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Regular Article

Effects of surface modification and size on oral drug delivery of mesoporous silica formulation

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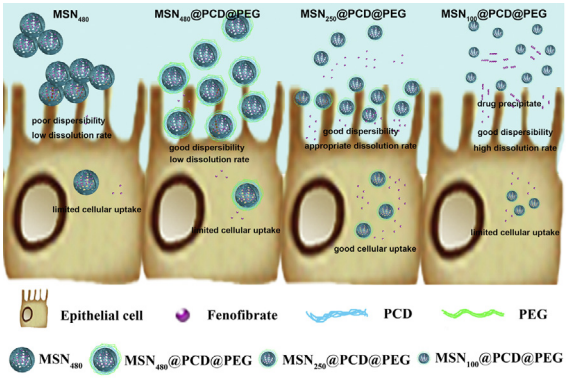
GRAPHICAL ABSTRACT



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ABSTRACT

The surface chemistry and size of nanoparticles can greatly impact their interaction with biological pathways and alter efficacy. However, the interplay between surface modification and particle size has not been well investigated especially for oral delivery. It is necessary to maximize the bioavailability of loading therapeutics. Here, we prepared different sized mesoporous silica nanoparticles (100–500 nm) and conjugated them with polyethylenimine-coated carbon dots (PCD) for effective transepithelial absorption. The nanoparticles were also coated with polyethylene glycol (PEG) polymers for improved mucus permeability. These mesoporous silica nanoparticles conjugated to PCD and coated in PEG (MSN@PCD@PEG) were used to study the influence of particle size and surface chemistry on transepithelial transport and bioavailability. Results demonstrated that the MSN@PCD@PEG with a diameter 250 nm had the highest transepithelial transport and oral bioavailability compared to other formulations. Drug release, endocytosis pathways, transepithelial transport and degradation of these different nanocarriers were systematically studied in order to investigate effects of size variety. The findings indicated that nanoparticle-based oral drug delivery can be potentially improved by adjusting physicochemical properties. We believe that understanding the importance of surface chemistry and particle size in the oral delivery will improve nanoparticle engineering and oral application.

1. Introduction

Oral delivery is a preferred administration pathway for most therapeutic cargos since it has the best patient compliance and

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fewer safety issues compared to intravenous delivery [1–3]. However, challenges for oral delivery still exist especially for drugs with weak stability and low solubility in the GI tract and poor permeability across epithelial tissue. For many years the goal has been to enhance the oral bioavailability of most therapeutics via simple drug delivery systems. To achieve the goal, nanoparticle-based drug delivery systems are attracting more attention since they can protect drugs from premature degradation and interaction with the physiological environment, enhance drug absorption into a special tissues, and increase intracellular penetration [4–6]. Mesoporous silica nanoparticles (MSNs), different from traditional organic polymers and lipid-based nanoparticles, possess high surface area, adjustable pore size, good biocompatibility and simple surface modification. For these reasons, MSNs have become a promising vehicle to enhance oral bioavailability of hydrophobic therapeutics [7–9]. Zhang et al. developed spherical MSNs through an organic template method and demonstrated that MSNs could effectively enhance loading efficiency of poorly water-soluble drug and improve drug dissolution rate and permeability [10,11]. Popat et al. further designed bioresponsive MSNs which were sensitive to pH and enzymes. The MSNs had programmable drug release in GI tract and high drug loading of sulfasalazine [12]. Several studies have shown the application of multifunctional modified MSNs in tumor targeted therapy and the promise of MSNs as drug delivery systems with adjustable surface chemistry and controlled drug release [13–15].

Since previous studies have reported that a slight change in physicochemistry of nanoparticles may significantly impact their interaction with biological pathways and alter efficacy, it is necessary to find new ways to maximize the bioavailability of loading therapeutics [16,17]. Lu et al. studied the effect of size on cancer cell uptake of MSNs (30–280 nm) and found that the maximum uptake occurred with 50 nm MSNs [18]. The effect of the shape of MSNs on the endocytosis, biodistribution, excretion and biocompatibility was separately studied by Li et al. and Shao et al. [19,20]. Most of these studies with MSNs were focused on intravenous administration and not on oral delivery. Without detailed studies on the impact of MSN physicochemistry on the GI tract and bioavailability, the application of MSNs towards oral delivery is limited.

In this study, we constructed a MSNs library composed of surface modification (bilayer polymer conjugated) and different size (100–500 nm) to explore the role of surface chemistry and particle size in oral drug delivery. As is reported, nanoparticles have to overcome the mucus barriers and penetrate the epithelial cells for efficient oral delivery. Hydrophilic/neutral nanoparticles are necessary for mucus permeation, but hydrophobic/cationic nanoparticles are important for efficient epithelial absorption. Therefore, we developed a bilayer modification on the surface of MSNs (d = 480 nm) consisting of polyethylenimine coated-carbon dots (PCD) for effective transepithelial absorption and polyethylene glycol (PEG) polymers for improved mucus permeability (called as MSN@PCD@PEG, @ means modified by). In addition, PCD can also be utilized to real-time monitor the nanoparticle distribution and trafficking in vivo. Bilayer modification showed that the surface chemistry of MSNs does affect biological interactions and bioavailability. The modification enhanced stability in the physiological environment, altered cell uptake mechanisms and increased distribution in various intestinal sections. However, this improvement in oral bioavailability was limited so we further focused on the size factor to determine whether the optimum effect could be obtained by adjusting particle size. MSN@PCD@PEG with different diameters (100 nm, 250 nm and 480 nm) were developed. The most significant enhancement in transepithelial transport, intestinal distribution and oral bioavailability was observed for MSN_{250}@PCD@PEG. MSN_{100}@PCD@PEG came in second while MSN_{480}@PCD@PEG, the formulation used to compare with unmodified MSNs, exhibited the least improvement. Drug release profiles, interactions with the cell membrane, endocytosis pathways, transepithelial transport and degradation of these engineered MSNs in gastric intestinal juice were systematically studied in order to investigate effects of size variety.

In summary, we confirmed the importance of surface chemistry and particle size in oral delivery applications of MSNs and established the proof of concept for further studies in optimizing oral bioavailability of nanoparticles by adjusting their physicochemical properties.

2. Experimental

2.1. Materials and reagents

Cetyltrimethylammoniumbromide (CTAB), tetraethoxysilane (TEOS), pluronic F127, citrate and ethylenediamine (EA) were obtained from Shan Dong Yu Wang Reagent Company (China). *N*-hydroxysuccinimide (NHS), polyethylenimine (PEI, MW:2000), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI), polyethylene glycol (PEG, MW:5000), bovine serum albumin (BSA) and fenofibrate (FBB) were purchased from Sigma-Aldrich Chemical (Shanghai, China). All chemical reagents utilized in study were analytic grade.

Caco-2 cell line was purchased from National Platform of Experimental Cell Resources for Sci-Tech (Beijing, China). Cells were cultured in minimum essential medium (MEM), containing 10% (v/v) fetal bovine serum, 1% (v/v) nonessential amino-acid, 1% (v/v) pyruvic acid sodium salt and 1% penicillin and streptomycin (100 IU/mL) at 37 °C with 5% CO_2.

SD rats (female, 6–8 weeks) were from Vital River Laboratory Animal Center (Beijing, China). All animal studies were performed with the approval of the Institutional Animal Care and Use Committee of Peking University.

2.2. Preparation of different sized MSNs

Different sized MSNs were prepared by adjusting the amount of F127 according to the previous reports [21]. Briefly, 0.5 g CTAB and triblock copolymer F127 (0 g, 1 g or 2 g) were dissolved in 98 mL distilled water, in which 12 mL 29 wt% ammonium hydroxide solution and 40 mL ethanol were added. Then, 1.9 mL TEOS was introduced to the mixture under intensive stirring, and the reaction was maintained at room temperature for 24 h. After that, an ATS AH110D homogenizer (ATS Engineer Inc., Shanghai, China) was performed to homogenize the resulting precipitate. The synthesized nanoparticles were collected by centrifugation and redispersed in 300 mL absolute ethanol containing 1 g NH_4NO_3 to reflux at 80 °C overnight for template extraction. The final particles were centrifuged, washed with ethanol and distilled water for 3 times and dried overnight at room temperature in vacuum. Here, 0 g, 1 g and 2 g of F127 were used respectively to obtain the different sized MSNs (called as MSN_{480}, MSN_{250} and MSN_{100}).

2.3. Surface modification of MSNs with PCD and PEG

The PCD was prepared by the hydrothermal method described in our earlier report [22]. Polyethylenimine (PEI), citric acid and ethylenediamine were added into a beaker, then the reaction mixture was heated to 160 °C and kept for 6 h. The final reaction products were dialyzed in a dialysis bag (molecular weight cut off: 3500) against water for 24 h to remove small molecules. Then PCD in the dialysis bag was freeze-dried to obtain the brown solid. To perform PCD coating, 10 mg of synthesized MSNs was