Progress in Natural Science: Materials International xxx (xxxx) xxx–xxx

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Progress in Natural Science: Materials International

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

Original Research

Hierarchical porous calcium carbonate microspheres as drug delivery vector

Hui Yang[a], Yunfeng Wang[a], Tongxiang Liang[a,*], Yiqun Deng[a], Xiaopeng Qi[a], Honghui Jiang[a], Yangjun Wu[a], Huichang Gao[b,c,*]

[a] School of Materials Science and Engineering, Jiangxi University of Science and Technology, Ganzhou 341000, China
[b] School of Medicine, South China University of Technology, Guangzhou, 510641, China
[c] A National Engineering Research Centre for Tissue Restoration and Reconstruction, Guangzhou 510006, China

ARTICLE INFO

Keywords:
Calcium carbonate
Microspheres
Phase transformation
Morphology-controlled growth
Biomedical application

ABSTRACT

$CaCO_3$ crystals with different hierarchical structure were fabricated by the precipitation of $CaCO_3$ in an aqueous solution containing guar gum (GG). Through adjusting a range of parameters, the size distribution and microstructure of $CaCO_3$ were well controlled. Results showed that GG facilitated the formation of the hierarchical hollow sphere through assembling of nanocrystals, while inhibited the growth of $CaCO_3$ crystals and restrained phase transition from calcite to vaterite at high concentration of GG (C_{GG}) condition; Moreover, increasing reaction temperature led to larger particles and stable crystalline phase formed. According to the results, a morphology map was presented. Furthermore, Drug loading and releasing results ensured porous $CaCO_3$ microspheres a promising vector for drug delivery.

1. Introduction

Recently, novel kinds of sustained-release drug delivery system, which can achieve long-term treatment of disease and reduce side effect compared with systemic administration by concentrating them at target regions, attracts intense attention [1,2]. Except for the constitution, the microstructure design of drug carriers to achieve high specific area is a key factor, and it determines the drug-loading capacity and releasing behavior of carriers [3]. Among them, porous drug carrier, especially porous hollow microsphere with different hierarchical structure through orderly assembled nano building blocks, have attracts an increasing interest [4,5]. Till now, various methods are applied to obtain porous hollow microsphere. Although templating methods (hard and soft templates) is one of the most common methods [6], the removing process of templates by washing with toxic organic solvents, calcinations, or other methods, these may affect the biocompatibility and microstructure of the products; besides, it is time and energy consuming as well. Because of the simple, low temperature, environmental friendly and easy operating properties, the self-assembly method gradually becomes the most widely used ways in preparation of porous hollow spheres [7].

Compared with synthetic polymer, which always involve in the use of toxic organic solvent and might bring about further toxic effects, inorganic and inorganic/natural polymer hybrid materials are more biocompatibility as their preparation conditions do not involve any organic solvent [8,9]. Hence, as a biomineral in general, $CaCO_3$, just like hydroxyapatite [10] and silica [11], attracts intense attention, and all of them with different hierarchical structure were successfully prepared by using biomolecules or biomolecular assemblies. Moreover, $CaCO_3$ naturally presents as calcite, aragonite and vaterite forms [12], and their stability are orderly decreasing; consequently, the dissolution rate of $CaCO_3$, which affects drug releasing rate and can be adjusted by controlling the crystal phase of $CaCO_3$ [13]. In addition, pH sensitive feature of $CaCO_3$ ensures tailorable drug releasing behavior as particles enter into cells or lysosomes. Hence, porous hollow $CaCO_3$ spheres with high specific surface area and different phase composition will be ideal candidate for various drugs' carrier. Moreover, GG is a natural polysaccharide and composed of galactan and mannan units combined through glycosidic linkages, and it is widely used as food additives and drug carriers because of its excellent biocompatibility [14,15]. What's more, GG will stabilize nanoparticles suspension through coating and creating a slightly negatively charged layer at particles' surface. Furthermore, GG alters the microstructure, size distribution and phase composition of $CaCO_3$ [16]. All of these ensure drug loading capacity and releasing property of $CaCO_3$ can be modified.

In this study, we prepared $CaCO_3$/GG hybrid porous hollow microspheres by precipitation of $CaCO_3$ within solution containing GG at low reaction temperature. And the morphology transformation of $CaCO_3$ in presence of GG will be described, in which GG was found to be particularly effective at leading the formation of porous hollow

Peer review under responsibility of Chinese Materials Research Society.
* Corresponding authors.
E-mail addresses: liang_tx@126.com (T. Liang), gaohuichang1986@163.com (H. Gao).

https://doi.org/10.1016/j.pnsc.2017.11.005
Received 16 September 2017; Received in revised form 20 November 2017; Accepted 20 November 2017

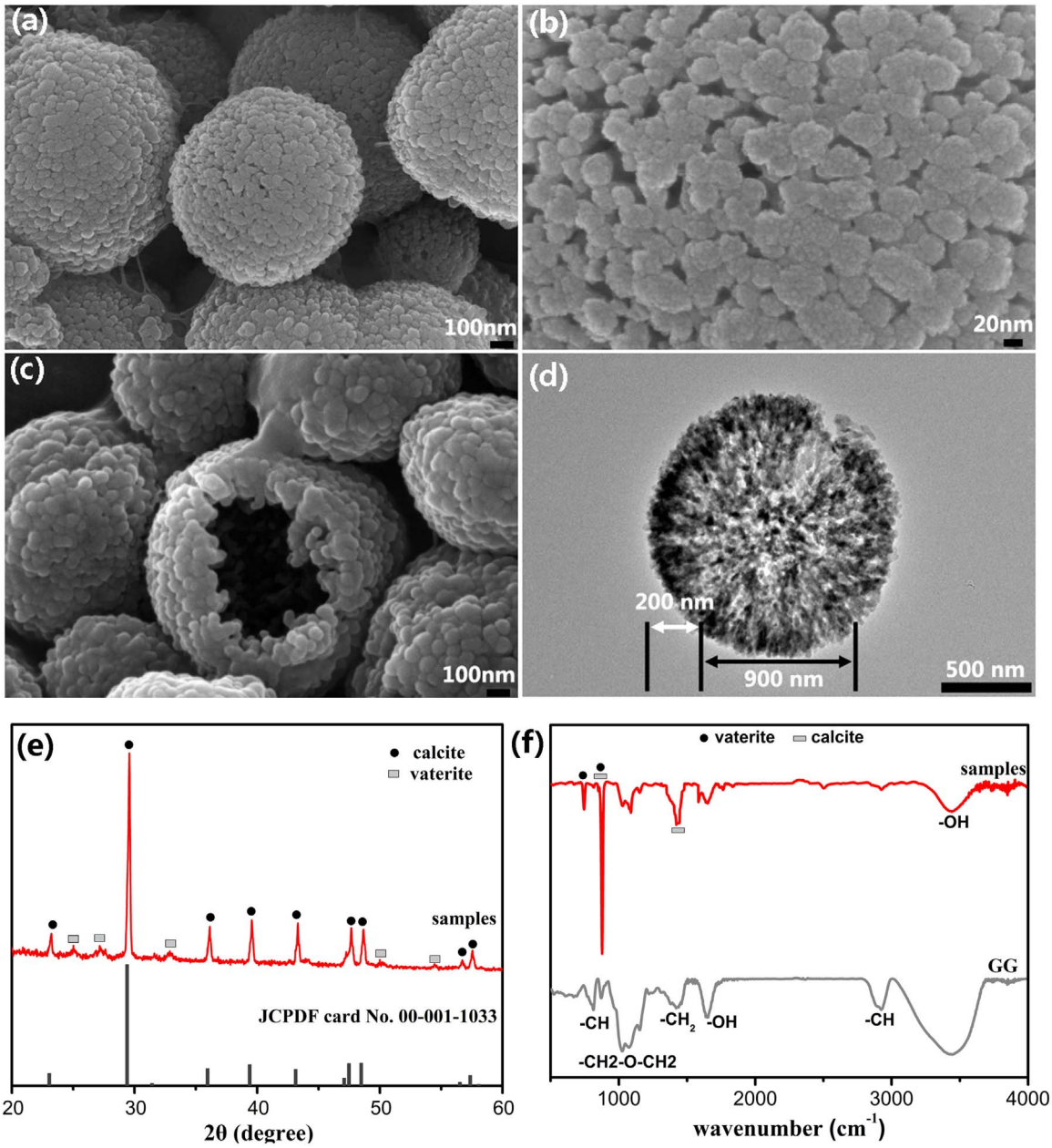

Fig. 1. SEM (a, b and c) and TEM (d) images of $CaCO_3$ spheres prepared at 20 °C. (e) XRD pattern and (f) FTIR spectra of the product. The initial C_{Ca} and C_{GG} is 2 mM and 0.025%, respectively.

structure of $CaCO_3$ spheres. Furthermore, A range of parameters, namely concentration of Ca^{2+} and GG (C_{Ca} and C_{GG}), reaction temperature, were investigated to shed light on the ways how the polymer influences the $CaCO_3$ growth. Encapsulation study, in which vancomycin hydrochloride was chosen as a model drug, was used to ensure whether the porous hollow sphere is suitable for using as capsules.

2. Material and methods

A typical product was synthesized as follows: 4 mM $CaCl_2$ was dissolved into 10 ml deionized water containing 0.05% GG, then a solution of Na_2CO_3 (4 mM, 10 ml) was injected into the former solution under vigorous stirring by using a magnetic stirrer. The mixture was kept in a water bath at certain temperature condition, after reacting for 24 h, the resulting precipitates were washed with deionized water, centrifuged and lyophilized. Then, 20 mg microsphere were well dispersed throughout the phosphate buffer solution (PBS, 1 mM) through magnetic stirring for 30 min; then 20 mg vancomycin (VCM) powder was added, and the mixture was further stirring for 12 h at room temperature. After that the vancomycin loaded $CaCO_3$ microsphere were washed three times with PBS and collected by centrifugal. The drug releasing behavior of VCM was conducted by immersing the VCM into PBS (10 ml, 4 g/L) with different pH value at 180 rpm and 37 °C for a given time. The supernatant (2 ml) was obtained at predetermined time intervals using a pipette through centrifugation at 5000 rpm, and an equal volume of the fresh medium was added. All of the samples were collected and stored at 4 °C for further characterizations. The loaded drug content was calculated by using the following equation [17].

$$\text{Drug loading}(\%) = (W_d - W_r)/W_s \times 100\%$$

where W_d, W_r and W_s represent the total weight of VCM, the weight of VCM in the supernatant and the total weight of $CaCO_3$ loaded with VCM, respectively.