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A doxorubicin delivery system: Samarium/mesoporous bioactive glass/alginate composite microspheres

Ying Zhang *, Xiang Wang, Yanli Su, Dongya Chen, Wenxing Zhong

College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China

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ABSTRACT

Samarium (Sm) incorporated mesoporous bioactive glasses (MBG) microspheres have been prepared using the method of alginate cross-linking with Ca^{2+} ions. The in vitro bioactivities of Sm/MBG/alginate microspheres were studied by immersing in simulated body fluid (SBF) for various periods. The results indicated that the Sm/MBG/alginate microspheres have a faster apatite formation rate on the surface. To investigate their delivery properties further, doxorubicin (DOX) was selected as a model drug. The results showed that the Sm/MBG/alginate microspheres exhibit sustained DOX delivery, and their release mechanism is controlled by Fickian diffusion according the Higuchi model. In addition, the delivery of DOX from Sm/MBG/alginate microspheres can be dominated by changing the doping concentration of Sm and the values of pH microenvironment. These all revealed that this material is a promising candidate for the therapy of bone cancer.

1. Introduction

Bone cancer is one of the devastating diseases. At present, the treatment of bone cancer includes surgical removal followed by a bone graft in the bone defect sites, as well as radiation and chemotherapeutic drugs that can also kill healthy cells and cause toxicity to the patient. An effective way to overcome this problem involves the design and construction of a controllable anti-cancer drug delivery system for the implant sites. Controllable drug delivery system is defined as a formulation or a device that enables the introduction of a therapeutic substance in the desired body location and improves the sake of safety and therapeutic efficacy by controlling the rate, time and location of drug delivery [1–3]. Functional drugs are playing a particularly critical role in inducing bone regeneration and preventing infection of wounds such as doxorubicin (DOX). DOX, as a model drug, is preferentially used for the treatment of variety of cancers, such as lung cancer, osteogenic sarcoma and malignant lymphoma [4,5]. The kinetics of DOX depends not only on the pH of the environment and drug-loading concentrations but also on the composition of matrix [6,7]. However, DOX is a universal anti-cancer drug that causes irreversible cardiac toxicity following multiple dosing in treatments for cancer [8,9]. To overcome this problem, the microsphere system has been developed for the targeted delivery of DOX. Compared to traditional block or film materials, the prominent advantage of microspheres is that they not only possess the higher specific surface area, pore volume and loading efficiency of drug, but also can be injected into targeted bone tumor sites [1,10]. This is a useful contribution from the point of view of clinical applications.

Previous studies have shown that multifunctional MBG microspheres may be used as drug delivery systems because they are biocompatible and degradation over time in the body compared to mesoporous SiO_2 nanoparticles [11,12]. It is difficult to prepare pure MBG microspheres through a traditional sol-gel method [1,13]. There are several studies about the synthesis of MBG microspheres [14,15], one of which is using the method of alginate cross-linking with Ca^{2+} ions [1]. Calcium alginate is considered as one of the promising materials as a bioactivity matrix [16–18]. When alginate cross-linked with calcium ions to form sphere materials can easily incorporate MBG powders to form composite microspheres. Moreover, the MBG/alginate composite microspheres have shown an in vitro drug loading and DEX release ability higher than conventional sol-gel glasses [1,13]. This major feature made the MBG microspheres be a favorite material for drug delivery system.

At the same time, refining the composition of glasses matrix has always been an area of interest in the field of biomaterial. The inorganic glass matrix of MBG could be refined by incorporating small quantity rare earth ions as trace elements, such as cerium [19,20], europium [21], gallium [20] and terbium [22]. The biological properties of the rare earth ions, primarily based on their similarity to Ca ions, have been the basis for research into potential therapeutic applications in recent years [23–25]. Samarium (Sm), as a rare earth element, with bear unique electronic and optical characteristics arising from their 4f electrons has received a lot of attention in many fields [26,27]. However, its potential role in biomedical application has been unnoticed. Especially, Sm (III) has a marked bioinorganic similarity to Ca in ionic radii and coordination properties. This key feature would make it be a bright and highly promising new development in the field of bone cancers. Therefore, the aim of this study was to incorporate Sm^{3+} ions into

* Corresponding author.
E-mail address: yingzhang@suda.edu.cn (Y. Zhang).

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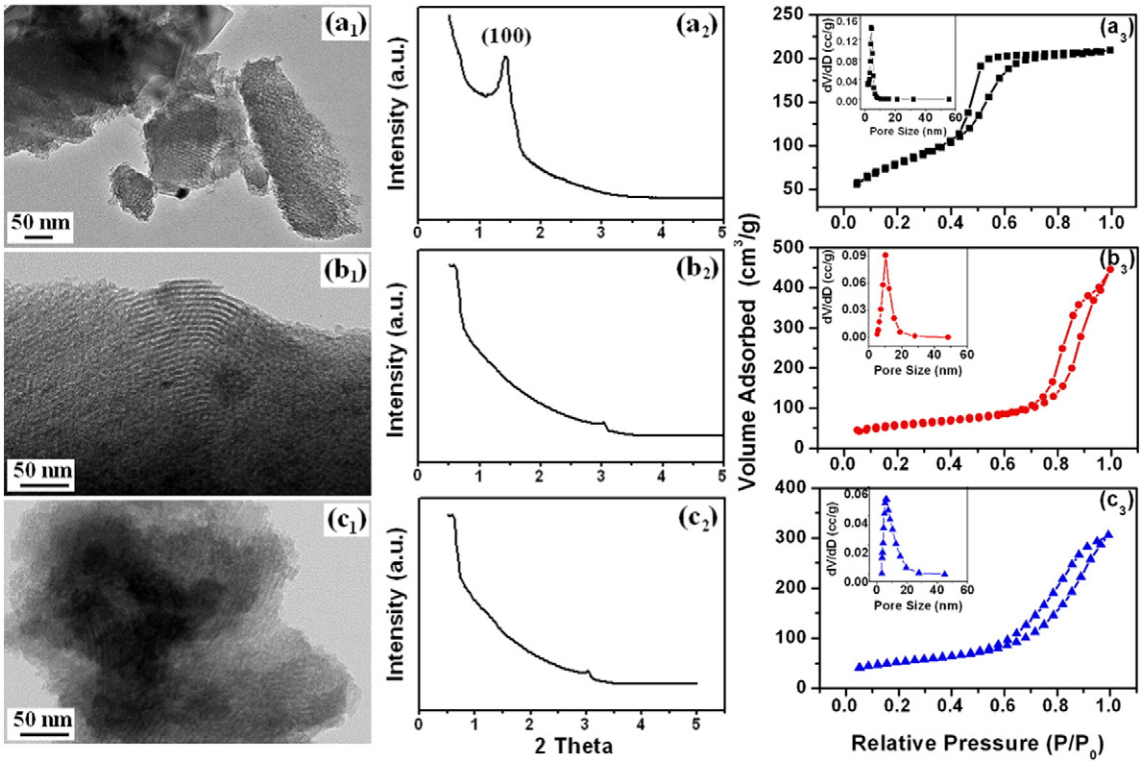

Fig. 1. TEM morphology of 0Sm/MBG powders (a_1), 0.5Sm/MBG powders (b_1), 1Sm/MBG powders (c_1); SXRD analysis of 0Sm/MBG powders (a_2), 0.5Sm/MBG powders (b_2), 1Sm/MBG powders (c_2); BET analysis of 0Sm/MBG powders (a_3), 0.5Sm/MBG powders (b_3), 1Sm/MBG powders (c_3).

MBG using the method of alginate cross-linking with Ca^{2+} ions to formed Sm/MBG/alginate composite microspheres, and optimize their physicochemical and biological properties to investigate DOX delivery properties for the therapy of bone cancer.

2. Materials and methods

2.1. Materials

Tetraethyl orthosilicate (TEOS), triethyl phosphate (TEP), Calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$), ethanol, hydrochloric acid (HCl, 37%), alginate (viscosity 20–40 cP), Calcium chloride anhydrous ($CaCl_2$) and samarium (III) nitrate hexahydrate ($Sm(NO_3)_3 \cdot 6H_2O$, 99.9%, Aladdin) were obtained from Sinopharm Chemical Reagent Co., Ltd. Non-ionic block polymer P123 (EO20-PO70-EO20, M_w 5800) was obtained from Sigma-Aldrich. All of the chemicals were used as received without further purification.

2.2. Synthesis of microspheres

2.2.1. Synthesis of Sm/MBG powders

Samarium doped mesoporous bioactive glasses powders (Sm/MBG) were prepared by incorporating 0.5 and 1Sm (mol%) into MBG to replace portions of the silicon (Si) using the P123 template [2]. In a typical synthesis of 0.5Sm/MBG, 4.0 g of P123, 6.55 g of TEOS, 1.4 g of Ca $(NO_3)_2 \cdot 4H_2O$, 0.73 g of TEP, 0.088 g of $Sm(NO_3)_3 \cdot 6H_2O$ and 1.0 g 0.5 M HCl were dissolved in 60 g of ethanol and stirred at room temperature for 24 h. The resulting sol was introduced into a petri dish for an evaporation-induced self-assembly process, and then the dry gel was calcined at 700 °C for 5 h to obtain the 0.5Sm/MBG powders. MBG powders without Sm (0Sm/MBG) and with 1% Sm (1Sm/MBG) were prepared using the same method except for their Sm content. The morphology and microstructure of the Sm/MBG powders was investigated using transmission electron microscopy (TEM, FEI Tecnai G-20, America). Brunauer-Emmett-Teller and Barrett-Joyner-Halenda analyses were employed to determine the specific surface area, the nanopore size distribution and the pore volume of Sm/MBG powders by the N_2 adsorption-desorption isotherms (BET, ASAP2020 (M + C), America). The small-angle X-ray diffraction (SAXRD) of samples was performed on an X-ray diffractometer (XRD, X'Pert-Pro MPD, Netherlands) using Cu Kα radiation (λ = 1.5406 Å). SXRD patterns were collected in the detection range between 0.5° and 5°, with a step size of 0.02° and a counting time of 5 s per step.

2.2.2. Synthesis of Sm/MBG/alginate composite microspheres

First, a certain amount of Sm/MBG powders was added into a 3% (w/v) concentration of alginate solution, stirred for 1 h and ultrasonicated for 5 min to form homogenous mixtures. The mass ratio of Sm/MBG powders/alginate is 1.67. Second, the mixtures were extruded dropwise with a 0.70 mm diameter needle into a 0.1 M $CaCl_2$ crosslinking solution to form spherical particles. The microspheres were hardened in the crosslinking solution for 30 min, then filtered and dried at 50 °C to obtain the Sm/MBG/alginate microspheres. The microstructures of the Sm/MBG/alginate microspheres was investigated using scanning electron microscopy (SEM, S-4700, Japan) and Fourier transform infrared spectroscopy (FTIR, VERTEX80, Germany).

2.2.3. Synthesis of DOX-loaded Sm/MBG/alginate composite microspheres

DOX-loaded Sm/MBG/alginate composite microspheres were synthesized according to the previous work [1]. The synthetic process is as follows. DOX (Sigma, 99%) served as a model drug, was dissolved in water at a final concentration of 0.1 mg/mL and then added to the Sm/