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Research paper

Betamethasone dipropionate intercalated layered double hydroxide and the composite with liposome for improved water dispersity

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ABSTRACT

A hierarchical nanocomposite of betamethasone dipropionate (BDP), a nonionic and lipophilic glucocorticoid drug, intercalated layered double hydroxide (LDH) encapsulated in liposome was constructed by combining host-gest chemistry with a core-shell strategy, to develop a LDH-based drug delivery system with remarkable water dispersity and good sustained-release performance. BDP molecules were first incorporated into sodium cholate (Ch) micelles, and the negatively charged BDP-loaded micelles were then coassembled with positively charged LDH single-layer nanosheets, forming a BDP/Ch intercalated LDH (BDP-Ch-LDH) gest-host nanohybrid. The BDP-Ch-LDH was further coated with liposome (LS) consisting of lecithin and cholesterol, gaining a core-shell nanocomposite, denoted as (BDP-Ch-LDH)@LS. The BDP-Ch-LDH and (BDP-Ch-LDH)@LS were characterized using small angle X-ray scanning, Fourier-transform infrared, transmission electron microscopy, and elemental analyses. Their water dispersity and stability as well as in vitro drug release behavior were investigated. The particle size and sedimentation rate of freeze-dried (BDP-Ch-LDH)@LS redispersed in water (~190 nm and 0.035 mm/h, respectively) are obviously lower than those of BDP-Ch-LDH (~761 nm and 1.028 mm/h, respectively). The maximum percentage releases of the (BDP-Ch-LDH)@LS in pH 7.4 and 4.8 PBSs (~60% and 80%, respectively) are also lower than those of the BDP-Ch-LDH (both ~90%) under the studied conditions. These results demonstrated that the (BDP-Ch-LDH)@LS has remarkable water dispersity and stability as well as enhanced drug sustained-release performance in comparison with BDP-Ch-LDH. The liposome-coating modification is an effective strategy for improving the practical performance of LDH-based drug delivery system.

1. Introduction

Betamethasone dipropionate (BDP), a nonionic and poorly water-soluble betamethasone derivative, is a glucocorticoid drug, mainly used in the treatment of allergic and autoimmune diseases (Tsuji et al., 1997; Zou et al., 2008; Zulfakar et al., 2012). However, its some side-effects such as electrolyte imbalance, sodium and water retention, and hypertension are unfavorable for its clinical application. To reduce its side-effects, prolong its effective duration, and enhance its curative effect, a variety of drug delivery and controlled release systems have been developed, such as liposomes (Gillet et al., 2011), polymeric microparticles (Ding et al., 2014), injectable hydrolipidic gels (Réeff et al., 2015), and lipid nanoparticles (Kong et al., 2016).

The usage of layered clays, such as montmorillonite, kaolinite, and layered double hydroxides (LDHs), and their nanocomposites with biocompatible polymers for drug delivery has been widely investigated (Patel et al., 2011; Rives et al., 2013, 2014; Jafarbeglou et al., 2016). Among the layered clays, LDHs (Mills et al., 2012; Wang and O'Hare, 2012), a large class of positively charged inorganic layered compounds, as a promising drug carrier are recently received great interest, owing to their biocompatibility, low toxicity, and biodegradation (Choy et al., 1999, 2000; Ambrogi et al., 2003; Xu et al., 2006; Bégu and Tichit, 2009; Li et al., 2013; Sahoo et al., 2013; Zhang et al., 2014a; Kuo et al., 2015; Senapati et al., 2016; Harrison et al., 2017). Anionic drugs or biomolecules can directly intercalate into LDH galleries to form drug- or bio-LDH gest-host nanohybrids (Choy et al., 1999, 2000; Li et al., 2013; Sahoo et al., 2013). The driving force for the intercalation is the electrostatic attraction between negatively charged drug ions and positively charged LDH layers. However, it is unable to achieve the direct intercalation for charge-neutral and poorly water-soluble drugs such as BDP, owing to the lack of the driving force (Tyner et al., 2004; Trikeriotis and Ghanotakis, 2007; Bégu and Tichit, 2009; Li et al., 2009; Wu et al., 2013a). A suitable strategy to achieve intercalation is to incorporate the drugs into negatively charged micelles derived from anionic surfactants such as sodium cholate (Ch), and the resulting drug-loaded micelles are then intercalated into the gallery of LDHs (Tyner

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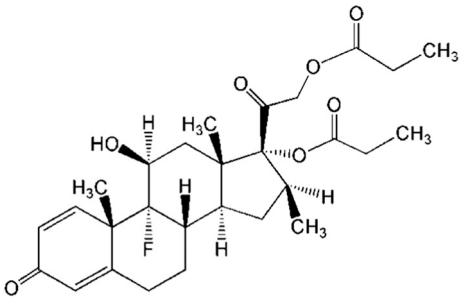
et al., 2004; Trikeriotis and Ghanotakis, 2007; Li et al., 2009; Wu et al., 2013a). Many methods have been used to fabricate drug- or bio-LDH nanohybrids, including co-precipitation (Li et al., 2009; Sahoo et al., 2013), ion exchange (Choy et al., 1999, 2000; Tyner et al., 2004; Trikeriotis and Ghanotakis, 2007; Li et al., 2013; Senapati et al., 2016), reconstruction (Gordijo et al., 2005), and hydrothermal (Ogawa and Asai, 2000) methods. Notably, a co-assembly strategy has been recently developed (An et al., 2009; Park et al., 2010; Bellezza et al., 2012; Wang and O'Hare, 2012; Lu et al., 2013; Wu et al., 2013a,b), in which positively charged LDH nanosheets and negatively charged drug ingredients or drug-loaded micelles co-assemble together into drug-LDH nanohybrids. In comparison with the conventional methods, the co-assembly strategy exhibits many remarkable advantages including simple procedure, short reaction time, mild condition, high drug loading, or easy control of drug-to-LDH ratio (Lu et al., 2013; Wu et al., 2013a,b). However, few researches have been performed so far on the co-assembly method for constructing intercalated LDH nanohybrids of charge-neutral and poorly water-soluble drugs (Wu et al., 2013a). In addition, the utilized LDH nanosheets for co-assembly are commonly prepared by delamination of LDHs in the toxic organic solvent formamide (Wang and O'Hare, 2012; Lu et al., 2013; Wu et al., 2013a,b), which is contrary to the requirements of green and sustainable chemistry (Wu et al., 2015). Recently, we developed a simple aqueous synthetic method to produce naked (unmodified) LDH nanosheets, using neither organic modifiers nor organic solvents (Zhang et al., 2016). It is of practical importance to explore the possibility of the LDH nanosheets used as building blocks.

A tricky problem for drug-LDH nanohybrids is their severe aggregation (Xu et al., 2006; Lu et al., 2013), especially for the case of dried nanohybrids re-dispersed in water, which limits their clinical application. Recently, a liposome-coating strategy has been developed to construct a core (nanohybrid)-shell (lipid bilayer) nanocomposite to improve their dispersity in water (Huang et al., 2013; Kankala et al., 2015; Yan et al., 2016). Huang et al. (Huang et al., 2013) reported a nanocomposite of "dextran-magnetic LDH-fluorouracil"/liposomes (DMFL) that showed high dispersion stability. Kankala et al. (Kankala et al., 2015) reported a nanocomposite of (LDH-indole-3-acetic acid) coated with liposomes (LDH-IAA-Lipo) that showed good sustained-release performance. Yan et al. (Yan et al., 2016) reported PEGylated phospholipid membrane coated methotrexate-LDH nanoparticles that showed high storage stability and good cell viability. These works demonstrate that the coating modification of drug-LDH nanohybrids with liposomes (or vesicles) may be an effective strategy to improve their water dispersity. However, there have been no reports on liposome-coating for nonionic and lipophilic drug intercalated LDH nanohybrids. In addition, the re-dispersity of dried nanocomposites in water has not been determined. A good re-dispersity is important for a drug delivery system.

Liposomes, a microscopic phospholipid bubbles with a bilayered membrane structure, are also a kind of drug delivery systems, which have been received remarkable attention owing to their biocompatibility, low toxicity, and targeting drug release (Samad et al., 2007; Chen et al., 2010). However, liposomes as drug delivery systems present drawbacks such as instability for long-term storage and in physiological media, and poor sustained-release performance (Bégu and Tichit, 2009). The combination of liposomes with LDHs can probably overcome their drawbacks.

In the present work, BDP is selected as a model for nonionic, poorly water-soluble drugs, and the liposome-coating strategy is used to improve the water dispersity, especially re-dispersity, of drug-LDH nanohybrids. BDP was first incorporated into Ch micelles, and the resultant BDP-loaded micelles then coassembled with LDH nanosheets to form BDP/Ch intercalated LDH (BDP-Ch-LDH) gest-host nanohybrids. The LDH nanosheets used here were pre-synthesized using the simple aqueous synthetic method we recently developed (Zhang et al., 2016). The BDP-Ch-LDH particles were further coated using liposomes (LSs) of lecithin and cholesterol, gaining a core-shell nanocomposite, denoted as (BDP-Ch-LDH)@LS. The water dispersity and drug-release performance of the hierarchical nanocomposite were examined. The results demonstrated that the liposome-coating not only can significantly improve the water dispersity of the nanohybrids but also can remarkably enhance their drug sustained-release performance. To the best of our knowledge, this is the first report on BDP intercalated LDH nanohybrids. This work provides useful information for developing LDH-based delivery and controlled release systems for nonionic and lipophilic drugs.



Scheme 1. Molecular structure of betamethasone dipropionate.

2. Materials and methods

2.1. Materials

Betamethasone dipropionate (BDP, 98% purity) was purchased from Shandong Taihua Bio. & Tech. Co., Ltd., China, and its molecular structure is shown in Scheme 1. Soybean lecithin (95% purity) and cholesterol (95% purity) were purchased from Heowns Biochem Technologies, LLC., China. Sodium cholate (Ch, 99% purity) was purchased from Alfa Aesar Chemical Co. Ltd., China. Magnesium nitrate hexahydrate (99% purity), aluminum nitrate nonahydrate (99% purity), and ammonia solution (~25 wt%) were obtained from Sinopharm Chemical Reagent Co., Ltd., China. All of the chemicals were used as received. Water was purified with a Hitech-Kflow water purification system (Hitech, China).

2.2. Experimental

2.2.1. Synthesis of LDH single-layer nanosheets

Mg_2Al-NO_3 LDH single-layer nanosheets (SLNSs) were synthesized via a simple aqueous coprecipitation-water washing-water re-dispersion (PWD) route (Zhang et al., 2016). Briefly, a mixed salt solution of $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$ was prepared with a Mg/Al molar ratio of 2.0 and a total salt concentration of 0.3 mol/L. The mixed salt solution and an ammonia solution (~6 wt%) were simultaneously added into a beaker under magnetic stirring and N_2 protection. During this process, the pH value of the reaction system was controlled to be ~10 by altering the relative addition rate of the two raw material solutions. The resultant precipitate was collected by centrifugation and washed with water, gaining LDH SLNS hydrogel with a solid content (C_s) of ~8.5 wt%. A certain amount of the LDH SLNS hydrogel was re-dispersed in a designed amount of water by ultrasonication for 10 min and then incubated at 40 °C for 5 h, producing a LDH SLNS dispersion (C_s = 10 g/L).

2.2.2. Synthesis of BDP intercalated LDH nanohybrids

BDP intercalated LDH nanohybrids were synthesized via a coassembly method, with reference to our previous work (Wu et al., 2013a). Briefly, a solution of BDP in chloroform (1 $g \cdot L^{-1}$, 25 mL) was added to an aqueous Ch solution (0.02 M, 50 mL) under magnetic stirring. The resultant system was stirred under N_2 to allow for the evaporation of chloroform, gaining a solution of BDP-loaded Ch micelles. The LDH

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