug, was developed by AstraZeneca to treat primary hypertension and chronic stable angina pectoris. Its poor water solubility results in a low dissolution rate and oral bioavailability [32,33]. We initially loaded FDP into 3DOMC to increase the dissolution rate, and then prepared FDP-3DOMC using a Push–Pull osmotic pump (PPOP) to control the release rate. The pharmaceutical performance of FDP-3DOMC self-made common tablets and FDP-3DOMC PPOP were evaluated by comparing them with commercially available FDP common tablets and FDP sustained-release tablets in a series of in vitro dissolution experiments and an in vivo pharmacokinetic study.

2. Materials and methods

2.1. Materials

FDP with a purity >99% was provided by Wuhan Dahua Weiye Pharmaceutical Chemical Co., Ltd. (Wuhan, China). FDP sustained-release tablets were supplied by Hefei Cubic Pharmaceutical Co., Ltd. (Hefei, China). Commercial common FDP tablets were provided by Beijing Union Pharmaceuticals (each containing 5 mg active pharmaceutical ingredient (API)). Soluble starch was obtained from Tianjin Guangfu Fine Chemical Research Institute Co., Ltd. (Tianjin China). Tetraethyl orthosilicate (TEOS) was obtained from Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin China). PEO was obtained from Dow Chemical (Shanghai, China), and cellulose acetate (CA) and PEG 6000 were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Ethanol, KCl, ammonia, chloroform, and hydrofluoric acid (HF) were provided by Tianjin Yong Sheng Fine Chemical Co., Ltd. (Tianjin, China), and all other chemicals used in this study were of analytical/HPLC grade.

Table 1
Compositions of FDP-3DOMC self-made common tablets.

	Ingredients	Formulation
Carrier	FDP-3DOMC	40 mg
Adjuvant	Lactose	40 mg
	PVP	18 mg
	CMC-Na	10 mg
	Magnesium stearate	2 mg

2.2. Preparation of 3DOMC

Step 1, synthesis of silica nanospheres: an appropriate amount of ammonia and TEOS were sequentially added to a mixed solution of ethanol and water with stirring at room temperature. After the completion of the reaction, the suspension was centrifuged at a high speed and then washed three times with anhydrous ethanol followed by deionized water. The obtained sample was our desired hard template, which was dried at 40 °C for 12 h in a vacuum oven (DZF6050, Shang hai boyuan, China).

Step 2: After the silica nanospheres were well dispersed in water, an 8% starch solution was injected as a carbon source into the voids between the closely packed silica nanospheres. The whole system was stirred for 4 h at 100 °C, centrifuged at 7000 rpm/min, and allowed to gel at 4 °C. The gel mixture was dried in a vacuum oven at 35 °C for 12 h and then calcined at 800 °C for 8 h. After this, the obtained samples were soaked in 10% hydrofluoric acid to remove the template. After washing three times with ethanol and drying under vacuum, the 3DOMC was obtained.

2.3. Drug loading

Solvent evaporation was used to load FDP into the pores of the 3DOMC. Firstly, the FDP was completely dissolved in methylene chloride and mixed with different proportions of 3DOMC (1:1, 1:3 and 1:5). The system was slowly stirred for 5 h under protection from light. After complete evaporation of the solvent at room temperature, samples of FDP-3DOMC (1:1, 1:3 and 1:5) were obtained. Finally, the samples were stored in a vacuum desiccator to prevent them from absorbing moisture.

2.4. Characterization of FDP-3DOMC

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

The surface topography of the samples was examined by SEM (JEOL JSM-7001F, operated at 20 kV), and the fine detail of the macroporous structure was obtained by TEM (Tecnai G2F30, FEI, USA, operated at 200 kV).

2.4.2. Solid-state characterization by PXRD and DSC

A powder X-ray diffractometry (PXRD, Rigaku Denki, Japan) was used to examine the change in FDP crystallinity in the 3DOMC. Samples were exposed to Cu-Kα radiation under 30 kV and 30 mA. The step size was 0.02°, the scan speed was 4°/min, and the range (2θ) was 3–60°. A differential scanning calorimeter (DSC-60, Shimadzu, Inc., Japan) was used to record the phase transition temperature or changes in crystallinity of the drug to determine the state of FDP in