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Efficient drug delivery using SiO_2-layered double hydroxide nanocomposites

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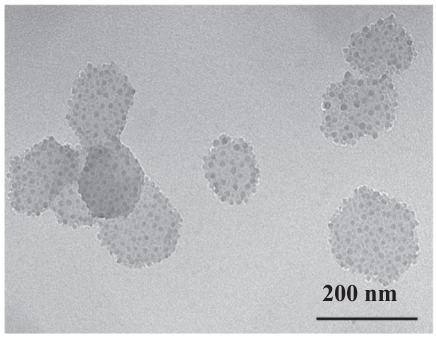
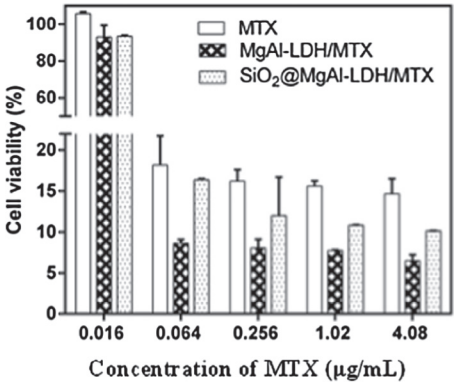
GRAPHICAL ABSTRACT





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ABSTRACT

MgAl-layered double hydroxide (MgAl-LDH) nanoparticles have great potentials in drug and siRNA delivery. In this work, we used a nanodot-coating strategy to prepare SiO_2 dot-coated layered double hydroxide (SiO_2@MgAl-LDH) nanocomposites with good dispersibility and controllable size for drug delivery. The optimal SiO_2@MgAl-LDH nanocomposite was obtained by adjusting synthetic parameters including the mass ratio of MgAl-LDH to SiO_2, the mixing temperature and time. The optimal SiO_2@MgAl-LDH nanocomposite was shown to have SiO_2 nanodots (10–15 nm in diameter) evenly deposited on the surface of MgAl-LDHs (110 nm in diameter) with the plate-like morphology and the average hydrodynamic diameter of 170 nm. We further employed SiO_2@MgAl-LDH nanocomposite as a nanocarrier to deliver methotrexate (MTX), a chemotherapy drug, to the human osteosarcoma cell (U2OS) and found that MTX delivered by SiO_2@MgAl-LDH nanocomposite apparently inhibited the U2OS cell growth.

1. Introduction

Nanocomposites, such as organic–inorganic, inorganic–inorganic and bioinorganic nanomaterials, have attracted considerable research interest in bioapplications such as drug delivery, biomedical imaging, biochemical sensing and biocatalysts owing to their structure features and unique properties [1,2]. In particular, recent investigations on nanocomposites with various structures such as core–shell structure and nanorattles have demonstrated unique release properties for drug/gene delivery due to their hierarchical structures [3,4]. These studies have shown that nanocomposites

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have great advantages in designing a smart drug delivery system with multifunctional properties for diagnostic and therapeutic applications [4].

Layered double hydroxides (LDHs), a family of anionic clay materials, consist of cationic brucite-like layers and interlayer anions with the general chemical composition of $M_{1-x}^{2+}M_x^{3+}(OH)_2(A_{x/n}^{n-})\cdot yH_2O$, where M^{2+} and M^{3+} are typical divalent and trivalent metal cations, respectively, A^{n-} an anion, and x the molar ratio of the trivalent cation to the total cation [5–11]. Among these LDH materials, MgAl-LDHs are very often used in drug and gene delivery owing to their low cytotoxicity, high anion exchange capacity, pH-controlled release, good biocompatibility, tunable particle size, and protection of drugs and genes in their interlayers [11–16]. A recent research has shown that various biofunctional molecules, including DNA, siRNA, drugs, and vitamins, have been successfully preserved by incorporation into LDHs with high delivery efficiency and bioactivity. Li et al. reported that co-delivery of 5-FU and siRNA by MgAl-LDH nanoparticles significantly inhibited the growth of various cancer cells including breast cancer cells (MCF-7), osteosarcoma cancer cell (U2OS) and colon cancer cells (HCT-116) [17]. Recently, hierarchical MgAl-LDH-based nanocomposites with controllable morphology and orientation have been constructed to enhance their performance. Zhang et al. synthesized an anti-inflammatory drug-loaded MgAl-LDH shell on the magnesium ferrite core via the coprecipitation method and claimed the prolonged control release of drugs from MgAl-LDH-magnesium ferrite nanohybrids [18]. Chen et al. developed the multifunctional upconversion luminescent LDH nanovehicles for tumor optical imaging and therapy via *in situ* growth of the LDH-5FU on the surface of silica-modified Y_2O_3:Er^{3+}, Yb^{3+} NIR nanoparticles and demonstrated that these nanohybrids exhibited strong red upconversion fluorescence and a better anticancer efficiency [19]. Liu et al. also reported a mesoporous silica-LDH nanorattle using mesoporous silica as a shell and MgAl-LDH as a core, and showed sustained release of the drug from the nanocomposites [4]. In addition, Hu et al. prepared MgAl-LDH-based nanocomposites with the flexible polycation brushes (2-(dimethylamino)-ethyl methacrylates) and demonstrated increased ability to condense plasmid DNA, and enhance cellular uptake and gene transfection efficiency in COS7 and HepG2 cell lines [20]. To date, though there are several types of LDH-based nanocomposites developed, cost-effective rational design of LDH-based nanocomposites with good dispersibility and high efficiency as nanocarriers that can be used in chemotherapy still remains a big challenge. Thus, we have recently developed amine-functionalized SiO_2 nanodot-coated MgAl-LDH (NH_2–SiO_2@MgAl-LDH) nanocomposites using the nanodot-coating strategy and employed these nanocomposites as a nanocarrier for siRNA delivery [21]. We have found that NH_2–SiO_2@MgAl-LDH nanocomposites can efficiently deliver cell death siRNA into U2OS cell line to inhibit cell proliferation. This nanocomposite combines the advantages of SiO_2 nanodots and MgAl-LDH nanoparticles to render the predominant properties for potential biomedical applications such as drug/gene delivery. However, the stability and dispersibility of SiO_2@MgAl-LDH nanocomposite in PBS and cell culture medium has not been explored and the drug delivery efficiency of this nanocomposite *in vitro* has not been examined.

Herein, we have optimized the SiO_2 nanodot-coating MgAl-LDH nanocomposites (SiO_2@MgAl-LDH) via the nanodot-coating strategy in terms of the dispersibility in culture medium and PBS. In brief, the pre-formed SiO_2 nanodots were coated on the surface of MgAl-LDH nanoparticles by directly mixing MgAl-LDH suspension with SiO_2 nanodot suspension under variable conditions, including the mixing time, temperature and the mass ratio of MgAl-LDH toSiO_2 mass ratio. We then employed the optimal SiO_2@MgAl-LDH nanocomposite as a nanocarrier to deliver methotrexate (MTX) into U2OS cells and found that MTX delivered by SiO_2@MgAl-LDH nanocomposite (SiO_2@MgAl-LDH/MTX) efficiently inhibited the U2OS cell growth and this nanocomposites itself showed low cytotoxicity at the MgAl-LDH concentration below 200 μg/mL. Thus, SiO_2@MgAl-LDH nanocomposite acts as a promising candidate for drug and gene delivery *in vitro* and *in vivo*.

2. Experimental

2.1. Chemicals

Magnesium nitrate hexahydrate ($Mg(NO_3)_2\cdot 6H_2O$), Aluminum nitrate nonahydrate ($Al(NO_3)_3\cdot 9H_2O$), Sodium hydroxide (NaOH), Octane, L-arginine, Methotrexate (MTX) and 21-bp dsDNA tagged with Cy3 (DNA-Cy3) were purchased from Sigma (USA) without purification. Fetal calf serum, penicillin (10 U/mL)/streptomycin (10 μg/mL) Dulbecco's Modified Eagle Medium (DMEM), (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) (MTT), 0.25% Trypsin-EDTA (1X) and PBS buffer (37 mmol/L NaCl, 2.7 mmol/L KCl, 8.1 mmol/L Na_2HPO_4, and 1.47 mmol/L KH_2PO_4, pH 7.4) were obtained from Life Technologies Corporation (Australia).

2.2. Synthesis of MgAl-layered double hydroxide (MgAl-LDH) and MTX-loaded MgAl-LDH (MgAl-LDH/MTX)

MgAl-LDH and MgAl-LDH/MTX suspensions were synthesized via co-precipitation approach following with hydrothermal treatment [8]. Briefly, a solution containing $Mg(NO_3)_2$ (3.0 mmol) and $Al(NO_3)_3$ (1.0 mmol) was quickly added to NaOH solution (6.0 mmol, 40 mL) with vigorous stirring at room temperature for 10 min. The resulting MgAl-LDH precipitate was separated and washed with distilled water twice via centrifugation. Then, the collected MgAl-LDH precipitate was redispersed in distilled water and hydrothermally treated in an autoclave (stainless steel with a Teflon lining) at 100 °C for 16 h. After hydrothermal treatment, a transparent, homogenous MgAl-LDH suspension was obtained. MgAl-LDH/MTX suspension was prepared similarly. As described above, after collecting the MgAl-LDH precipitate via centrifugation, the MgAl-LDH precipitate was mixed with MTX solution (0.1 mmol MTX in NaOH solution, pH 8–9) with shaking for 1 h. After separating and washing via centrifugation, the MgAl-LDH/MTX mixture was dispersed in distilled water and transferred to an autoclave for hydrothermal treatment at 100 °C for 16 h.

2.3. Synthesis of SiO_2@MgAl-LDH and SiO_2@MgAl-LDH/MTX

The SiO_2@MgAl-LDH and SiO_2@MgAl-LDH/MTX suspensions were prepared via SiO_2 nanodot-coating stragety, as reported previously in our work [21]. Briefly, a certain amount of TEOS was added to a solution containing octane (730 mg) and L-arginine (14 mg) with vigorous stirring at 60 °C for 4 h via a microemulsion method [22]. Then, MgAl-LDH and MgAl-LDH/MTX suspension was added to the above solution at various temperatures under stirring for different time, respectively. After washing with distilled water for 4 times, as-obtained SiO_2@MgAl-LDH and SiO_2@MgAl-LDH/MTX nanocomposites were redispersed in distilled water with ultrasonication.

2.4. Colloidal stability of SiO_2@MgAl-LDH in PBS and cell culture medium

The dispersibility of the nanocarrier in PBS or culture medium is one of the critical parameters for *in vivo* drug/gene delivery. A certain volume of MgAl-LDH and SiO_2@MgAl-LDH suspensions were