Materials Letters 143 (2015) 252–255

Contents lists available at ScienceDirect

Materials Letters

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

Nanostructured calcium phosphate carriers for deliver of poor water-soluble drug silybin

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ARTICLE INFO

Article history:
Received 3 December 2014
Accepted 24 December 2014
Available online 2 January 2015

Keywords:
Biomaterials
Nanocrystalline materials
Silybin
Calcium phosphate
Drug delivery

ABSTRACT

Silybin, the main component of silymarin, has been widely used as a hepatoprotective agent for a variety of acute and chronic liver diseases. However, its poor aqueous solubility lead to poor oral absorption and low bioavailability, which strongly limit its applications. The amorphous calcium phosphate (ACP) nanosphere and hydroxyapatite (HAP) nanorod have been prepared and used for the investigation of the silybin loading and release. The results indicate that both ACP nanosphere and HAP nanorod have relatively high silybin-loading capacities which reach to 900 and 825 mg g^{-1}. Moreover, the as-prepared silybin delivery systems exhibit sustained drug release performance in simulated gastric fluid and simulated intestinal fluid.

1. Introduction

Silybin is one of the ideal therapeutic agent for the treatment of various diseases, including acute and chronic viral hepatitis, alcoholic liver disorders, toxin- /drug-induced hepatitis, as well as liver fibrosis/cirrhosis [1–3]. However, the application of silybin has been limited, due to the poor solubility and low bioavailability [4,5]. Therefore, the development of novel drug carrier for delivering silybin is meaningful. To enhance the effectiveness of silybin, various carriers such as porous silica [6,7], nanostructured lipids [8,9], mixed micelles [10,11], and poly (ethylene glycol) [12] have been reported.

Calcium phosphate (CaP) has been widely investigated in biomedical areas [13,14]. Comparing with other drug carriers (porous silica, nanostructured lipids, micelles, and so on), the CaP has outstanding biocompatibility, good biodegradability and favorable chemical properties similar to the native inorganic constitution in natural bone tissue [15,16]. Moreover, the solubility of synthetic CaP increased with the decrease of pH value in aqueous solution. The CaP nanostructures can be designed and used as a pH sensitive drug nanocarrier to control the drug release [17,18].

Herein, amorphous CaP (ACP) nanospheres and hydroxyapatite (HAP) nanorods have been prepared and used for the investigations of silybin loading and release. The results indicate that the silybin-loading capacity can be enhanced by using ACP nanospheres and HAP nanorods. Moreover, the as-prepared delivery systems exhibited sustained drug release performances in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF).

2. Experiment

Materials: The polylactide–block–monomethoxy (polyethyleneglycol) (PLA−mPEG) (PLA_{MW}=3000 and $mPEG_{MW}$=5000) were purchased from Jinan Daigang Biomaterials Co. Ltd. and Silybin was purchased from Sigma (USA). All other chemicals were purchased from Sinopharm Chemical Reagent Co. (China), and used as received without further purification.

Synthesis: For the synthesis of ACP nanospheres, 0.355 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.025 g of PLA−mPEG were dissolved in 60 ml of deionized water to form Solution A. Meanwhile, 0.166 g of $CaCl_2$, 0.025 g of PLA–mPEG and 10 ml of ammonia were dissolved in 60 ml of deionized water to form Solution B. Then, solution B was slowly added into Solution A, and the resultant solution is stirred for 1 h at room temperature. For the synthesis of HAP nanorods, the 60 ml of the resultant solution was transferred into a 100 ml sealed Teflon autoclave, and heated in an oven at 200 °C for 24 h. After cooling down to room temperature, the product was separated by centrifugation, and separately washed with deionized water and ethanol several times.

Characterization: X-ray powder diffraction (XRD) patterns were recorded using a Rigaku D/max 2550 V X-ray diffractometer with a graphite monochromator (Cu Ka radiation, λ=1.54178 Å). FTIR spectroscopy was recorded using a Thermo Nicolet Nexus FTIR spectrophotometer at wavelengths ranging from 500 to 4000 cm^{-1}.

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http://dx.doi.org/10.1016/j.matlet.2014.12.118
0167-577X/

The silybin concentrations was analyzed using UV–vis absorption spectrophotometer (UV-2300, Techcomp) at wavelengths of 301 nm. Transmission electron microscopy (TEM) micrographs were taken with a JEOL JEM 2100 field-emission transmission electron microscope.

Drug loading and release: The silybin-loading experiments were performed as follows: ACP nanospheres and HAP nanorods (5 mg each) were separately immersed in silybin-containing ethanol solution (75%, 8 ml) with a varied concentration of 0–6.0 mg mL^{-1}. After ultrasonic treatment for 20 min in a conventional ultrasonic cleaner (Guangdong GT Ultrasonic Co., Ltd., China), each solution was shaken (160rpm) at 37 °C for 6 h. Then, the solution was centrifuged, and the amount of silybin in the supernatant was measured by UV–vis absorption at a wavelength of 301 nm. The silybin loading experiments at different time were performed as follows: ACP nanospheres and HAP nanorods (5 mg each) were immersed in silybin-containing ethanol solution (5 ml, 3.0 mg mL^{-1}). After ultrasonic treatment for 20 min, each solution was shaken (160rpm) at 37 °C for different time. Then, the solution was centrifuged, and the amount of silybin in the supernatant was measured by UV–vis absorption.

For the drug-release assay, silybin-contained ACP or HAP (40 mg) were immersed into the SIF (100 mL, pH 6.8) and SGF (100 mL, pH 1.2) at 37 °C under constant shaking (120rpm). The

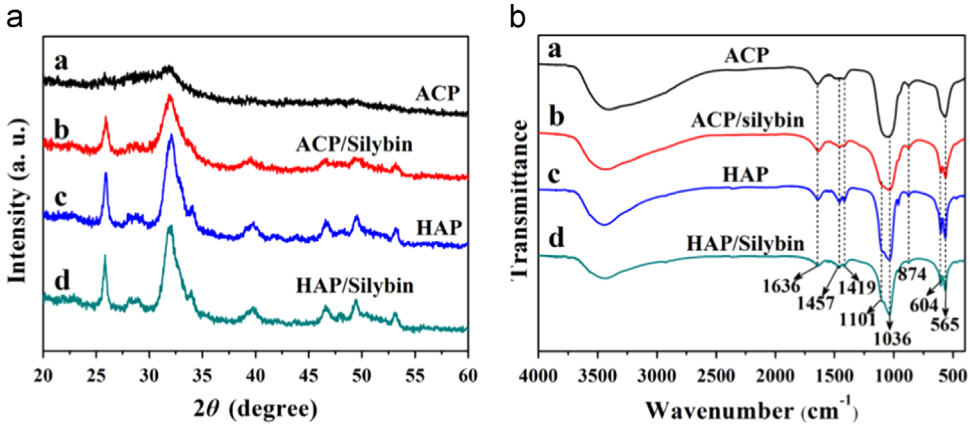

Fig. 1. XRD patterns (A) and FTIR spectra (B) of calcium phosphate before and after silybin loading: (a) ACP nanosphere; (b) silybin-loaded ACP nanosphere; (c) HA nanorods and (d) silybin-loaded HA nanorods.

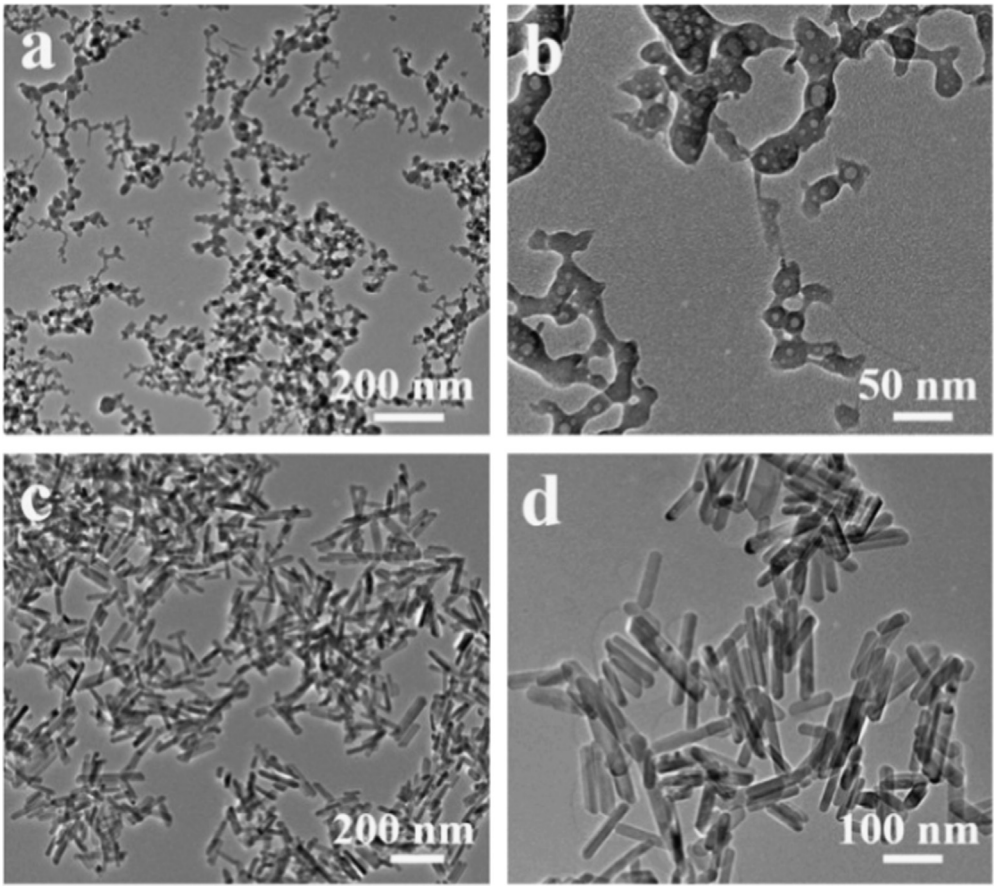

Fig. 2. TEM micrographs of the ACP prepared at room temperature (a, b) and the HAP synthesized by hydrothermal method at 200 °C for 24 h (c, d).