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Highly stable molybdenum dioxide nanoparticles with strong plasmon resonance are promising in photothermal cancer therapy

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ABSTRACT

Photothermal therapy (PTT) is one of promising cancer therapy with high efficiency and minimal invasiveness. Exploiting of perfect PTT agent is vital to improve the therapy. In this study, a new type of bow tie-like molybdenum dioxide (MoO_2) nanoparticles was successfully synthesized. These nanobowties had strong localized surface plasmon resonance (SPR) effect from visible to near infrared regions, and exhibited ultrahigh chemical stability. They could not only withstand high temperature heating without oxidation, but also resist the corrosion of strong acid and alkali. Meanwhile, the MoO_2 nanoparticles were highly stable in protein-containing biological medium, though they partly degraded in PBS solution. Both *in vivo* and *in vitro* experiments indicated that they exhibited inappreciable toxicity. Under illumination of near infrared laser, they showed excellent PTT effect, as revealed by significant inhibition of cancer cell viability *in vitro* and efficient destruction in tumor tissue growth *in vivo*. These MoO_2 nanoparticles possessed highly chemical stability and low toxicity with high PTT efficiency, thus promising them high potential as nanoagent in cancer treatment.

1. Introduction

Nanomaterials and nanotechnology were rendered attractive for their oncological applications, owing to their unique features for drug delivery, miniature medical devices and therapeutic nature [1–5]. Nowadays, enormous progress has been made in the development of cancer nanomedicine, and some nanotherapies have been successfully in use [6–13]. For example, liposomes, albumin NPs and polymeric micelles have been approved for cancer treatment as therapeutic nanoparticle platforms [14], and many others are under investigation and show great potentials in clinical application [15].

Photothermal therapy based on near infrared (NIR) radiation is a promising alternative or supplement to traditional cancer therapy. Nanomaterials, such as noble-metal nanostructures, sulfide nanoparticles, and graphene have been explored as photothermal agents because of their therapeutic function upon the stimulation of near infrared (NIR) [16–25]. Among these materials, oxygen vacancy-rich transition metal oxides are particularly appealing due to their metallic features, strong surface plasmon resonance (SPR) effect, low cost and easy synthesis. For example, ultrathin $W_{18}O_{49}$ nanowires could be used as a 980 nm-laser-driven photothermal agent for efficient ablation of cancer cells *in vivo* [26,27]. Non-stoichiometric MoO_{3-x} nanosheets showed efficient tumor homing capabilities due to their strong localized-SPR effects in the near-infrared (NIR) region [28–30]. Although these oxygen vacancy-rich metal oxides showed attractive therapeutic capacities in cancer photothermal treatment, their chemical stabilities were poor, and could not resist the oxidation. As pointed out by previous studies, $W_{18}O_{49}$ and MoO_{3-x} nanomaterials are were easily oxidized by airbone oxygen even at room temperature due to high redox or catalytic activities of their oxygen vacancies [31–35]. Once the oxygen vacancies in crystal lattices were filled with oxygen, these metal oxides would rapidly lose localized-SPR effects, resulting in the vanishment of photothermal therapeutic properties. Therefore, it is of great importance to develop new effective and stable alternatives as photothermal agents for tumor treatments.

In this study, we successfully synthesized a new type of bow tie-like MoO_2 nanoparticles with strong localized-SPR effect, high photothermal conversion efficiency, and low toxicity. They had excellent chemical stability and biocompatibility. Both *in vitro* and *in vivo* experiments showed that MoO_2 nanoparticles could be used as an efficient photothermal therapy agent for the treatment of tumor tissues.

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2. Results and discussion

2.1. Morphology and chemical stability of MoO_2 nanoparticles

MoO_2 nanoparticle samples were synthesized by a simple hydrothermal method as illustrated in schematic 1. In short, molybdenyl acetylacetonate was added to 100% ethanol solution, and heated at 180 °C in a Teflon-lined stainless steel autoclave for 10 h. The resultant black powders were collected by centrifugation (more experimental details see supporting information).

The crystal phase and crystallinity of MoO_2 nanoparticle powder were characterized by X-ray diffraction (XRD) (Fig. 1a). All diffraction peaks could be accurately indexed as monoclinic phase MoO_2 (JCPDS. 78−1069), and no other impure crystals were found. These sharp diffraction peaks showed that the as-synthesized MoO_2 nanoparticles had good crystallinity. In addition, Raman spectrum further confirmed that these products had high pure monoclinic phase MoO_2 (Fig. 1b) [36].

The morphology of MoO_2 nanoparticle samples observed by scanning electron microscopy (SEM) showed they appeared in a bow tie-like shape with a length of about 200 nm and a narrowest diameter of about 50 nm (Fig. 1c). Transmission electron microscope (TEM) also demonstrated the bow tie-like shape of MoO_2 nanoparticles (Fig. 1d−f). High resolution-TEM (HRTEM) image showed that these nanoparticles had clear two-dimensional lattice fringes (Fig. 1g−h). Among them, the lattice fringe with a spacing of 0.48 nm could be indexed as the (101) crystal planes, while the lattice fringe with a spacing of 0.41 nm could be indexed as the (200) crystal planes. This was confirmed by the corresponding fast Fourier transform (FFT) pattern (Fig. 1i). According to the characterization results above, the as-prepared MoO_2 nanoparticles had highly crystalline and homogeneous bow tie-like monoclinic phase.

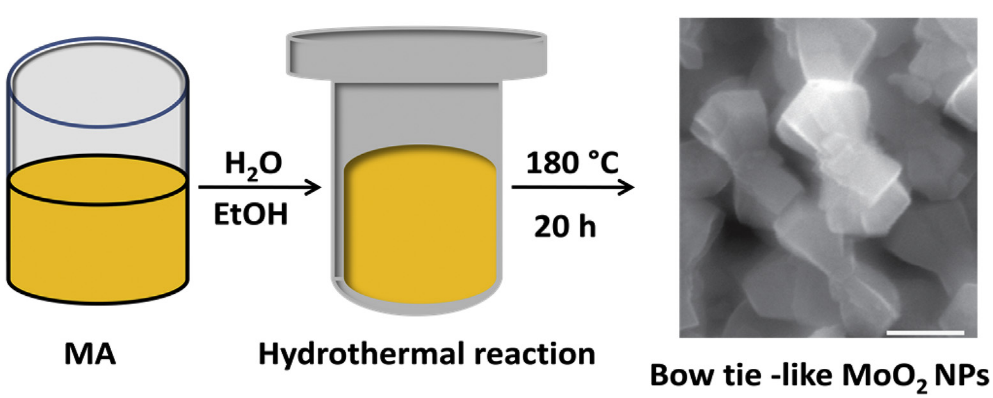
The analysis of surface molybdenum atom valance using X-ray photoelectron spectroscopy (XPS) showed a typical four-peak-shaped of Mo3d spectrum, that is, a pair of strong peaks was accompanied by a pair of weak peaks (Fig. 2a). The pair of strong peaks located at 229.3 and 232.5 eV could be referred to the characteristic peaks of Mo^{4+} oxidation state, while the pair of weak peaks located at 231.2 and 234.5 eV could be attributed to Mo^{6+}. The sharp difference between the strong peaks and the weak peaks demonstrated that the amount of surface Mo^{6+} was small. XPS results indicated that a large number of free d-electrons were contained in the MoO_2 nanoparticles with intermediate valence [37].

Interestingly, in contrast to UV-active wide band-gap MoO_3, which only absorbed UV light with the wavelength less than 390 nm, these bow tie-like MoO_2 nanoparticles exhibited a strong absorption from visible to NIR regions (Fig. 2b). Density functional theory (DFT) calculations on the band structure of MoO_2 nanoparticles showed that their Fermi level entered the conduction band level, and had a certain degree of metallic characteristics, revealing that MoO_2 nanoparticles possessed high density of free d-electrons [37]. Considering this metallicity, and then combined with the XPS results, it was reasonable to assume that this strong visible absorption could be attributed to a localized SPR effect caused by free electron electromagnetic resonance, which is similar to the Au and Ag nanostructures.

Nanomedicine need to keep stable in processes of producing, storage, transporting and usage in order to make sure that their photothermal property does not lose in these processes. Besides, the photothermal nanoagents are going to be used inside the tumor, which is in acidic microenvironment (acidic TME). Generally, the chemical stability of semiconducting photothermal agents was poor when compared with noble metal gold [38]. For example, $W_{18}O_{49}$, a very excellent photothermal agent for inhibiting cancer cells, could be yet easily oxidized by oxygen in air even at room temperature, thus losing SPR effect and the corresponding photothermal performance. As for sulfide-based photothermal agents, they had relatively high toxicity, and could be easily decomposed by acid to form hydrogen sulfide [39]. Nevertheless, as-prepared MoO_2 nanoparticles exhibited extraordinarily high chemical stability. The differential thermal analysis (DTA) curve showed that this material could even withstand high temperature heating at 300 °C without any oxidation. In addition, their SPR properties wouldn't be influenced by the treatments of strong acid or alkali, showing they had anti-chemical corrosiveness (Fig. 2b).

2.2. The photothermal conversion efficiency of the bow tie-like MoO_2 nanoparticles

Mo based nanomaterials are explored as a useful therapeutic agent for cancer. The molybdenum trioxide (MoO_3) nanoplates induces apoptosis and generates reactive oxygen species in invasive breast cancer cells, revealing the potential utility of Mo based nanomaterials for treating metastatic cancer cells [40]. Molybdenum oxides with an oxygen deficiency, MoO_{3-x}, showed strong localized surface plasmon resonance absorption in the NIR region [30]. However, the MoO_{3-x} is not chemical stable for storage. They easily oxidized in air condition [33]. Irregular carbon layer-coated molybdenum dioxide nanoparticles and MoO_2 irregular nanospheres exhibit strong photo-absorption in the near infrared (NIR) region and pose good photostability [41,42]. In order to compare the light-to-heat conversion capability of the MoO_2 bow tie-like nanoparticles with other Mo based PTT nanoagents, the



Scheme 1. A synthetic scheme of the synthesis route for the bow tie-like MoO_2 nanoparticles.