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Outside-in synthesis of mesoporous silica/molybdenum disulfide nanoparticles for antitumor application

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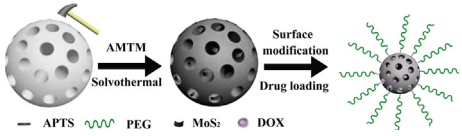
HIGHLIGHTS

- An outside-in synthesis of mesoporous silica nanoparticle/MoS_2.
- It is surface modified with polyethylene glycol.
- The method is based on solubility difference of ammonium tetrathiomolybdate.
- The product exhibits high drug loading efficiency and photothermal performance.
- The product can be used for combined tumor therapy both *in vitro* and *in vivo*.

GRAPHICAL ABSTRACT



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ABSTRACT

Very different from traditional inside-out method, which used guest material as the inside core and then surface-coated outer layer, herein, we propose a facile and unique outside-in approach for the synthesis of high dispersive mesoporous silica nanoparticle (MSN)/MoS_2-PEG nanoparticles (SMPs) based on the differences of precursor solubility in different solvents, for the first time. The prepared SMPs exhibit both higher drug loading efficiency of 64.7% owing to the pore structure of mesoporous silica, and excellent photothermal performance with photothermal efficiency of 41.5% due to the inside decorated MoS_2 nanosheets, which could be used for the combination of tumor hyperthermia and chemotherapy. The *in vivo* results indicate that SMPs show great synergistic effect, *i.e.*, the heat produced during PTT can increase the chemotherapy sensitivity of DOX and synergistically improve its therapeutic effect. Such a facile strategy provides a new facile way to construct a novel theranostic agent by integrating different functions into one dosage, and shows a promising approach for the construction of nanomaterials using MSN as a template.

1. Introduction

Although numerous studies aimed at promoting cancer therapy efficiency have been carried out, cancer remains a worldwide devastating disease with high mortality [1]. Chemotherapy, alone or combining with radiotherapy, is still the standard tumor treatment approach following surgical resection [2]. However, there remained some unavoidable deficiencies, such as damage to normal tissue, poor

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selectivity, multi-drug resistance to chemotherapy [3,4], and radio-resistance to radiotherapy [5,6], generally result in a poor prognosis. Over the past decades, several physical cancer treatment protocols including photothermal therapy (PTT), photodynamic therapy, magnetic-hyperthermia regression, microwave ablation, and high intensity focused ultrasound ablation, etc., have been developed as alternatives to overcome the aforementioned shortcomings [7–13]. Thereinto, PTT has attracted considerable attention for localized hyperthermia cancer therapy. The first prerequisite for efficient tumor PTT is to design intelligent photo-absorbing agent (PTA) that is thermally durable and biocompatible to efficiently transduce the absorbed near-infrared (NIR) laser into heat and ablate the tumor. However, to achieve a desirable tumor ablation outcome, high light intensity, high PTA concentration, or repeated administration of PTA is needed [14]. Thus, it is highly desirable that a PTA system possesses both chemo- and photothermal therapeutic functions to avoid complex administration and improve patient compliance [15]. The combination of hyperthermia and chemotherapy is a promising approach to achieve optimized antitumor efficacy, leading to synergistic effects that are greater than each treatment alone [16]. Moreover, the heat produced during PTT can increase the sensitivity of chemotherapy and synergistically improve therapeutic effects [17].

Representatively, biocompatible MoS_2 nanosheets, which can be synthesized using either top-down or bottom-up strategy, have been reported and expanded rapidly as PTAs because of their good biocompatibility and excellent photothermal performance [7,18,19]. The top-down exfoliated polyethylene glycol (PEG) and chitosan-modified MoS_2 showed effective loading of a variety of therapeutic molecules and were successfully used for synergistic tumor photothermal and chemotherapy ablation in lab [18,19]. To date, a simple method for mixing bottom-up synthesized MoS_2 with drugs to attain drug loading, however, remains challenging, because this kind of MoS_2 often stacks with each other to form a multi-layer structure that limits the loading efficiency [7]. On this occasion, searching a facile approach for integrating the drug-loading and photothermal effectiveness of bottom-up synthesized MoS_2 nanosheets into one dosage would be of great interest in facilitating the biomedical translational trials of MoS_2 based nanoplatforms.

Mesoporous silica nanoparticles (MSNs), which have a large surface area and pore volume, have attracted considerable attention for their applications in drug delivery and biomedicine [9]. Over the past decades, MSNs played important role in immediate/sustained drug transport systems for targeted delivery of biotherapeutic agents, bioimaging agents, and other bioactive materials [20–23]. In light of the ease in handling, scalability, low cost, and high drug load capacity of MSNs and the attractive photothermal properties of MoS_2 nanosheets, we herein develop a simple outside-in method to direct grow well-dispersed MoS_2 nanosheets within MSN pores. MSN pore was used not only as a vehicle for drug loading and transporting, but also as a micro-reactor for the solvothermal synthesis of MoS_2 nanosheets based on differences in solubility of precursor that used to synthesize MoS_2 nanosheets (ammonium tetrathiomolybdate, $(NH_4)_2MoS_4$), AMTM) in different solvents. To improve physiological stability, the MoS_2 nanosheets decorated MSNs were further surface modified with PEG, to form modified, *i.e.*, MSN/MoS_2-PEG nanoparticles (denoted as SMPs), via the mediation of silane coupling agents (e.g., 3-aminopropyltriethoxysilane, APTS). Unlike traditional attempts to synthesize MNSs based composites, which used guest materials such as graphene, gold nanorods, and Fe_3O_4, etc., as the inside core and then surface coated with MSNs layer using a complicated process [17,24–26], we herein used MSNs as the outside template for the facile *in-situ* growth of guest MoS_2 nanosheets. Such a unique outside-in strategy features with low-cost, easy and scalable synthesis and more importantly, the MoS_2 nanosheets growth inside the pore have no influences on the mesoporous structure of MSNs. Therefore, the synthesized SMPs inherit both the drug loading features of MSNs and the photothermal efficiency of MoS_2, which could be employed for the ablation of colorectal carcinoma both *in vitro* and *in vivo* via the combination of PTT and chemotherapy. In addition, the heat produced from NIR irradiation could also trigger the drug release, thus enabling on-demand drug release and enhancing DOX chemotherapy sensibility. To the best of our knowledge, this is the first report of an outside-in solvothermal method for synthesis of MSNs/MoS_2-based nanoplatform for *in vitro* and *in vivo* tumor synergistic therapy.

2. Experimental

2.1. Materials

AMTM and APTS were purchased from J&K Chemical Co., Ltd. (Shanghai, China). Cetyltrimethylammonium Bromide (CTAB), triethanolamine (TEA), and tetraethoxysilane (TEOS) were purchased from Aladdin Reagent Co., Ltd (China). mPEG-Succinimidyl carbonate (mPEG-SC, MW = 10,000), Capstone FS-66 and trypan blue were purchased from Sigma-Aldrich (USA). PEG with a molecular weight of 400 Da (denoted as PEG-400), acetone, ethanol, phosphate acid, HF, HNO_3 and monoethanolamine were purchased form Sinopharm Chemical Reagent Co., Ltd., (China). Human colorectal carcinoma (HT29) cell line was obtained from the Institute of Biochemistry and Cell Biology (the Chinese Academy of Sciences, Shanghai, China). Cell culture reagents including Roswell Park Memorial Institute 1640 medium (RPMI-1640), fetal bovine serum (FBS), penicillin, streptomycin and phosphate buffer (PBS) were purchased from Gibco (Shanghai, China). The cell counting kit-8 (CCK-8) was purchased from Dojindo Laboratories (Japan). Cell culture flasks and plates were purchased form Corning Co., Ltd., (Shanghai, China). Balb/c nude mice and Kunming mice (KM, with a body weight of ~20*g*) were purchased from Shanghai Slac Laboratory Animal Center (Shanghai, China). Water used in this study was treated using the Pall Cascada laboratory water system to obtain a resistivity > 18.2 MΩ·cm. All chemicals were used as received.

2.2. Preparation of MSNs and SMPs

MSNs were synthesized according to our previous study [27]. Briefly, 1.92 g of CTAB, 0.32 g of Capstone FS-66, and 0.35 g of TEA were added to 100 mL water. The pH of the formed solution was adjusted to 7.4 with phosphate acid. Then, 15 mL TEOS was added dropwise to the solution and stirred for 4 h at 60 °C. The obtained particles were centrifuged and washed twice with ethanol and once with acetone. CTAB and Capstone FS-66 were removed by calcining at 550 °C for 5 h under air atmosphere.

MSNs/MoS_2 nanoparticles were prepared by adding 50 mg of MSNs and 325 mg of AMTM into 32.5 mL of an ethanol and water mixed solution (v:v = 7:3) followed by ultrasonic treatment for 30 min (300 w, SK1200H, Shanghai KUDOS Inc., China). Then, the dispersion was vacuumed at 15 °C in a rotary evaporator for 24 h to ensure the AMTM thoroughly occupied the mesoporous pores of the MSNs. The resulting red paste (MSNs/AMTM) was then transferred to a 100 mL polyphenylene-lined stainless steel autoclave containing 20 mL PEG-400 and heated at 220 °C in an oven for 12 h. The formed MSNs/MoS_2 nanoparticles were thoroughly washed once with a monoethanolamine solution (50%, in water, v/v) and three times with water and then lyophilized for further use.

For surface PEG modification, 50 mg of MSNs/MoS_2 nanoparticles were dispersed in 25 mL ethanol to which 100 μL APTS had been added in advance. The mixed solution was refluxed at 80 °C and then added to 80 mg mPEG-SC. The mixture was allowed to react with stirring for 12 h at room temperature (15 °C) to obtain SMPs.

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