Powder Technology 261 (2014) 241–249

Contents lists available at ScienceDirect

Powder Technology

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

Preparation and application of monodispersed mesoporous submicron carbon particles as a drug carrier

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ARTICLE INFO

Article history:
Received 2 January 2014
Received in revised form 7 April 2014
Accepted 10 April 2014
Available online 18 April 2014

Keywords:
Monodisperse
Mesoporous carbon
Drug carrier
Spray drying

ABSTRACT

Monodispersed mesoporous carbon (MMPC) submicron carbon particles have been fabricated by co-spray drying of SBA-15 submicron particles and sucrose, followed by carbonization in a nitrogen environment and removal of the hard SBA-15 template in NaOH solution. The ratio of sucrose/SBA-15 used for the co-spray drying affected the integration and dispersibility of the obtained mesoporous carbon particles and sucrose/SBA-15 ratios at 1.0–1.5 resulted in monodispersed mesoporous carbon submicron particles. The surface properties of MMPC could be modified by treatment in nitric acid solution to create oxygen groups and thus increase wettability of MMPC powder. MMPC particles were used as drug carrier to enhance the dissolution rate of a poorly soluble drug, indomethacin (IDMC) via co-spray drying. The morphology of MMPC was not changed after drug loading as most IDMC molecules were encapsulated into its pore channels in amorphous state, which was characterized by X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Due to the ordered mesoporous structure, the pore walls separate the IDMC particles and prevent recrystallization from happening. The amorphous IDMC/MMPC solid dispersion exhibited excellent stability under stress storage conditions of 40 °C/75% RH for six months. The amorphous formulation contributed to the significantly enhanced dissolution rate of IDMC from solid dispersion.

1. Introduction

Since the discovery of mesoporous silica, many mesoporous materials have been synthesized for various applications involving large molecules or for biomolecular engineering, which was not achieved by using conventional microporous zeolitic materials [1–4]. Among these mesoporous materials, ordered mesoporous carbons with various pore structures have mainly been synthesized by nano-casting technology using appropriate ordered mesoporous silica as hard templates. They have been successfully fabricated and modified for potential applications as catalysts [5–8], adsorbents [9], separation media [10], energy storage [11–15] and advanced electronic materials [16] in many scientific disciplines [17] since Ryoo et al. reported the synthesis of CMK-1 mesoporous carbon [18]. Among the various applications, the utilization of mesoporous carbon as drug carriers has attracted much attention as they have shown great potential applications in drug formulation because of their well-ordered pore structure, very high specific pore volume, specific surface area, tunable pore diameter and biocompatibility [19,20]. The large surface area to volume ratio of these nanostructured materials provides the potential for significant drug loading through surface adsorption [21]. Mesoporous carbon materials are also highly tolerant in aqueous environments as compared to silica materials. The stable nanostructures of mesoporous carbon could ensure that it preserves their drug cargo in the body to enable effective targeting and release at the diseased site [22,23]. Gu et al. [24] applied mesoporous carbon as carriers for the delivery of hydrophobic anti-cancer drug, camptothecin, which efficiently inhibited the growth of MCF-7 cancer cells due to its sustained release. Wang et al. [25] reported that ibuprofen loaded on mesoporous carbon exhibited a two-step release profile of an initially fast release followed by a slower release. Zhao et al. [26] found that mesoporous carbon could achieve a higher degree of drug loading and dissolution of poorly soluble drugs could be markedly increased. Moreover, mesoporous carbon exhibited a weak cytotoxicity at tested concentrations (10–800 μg/ml). Labiano et al. [27] studied the slow release kinetics of mitoxantrone from ordered mesoporous carbon films where the high porosity and surface areas of ordered mesoporous materials provide substantial capacity for the loading of guest molecules, and could achieve a controlled release.

The preparation of mesoporous carbon usually uses mesoporous silica as the hard template and followed by a replication process. The harvested mesoporous carbon generally preserves the morphology of mesoporous silica [17]. Most mesoporous carbon materials usually exhibit the common fiber morphology although various pore structures were fabricated [28–31]. To our best knowledge, mono-dispersed mesoporous carbon

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http://dx.doi.org/10.1016/j.powtec.2014.04.044
0032-5910/

materials have rarely been reported. In this study, sucrose was filled to mesoporous silica by a co-spray drying process at different ratios of sucrose/SBA-15. Following carbonization in a nitrogen environment and subsequent removal of the hard SBA-15 template by NaOH, the obtained monodispersed mesoporous carbon were used as drug carriers for loading a poorly soluble drug, IDMC to improve IDMC's dissolution rate and bioavailability. The drug loading performance of MMPC was compared with porous activated carbon (AC) with non-uniform pore structures and non-porous microspheres of carbon (MSC). The molecular state of drug in the IDMC/MMPC solid dispersion was studied by scanning electron microscopy (SEM), DSC, XRD and N_2 adsorption.

2. Materials and methods

2.1. Synthesis of mesoporous submicron particles

Mesoporous SBA-15 with submicron particle size was synthesized by a rapid condensation process. 4.0 g of template, EO_{20}–PO_{70}–EO_{20} (P123, pluronic 123, Aldrich) was dissolved in 150 g of a 2 N HCl solution under stirring at 40 °C for 2 h. 8.5 g of Tetraethylorthosilicate (TEOS, Aldrich, 98%) was added to the solution under vigorous stirring for 2 min. The hydrolysis of TEOS was performed at 40 °C for 2 h without stirring. The mole ratio of components in the mixture is SiO_2:P123:HCl:H_2O = 1.0:0.016:6.9:178.6. The mixture was transferred to a polypropylene bottle and aged in an oven at 100 °C for 24 h. The resulting material was filtered and washed with deionized water, then dried at 55 °C for 12 h. To remove the template molecules, the material was heated from room temperature to 550 °C for 6 h in air at a heating rate of 2 °C/min.

2.2. Preparation of monodisperse mesoporous carbon

Monodispersed mesoporous carbon was prepared by using submicron SBA-15 as hard templates and sucrose was used as the carbon precursor. Sucrose was filled to mesoporous structure of SBA-15 by co-spray drying process. Typically, 1.0 g of sucrose was dissolved in a mixed solvents of 80 ml of methanol and 20 ml of water as well as 0.18 g of H_2SO_4 (98%). The 1.0 g of SBA-15 submicron particles was mixed with sucrose solution under stirring. The suspension was co-spray dried with a mini spray dryer (BÜCHI B-290, BÜCHI Labortechnik AG, Flawil, Switzerland) operated with an inlet temperature of 68 °C and feeding rate of 4 ml/min. Carbonization experiments were performed with a tubular furnace in purified N_2 flow at 900 °C for 6 h and a heating rate of 10 °C/min. The obtained carbon–silica composite was washed with 1 M NaOH solution of 50% ethanol-50% H_2O twice at 90 °C, in order to dissolve the silica template followed by washing with de-ionized water to remove trace NaOH completely. Four mesoporous carbon samples were prepared by co-spray dried sucrose/SBA-15 with ratios of 0.5, 1.0, 1.5 and 2.0, and the resulting MMPC was denoted as MMPC-1, MMPC-2, MMPC-3 and MMPC-4, respectively.

2.3. Nitrogen adsorption

Nitrogen adsorption/desorption isotherms were measured by using a gas adsorption analyzer (Autosorb-6B, Quantachrome Instruments, Boynton Beach, FL, USA) at a temperature of −196 °C. Before nitrogen adsorption-desorption measurements, each sample of monodisperse mesoporous carbon was heated at 100 °C under vacuum overnight. For samples of drug loaded carbon, each sample was degassed at 40 °C under vacuum overnight. The specific surface areas of the samples were determined from the linear portion of the Brumauer–Emmett–Teller (BET) plots. The mesoporous carbon pore size (diameter DBET) distribution (with and without drug loading) was calculated from the desorption branch of N_2 adsorption-desorption isotherms using the conventional Barrett–Joyner–Halenda (BJH) method. The total pore volume, V_T, was estimated from the amount adsorbed at a relative pressure of 0.95.

2.4. Scanning electronic microscopy

The morphology of monodisperse mesoporous carbon was examined by high resolution field emission scanning electron microscopy (FESEM, JSM-6700F, Jeol Ltd., Tokyo, Japan). Samples were loaded and adhered to double faced carbon tape on the sample stub then sputter coated with gold by a sputter coater (High Resolution Sputter Coater 208h, Cressington Scientific, Watford, UK). The SEM was operated with an accelerating voltage of 5 kV and specimen working distance of 8 mm.

2.5. Transmission electron microscopy

The morphology and structures of mesoporous carbon were also examined by transmission electron microscopy (TEM, G2 F20, Tecnai, Hillsboro, OR, USA) at 200 kV. The specimens for high resolution transmission microscopy studies were prepared by suspending a solid sample in acetone with ultrasonic dispersion in a water bath.

2.6. Fourier transform infrared spectroscopy

The framework vibration Fourier transform infrared (FTIR) spectra were recorded on an infrared spectrophotometer (Bio-Rad, TFS 3000MX, Hercules, CA, USA) at a resolution of 2 cm^{-1}. The samples were thoroughly ground with KBr pellets before being pressed at 4 t to form a thin wafer.

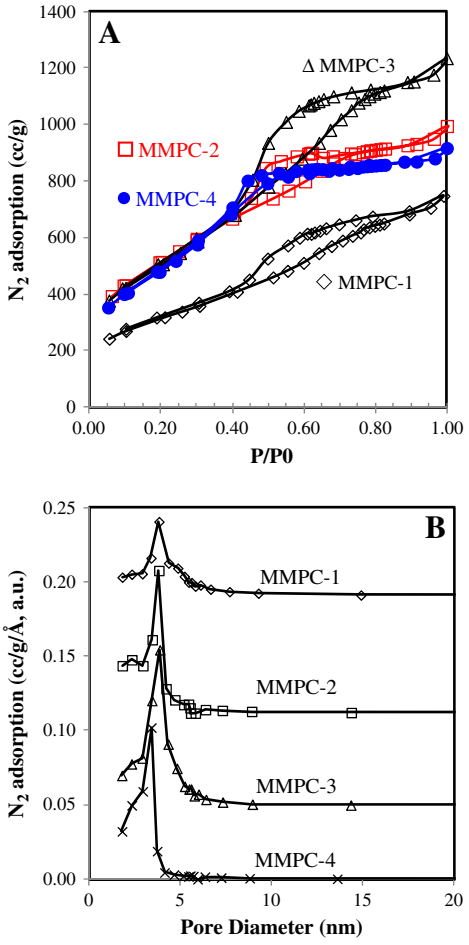

Fig. 1. (A) Nitrogen adsorption and desorption isotherms for MMPC-1, MMPC-2, MMPC-3 and MMPC-4; (B) pore size distribution of MMPC-1, MMPC-2, MMPC-3 and MMPC-4.