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Comparison of bare and amino modified mesoporous silica@poly(ethyleneimine)s xerogel as indomethacin carrier: Superiority of amino modification

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ABSTRACT

The purpose of this study was to facilely develop amino modified mesoporous silica xerogel synthesized using biomimetic method (B-AMSX) and to investigate its potential ability to be a drug carrier for loading poorly water-soluble drug indomethacin (IMC). For comparison, mesoporous silica xerogel without amino modification (B-MSX) was also synthesized using the same method. The changes of characteristics before and after IMC loading were systemically studied using fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), small angle X-ray scattering (SAXS) and nitrogen adsorption/desorption analysis. The results showed that B-MSX and B-AMSX were spherical nanoparticles with mesoporous structure. Compared with B-MSX, IMC loading capacity of B-AMSX was higher because more drug molecules can be loaded through stronger hydrogen bonding force. DSC and SAXS analysis confirmed the amorphous state of IMC after being loaded into B-MSX and B-AMSX. The in vitro drug release study revealed that B-MSX and B-AMSX improved IMC release significantly, and B-AMSX released IMC a little faster than B-MSX because of larger pore diameter of IMC-AMSX. B-MSX and B-AMSX degraded gradually in dissolution medium evidenced by color reaction and absorbance value, and B-AMSX degraded slower than B-MSX due to amino modification. In conclusion, B-AMSX with superiority of higher loading capacity and enhanced dissolution release can be considered to be a good candidate as drug carrier for IMC.

1. Introduction

Porous silica with amorphous state has been long recognized as very promising excipient for drug delivery application due to its simple, inexpensive, versatile synthesis, physiologically inert and non-toxic nature. It is widely accepted that there are three types of porous silica structures: microporous, mesoporous, and macroporous based on the diameter of the pores. The term "microporous" refers to pore diameters of less than 2 nm, "mesoporous" is defined as diameters between 2 and 50 nm and "macroporous" refers to pore size range of greater than 50 nm [1]. To date, mesoporous silica materials with different pore characteristics and a variety of morphologies have been widely described in the literature, where a variety of drug molecules have been successfully incorporated and then delivered in a controlled or immediate manner [2–6].

As one of the formation states of silica materials, xerogel can be applied in pharmaceutical field and medical intelligent devices, including drug carrier, implanting devices, tissue engineering, and nanomedical or micromedical devices [7]. It has been reported that sol–gel derived silica xerogel is considered as promising carrier materials owing to its biodegradability, high drug loading efficiency, low processing temperature, and the ability to allow in situ incorporation of drug molecules into the silica. Normally, acetic acid, nitric acid, and hydrochloric acid can be used as catalysts to synthesize silica xerogel [7]. Therefore, it has great significance to explore functional template to synthesize mesoporous silica xerogel as drug carrier.

Diatoms are the predominant organisms engaged in biosilicification [8], and biosilicification of mesoporous silica inspired by diatoms has completely changed the way of designing novel mesoporous silica [9]. For biosilicification mechanism, it is highlighted that amines actively catalyze the condensation of silica precursors (tetramethoxysilane and tetraethoxysilane) [10]. Therefore, a number of amine-containing molecules, including polypeptides, synthesized polymers/oligomers and small molecules, have been explored for the biomimetic synthesis of silica [11]. Recently, biomimetic synthesis of porous silica mediated by polyamines has attracted great attention [12]. Polyamines catalyze the silica formation due to the alternating presence of protonated and nonprotonated amine groups in the polyamine chains to form hydrogen bonds with the oxygen adjacent to Si and thus facilitate Si–O–Si bond formation [13].

To the best of our knowledge, a certain number of functional groups, such as amino-, carboxyl- [14], alkyl- [15], polyethylene glycol (PEG)

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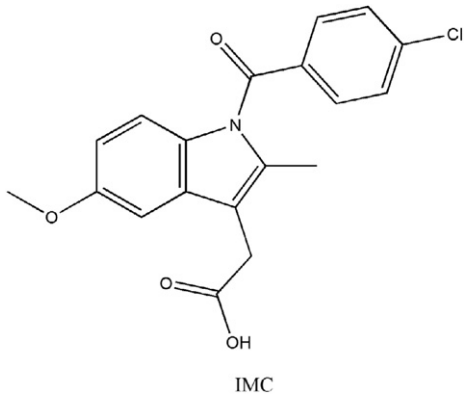


IMC

Fig. 1. Chemical structure of model drug IMC.

[16] and chitosan [17], are utilized to modify the surface of mesoporous silica. Surface modification of mesoporous silica can be realized by any of the following three methods: co-condensation (one-pot synthesis), grafting (post-synthesis modification), and imprint coating method [18]. Co-condensation and post-grafting are the two commonly available options for surface modification. The former designates the simultaneous hydrolysis and polycondensation of silica and organic silanes in one-pot, while the latter refers to the grafting of organic functional species on the surface of silica after the synthesis of mesoporous silica matrix [19]. Amino modified mesoporous silica prepared by co-condensation method using 3-aminopropyltriethoxysilane (APTES) has higher distribution homogeneity of functional groups compared to post-grafting method [19].

Indomethacin (IMC, see Fig. 1) is a poorly water-soluble and acidic non-steroidal anti-inflammatory drug that can cause irritation of the gastrointestinal mucosa [20]. Incorporation of IMC into mesoporous silica can improve its drug dissolution and reduce side effect of causing local irritation due to the direct contact of free carboxyl group and local inhibition of cytoprotective action of prostaglandins on gastric mucosa [20,21]. In the present work, amino modified mesoporous silica xerogel was facilely synthesized using biomimetic method (B-AMSX) with branched PEIs as the template and APTES as organic functional species. The obvious highlights and advantages of as-synthesized B-AMSX were as follows. (1) The PEIs used can be retained in synthesized mesoporous silica due to their nontoxicity at low molecular weight (<25 kD) [22]; (2) Biomimetic synthesis method can be accomplished through the process from sol to gel at ambient conditions (ambient temperature and ambient pressure); (3) Amino modification was involved aiming to bind the carboxyl group of IMC, which may improve drug loading capacity. For comparison, mesoporous silica xerogel without amino modification (B-MSX) was also synthesized using the same method. The changes of characteristics before and after IMC loading were systemically studied using fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), small angle X-ray scattering (SAXS) and nitrogen adsorption/desorption analysis. We believe that this research will be of significant help in designing oral drug delivery systems for poorly water-soluble drug and developing material science of mesoporous silica.

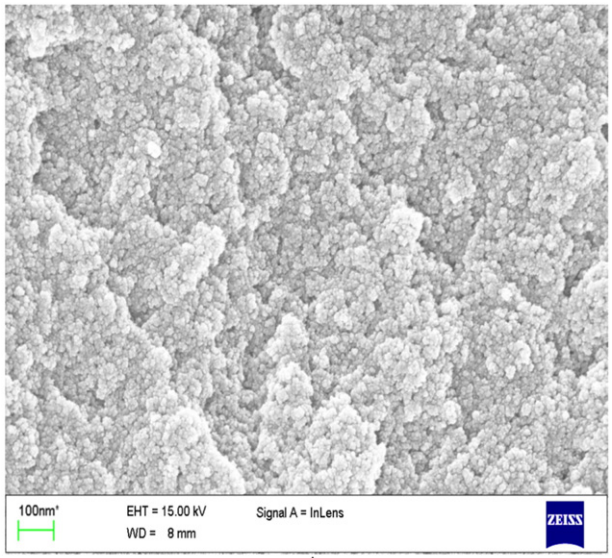
2. Materials and methods

2.1. Materials

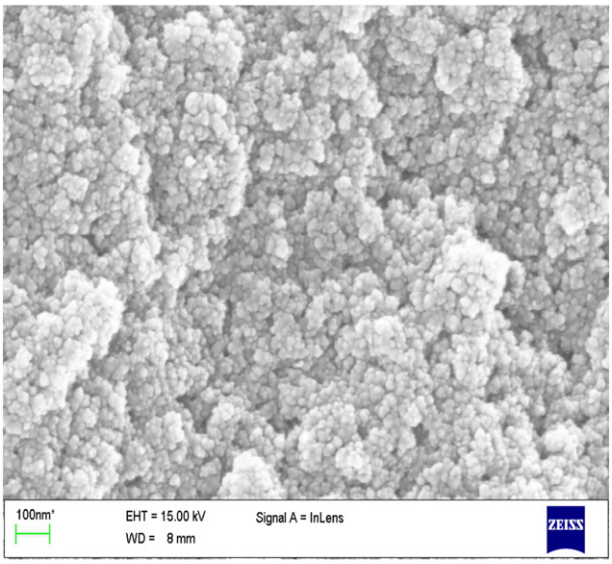
Tetramethoxysilane (TMOS) and 3-aminopropyltriethoxysilane (APTES) were purchased from Aladdin (Shanghai, China), branched poly(ethyleneimine)s (PEIs) with weight-average molecular weight of 20 kDa was kindly donated by Qianglong new chemical materials (Wuhan, China). All of the other reagents were purchased from Yu Wang Chemical Reagent Corporation (Shandong, China). Deionized water was prepared by ion exchange.

2.2. Facile preparation of B-MSX and B-AMSX

B-AMSX was facilely synthesized with biomimetic method using PEIs as the template, and its amino modification method belonged to co-condensation (one-pot synthesis) method with the advantage of high distribution homogeneity of functional groups [19]. For this, 0.4 mL PEIs was dissolved in 40.8 mL aqueous solution and the mixed solution was left statically for 48 h. Then 1 mL as-synthesized template solution was added into mixed solution consisting of 1 mL TMOS, 1 mL absolute ethyl alcohol and 20 μL APTES, and left the sol system at ambient conditions statically until the formation of wet gel. Finally, wet gel was dried at 40 °C vacuum drying oven to remove volatile solvent.



A



B

Fig. 2. SEM photographs of A, B-MSX; B, B-AMSX. TEM images of C, B-MSX; D, B-AMSX.