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Core-shell structure of Fe_3O_4@MTX-LDH/Au NPs for cancer therapy

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ABSTRACT

Nearly monodispersed magnetic Fe_3O_4@MTX-LDH/Au nanoparticles (NPs) containing the anticancer agent of methotrexate (MTX) were prepared via a coprecipitation-electrostatic interaction strategy. Firstly, layered double hydroxide (LDH) materials were deposited over the surface of Fe_3O_4 NPs by the coprecipitation method. Secondly, Au NPs were successfully conjugated onto the surface of LDH through electrostatic interaction. Herein, MTX was used both as the agent for surface modification and the anticancer drug for chemotherapy. These particles presented well-defined core-shell structure, strong magnetization and a high drug-loading capacity. Furthermore, the combined treatment of cancer cells by using Fe_3O_4@MTX-LDH/Au for synergistic hyperthermia ablation and chemotherapy was demonstrated to exhibit higher therapeutic efficacy than either single treatment alone, underscoring the great potential of the platform for cancer therapy.

1. Introduction

During the past decades, remarkable progress has been achieved in developing the multilevel platforms for cancer therapy [1,2]. Among them, the integration of three or more strategies in one system, which now becomes a representative challenge in the field of biomedicine [3,4], is very attracting and draws attention to many researchers. If anticancer drugs could be integrated with such functional system, it would give a new insight into fabrication of a promising platform for the combined treatment. In particular, magnetic materials, like Fe_3O_4 nanoparticles (NPs), exhibited promising properties in biomedical uses, such as biocompatibility, relatively low toxicity, more stability in magnetic response, targeted drug delivery and so on [5]. Equally attractive in the area of other metals are Au NPs, which can scatter and absorb incident light efficiently at the resonance wavelength and this is the so-called SPR effect [6], and their therapeutic strategy was based on the conversion of absorbed light energy into heat for hyperthermia [7]. This property allowed the use of Au NPs for lots of applications, e.g., Raman sensors [8,9], photocatalysts [10], photo electrochemical materials [11,12], drug delivery [13], cancer diagnostics and therapeutics etc. [14].

Layered double hydroxide (LDH), whose positive charge on the metal hydroxide sheets was balanced by interlayer anions, had currently attracted extensive attention as carriers for delivering drugs and biomolecules because of their high anionic exchange capacity, negligible toxicity, favorable biocompatibility and so on [15–17]. Therefore, LDH would be one of the most potential ideal candidates to build up synergistic platform with Au and Fe_3O_4 NPs. It was thought that the combination of photothermal therapy, chemotherapy together with magnetic targeting would show tremendous application prospect because of their synergistic effects. Unexpectedly, no literature on combining LDH with Au and Fe_3O_4 NPs for synergistic treatment could be found to date.

Among various possibilities, the core-shell type of nanostructures occupies an important position, as they can offer structures with extra stability and multifunctionality [18]. Previously, we reported a composite consisting of Au yolk/LDH shell loaded with methotrexate (MTX), and the obtained products possessed a plausible core-shell structure [19]. Dhirendra Bahadur also reported the similar conjugated system which disappointed about its dispersibility [20]. In addition, Saumya Nigam researched the Dendrimer-conjugated iron oxide nanoparticles with high cost, complicated and cytotoxicity to normal cells [21]. Sunil Pandey studied carbon-dots clathrates with MTX and folic acid (FA), but owned different particle sizes [22]. In this paper, by choosing the anticancer agent MTX as a guest drug, nearly monodispersed submicro particles of Fe_3O_4@MTX-LDH/Au with well-defined core-shell structure were firstly prepared via a coprecipitation-electrostatic interaction route, where LDH deposited on the surface of Fe_3O_4 spherical particles through coprecipitation method and Au NPs adsorbed on the surface of LDH materials via electrostatic interaction.

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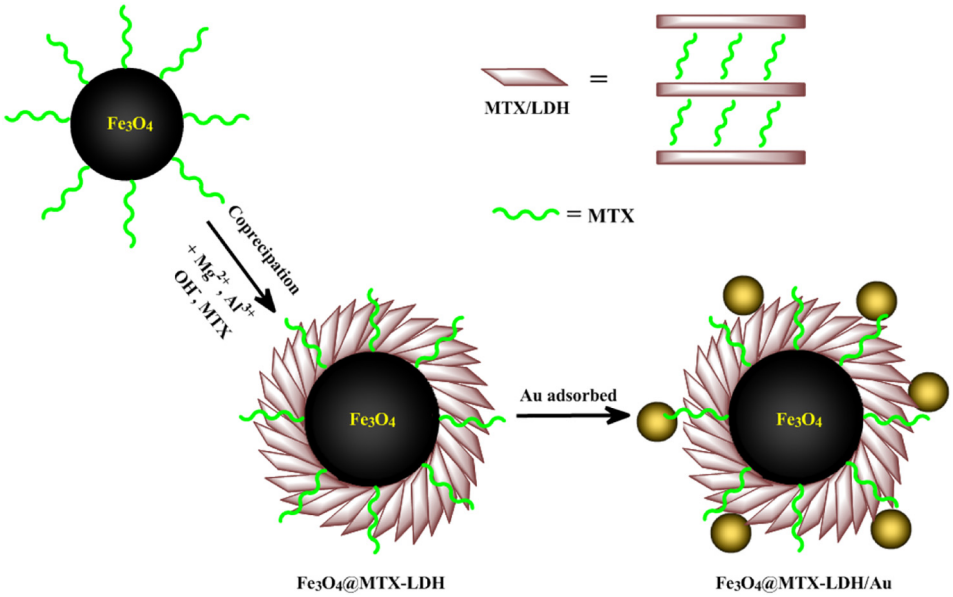

Scheme 1. Schematic procedure for the preparation of Fe_3O_4@ MTX-LDH/Au NPs.

Herein, LDH was used to carry and deliver the anticancer drug of MTX (Scheme 1). The magnetic Fe_3O_4 particles (ca. 250 nm) were synthesized using a modified hydrothermal growth method [23]. After being coated by a thin layer of LDH material using a typical coprecipitation method, positively charged Fe_3O_4 core/inorganic LDH shell structure was built up. Then the negatively charged Au NPs were assembled onto the surface of LDH material through electrostatic interaction to afford the multilevel platform of Fe_3O_4@MTX-LDH/Au. In this design, MTX was not only used as a specific anticancer drug but also served as a surface stabilizing agent of Fe_3O_4 and Au NPs, and the functional groups of diamino, pteridinyl, acyl and dicarboxyl of MTX made it a good candidate to conjugate onto the surface of inorganic particles [24]. Compare to the reported literature [25], the release of anticancer drugs in this article was primarily a magnetically controlled release, rather than relying on the rate of dissolution of the materials and uncontrollable. Moreover, the resultant particles exhibited strong magnetization, high drug loading capacity, and enhanced therapeutic efficacy, thus presenting a promising drug delivery platform for magneto-chemo-photothermal therapy.

2. Materials and methods

2.1. Materials

Magnesium nitrate ($Mg(NO_3)_2{\cdot}6H_2O$) was obtained from Shantou Xilong Chemical Co. (Guangdong, CN). $Al(NO_3)_3{\cdot}9H_2O$ was purchased from ShangHai Sinpeuo Fine Chemical Co. Hydrogen tetrachloroaurate (III) hydrate ($HAuCl_4{\cdot}4H_2O$, Au ≥ 47.8%), Iron(III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), sodium citrate dihydrate ($Na_3C_6H_5O_7{\cdot}2H_2O$), and $NH_3{\cdot}H_2O$ were all purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). MTX was purchased from Huzhou Prospect Pharmaceutical Co. (Zhejiang, CN), human lung adenocarcinoma cells (A549) were purchased from Shanghai cell bank (Shanghai, CN). All reagents were of analytical grade and used without further purification. All the aqueous solutions were prepared with Millipore water having a resistivity of 18.2 MΩ (Purelab Classic Corp., USA).

2.2. Preparation of Fe_3O_4 NPs

Fe_3O_4 NPs were synthesized using the previously reported procedure after slight modification [23]. Briefly, 1.35 g of $FeCl_3{\cdot}6H_2O$ was dissolved into 40 mL of ethylene glycol, followed by the addition of 3.6 g of NaAc, 1 g of polyethylene glycol and 30 mg of MTX. After being stirred vigorously for 30 min, the mixture was sealed in a Teflon-lined stainless-steel autoclave and heated at 180 °C for 24 h. After being cooled to the ambient temperature, the black products were collected, washed several times with ethanol and water, and dried at 60 °C for further use.

2.3. Preparation of Fe_3O_4@MTX-LDH hybrids

Fe_3O_4@MTX-LDH hybrids were synthesized as follows: 50 mg of freshly-prepared Fe_3O_4 NPs were added into 50 mL of mixed solvent of ethanol/water (a volume ratio of 1:3). Then, 0.0341 g of MTX was dissolved into 8 mL of 10% $NH_3{\cdot}H_2O$ and the resulting solution was added into 50 mL of the above Fe_3O_4 solution. The final mixture solution was named as solution A. Solution B, containing 0.07692 g of $Mg(NO_3)_3{\cdot}6H_2O$ and 0.05627 g of $Al(NO_3)_3{\cdot}9H_2O$ in the mixed solvent of ethanol/water, was also prepared. At last, solution B was dropped into solution A at a constant rate of 3 mL/min, and the final solution was adjusted to pH 9.5 by adding a certain amount of 10% $NH_3{\cdot}H_2O$. Throughout the operation, N_2 gas was bubbled into the solutions. Followed by vigorously stirring for 1 h at 60 °C, the products were washed with deionized water and ethanol for several times, and dried at 60 °C for further use.

2.4. Preparation of Fe_3O_4@ MTX-LDH/Au

Au NPs were synthesized using the previously reported procedure [24]. Briefly, 150 mL of sodium citrate (0.0022 mol/L) in Milli-Q water was heated in a three-necked round-bottomed flask under vigorous stirring and a condenser was utilized to prevent the evaporation of the solvent. After boiling had commenced, 1 mL of $HAuCl_4$ (0.025 mol/L) solution was dropped. Then color of the solution changed from yellow to deep red in 15 min, indicating the formation of Au seeds. Then the temperature was cooled to 90 °C. After that, 3 mL of sodium citrate (0.06 mol/L) and 1 mL of $HAuCl_4$ (0.025 mol/L) were sequentially added and reacted for another 1 h again. 20 mL of the as-prepared Au NPs was centrifuged, redispersed in 20 mL of water and then added into the Fe_3O_4@MTX-LDH solution (10 mg/mL). After stirring for 5 h at room temperature, the products were washed with deionized water and ethanol for several times, and dried at 60 °C for further use.