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Hydroxyapatite/mesoporous silica coated gold nanorods with improved degradability as a multi-responsive drug delivery platform

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ABSTRACT

In this study, gold nanorods/mesoporous silica/hydroxyapatite (Au/SiO_2/HAP) hybrid nanoparticles with AuNR core and SiO_2/HAP hybrid inorganic shell for multi-responsive drug delivery had been prepared. The morphology and structure of the nanoparticles were characterized by TEM, XPS, XRD, FT-IR and N_2 adsorption-desorption isotherms. The degradation of the hybrid nanoparticles could be significantly improved by the dissolution of HAP from the hybrid skeleton in acid environment. In vitro drug release results indicated that Au/SiO_2/HAP nanoparticles exhibited high drug loading efficiency, excellent near-infrared (NIR)- and pH-responsive drug release properties. Compared to the drug release of Au/SiO_2 nanoparticles over 12 h (about 6.35%), Au/SiO_2/HAP nanoparticles displayed a higher drug release of 37.62% upon NIR irradiation at pH 4.5 due to the NIR-responsiveness of AuNRs and the pH-responsiveness of HAP in acid media. The cell viability results also indicated that the Au/SiO_2/HAP nanoparticles exhibited the excellent biocompatibility. The present paper provides a facile route to fabricate a hybrid drug carrier with high drug loading efficiency, excellent pH sensitivity, NIR-sensitivity, biodegradability and biocompatibility.

1. Introduction

Nanomaterials have recently attracted increasing attention in drug delivery systems (DDS) due to their remarkable physicochemical properties [1–5]. A number of nanoscale materials including polymeric nanoparticles [6], gold nanoparticles [7,8], liposomes [9], inorganic materials [10,11], and magnetic nanoparticles have been developed as drug carriers to enable chemotherapies to be securer, more intelligent and efficient [12]. Among these materials, gold nanorods (AuNRs) [13–15] have been widely employed in the nanoscale drug carrier area due to their inherently adjustable size, various shapes and superb optothermal properties associated with the localized surface plasmon resonance [16,17]. However, AuNRs with nonporous structure exhibit the low loading capacity, which restricts their applications in effective drug delivery [18].

Mesoporous silica is pretty suitable as a coating material for AuNRs, in light of its convenience for functionalization, high specific surface area, high pore volume and excellent biocompatibility [19]. AuNRs individually coated with mesoporous silica shell (Au/SiO_2) [20] exhibit great potentials to achieve improved stability and high drug loading capacity, and they also have become a hot research topic [21]. It is well known that Au/SiO_2 nanoparticles are possessed of the response to near-infrared (NIR) light by introducing AuNRs as photothermal convertors [22]. Therefore, Au/SiO_2 nanoparticles had been developed by surface modification or in situ functionalization to achieve multiple-responsive delivery property. For example, Zhang et al. reported a pH-sensitive Au/SiO_2, after introducing Schiff base linker (−C═N−) onto the surface of mesoporous silica shell. Then, the acidic environment makes the Schiff base linker break, which leads to a distinct drug release. Zhang et al. fabricated Au/SiO_2 with thermo-, NIR- and pH-responsive properties by coating a thermoresponsive polymer shell consisting mainly of poly (*N*-isopropyl acrylamide) [23]. However, Au/SiO_2 also has some limitations and drawbacks. As a result of the stable network structure of SiO_2, its degradation is quite poor, and SiO_2 has been found to accumulate in some living organs such as liver, bladder, kidneys, spleen, and lungs, which may be harmful to living organs [24,25]. Therefore, there still remains a challenge to develop Au/SiO_2-based drug delivery vehicles with improved biocompatibility, excellent degradability and controllable release properties [26–28].

In recent years, a variety of methods have been explored to improve the degradability of Au/SiO_2 and investigate their multiple-responsive properties [29–31]. As a major inorganic constituent of teeth and bones, hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HAP) has been an excellent candidate for drug delivery vehicles because of its outstanding

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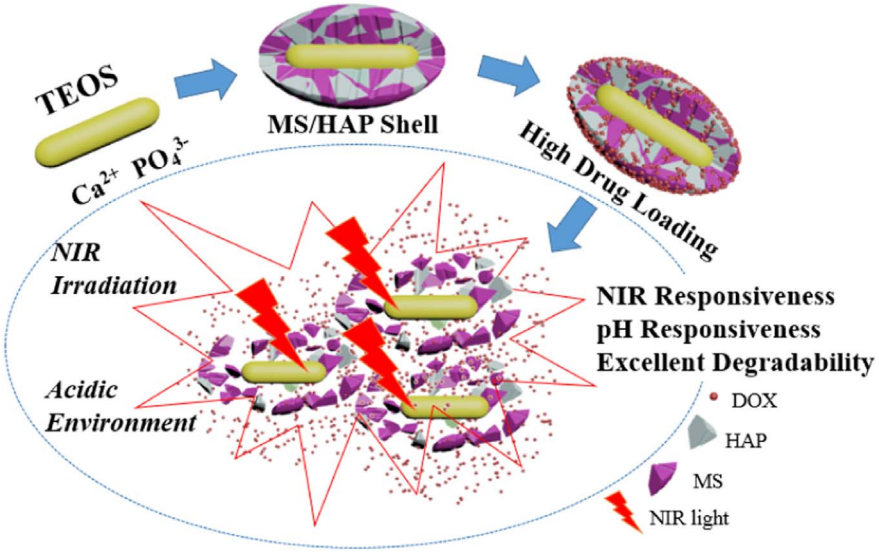

Scheme 1. Preparation and property illustration (high drug loading efficiency, excellent pH-sensitivity, NIR-sensitivity and biodegradability) of Au/SiO_2/HAP nanoparticles.

biological activity, biocompatibility and biodegradability. Incorporating conventional nanomaterials with HAP can endow the nanomaterials with better degradability and pH-sensitive drug release property [32,33]. Meanwhile, owing to these excellent biological properties, the introduction of HAP obviously has a great potential to improve the biocompatibility and reduce the cell cytotoxicity which is caused by the biotoxicity of mesoporous silica and the standard antineoplastic drug. Therefore, HAP-based drug delivery nano-vehicles can effectively reduce the damage to normal human tissues and keep a sustained lethality to cancer cells [34,35]. Hao et al. had doped HAP into mesoporous silica nanoparticles and obtained hybrid nanoparticles which can be degraded in acidic environment by the dissolution of HAP [36]. The prepared nanoparticles not only had improved drug loading efficiency but also exhibited distinct degradability and pH-responsive drug delivery property. Nevertheless, to the best of our knowledge, multi-responsive Au/SiO_2 nanoparticles with improved degradability have not been reported so far.

Herein, a novel nanoscale hybrid drug carrier with AuNR core and SiO_2/HAP shell (Au/SiO_2/HAP) for multi-responsive drug delivery has been prepared, as illustrated in Scheme 1. AuNRs coated by SiO_2/HAP were obtained through base-catalyzed hydrolysis of tetraethyl orthosilicate (TEOS) and in situ formation of HAP via the reaction between calcium salt and phosphate. The introduction of HAP altered the mesoporous constitution of the original silica shell, resulting in the relatively higher drug loading capability of Au/SiO_2/HAP nanoparticles. In addition, the degradation of the hybrid nanoparticles could be significantly improved by the dissolution of HAP from the hybrid skeleton in acid environment. More importantly, doxorubicin hydrochloride (DOX) release results demonstrated that the prepared Au/SiO_2/HAP nanoparticles exhibited distinguished NIR- and pH-responsive drug release properties, as illustrated in Scheme 1. Totally, the studied Au/SiO_2/HAP nanoparticles provided a facile route to fabricate SiO_2-based drug delivery vehicles with multi-responsiveness, high drug loading ability and excellent biodegradability, which is highly attractive for smart drug delivery domain.

2. Experimental section

2.1. Materials

Doxorubicin hydrochloride (DOX, Beijing Huafenglianbo Chemical, China), calcium chloride ($CaCl_2$, Tianjin Chemical Reagent Factory, China), disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4{\cdot}12H_2O$, Tianjin Dengke Chemical, China), chloroauric acid tetrahydrate ($HAuCl_4{\cdot}4H_2O$, Sinopharm Chemical Reagent Co., China), tetra-ethylorthosilicate (TEOS, Tianjin Kermel Chemical, China), cetyltrimethylammonium bromide (CTAB, Tianjin Kermel Chemical, China), silver nitrate ($AgNO_3$, Aladdin Reagent Co. Ltd., China), sodium borohydride ($NaBH_4$, Tianjin Kermel Chemical, China), ascorbic acid (AA, Tianjin Kermel Chemical, China).

2.2. Preparation of AuNRs

AuNRs were prepared via conventional seed-mediated growth method, developed by the method of El-Sayed [37] with some minor modifications. Firstly, a $HAuCl_4$ solution (0.1 mL, 25 mM) was mixed with a CTAB solution (9.9 mL, 200 mM) in a conical flask under stirring at 25 °C. Then, an ice-cold $NaBH_4$ solution (0.6 mL, 10 mM) was injected to the mixed solution quickly for 2 min under vigorous magnetic agitation. After the solution was stirred, it was kept for 2 h at 28 °C. Secondly, the growth solution for AuNRs consisted of a mixture of CTAB (98 mL, 200 mM), $HAuCl_4$ (2 mL, 25 mM) and $AgNO_3$ (2.5 mL, 4 mM) was added into a 500-mL round-bottom flask under stirring for 15 min. Then ascorbic acid (0.7 mL, 78.8 mM) was injected quickly. Once the solution became colourless, the seed solution (1 mL) was added immediately under stirring for 2 min and then the growth solution stayed in a thermostat water bath at 28 °C for 6 h.

2.3. Preparation of Au/SiO_2 nanoparticles

Mesoporous silica shell coating on AuNRs was carried out according to Gorelikov and Matsuura method with some modifications [38]. The as-synthesized 50 mL AuNRs were centrifuged at 10,000 rpm for 30 min and then the precipitate was re-dispersed in same volume Milli-Q water. NaOH solution (1 mL, 100 mM) was added upon stirring to adjust the pH value to ca. 10. Following this step, 300 μL injection of 20% TEOS in methanol was added at 30 min intervals under gentle stirring. The reaction mixture was reacted at 30 °C for 2 days.

2.4. Preparation of Au/SiO_2/HAP nanoparticles

For the synthesis of Au/SiO_2/HAP, $CaCl_2$ and $Na_2HPO_4{\cdot}12H_2O$ were used to offer Ca^{2+} and PO_4^{3-} ions for the fabrication of HAP. 100 mL as-synthesized AuNRs were centrifuged at 10,000 rpm for 40 min to remove the excess CTAB surfactant. In a typical procedure, the supernatant was discarded, followed by re-dispersing the precipitate into 100 mL Milli-Q water. Then the addition of NaOH upon stirring adjusted the pH to ca. 10 in a 250 mL round-bottom flask. After the