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Size effect on oral absorption in polymer-functionalized mesoporous carbon nanoparticles

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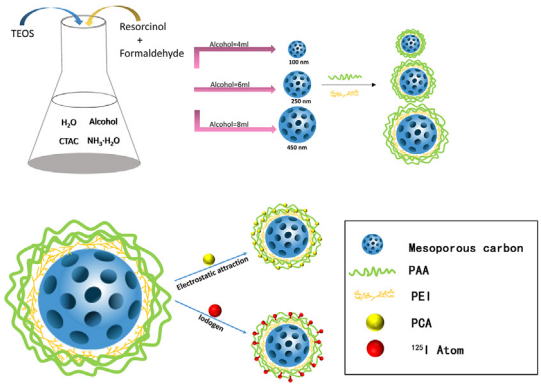
GRAPHICAL ABSTRACT



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ABSTRACT

In this manuscript, the effect of the particle size of polymer-functionalized mesoporous carbon (MPP) nanoparticles on enhancing oral absorption of a water-insoluble drug is first investigated. The insoluble drug, fenofibrate (Fen), was selected as the model drug loaded in the MPP nanoparticles. MPP nanoparticles with different particle sizes were designed for improving the oral bioavailability of drugs, in which the branched polyethyleneimine (PEI) and polyacrylic acid (PAA) were modified on the surfaces of mesoporous carbon nanoparticles (MCNs) with amide bonds. In addition, PEI-functionalized carbon quantum dots (PCA) and radioisotope ^{125}I were applied to label the MPP nanoparticles to trace in the vivo process. According to the data, the MPP nanoparticles could markedly improve the dissolution rate and oral bioavailability of Fen. Interestingly, the MPP nanoparticle size had a notable effect on Fen oral absorption, and intermediate sized MPP nanoparticles were expected to be more ideal oral drug carriers. The nanoparticles were safe and easily excreted. These findings present the prospect of MPP nanoparticles for oral application, and guides the rational design of an oral delivery system with respect to particle size.

1. Introduction

Physicochemical properties, such as size, shape, surface chemistry and structure, play important roles in determining nanoparticle behaviors in vitro and in vivo [1,2]. For an oral delivery system, particle size is a key factor, which ultimately affects the gastrointestinal uptake, in vitro digestion and drug release from nanoparti-

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cles [3,4]. Although there are many reports on the oral absorption effects of particle size, these researches were mainly focused on polymeric nanoparticles [5]. Researchers seldom paid attention to the effect that the particle size of inorganic nanoparticles had on an oral drug delivery system, especially mesoporous carbon nanoparticles (MCNs) [6]. Compared with traditional lipid-based nanoparticles or polymeric nanoparticles, MCNs exhibit prominent characteristics, such as a large surface area, controllable shape, favorable biocompatibility, good stability, and especially their easily functionalized surface, making them ideal candidates for drug delivery [7,8]. Additionally, some studies confirmed that MCNs could effectively improve the oral absorption of poorly water-soluble drugs [9,10].

However, the effect of particle size on oral drug delivery has rarely been studied due to the difficulties in the preparation of size-controlled MCNs. In addition, π-π stacking interactions between the fluorescent dyes and the walls of carbon spheres could make the fluorescence quench through photoinduced electron transfer, which makes it difficult to trace the MCNs' in vivo process [11,12]. Therefore, a novel and multifunctional drug delivery system should be established to solve these problems. According to some reports, advantages of the surface functionalized nanoparticles with hydrophilic polymers are as follows: (1) improved dispersibility and stability, such as polyethyleneimine (PEI) [13,14], polyacrylic acid (PAA) [15,16]; (2) enhanced mucoadhesion and intestinal uptake, such as poly (ethylene glycol) (PEG), polyvinyl alcohol (PVA); (3) reduced the toxicity of nanoparticles; and (4) decreased π-π stacking interaction [17–20]. Thus, it is extremely important to select appropriate polymers.

Recently, compared with commercial fluorescent dyes and semiconductor quantum dots, carbon quantum dots (CQDs) have attracted the attention of researchers as being one of the most popular photoluminescent materials due to their low toxicity and environmental friendliness. Additionally, it has been confirmed that surface passivation was critical to improve the fluorescent efficiency of CQDs, and the surface groups of passivating agents could connect with a suitable drug delivery to play an important role in tracing [21,22].

In this work, novel polymer-functionalized mesoporous carbon nanoparticles of various sizes were developed to investigate their effects on improving the oral absorption of poorly water-soluble drugs. For the first time, MCNs with tunable particle sizes were synthesized by adjusting volume of ethanol during preparation. PEI and PAA grafted on the surface of MCNs were applied as the biocompatible materials as well as barriers to decrease π-π stacking interaction between MCNs and CQDs, which made CQDs trace MCNs in vivo. Interestingly, the in vivo process of nanoparticles was observed with two methods as follows: one method involves coating with PEI-functionalized carbon quantum dots (PCA), which uses citric acid (CA) as a carbon source and PEI as surface passivating agents, and the other method was associated with the radioactive isotope ^{125}I, as shown in Scheme 1. To prevent the interference of surface charges in the drug loading process, fenofibrate, a biopharmaceutics classification system II (BCS II) and a neutral drug, was selected as a model drug. In addition, the in vitro dissolution behavior, in vivo pharmacokinetics, and gastrointestinal mucosa irritation were also discussed.

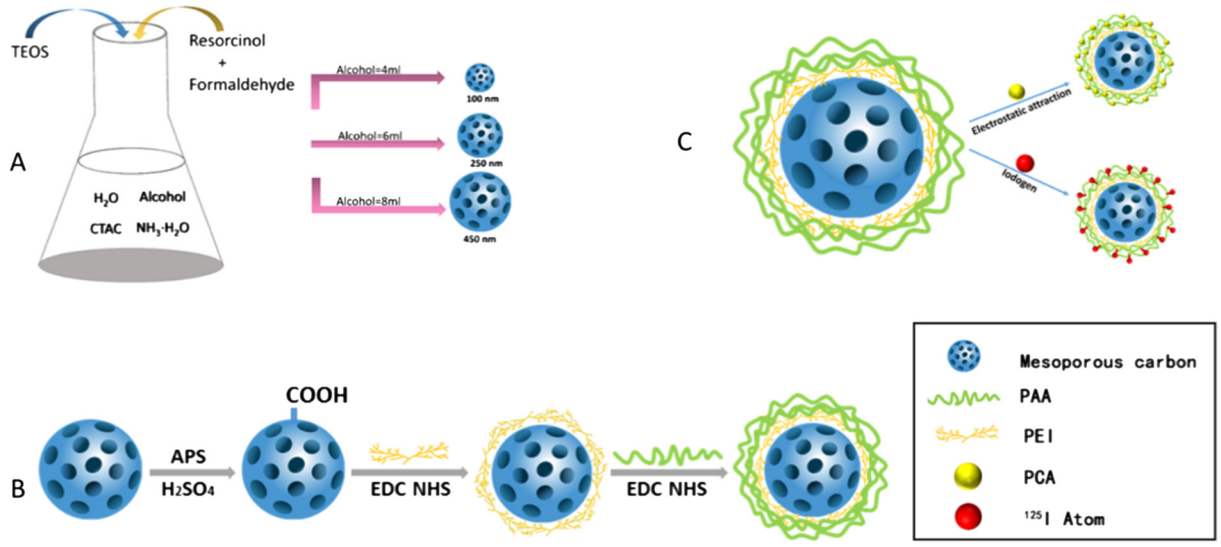
2. Materials and methods

2.1. Materials

Formaldehyde solution, resorcinol, citric acid (CA), ammonium persulfate, sulfuric acid (98%), tetraethoxysilane (TEOS, 98%), and hexadecyl trimethyl ammonium chloride (CTAC, >99%) were obtained from Shan Dong Yu Wang Reagent Company (China). Poly (acrylic acid) (PAA, M_W = 2000 Da), polyethyleneimine (Branched PEI, M_W = 25 kDa), p-aminophenol were purchased from Sigma-Aldrich Chemical (Shanghai, China). All other chemicals were analytical grade and were used without further purification.

2.2. Preparation of MPP nanoparticles

According to the preceding method, MCNs with tunable particle sizes were prepared by altering the amount of absolute ethanol [23]. First, CTAC (1.04 g, 25 wt% in water) and ammonia (0.1 ml) were added to the solution containing deionized water (H_2O, 19 ml) and anhydrous alcohol (E_tOH, 4–8 ml) with stirring at room temperature. After 30 min, resorcinol (0.2 g) was dissolved in the aforementioned solution and continually stirred for 30 min. Subsequently, TEOS (0.36 ml) and formaldehyde solution (0.28 ml) were introduced dropwise to the reaction solution with intensive stirring, and the system continued stirring at 30 °C for 24 h. The as-prepared products were purified by centrifugation, washed with deionized water and ethanol several times, and dried under vac-



Scheme 1. Schematic illustration of (A) synthetic route of MCNs with different particle sizes; (B) synthetic route of MPP, and (C) two kinds of in vivo tracing strategies.