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Folate-polyethyleneimine functionalized mesoporous carbon nanoparticles for enhancing oral bioavailability of paclitaxel

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ABSTRACT

Polymer-functionalized carbon nanoparticles hold great promise for their use in enhancing the oral absorption of drugs with poor oral bioavailability. And since the abundant expression of folate receptors in intestinal tract, folic acid (FA) modified uniform mesoporous carbon spheres (UMCS) was used to improve oral absorption of paclitaxel, a chemotherapeutic drug with poor oral bioavailability. In this research, folate-polyethylenimine (FA-PEI) was grafted onto acid-treated uniform mesoporous carbon spheres through one-step electrostatic attraction. PTX was loaded into mesopores of nanoparticles through solvent evaporation, present as amorphous. The release of PTX from the FA-PEI-UMCS nanoparticles exhibited an initial rapid release, followed by a sustained release. And release rate could be regulated by changing amount of FA-PEI complex on the UMCS. The uptake of PTX-encapsulated nanoparticles was studied exploiting Caco-2 cells as an in vitro model. The results of confocal microscopy and flow cytometry demonstrated that folate functionalization enhanced internalization of nanoparticles by the cells. Moreover, PTX loaded in FA-PEI-UMCS nanoparticles resulted in a 5.37-fold increase in apparent permeability (P_{app}) across Caco-2 cell monolayers compared to Taxol®. And the in vivo results showed that FA-PEI-UMCS nanoparticles did not only improve the oral bioavailability of PTX, but also decrease the gastrointestinal toxicity of PTX. In conclusion, the FA-PEI-UMCS nanoparticles might be a potentially applicable system to improve oral absorption of drugs with poor oral bioavailability.

1. Introduction

Oral delivery is the most convenient route for the administration of drug with the best compliance. However, poor water-solubility, low permeability through cell membranes, transport of efflux, and drastic intestinal/hepatic metabolism restrain the oral bioavailability of many drugs. (Lipinski et al., 1997; Scripture et al., 2005; Vasconcelos et al., 2007) In last decades, various nano-carriers have been broadly proposed and studied in oral nanomedicine delivery. (des Rieux et al., 2006; El-Sayed et al., 2005; Roy et al., 1999) Compared to conventional organic lipids or polymer-based nanoparticles, inorganic nanoparticles show distinctive properties such as stability, inertness and ease of modification, which is more conductive to overcome those barriers limiting oral bioavailability. (Bindl et al., 2010; Meng et al., 2009; Valle-Vigón et al., 2010; Zhang et al., 2007, 2010b) Especially, mesoporous carbon nanoparticles with large specific surface areas, tunable particle sizes as well as pore structures, and controllable surface chemistry make it as an ideal reservoir for drug delivery. Moreover, the mesoporous carbon matrix could protect the payload agents effectively from degradation during delivery, as well as improve solubility and membrance-permeability of the drug with poor bioavailability. (Zhao et al., 2012b)

There have been some reports about utilizing mesoporous carbon nanoparticles to enhance oral bioavailability of the Biopharmaceutical Classification System (BCS) class II drugs. (Niu et al., 2013; Zhao et al., 2012a,b) Drugs were loaded in the mesopores of carbon nanoparticles to maintain amorphous state that is in favor of increasing the solubility and accelerating dissolution rate. Consequently, many hydrophobic drugs show a relatively better absorption from the gastrointestinal tract. However, there are few reports on increasing uptake and transcytosis of mesoporous carbon nanoparticle-encapsulated drug across enterocytes to enhance oral absorption, which is

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one major factor in improving oral bioavailability of hydrophobic drugs. (Rieux et al., 2005; Roger et al., 2009) And it is not meaningful for the improvement of oral absorption of another poorly-water soluble drugs (BCS class IV drugs) just by increasing the solubility and accelerating dissolution rate.

In this article, mesoporous carbon nanoparticles UMCS with a mean particle size of 350 nm have been fabricated as drug nanocarriers. PTX, a drug with poor oral bioavailability, (Barrand et al., 1997; Scripture et al., 2005) was encapsulated into the pore channels of mesoporous carbon nanoparticles UMCS. Polymer PEI was grafted onto the surface of UMCS nanoparticles to control the release rate of PTX and increase the adhesion between gastrointestinal tract (negative) and nanoparticles (positive). In addition, folate receptors (FRs) are abundantly expressed at the apical (luminal) surface of intestinal cells. (Elnakat and Ratnam, 2004; Parker et al., 2005; Weitman et al., 1992) Therefore, we functionalized ligand folic acid onto PEI-UMCS nanoparticles that would bind to the cell surface proteins to enable transcytosis of nanoparticles and improve oral absorption of the encapsulated drug. It would be very interesting to incorporate FA-PEI-UMCS nanoparticles to improve oral bioavailability of PTX, especially as, to the best of our knowledge, there are few reports on FA-PEI modified mesoporous carbon nanoparticles as the delivery system for enhancing oral absorption of PTX. Caco-2 cell monolayers were used to simulate a model intestinal barrier for studying the effect of folate modified PEI-UMCS nanoparticle transcytosis on facilitating oral absorption of paclitaxel. And SD rats were used as an in vivo model to evaluate the effect of FA-PEI-UMCS nanoparticles improving the oral bioavailability of PTX.

2. Materials and methods

2.1. Materials

Hexadecylamine, Tetraethyl orthosilicate (TEOS) and Coumarin-6 and fluorescein isothiocyanate (FITC) were purchased from Sigma–Aldrich (St. Louis, MO, USA). Fluorescent probes containing Hoechst 33258, rhodamine-phalloidin were bought from Molecular Probes Inc. (Eugene, OR, USA). MTT was a product of Amreso (USA). Cell culture media folate-free RPMI 1640, penicillin-streptomycin, fetal bovine serum (FBS) were purchased from GIBCO, Invitrogen Co. (Carlsbad, USA). All the other reagents in the experiments were of analytical grade and used without additional purification. Deionized water was used in all procedures.

Sprague-Dawley (SD) rats (220 ± 10 g) were purchased from the Experimental Animal Center of Shenyang Pharmaceutical University. Animal experiments were carried out in accordance with the Guidelines for Animal Experimentation of Shenyang Pharmaceutical University, and the protocol was approved by the Animal Ethics Committee of this institution.

2.2. Preparation of nanoparticles

Uniform mesoporous carbon spheres (UMCS) of 350 nm diameter were prepared by using spherical nanosilica matrix (SNM) as template. SNM was fabricated through the modified fine-tuning method of Xindu et al. (Du and He, 2010) as previously described. (Sun et al., 2012) An ATS AH100D homogenizer (ATS Engineer Inc., China) was used to increase the homogeneity of SNM. Then, the SNM was filtered and dried at 60 °C overnight. At

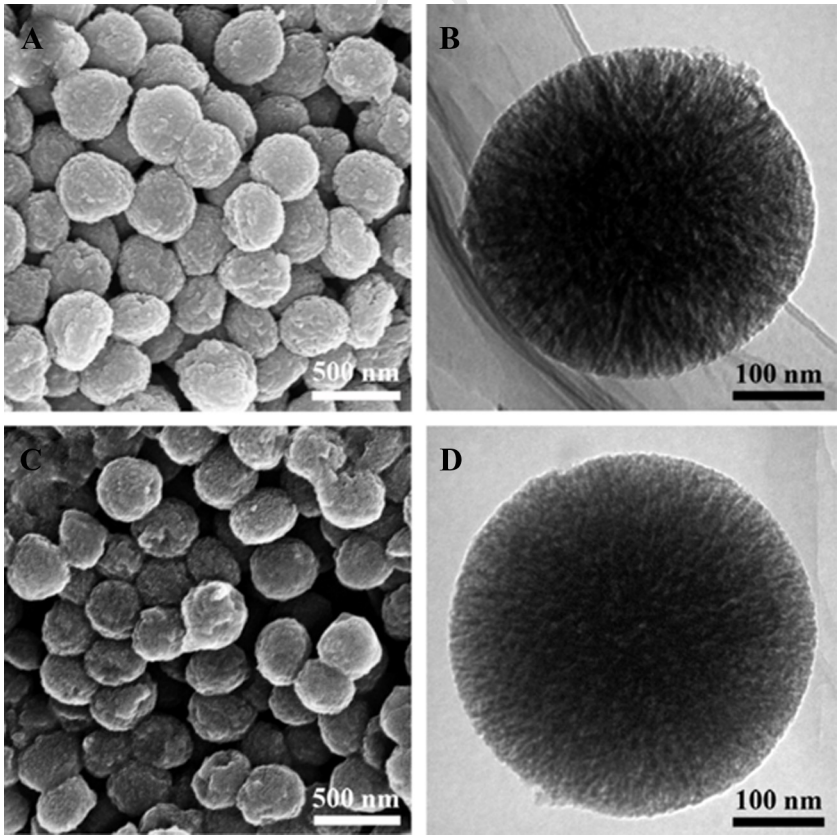

Fig. 1. SEM and TEM micrographs of (A, B) COOH-UMCS, (C, D) FA-PEI-UMCS.

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