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Sustained release of simvastatin from hollow carbonated hydroxyapatite microspheres prepared by aspartic acid and sodium dodecyl sulfate

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ABSTRACT

Hollow carbonated hydroxyapatite (HCHAp) microspheres as simvastatin (SV) sustained-release vehicles were fabricated through a novel and simple one-step biomimetic strategy. Firstly, hollow $CaCO_3$ microspheres were precipitated through the reaction of $CaCl_2$ with Na_2CO_3 in the presence of aspartic acid and sodium dodecyl sulfate. Then, the as-prepared hollow $CaCO_3$ microspheres were transformed into HCHAp microspheres with a controlled anion-exchange method. The HCHAp microspheres were 3–5 μm with a shell thickness of 0.5–1 μm and were constructed of short needle nanoparticles. The HCHAp microspheres were then loaded with SV, exhibiting excellent drug-loading capacity and sustained release properties. These results present a new material synthesis strategy for HCHAp microspheres and suggest that the as-prepared HCHAp microspheres are promising for applications in drug delivery.

1. Introduction

Hydroxyapatite (HAp) is widely employed in various biomedical materials, in environmental engineering, and in the chemical and technological fields [1–5]. Because of its numerous advantages, HAp has attracted considerable attention as a drug delivery system [6–8], where its effect and applications depend greatly on its morphology and size [1]. Carbonated HAp (CHAp) is the main inorganic constituent of bone and therefore has excellent biocompatibility and osteoconductivity. The inorganic constituent of human teeth is CHAp with a calcium and hydroxyl ions deficiency [9,10]. Furthermore, hollow HAp microspheres have attracted great interest due to their large inner volume, nanoscale shell, high specific surface area, and low density [11,12]. These advantages allow for technical improvements such as the incorporation of higher drug dosages, surface adsorption, and better controlled release [13]. Therefore, the design and synthesis of HCHAp nanoparticle microspheres is of great significance.

Recently, several methods have been developed to prepare HCHAp structures. These approaches can mainly be classified into three types: the assistant- or template-directed method [14–17], the chemical etching method [18], and the spray drying method [11]. Assistant- or template-directed synthesis has been needed to fabricate hollow structures until now. For example, polymer micelle-templated syntheses of HCHAp microspheres have been frequently reported [14,15,17]. In addition, Ma and Zhu [16] used potassium sodium tartrate as a chelating ligand in water and *N*,*N*-dimethylformamide mixed solvents. Qi et al. [12] used creatine phosphate as an organic phosphorus source. However, large amounts of unhealthy organic templates and organic solvents, which are hazardous to health and the environment, are used in the above methods. Therefore, many researchers have recently focused their attention on a novel hydrothermal transformation method to fabricate HCHAp microspheres using similarly structured $CaCO_3$ microspheres as a precursor [19,20].

Simvastatin (SV), a hydroxymethylglutaryl-coenzyme a reductase inhibitor, is used clinically to reduce blood cholesterol levels [21,22]. It has also been reported to have multiple biological effects, including anti-inflammation, promoting bone formation [23], odontogenic differentiation induction of human dental pulp stem cells (DPSCs) [24,25]. Orally administered SV can be degraded during first-pass metabolism in the liver, resulting in poor bioavailability [24]. Extremely high dosages of orally administered drugs have more serious side effects on the liver, muscle, and other tissues. In addition, a high concentration of SV could significantly suppress the proliferation of DPSCs [24]. Therefore, SV should be loaded onto a carrier for its controlled release in an effective concentration range appropriate for the enhancement of proliferation or differentiation of DPSCs. In previous studies, Tanigo et al. [26] developed a gelatin hydrogel that incorporated water-insoluble SV, thus obtaining sustained release. Tai et al. [27] described the controlled-release kinetics of SV from poly(lactic-*co*-glycolic acid)/HAp microspheres *in vitro*. Similarly, Naito et al. [28] presented a

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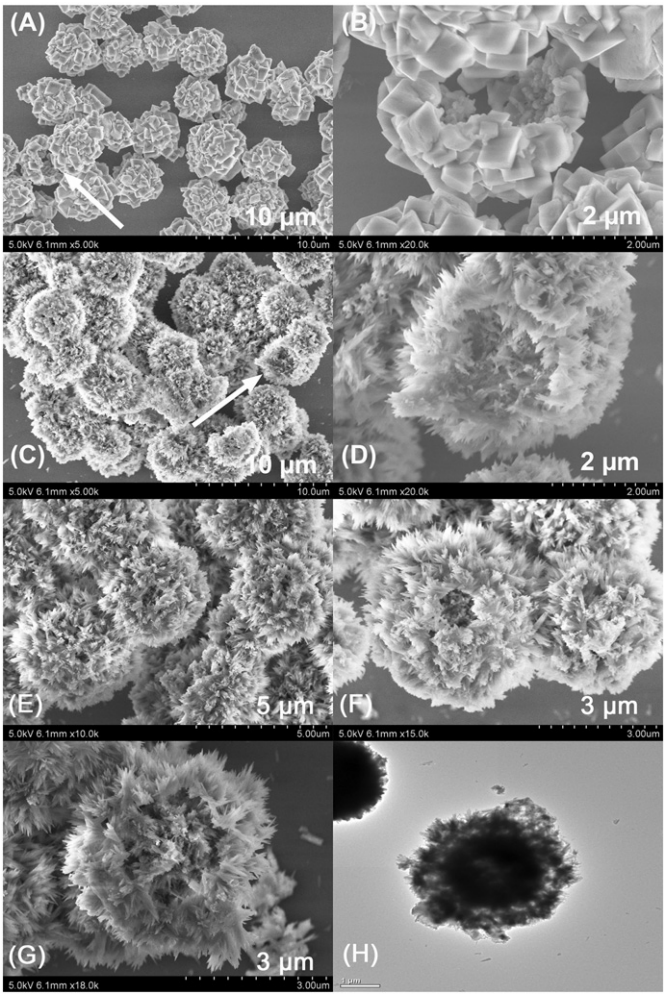

Fig. 1. FESEM micrographs of hollow samples: (A), (B) hollow $CaCO_3$ microspheres; (C), (D), (E), (F), (G) HCHAp microspheres. (B) and (D) are the high magnification images of A and C, respectively. (H) high resolution TEM micrographs of HCHAp.

sustained-release system by incorporating SV into poly(lactic-*co*-glycolic acid) microspheres. HAp is native to the body, and problems with the metabolic pathway can be greatly reduced compared to other delivery systems [29].

In our work, aspartic acid (Asp) and sodium dodecyl sulfate (SDS) were used as the hollow template for a one-step synthesis of HCHAp microspheres at atmospheric pressure and a relatively low temperature (50 °C). Our reasons for putting forward this route are not only the fact that both SDS and Asp can act as active sites for HAp nucleation through the electrostatic interaction between polar groups and calcium ions [30,31], but also the carboxyl of the amino acid can also provide calcium ion binding sites [32]. The major purpose of the present study is to synthesize HCHAp microspheres with a simple one-step biomimetic strategy and load these with SV in order to investigate the microsphere drug loading capacity and drug release properties.

2. Materials and methods

2.1. Materials

Chemicals, including calcium chloride anhydrous ($CaCl_2$), sodium carbonate anhydrous (Na_2CO_3), disodium phosphate dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$), sodium hydroxide (NaOH), and sodium lauryl sulfate (SLS) were of analytical grade and purchased from Tianjin Guangfu Technology Development Co. Ltd. SDS was chemical grade and provided by Sinopharm Chemical Reagent Co. Ltd. Absolute ethanol and acetonitrile were bought from Beijing Chemical Works. Asp and SV were purchased from J&K Scientific Ltd. Distilled water used throughout the experiments was produced in our own laboratory.

2.2. Synthesis of HCHAp microspheres

The HCHAp microspheres were prepared by an anion-exchange process with the as-prepared $CaCO_3$ precipitate as the sacrificial template. In a typical experimental process, equal volumes of $CaCl_2$ (0.1 mol/L) and Na_2CO_3 (0.1 mol/L) solutions were added to solution I and solution II, respectively, stirring continuously at a constant rate of 200 rpm. Solution I contained 0.01–0.5 g/L of Asp, while solution II was a mixed solution of 0.01–0.5 g/L Asp and 30 mmol/L SDS. $CaCO_3$ crystals were precipitated by rapidly pouring solution I into solution II, followed by stirring for 1 h at 40 °C. Afterwards, the mixtures were placed at 50 °C with a corresponding amount of aqueous solution of 0.03 mol/L $Na_2HPO_4 \cdot 12H_2O$ added dropwise. The system was stirred for 2 h at 50 °C and at a constant rate of 200 rpm. The pH of the mixed solution was controlled to approximately 10 with a 20 wt% NaOH solution. When the reaction was finished, the collected products were filtered off, rinsed with distilled water, then drip washing with ethanol, and

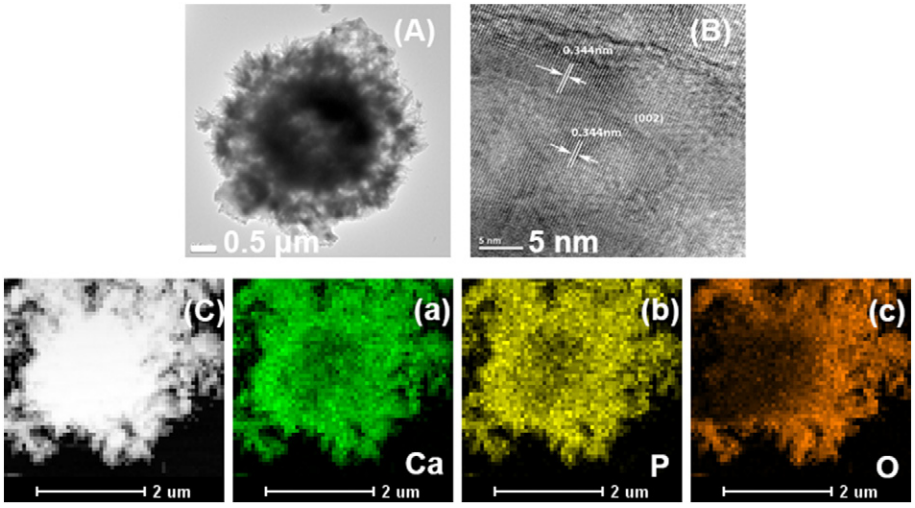

Fig. 2. High resolution TEM micrographs and EDX elemental maps of HCHAp: (A) low magnification; (B) high magnification; (C) STEM image and EDX mappings (a) Ca, (b) P, (c) O.