Microporous and Mesoporous Materials 213 (2015) 134–141

Contents lists available at ScienceDirect

Microporous and Mesoporous Materials

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

Mesoporous silica core–shell composite functionalized with polyelectrolytes for drug delivery

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ARTICLE INFO

Article history:
Received 19 April 2014
Received in revised form
25 January 2015
Accepted 3 February 2015
Available online 11 February 2015

Keywords:
Mesoporous silica
Core–shell composites
Ibuprofen
Controlled release
SAXS

ABSTRACT

Porous, spherical (d ≈ 400 nm) polyelectrolytes-coated silica particles (SiPs) with high surface area (1254 m^2/g) have been synthesized for controlled release of ibuprofen (IBU) in aqueous dispersion. The zeta potential of the SiPs was negative (−77 mV) at pH 5.5, so the shells, as a positively charged polyethylenimine (PEI) and a negatively charged poly(sodium-4-styrenesulfonate) (PSS) bind through electrostatic interactions. The adsorbed amount of IBU is 1666 mg/g and 1618 mg/g SiPs based on adsorption method in aqueous media and thermogravimetric (TG) measurement, respectively. The SiPs was characterized by using low temperature N_2 adsorption/desorption method. The well-ordered structure of SiPs and the fractal dimensions of the core–shell composites were determined by small angle X-ray scattering (SAXS) measurement. Finally the release properties of the IBU have been investigated; kinetic models were used to describe the release mechanism. The results of this study highlighted that the SiPs and the core–shell particles are well applicable as dissolution-enhancing systems for encapsulation of poorly soluble drugs.

1. Introduction

High porosity and large porous surface materials with different morphology have been one of the main topics of research into inorganic particles [1–3]. Due to these properties to have been applied in many field for example catalysis, separation, sensing and biomedicine [4–6]. These materials are able to pick up and store the drug molecules with high affinity and efficiency. There are two types of SiPs, the nonporous and the porous, commonly named as the mesoporous structure [7]. Many methods are available for the synthesis of the mesoporous silica [8–11]. Encapsulating of many drugs (fluoxetine, lidocaine, gentamicine, morphine, nifedipine, paracetamol, tetracyclin and ibuprofen are reported in the literature [12–14].

IBU is a non-steroidal inflammatory drug used in treatment of pain and inflammation in rheumatic disease and other musculoskeletal disorders [15]. It has a short biological half-life time (2 h) so it's a good candidate for controlled drug release [16].

The formation of core–shell structure on silica core improves the sustained and controlled release of the drug or other molecules [7,17]. The shell is usually non-toxic, biodegradable, inert and biocompatible, such as polyethylene-glycol (PEG), poly(D,L-lactic acid) and poly(D,L-lactic-co-glycolic acid) (PLGA) [18,19]. PEI has been used in gene therapy as a delivery agent because it can bind to anionic cell surface [20,21]. Polyanionic polyelectrolyte, such as PSS is a water-soluble, thermal-stable and biodegradable polymer, also commonly used in biological systems [22].

The N_2 adsorption/desorption methods are used to determine the surface area and the pore size distribution of the porous materials [10,23,24], while the thermoanalytic analysis are used to determine drug content [25]. The FT-IR is a very easy way to follow the reaction progress [26–28].

The most important data is how fast the drug dissolves from the core–shell structure. Horcajada and et al. studied how the release rate depends on of the pore size [14]. Feng and et al. determined how the ionic strength of the media effects the in vitro drug release [29]. Many of the kinetic models are useful to describe the release mechanism. The conformity between experimental data and each model predicted values was expressed by the correlation coefficient (R^2) [30–32].

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http://dx.doi.org/10.1016/j.micromeso.2015.02.008
1387-1811/

We represent a mesoporous silica particles high surface area as a drug carrier. The well-ordered structure and the fractal dimensions were verified by SAXS measurement. The adsorbed amount of the IBU was determined by classical batch equilibrium method and by TG measurements. The release profiles of the IBU were carried out in phosphate buffer with vertical diffusion cell. Empirical kinetic models, based on simple power–low correlation and a mechanistic kinetic models were used to describe the release mechanism of the IBU molecules.

2. Experimental

2.1. Materials

Tetraethyl-ortosilicate (TEOS) (98%) and the poly(ethylenimine) (PEI) (50 w/v%) was purchased from Fluka. The IBU ($C_{13}H_{18}O_2$), the poly(sodium-4-styrene-sulphonate) (PSS) of MW 70.000 g/mol and the cetyltrimethyl-ammoniumbromide (CTAB) were purchased from Sigma Aldrich. The sodium-hydroxide (NaOH) and the hydrogen chloride (HCl) were obtained from Molar Chemicals. McIlvaine buffer (pH = 5.4): citric acid and sodium chloride (NaCl) were ordered from Molar Chemicals, while the disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4 \times 12H_2O$) was purchased from Sigma Aldrich. Highly purified water was obtained by deionization and filtration with a Millipore purification apparatus. All solvents and reagents used were of analytical grade, and no further purifications were made.

2.2. Methods

2.2.1. Synthesis of porous SiPs

The SiPs were prepared in aqueous media. The structure-directing agent was a cationic surfactant, the CTAB. The surfactant (2.74 mmol) was dissolved in water (240 ml) and then NaOH (2 M) was added to the CTAB solution. The temperature was adjusted to 80 °C. After 30 min we dropped the TEOS (27.09 mmol) to the solution. We stirred the solution for 2 h further. The product was obtained by centrifugation and washed with distilled water three times. The product was dried for 2 h at 140° and then calcination was carried out at 550 °C for 5 h to remove the template.

2.2.2. Synthesis of the core–shell particles

The SiPs (0.7 w/v%) and the IBU (1.6 w/v %) were dissolved in different beaker in 7.5 ml 0.9 w/v % NaCl content buffer solution. The pH was adjusted to around 5.5. When the SiPs and the IBU were dissolved completely we have combined the two solutions. The solution was stirred for ca. 10–12 h, after that it was centrifuged (15 min, 14,000 rpm). The SiPs were dispersed in PEI (1.7 w/v%, 15 ml) solution and was stirred for one more hour then centrifuged again. The PSS solution has been treated the same way. Each step, samples were set aside to further investigation. The products were liophylized and stored at −80 °C. The formation of core–shell composites and the release processes are shown in Fig. 1.

2.2.3. Adsorption isotherm

The concentration of IBU in aqueous solution on SiPs surface was defined by the classical batch equilibration method. In each adsorption experiment 0.1 g SiPs was added to IBU solutions with different concentration (0.005; 0.02; 0.06; 0.1; 0.17; 0.2 M). The solutions were stirred for 20 h continuously at room temperature. The aqueous phase was separated from the silica by centrifugation. The concentrations of the IBU solutions were calculated by an UV spectrophotometer at 272 nm. The absorbed amount of IBU (mg/g) on the silica surface per one gram silica is: $n^s = V^o (c_o - c_e)/m$. The V^o is the volume of the solution, c_o the initial concentration of the IBU, c_e is the equilibrium concentration of the IBU and m is the weight of the sorbent [33,34].

The monolayer adsorption capacity (n_m^s) was calculating with the Langmuir equation:

$c_e/n^s = c_e/n_m^s + 1/n_m^s b$, where the n_m^s is the monolayer adsorbed amount of IBU and the b is the Langmuir constant [35,36].

2.2.4. In vitro drug release

This experiment is described in details previously [37]. Briefly, the core–shell composites containing IBU were dispersed in phosphate solution (PBS, pH = 7.4). We poured this sample in a vertical diffusion cell (Franz cell). The dispersion was stirred continuously with a magnetic stirrer and peristaltic pump at 25 °C. The cell was connected to a UV-1800 spectrophotometer. The absorbance of the dissolved IBU was detected at 272 nm. Samples were taken every 10 min in the first hour, then once every hour. We continued the measurement for 500 min. We repeated every measurement twice.

2.2.5. Materials characterization

The specific surface area and the pore volume of the silica were determined by nitrogen adsorption at 77 K by a *Micromeritics* gas adsorption analyzer (*Gemini Type* 2375). The specific surface area was calculated using the BET method, while the pore size distribution using by BJH method [1]. The micropores volume and the external surface area were determined with the de Boer's t-method.

The streaming potential of SiPs and the PSS was measured by a PCD-04 Particle Charge Detector (Mütek Analytic GmbH, Germany).

The absorption spectra of IBU were studied by UV-1800 (Shimadzu) spectrophotometer. The concentration of the IBU had been determined according to the absorption at 272 nm.

The XRD patterns of the SiPs were generated in a Bruker D8 Advance X-ray diffractometer with CuKα radiation (λ = 0.1542 nm, 40 kV, 30 mA).

Small angle X-ray scattering (SAXS) measurements were used to analyze the inner structure of the materials. SAXS curves were recorded with a slit-collimated Kratky compact small-angle system (KCEC/3 Anton-Paar KG, Graz, Austria) equipped with a position-sensitive detector (PSD 50M from M. Braun AG. Munich, Germany). Cu Kα radiation was generated by a Philips PW1830 X-ray generator operating at 40 kV and 30 mA.

Transmission electron microscopy (TEM) measurements were performed using a FEI Tecnai G^2 20 X-TWIN microscope with the tungsten cathode operated at 200 kV.

Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy measurements were performed in a Biorad FTS-60A FT-IR spectrometer by accumulation of 256 scans at a resolution of 4 cm^{-1} between 4000 and 400 cm^{-1}. All spectral manipulations were performed by using Thermo Scientific GRAMS/AI Suite software.

TG measurements were carried out in a Mettler Toledo TGA/SDTA 841e thermoanalytical instrument. The samples were between 25 and 600 °C at a heating rate of 5 °C/min.

3. Results and discussion

3.1. Silica particles

The SiPs samples were characterized using several different techniques before the forming of the core–shell particles. We determined the surface area and the pore size distribution of the core. The nitrogen adsorption isotherm and the size distribution are shown in Fig 2. The surface area of the SiPs is 1254 m^2/g. The pores are relatively in a narrow range of size, the average pore size is