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Facile synthesis of yolk–shell structured monodisperse mesoporous organosilica nanoparticles by a mild alkalescent etching approach

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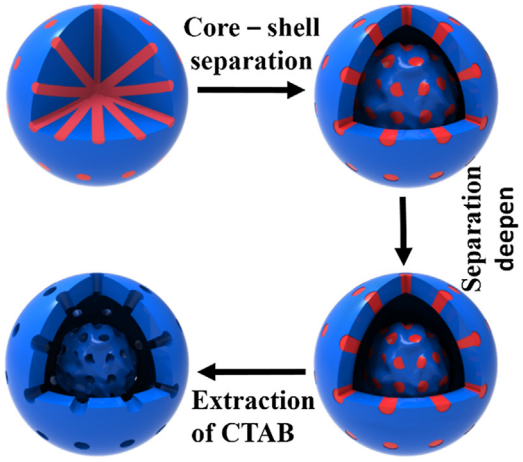
GRAPHICAL ABSTRACT

The yolk–shell structured mesoporous organosilica nanoparticles are successfully prepared by a mild alkalescent etching approach.



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ABSTRACT

In the work, yolk–shell structured mesoporous organosilica nanoparticles (YSMONs) are successfully prepared by a mild alkalescent etching approach. The method is very convenient, in which mesostructured organosilica nanospheres are directly transformed into yolk–shell structures after etching with mild alkalescent solution (e.g. sodium carbonate solution). The prepared YSMONs have ethane-bridged frameworks, a monodisperse diameter (320 nm), a large pore volume (1.0 $cm^3 g^{-1}$), a uniform mesopore (2.4 nm) and a high surface area (1327 $m^2 g^{-1}$). *In vitro* cytotoxicity and hemolysis assays demonstrate the ethane-bridged YSMONs possess excellent biocompatibility and low hemolysis activity. In addition, the YSMONs show a high loading capacity up to 181 μg mg^{-1} for anti-cancer drug doxorubicin (DOX). Confocal laser scanning microscopy and flow cytometry analyses show that the DOX loaded YSMONs (YSMONs-DOX) can be effiectively internalized by multidurg resistant MCF-7/MDR human breast cancer

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cells. The chemotherapy against MCF-7/MDR cells demonstrate that the YSMONs-DOX possess higher therapeutic efficacy compared to that of free DOX, suggesting that the YSMONs synthesized by the mild alkalescent etching method have great promise as advanced nanoplatforms for biological applications.

1. Introduction

Yolk–shell structures with interior core, large void space, and outer shell have attracted increasing interests because of their appealing properties such as low density, high surface area, and confined environment for various applications including catalysis [1,2], nanoreactors [3,4], energy storage [5,6], and drug delivery [7–9]. Conceptually, yolk–shell structures can be prepared by hard- or soft-templating methods, in which organic/inorganic materials or vesicles are generally used as the intermediate sacrificial layers [10–14]. For instance, Zhao and co-workers consecutively coated magnetite nanoparticles with silica and titania shells, and then etching the intermediate silica layer to form yolk–shell microspheres [15]. Xu and co-workers prepared yolk–shell structures through deposition of silica shell on nanoparticle encapsulated vesicles [13]. However, the hard-templating methods involving multiple coating and etching procedures are cumbersome, uneconomic, and time-consuming [16]. The vesicles used in the soft-templating methods represent low thermodynamic stability and the obtained yolk–shell structures are often ill-defined in shape and polydispersed in size [17,18].

Self-templating methods are more simple, effective, and able to produce highly monodisperse yolk–shell structures because additional templates or coating processes are not required in the preparation procedures [19–21]. For example, Li et al. directly prepared yolk–shell structured semiconducting microparticles *via* rapid nucleation and recrystallization of metal oxide in hydrothermal conditions [22]. Our group demonstrated that nano-sized organosilicas can transform to yolk–shell structures *via* dissolution and reassembly of their frameworks during hydrothermal treatment. However, the self-templating methods for fabrication of the yolk–shell structures via hydrothermal treatment procedures require high pressure and temperature (~180 °C), which are energy-consuming and difficult to scale-up. Therefore, development of a mild method to fabricate yolk–shell structures is very desirable and valuable for different applications [23–27].

Herein, a mild alkalescent etching approach has been successfully developed to prepare yolk–shell structured mesoporous organosilica nanoparticles (YSMONs). This method is accomplished by selectively etching the intermediate layer of ethane-bridged organosilica nanospheres in an alkalescent solution (e.g. sodium carbonate solution), during which a structural transformation from solid to yolk–shell occurs. The prepared YSMONs possess a uniform diameter (320 nm), a large surface area (1327 $m^2 g^{-1}$), a high pore volume (1.0 $cm^3 g^{-1}$) and accessible pores (2.4 nm). The intermediate cavity in the YSMONs provides a large space for efficient drug loading, and the weight of YSMONs is lighter than MONs in the same number of particles which is beneficial to biological metabolism. In addition, the organic groups doped in the frameworks can enhance its biocompatibility [8,21]. *In vitro* hemolysis and toxicity assays show the YSMONs exhibit excellent biocompatibility. Furthermore, the YSMONs have a high loading capacity for anticancer drug doxorubicin (DOX) (181 μg mg^{-1}). Confocal laser scanning microscopy (CLSM) and flow cytometry (FCM) analyses demonstrate the YSMONs can effectively delivery DOX into MCF-7/MDR human breast cancer cells and significantly improve chemotherapeutic efficay.

2. Experiment

2.1. Materials

Cetyltrimethylammonium bromide (CTAB, ≥99%), anhydrous ethanol, concentrated ammonia aqueous solution (25 wt%), tetraethyl orthosilicate (TEOS, ≥28.4%), concentrated HCl (37%) sodium carbonate (Na_2CO_3, ≥98%), sodium phosphate (Na_3PO_4, ≥98%) and potassium carbonate (K_2CO_3, ≥99%) were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). 1,2-Bis(triethoxysily) ethane (BTSE, ≥96%) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Deionized water (Millipore) with a resistivity of 18.2 MΩ cm was used in all experiments. Roswell Park Memorial Institute (RPMI)-1640, phosphate buffered saline (PBS) and fetal bovine serum (FBS) were bought from Gibco/Life Technologies (Grand Island, New York, USA). 4,6-Diamidino-2-phenylindole (DAPI) was purchased from Santa Cruz Biotechnology (Santa Cruz, USA). DOX was obtained Beijing Hvsf United Chemical materials Co., Ltd. (China). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Nanjing Keygen Biotech. Co., Ltd. (Nanjing, China). Dimethyl sulfoxide (DMSO) was bought from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). MCF-7 and MCF-7/MDR human breast cancer cells were purchased from American Type Culture Collection (ATCC).

2.2. Preparation

Typically, ethane-bridged mesostructured organosilica nanospheres were first prepared *via* a CTAB-directing sol–gel process employing BTSE and TEOS as co-precursors. In typical, CTAB (0.16 g) was dissolved in a mixture of water (75 ml), ethanol (30 ml) and ammonia aqueous solution (1 ml, 25 wt%). The solution was stirred at a speed of 1100 rpm for 30 min at 35 °C, then a mixed precursors of BTSE (0.25 ml) and TEOS (0.25 ml) was rapidly added. After stirring for 24 h, mesostructured organosilica nanospheres were collected by centrifugation at 8000 rpm for 10 min and washed with water two times. The mesostructured organosilica nanospheres were subsequently dispersed in 30 ml of sodium carbonate solution (2.4 M, pH = 11.29) and shook at room temperature for 2 h. At last, the products were collected by centrifugation and the CTAB templates were extracted in a mixed solution containing ethanol (200 ml) and HCl (400 μl) three times at 60 °C. In addition, sodium phosphate solution (1 M, pH = 12.09) and potassium carbonate solution (1 M, pH = 12.18) were also used as the mild alkalescent etching agents to prepare the YSMONs.

2.3. Hemolytic assay

One milliliter of blood obtained from Jinling Hospital was centrifuged at 2000 rpm for 5 min to collect the red blood cells (RBCs). The obtained RBCs were diluted with physiological saline to 2 ml. The RBCs suspension (0.2 ml) was incubated with the ethane-bridged YSMONs in physiological saline (0.8 ml) at 37 °C for 2 h. RBCs incubated with water and physiological saline were set as the positive and negative control, respectively. Finally, the supernatants were collected to measure the absorbance at 630 nm. The hemolysis percentage of RBCs (%) were calculated by the