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Chemical template-assisted synthesis of monodisperse rattle-type Fe_3O_4@C hollow microspheres as drug carrier

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ABSTRACT

A chemical template strategy was put forward to synthesize monodisperse rattle-type magnetic carbon (Fe_3O_4@C) hollow microspheres. During the synthesis procedure, monodisperse Fe_2O_3 microspheres were used as chemical template, which released Fe^{3+} ions in acidic solution and initiated the in-situ polymerization of pyrrole into polypyrrole (PPy) shell. With the continual acidic etching of Fe_2O_3 microspheres, rattle-type Fe_2O_3@PPy microspheres were generated with the cavity appearing between the PPy shell and left Fe_2O_3 core, which were then transformed into Fe_3O_4@C hollow microspheres through calcination in nitrogen atmosphere. Compared with traditional physical template, the shell and cavity of rattle-type hollow microspheres were generated in one step using the chemical template method, which obviously saved the complex procedures including the coating and removal of middle shells. The experimental results exhibited that the rattle-type Fe_3O_4@C hollow microspheres with different parameters could be regulated through controlled synthesis of the intermediate Fe_2O_3@PPy product. Moreover, when the rattle-type Fe_3O_4@C hollow microspheres were investigated as drug carrier, they manifested sustained-release behaviour of doxorubicin, justifying their promising applications as carriers in drug delivery.

Statement of Significance

The aim of the present study was first to synthesize rattle-type Fe_3O_4@C hollow microspheres through a simple synthesis method as a drug carrier. Here a chemical template synthesis of rattle-type hollow microspheres was developed, which saved the complex procedures including the coating and removal of middle shells in traditional physical template. Second, all the influence factors in the reaction processes were systematically investigated to obtain rattle-type Fe_3O_4@C hollow microspheres with controlled parameters. Third, the rattle-type Fe_3O_4@C hollow microspheres were studied as drug carriers and the influences of their structural parameters on drug loading and releasing performance were investigated.

1. Introduction

Hollow microspheres are of great interest in many current and emerging areas of technology, which have displayed new phenomena and applications for combining the merits of hollow and porous shell structures [1]. Recently, lots of hollow capsules have been designed with the shell composition either organic or inorganic species according to different application fields [2–4]. At present, hollow carbon microspheres have attracted much attention for their high surface area, low density, good electric conductivity, thermal and chemical stabilities, which exhibited excellent performance as adsorbents, catalyst supports, storage materials, sensors, supercapacitors, and lithium-ions batteries, and even served as building blocks for complex structures [5–12].

Recently, carbon materials for drug delivery have attracted researchers' attention, for they possess sufficient surface-to-volume ratio, thermal conductivity, rigid structural properties capable of post-chemical modification, and excellent biocompatibility [13]. Carbon hollow microspheres have also been demonstrated to be an excellent drug carrier for their large drug-loading capacity in recent years [14–17]. However, hollow carbon microspheres suffered from some inherent limitations as a drug carrier, such as

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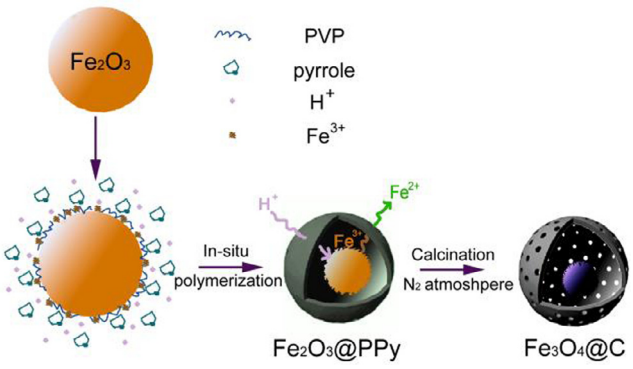
how to separate them efficiently or carry a drug to the target locations in the body. A possible solution is to create a cavity between the mesoporous shell and the inner magnetic core [18–23], for example, a rattle-type magnetic hollow carbon microsphere, which combined the merits of the high drug loading capacity and the targeted delivery property. As an important extension of core-shell particles, rattle-type hollow microspheres have recently been synthesized by template strategies that involve the preparation of a middle layer and outer shell on a preformed inner core and subsequent removal of the middle layer [24–31]. For example, Wan and Yin et al. reported the synthesis of rattle-type magnetic Fe_3O_4/C hollow microspheres through successive coating of silica and carbon precursor shell (C_{18}TMS) around Fe_3O_4 template, and the subsequent treatment including thermal reduction under N_2 atmosphere and removal of the middle layer transformed $Fe_3O_4/SiO_2/C_{18}$TMS into rattle-type magnetic Fe_3O_4/C hollow microspheres [30,31]. Guo et al. fabricated rattle-type Fe_3O_4@C hollow microspheres through calcination of multi-shelled Fe_3O_4@PF@PS@PF microspheres, where hollow cavity could be generated through decomposition of the PS shell and carbon shell through carbonization of PF shell [26].

However, the above-mentioned traditional methods often required insertion of the middle layer and their following selective removal by just using Fe_3O_4 microspheres as physical template. Besides, the disadvantages related to tedious synthetic procedures and low yields have also impeded the scale-up production and large-scale applications. Therefore, how to develop a facile and efficient route becomes the major aim for the fabrication of magnetic rattle-type hollow microspheres. Herein, we present a novel strategy for the synthesis of magnetic carbon (Fe_3O_4@C) rattle-type hollow microspheres through chemical template method, rather than the traditional multi-step coating and subsequent treatment. In our method, the synthesis strategy using uniform Fe_2O_3 microspheres as chemical template is illustrated in Scheme 1, the PVP-modified monodispersed Fe_2O_3 microspheres were firstly dispersed in pyrrole solution; and then lots of Fe^{3+} ions were released from Fe_2O_3 microspheres through acidic etching and initiated the polymerization of pyrrole monomers in-situ around the Fe_2O_3 microspheres. The continual etching of Fe_2O_3 microspheres and in-situ polymerization of pyrrole lead to the generation of rattle-type Fe_2O_3@PPy hollow microspheres. At last, the as-obtained intermediate Fe_2O_3@PPy products were transformed into rattle-type Fe_3O_4@C hollow microspheres through calcination in nitrogen atmosphere. To explore their capability as drug carriers, doxorubicin (DOX), a typical anticancer drug, was introduced into the cavity of the rattle-type Fe_3O_4@C hollow microspheres, which exhibited pH-controlled sustained drug release property. The above chemical template strategy has three advantages when compared with traditional methods reviewed above, including (1) the non-magnetic Fe_2O_3 cores are easier to control in aqueous solutions compared with magnetic Fe_3O_4 cores; (2) the PPy shells are generated through in-situ polymerization, which is simpler than traditional heterogeneous deposition; (3) the chemical template method avoids multi-step coating and the removal process of middle layer in traditional physical template method. Therefore, the developed strategy is potential for scale-up production of rattle-type Fe_3O_4@C hollow microspheres as drug carrier.



Scheme 1. Synthesis of rattle-type Fe_3O_4@C hollow microspheres using Fe_2O_3 as chemical template.

2. Experimental section

2.1. Chemicals

Iron(III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), pyrrole, urea, sodium polyacrylate (PAAS), polyvinyl pyrrolidone (PVP), sodium citrate and ethanol were purchased from Sinopharm Chemical Reagent Co., Ltd. Phosphate buffered saline (PBS, 0.02 M) solutions with different pH values were prepared according to the well-documented procedures. All the reagents were of analytical grade.

2.2. Preparation of Fe_3O_4@C microspheres

The monodisperse Fe_2O_3 microspheres with a diameter of about 200 nm were prepared through a modified hydrothermal reaction [32]. In a typical synthesis, after $FeCl_3{\cdot}6H_2O$ (1 g), sodium citrate (2.4 g), and urea (0.8 g) were dissolved in distilled water (80 mL), PAAS (0.6 g) was added under continuous stirring until it was totally dissolved. The mixture was transferred to a 100 mL Teflon-lined autoclave with magnetic stirrer, which was sealed and maintained at 200 °C for 3 h. Then red product was collected after repeated washing with deionized water and dried in a vacuum oven at 60 °C.

The as-obtained Fe_2O_3 microspheres (0.1 g) were then dispersed in a water-ethanol mixture including PVP (0.2 g) under a magnetic stirrer for 30 min at room temperature (20 °C). After the above solution was stirred for 2 h, pyrrole and 3 mL HCl solution (12 M) was added in turn. After the above solution was gently stirred for 90 min, the product was collected by centrifugation at 7000 rpm for 3 min and washed thoroughly with deionized water and ethanol, and finally dried in a vacuum oven at 60 °C overnight. The product was calcined at 500 °C for 3 h under nitrogen atmosphere, and the black powder was rattle-type Fe_3O_4@C hollow microspheres, which could be easily collected by a magnet.

2.3. Characterizations

The size and morphology of the as-synthesized materials were measured using a Hitachi S-5500 Field-emission scanning electron microscope (FE-SEM, Tokyo, Japan), JEOL JEM-2010 high-resolution transmission electron microscope (HRTEM, Kyoto, Japan). The composition of products were analyzed by X-ray diffraction (XRD, Philips X'pert diffractometer), in a 2θ range from 20° to 80° and Infrared Fourier Transform Spectrometer (FT-IR, AVATAR360, Nicolet, U.S.). Magnetic measurements were performed with a superconducting quantum interference device (SQUID, Quantum Design MPMS) magnetometer at room temperature (300 K). Nitrogen sorption isotherms were obtained at 273 K with a Quadrasorb TM SI Four Station Surface Area Analyzer and Pore Size Analyzer (Quantachrome Instruments, Boynton Beach, FL). UV–Vis spectra were recorded using a Beckman DU 800 nucleic acid/protein analyzer (Beck-man Instruments, Inc., Rosemead, CA). The chemical composition and chemical states of the final products were further investigated by X-ray photoelectron spectroscopy (XPS, Axis Ultra).