Available online at www.sciencedirect.com

ScienceDirect

Ceramics International 42 (2016) 2281–2288

CERAMICS INTERNATIONAL

www.elsevier.com/locate/ceramint

Preparation of calcium carbonate@graphene oxide core–shell microspheres in ethylene glycol for drug delivery

Zhihang Zhou, Yanbao Li*, Song Yao, Haichen Yan

College of Materials Science and Engineering, Nanjing Tech University, Nanjing 210009, China

Received 9 August 2015; received in revised form 4 October 2015; accepted 5 October 2015
Available online 21 October 2015

Abstract

Calcium carbonate@graphene oxide core–shell microspheres were prepared through encapsulation of graphene oxide (GO) sheets on the surface of calcium carbonate ($CaCO_3$) microspheres. Ethylene glycol was used as encapsulation medium to prevent GO aggregation in the dispersion system. The optimum encapsulation condition was determined through experiments to ensure that GO can be completely encapsulated on the surface of $CaCO_3$ microspheres. The optimum encapsulation temperature was 50 °C, and the optimum encapsulation time was 4 h. The structure of $CaCO_3$@GO microspheres was examined via field emission scanning electron microscopy. Results show that the core–shell microspheres had a uniform size of 3–4 μm when encapsulated under optimum encapsulation condition. The saturated encapsulation ratio of GO, which was calculated via UV–vis spectroscopy, was approximately 28%. The GO sheets were reduced with increasing encapsulation temperature during the preparation of $CaCO_3$@GO microspheres. GO reduction was examined via Raman spectroscopy and UV–vis spectroscopy. The GO sheets in ethylene glycol reduced at high encapsulation temperature. Furthermore, the drug-loading capacity of $CaCO_3$@GO microspheres increased from 38% to 52%, and the drug release time increased from 4.5 h to 6 h. Given these results, $CaCO_3$@GO microspheres have potential application as new drug carriers.

Keywords: Calcium carbonate; Graphene oxide; Ethylene glycol; Core–shell structure; Drug carrier

1. Introduction

Studies on novel kinds of sustained-release drug carriers have been developed to achieve long-term treatment of lesions and diseases. The structure design of drug carriers is important for their synthesis and affects drug-loading capacity and drug release time. Microspheres are commonly used as drug carriers [1–3] because of their high specific surface area. The application of microspheres as drug carriers began in the last century. Among the several types of microspheres (e.g., solid, porous, mesoporous, and core–shell), core–shell microspheres have attracted considerable attention because of their unique structure. Core–shell microspheres are well-ordered assembly structures that are synthesized through chemical bonding or other forms of interaction between two materials. Core–shell microspheres can be prepared through several methods, such as self-assembly [4], surface deposition [5], emulsification [6], and stepwise heterocoagulation methods [7]. The self-assembly method is the most widely used among other methods in the preparation of core–shell microspheres because of its easy operability. Moreover, selecting core and wall materials is important in the preparation of high-performance core–shell microspheres because it can affect both drug-loading capacity and drug release time.

Calcium carbonate ($CaCO_3$) has been studied for many years as a traditional core material to prepare core–shell microspheres [8,9]. $CaCO_3$ possesses high specific surface area, good biocompatibility, and good dispersion in aqueous solutions. These advantages have considerable potential for industrial, medical, and biological applications [10]. $CaCO_3$ is also a suitable material to be encapsulated with wall materials in the preparation of core–shell microspheres for drug delivery because of their advantages. The utilization of $CaCO_3$ for drug delivery has already been studied. Volodkin et al. [11] employed porous $CaCO_3$ microspheres with a size of 4.75 μm to load

*Corresponding author.
E-mail addresses: lyanbao@163.com, ybli@njtech.edu.cn (Y. Li).

http://dx.doi.org/10.1016/j.ceramint.2015.10.022
0272-8842/

lactalbumin. Li et al. [12] examined the drug release profiles of ibuprofen-loaded $CaCO_3$ hollow microspheres. The results of Li et al.'s study showed that the $CaCO_3$ microsphere drug delivery system has high drug-loading capacity and good sustainable release. Although $CaCO_3$ microspheres demonstrate efficient drug delivery performance, one type of suitable material should be considered to encapsulate on the surface of $CaCO_3$ microspheres to improve their drug delivery performance.

Graphene oxide (GO) has drawn the interest of several researchers because of its unique properties. GO sheets possess typical 2D structure and numerous oxygen-containing groups, such as hydroxyl, carboxyl, and epoxy groups [13]. Because of these functional groups, GO exhibits good hydrophilic property, which enables dispersion stability in water or in several organic polar solvents. GO has potential applications in electrochemical devices [14,15], energy storage [16,17], catalysis [18], enzyme adsorption [19], cell imaging [20], drug delivery [21,22], biosensors [23], and antibacterial papers [24]. Furthermore, $CaCO_3$ microspheres can be wrapped and interconnected by a GO network because of the oxygen-containing functional groups [25]. However, the dispersion of GO in water containing calcium ions is problematic because of the carboxylic groups that interact with these calcium ions [26,27]. When the GO sheets encapsulate the $CaCO_3$ microspheres with water as the dispersion medium, the GO sheets agglomerate during encapsulation, which ultimately causes the failure of this process. This agglomeration, which comes from the reaction of GO with $CaCO_3$ through the formation of –COOCaOOC–, limits the preparation and application of composite microspheres. Researchers have conducted studies to prevent this problem. Fan et al. [28] initially encapsulated $CaCO_3$ microspheres with polyethylenimine. The surface of the composite microspheres was then encapsulated with the GO sheets. Kurapati et al. [29] used poly(allylamine hydrochloride), which is a stable material, to encapsulate $CaCO_3$ core, and GO sheets were then used to encapsulate the microspheres. Both of these studies used one type of polymer that can provide the positive charge necessary to attach the GO sheets for the preparation of core–shell microspheres via layer by layer self-assembly. Meanwhile, these positively charged materials may prevent the contact of the GO sheets with the $CaCO_3$ core, which can lead to agglomeration. Therefore, the GO sheets can be encapsulated on the microsphere surface, and the redundant GO sheets can be easily separated. However, studies about the direct encapsulation of $CaCO_3$ with GO sheets are rare.

The aforementioned issues are resolved using organic solvents as dispersion media in place of water. Organic solvents are common dispersion media; however, most of these solvents are harmful to the environment because of their toxicity and difficulty in recycling. Considering whether or not the dispersion medium can protect drugs, wall materials, and core materials is also an important factor in preparing core–shell drug-loaded microspheres. Ethylene glycol is a common organic solvent and has low toxicity and easy recyclability. Moreover, the $CaCO_3$ microspheres are easily dispersed in ethylene glycol, which can also protect the crystalline phase of vaterite [30]. The GO sheets can also be dispersed in ethylene glycol better than in other organic solvents [31]. Ethylene glycol is therefore a good choice of dispersion medium in the preparation of $CaCO_3$-based core–shell structure.

In this work, the $CaCO_3$ microspheres were encapsulated with the GO sheets in ethylene glycol by the self-assembly method to prepare $CaCO_3$@GO microspheres. This strategy can also prevent GO agglomeration in the presence of calcium ions. The strategy may have potential application in the biomedical and absorption treatment fields.

2. Experimental section

2.1. Materials

Graphite powder, hydrogen peroxide (H_2O_2, 30.0%), tris (hydroxymethyl) aminomethane (Tris), and anhydrous sodium sulfate (Na_2SO_4) were purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Sulfuric acid (H_2SO_4, 98.0%), potassium permanganate ($KMnO_4$), hydrochloric acid (HCl, 37.0%), sodium carbonate (Na_2CO_3), sodium hydrogen carbonate ($NaHCO_3$), di-potassium hydrogen phosphate trihydrate ($K_2HPO_4 \cdot 3H_2O$), and ammonium hydroxide ($NH_3 \cdot H_2O$, 25–28%) were obtained from Shanghai LingFeng Chemical Reagent Co. Ltd. Sodium nitrate ($NaNO_3$), sodium chloride (NaCl), calcium chloride anhydrous ($CaCl_2$), magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$), and calcium acetate monohydrate ($Ca(CH_3COO)_2 \cdot H_2O$) were acquired from XiLong Chemical Co. Ltd. (Guangzhou, China). Ethylene glycol, ethanol, and n-hexane were purchased from Shanghai No. 4 Reagent & H.V. Chemical Co. Ltd. (Shanghai, China). Ibuprofen and poly(styrene sulfonic acid) sodium salt were obtained from Wuhan Bright Chemical Co. Ltd. (Wuhan, China) and Alfa Aesar Chemical Co. Ltd. (Shanghai, China), respectively. All reagents were of analytical grade and used without further purification.

2.2. Preparation of graphene oxide

GO was prepared using a modified Hummers' method [32,33]. Approximately 46 mL of H_2SO_4 was added into a 500 mL round-bottom flask under agitation. Subsequently, 1 g of graphite powder and 1 g of $NaNO_3$ were successively added into the round-bottom flask in an ice bath. The mixture was stirred for 30 min and 6 g of $KMnO_4$ was then slowly and gradually added. Afterward, the round flask was transferred into a 35 °C water bath, and the suspension was stirred for approximately 1 h. Distilled water (92 mL) was gradually added to the mixture to maintain the temperature below 100 °C. The flask was then placed into an oil bath at 100 °C, and the reaction was maintained at this temperature for 15 min. The mixture was further treated with 150 mL of distilled water and 5 mL of H_2O_2 solution (30%) until the color changed from brown to bright yellow. The prepared graphite oxide could be easily isolated from the solution through filtration. The product was washed and centrifuged using 5 wt% aqueous hydrochloric acid solution and distilled water to remove metal ions. The washing procedure was repeated until the supernatant was neutral. GO was obtained through ultrasonic drying and freeze drying. GO