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Research paper

Carboxymethyl cellulose capsulated layered double hydroxides/drug nanohybrids for Cephalexin oral delivery

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ABSTRACT

In this paper, pH sensitive carboxymethyl cellulose (CMC) beads were proposed as a protective capsule for layered double hydroxides-drug (LDH-Drug) nanohybrids in gastrointestinal tract conditions. Cephalexin (CPX), as a model drug, was intercalated between LDH layers through co-precipitation method. The resulting nanohybrid (LDH-CPX) was used to prepare nanocomposite hydrogel beads by association with carboxymethyl cellulose. The synthesized products were characterized using FTIR, XRD and SEM analysis. In vitro drug delivery tests were carried out in conditions simulating the gastrointestinal tract to prove the effectiveness of these novel nanocomposite beads as a controlled drug delivery system. The drug release tests revealed a better protection against stomach pH and a controlled liberation in the intestinal tract conditions for CMC encapsulated LDH-CPX nanohybrids.

1. Introduction

In recent years, there has been an increased interest in the controlled release of drugs, which is an efficient technique for the use of medicines. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving a high drug loading for the required blood levels, immune to accidental release, simple to apply, and easy to fabricate (Yoo et al., 2011; Chacko et al., 2012; Yadollahi et al., 2015a). Among the many different nanoparticles that have been shown to facilitate gene and/or drug delivery, layered double hydroxide (LDH) nanoparticles have attracted particular attention owing to their many desirable properties. The LDH, as a new drug carrier, are easily synthesized in the laboratory, have a high drug transportation efficiency, high drug loading density, low toxicity to target cells or organs and excellent protection to loaded molecules from undesired enzymatic degradation (Choi and Choy, 2011; Zhang et al., 2014). A plethora of drugs and bio-molecules have been reported to either attach to the surface of or intercalate into LDH materials through co-precipitation or anion-exchange reaction, including anti-inflammatory drugs (Rives et al., 2013), anticancer drugs (Choi et al., 2008), amino acid and peptides (Reinholdt and Kirkpatrick, 2006), nucleotides (Nakayama et al., 2010), vitamins (Gasser, 2009), and even polysaccharides (Yadollahi and Namazi, 2013; Yadollahi et al., 2014). Owing to their alkalinity, however, their use as orally available drug-delivery systems could be difficult. However, LDH are very sensitive to acid environments, and the drug is often completely released in the stomach media (pH 1.2) (Ambrogi et al., 2001; Khan et al., 2001). Thus, the preparation of LDH-drug hybrids coated with a protective polymeric matrix had been recently proposed to preserve the release properties through the gastrointestinal tract (Alcantara et al., 2010; Barkhordari et al., 2014; Zhang et al., 2010). Li et al. (2004) described a promising approach to improve the passage of LDH hybrids through the gastrointestinal tract by coating fenbufen- intercalated LDH with enteric polymers, for example Eudragit S 100. Under in vitro conditions, these core–shell materials showed a controlled release profile for the incorporated drug. Alcantara et al. (2010) encapsulated LDH by zein, and alginate in order to survive in stomach-like environment. Valarezo et al. (2013) employed poly (ε-caprolactone) to coat LDH via the electrospinning technique. The release curves present a sustained release behavior, although an initial rapid drug release was found, indicating that the presence of the poly (ε-caprolactone) could extend the drug release rate.

Carboxymethyl cellulose (CMC) is an anionic, water-soluble cellulose derivative obtained by introducing —CH_2COOH groups into cellulose molecular chain. Due to its unique characteristics such as pH-sensitivity, transparency, hydrophilicity, non-toxicity, biocompatibility, and biodegradability as well as its gel and film forming properties, CMC has a great potential for use in biomedical applications (Yadollahi et al., 2015b, 2015c). On the other hand, in the presence of Fe^{3+} and Al^{3+}, CMC can form spherical gel beads. CMC in the form of the bead has attracted much attention as a drug controlled release formulation

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owing to the simplicity and mildness of this process and formation of uniform and small size shape as compared with the conventional CMC hydrogels (Bhattacharya et al., 2013; Rao et al., 2012; Wang et al., 2011).

Cephalosporins are lactam antibiotics with the same fundamental structural requirements as penicillin. They are used for the treatment of infections caused by Gram-positive and Gram-negative bacteria. They act by inhibiting the synthesis of essential structural components of bacterial cell wall. They are among the most effective broad-spectrum bactericidal antimicrobial agents, being the most prescribed of all antibiotics. Cephalexin is a first-generation cephalosporin. Cephalexin is a semisynthetic antibiotic derived from cephalosporin and is almost completely absorbed from the gastrointestinal tract, with a bioavailability of 95%. Cephalexin has a half-life of around 1.1 h. To maintain therapeutic range, the drug should be administered 3–4 times a day, which leads to sawtooth kinetics and resulting in ineffective therapy (Legnoverde et al., 2014; Jishnu et al., 2011).

Based on the above-stated background, in this study, pH sensitive carboxymethyl cellulose proposed as a protective capsule for LDH-Drug nanohybrids in conditions simulating the gastrointestinal tract. Cephalexin, as a model drug, was intercalated between LDH layers through co-precipitation method. The resulting nanohybrid is used to prepare nanocomposite hydrogel beads by association with carboxymethyl cellulose. In vitro drug delivery tests in conditions simulating the gastrointestinal tract were carried out to prove the effectiveness of this novel nanocomposite beads as controlled drug delivery system.

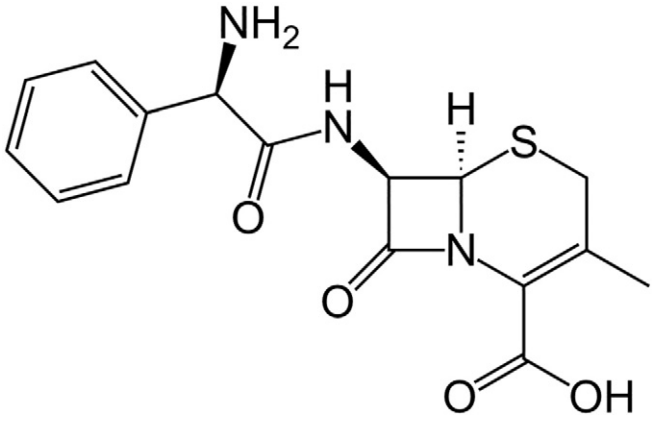
2. Experimental

2.1. Materials

Sodium carboxymethyl cellulose (CMC), degree of substitution (DS) 0.55–1.0 and viscosity of 15,000 mPas/s (1% in H_2O, 25 °C), obtained from Nippon Paper Industries (Japan). $Mg(NO_3)_2 \cdot 6H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, $FeCl_3 \cdot 6H_2O$ and NaOH were purchased from Merck. Cephalexin (Scheme 1) was purchased from Danna Pharma Co. (Tabriz, Iran) and used as received. All the chemicals used as received without further purification. Bi-distilled water used throughout this work.

2.2. Preparation of Mg–Al-LDH

Mg–Al-LDH was prepared by co-precipitation method. First, an aqueous solution (50 ml) of $Mg(NO_3)_2 \cdot 6H_2O$ (33.5 mmol) and $Al(NO_3)_3 \cdot 9H_2O$, (16.5 mmol) were prepared. To this solution, 50 ml of NaOH solution (2 M) added drop-wise with constant stirring under N_2 atmosphere. Afterwards, the slurry aged for 24 h at 95 °C, keeping the pH at 9–10 by adjusting with NaOH (2.0 M) solution. Then, the precipitates were centrifuged and washed with 500 ml of bi-distilled water and finally dried at 50 °C under vacuum for 24 h.



Scheme 1. Chemical structure of Cephalexin molecule.

2.3. Preparation of LDH-CPX nanohybrids

LDH-CPX nanohybrid was synthesized by reacting mixed aqueous salt solutions with a basic solution containing the dissolved drug. The LDH-CPX nanohybrid was prepared with the Mg^{2+} to Al^{3+} ratios of 2. In a three-necked flask, 10.31 g of Cephalexin (0.05 mol) and 4.00 g NaOH was dissolved in 100 ml of bidistilled water. 2.86 g of nitrate salt of $Mg(NO_3)_2 \cdot 6H_2O$ and 2.10 g of $Al(NO_3)_3 \cdot 9H_2O$ was dissolved in 15 ml bi-distilled water. This solution was added drop-wise to the Cephalexin solution with constant stirring under N_2 atmosphere. The pH of the final mixtures was controlled within the range of 9–10. The obtained slurry was aged for 24 h in the mother liquid at 90 °C. The precipitates centrifuged and washed with 500 ml of bi-distilled water and finally dried at 50 °C under vacuum for 24 h.

2.4. Encapsulation of LDH-CPX nanohybrids

CMC/LDH-CPX nanocomposite beads were prepared using the procedure described by Wang et al. (2011). Typically, 2 g of CMC and the necessary amount of the LDH-drug nanohybrid compound containing 60 mg of Cephalexin were incorporated into 100 ml bi-distilled water and sonicated in a sonication bath for 60 min. The obtained mixture heated at 75 °C for 6 h until a homogenous solution obtained. Thereafter, the solution was extruded in the form of droplets, using a syringe, into 2 M $FeCl_3$ solution. The beads were allowed to crosslink with Fe^{3+} in solution for 20 min. After that, the beads were filtered and washed with bi-distilled water to remove un-reacted $FeCl_3$ on the surface of the beads and dried 50 °C under vacuum for 24 h.

2.5. Characterization

Infrared spectra obtained on a FTIR spectrometer (Bruker Instruments, model Aquinox 55, Germany) in the 4000–400 cm^{-1} range at a resolution of 0.5 cm^{-1} as KBr pellets. The X-ray diffraction pattern of the samples was obtained by Siemens diffractometer with Cu-Kα radiation at 35 kV in the scan range of 2θ from 2 to 70°. All the analyzed samples were in the powdery form. The d-spacing was calculated by Bragg's equation where λ was 0.154 nm. Scanning electron micrographs (SEM) were obtained with a TESCAN MIRA3 scanning electron microscope operating at 5 kV.

2.6. Swelling ratio determination of nanocomposite beads

There are many electrolytes in the gastrointestinal tract which have great influences on swelling kinetics of the gel beads and the release of drugs once orally administrated. Thus, it is very important to investigate the swelling kinetics of these hybrid beads in conditions similar to the gastrointestinal tract. The swelling ratios of the nanocomposite beads were measured in buffer solutions with pH of 1.2, 6.8 and 7.4 at room temperature. Typically, 0.1 g of CMC/LDH-CPX nanocomposite beads was immersed in 50 ml of buffer solutions with desired pH at room temperature for 500 min to reach swelling equilibrium. The swelling ratio of CMC/LDH-CPX nanocomposite beads was determined according to Eq. (1).

$$\text{Swelling}\ (\%) = (W_2 - W_1)100/W_1 \quad (1)$$

where W_1 is initial weight of sample, and W_2 is the weight of the sample after swelling for 500 min. All the experiments were carried out in triplicate.

2.7. Estimation of Cephalexin loading of LDH-CPX nanohybrids

Cephalexin content of LDH-CPX nanohybrids was determined by Uv–vis spectroscopy.