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Featured Letter

Amino-modified mesoporous silica SBA-15 as bifunctional drug delivery system for cefazolin: Release profile and mineralization potential

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ABSTRACT

In this paper the amino-modified mesoporous silica (SBA-NH_2) was investigated as a potential bifunctional drug delivery system for cefazolin with both prolonged drug release and mineralization properties. The primary SBA-15 was synthesized using sol-gel method and surface functionalization was carried out using post-synthesis grafting. The obtained SBA-NH_2 was characterized by higher adsorption efficiency of cefazolin with drug release prolonged to 7 days compared to primary SBA-15. The amino-modified SBA-15 exhibited also mineralization potential after immersion in simulated body fluid (SBF) with delayed hydroxycarbonate apatite (HCA) formation compared to SBA-15 which did not interrupt the cefazolin release in controlled manner. A bone-mineral-mimicking layer of HCA was formed on the SBA-NH_2 surface after 28 days in SBF.

1. Introduction

Ordered mesoporous silica materials SBA-15 understood as novel drug carriers which play an important role as biomaterial in orthopaedics are present in literature [1], due to their mineralization potential in simulated body fluid (SBF) leading to self formation of surface hydroxycarbonate apatite (HCA) with morphology and chemical composition similar to human bone apatite. Moreover SBA-15 are proven to be biocompatible and bioinert in tissue [2].

We are interested in the investigation of *in vitro* potential of amino-modified SBA-15 mesoporous silica (SBA-NH_2) as bifunctional drug delivery system for cefazolin which is a semi-synthetic cephalosporin for parenteral administration use in bacterial bone infections. The preferable electrostatic attraction between positively charged silica surface (R-NH_3^+) and negatively charged cefazolin ions (Cef-COO^-) might increase the drug loading capacity and prolong the release profile. After surgical implantation the proposed SBA-NH_2 bifunctional system should release the cefazolin in prolonged manner directly in the infected bone tissue and after complete drug release it should support the bone regeneration *via* delayed HCA formation. Such system will reduce the systemic side effects of administered drug and its later removal is not necessary because of its biocompatible composition with human bone apatite.

2. Materials and methods

2.1. Synthesis and surface functionalization of SBA-15

The SBA-15 synthesis was performed according to the procedure proposed by Zhao et al. [3]. Material was obtained in sol-gel method using Pluronic P123 surfactant (Sigma-Aldrich, average M_n = 5800) as a structure directing agent and tetraethyl orthosilicate (TEOS, Sigma-Aldrich) as the precursor of silica. The synthesized and calcinated SBA-15 was filtered, rehydroxylated in HCl (18 wt%, POCH) for 24 h, then sieved through a 500 μm mesh to uniformize the silica grains (fraction 200–500 μm) and vacuum-dried.

The SBA-15 surface modification was performed using grafting method [4] in anhydrous toluene under reflux and nitrogen atmosphere with (3-aminopropyl)trimethoxysilane (APTMS) as surface modifier. The amount of added APTMS was calculated based on the surface area of SBA-15 (nitrogen adsorption–desorption analysis on Micromeritics ASAP 2405N instrument, data not shown) and silanol surface excess value of 9.0 μmol/m^2. The obtained materials were filtered, sieved through a 500 μm mesh (fraction 200–500 μm) and vacuum-dried.

The both obtained SBA-15 and SBA-NH_2 were preliminary investigated (data not shown) using Fourier transform infrared spectroscopy (FTIR, Jasco 4700 model) and small-angle X-ray diffraction (XRD, Empyrean, PANanalytical) to confirm the 3-aminopropyl groups attachment to silica surface and the ordered mesoporous structure for both materials, respectively.

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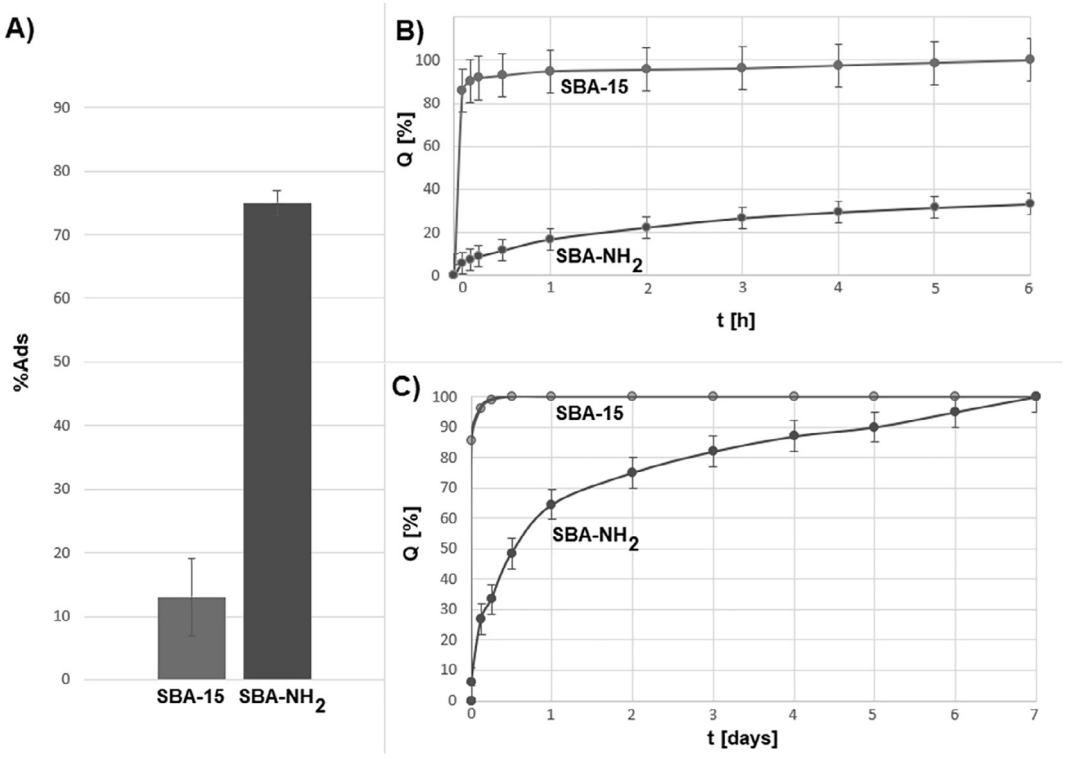

Fig. 1. The adsorption efficiency (A) and drug release profiles (B-C) for SBA-15 and SBA-NH_2.

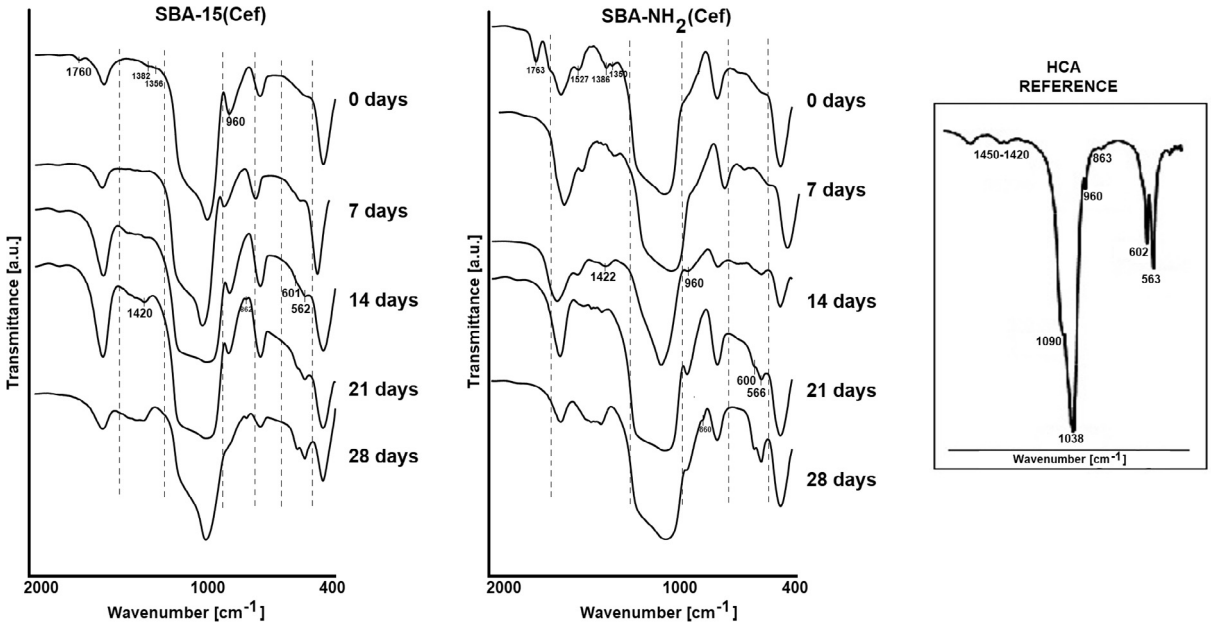

Fig. 2. The FTIR spectra of hydroxyapatite formation for SBA-15(Cef) and SBA-NH_2.

2.2. Cefazolin adsorption and release studies

Each 100 mg of SBA-15 and SBA-NH_2 were soaked in 2 mL of the cefazolin sodium (Biofazolin, Polpharma) solution (5 mg/mL) prepared in 0.05 M phosphate buffer (pH = 4.5) and incubated in water bath (25 °C, 300 rpm) for 24 h to ensure the equilibrium adsorption state. Then materials were centrifuged and dried at 25 °C. The total amount of cefazolin ions (Cef) adsorbed on SBA-15 and SBA-NH_2 was calculated spectrophotometrically (UV–Vis spectrophotometer Shimadzu, UV-1800) by monitoring the changes in absorbance at 271 nm, next confirmed by thermogravimetric analysis (TGA/SDTA 851e Mettler Toledo, data not shown).

The release studies were performed for SBA-15 and SBA-NH_2 with adsorbed Cef (SBA-15(Cef) and SBA-NH_2(Cef), respectively) using a pharmacopoeial dissolution paddle apparatus (Dis 6000 Copley, 50 rpm, 37 °C). 1.0 g of each material was soaked in SBF [5] providing sink conditions – there was no statistically significant differences in %Q released using different mass of drug-loaded silica materials. SBF was changed after each 24 h to provide Cef stability (USP Pharmacopeia). At suitable time intervals 2.0 mL of