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Three dimensional macroporous hydroxyapatite/chitosan foam-supported polymer micelles for enhanced oral delivery of poorly soluble drugs

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ABSTRACT

In the current study, a novel three-dimensional macroporous hydroxyapatite/ chitosan foam (HA/CS)-supported polymer micelle (PM/HA/CS) was developed, and its potential as an oral drug delivery system to enhance the solubility and oral bioavailability of poorly soluble compounds was systemically studied. Candesartan cilexetil (CC) was selected as a poorly soluble model drug. Firstly, HA/CS foam was synthesized using a wet chemical co-precipitation approach and poly-(methyl methacrylate) colloidal crystals as a macropore template. Subsequently, the CC-loaded polymer micelles were efficiently encapsulated into the macropores of the HA/CS foam and freeze-dried to produce powdery CC-loaded PM/HA/CS composites (CC-PM/HA/CS). The resulting CC-PM/HA/CS particles were then characterized in terms of porous structure, morphology, angle of repose, crystallinity, drug loading, dissolution profiles, and physical stability. Differential scanning calorimetry (DSC) analysis confirmed that CC-PM/HA/CS was present in an amorphous form and has an excellent physical stability. Under both simulated gastric and intestinal conditions, the aqueous solubility and dissolution rate of the PM/HA/CS-based CC formulation were significantly increased compared with the pure drug powder. In addition, PM/HA/CS is almost completely non-cytotoxic. The PM/HA/CS-based CC formulation produced approximately 1.9-fold increased bioavailability when compared to the marketed tablets (Blopress®) administered to fasted Sprague-Dawley rats. On the whole, PM/HA/CS benefits from the advantages of three dimensional macroporous HA/CS foam and polymer micelles, and exhibits great potential as a drug delivery system for increasing the solubility and oral bioavailability of a poorly soluble compound, like CC.

1. Introduction

Oral solid formulations are considered to be the most acceptable and convenient for the delivery of drugs. However, up to 40% of new drug candidates have very poor aqueous solubility. The poor aqueous solubility and incomplete dissolution in gastrointestinal fluids of such compounds often leads to poor oral bioavailability and lack of dose proportionality [1]. Consequently, many different techniques have been employed to improve the dissolution rate in order to attain better oral bioavailability of poorly soluble drugs, including nanocrystals, solid dispersions, polymer micelles, inclusion compounds, microemulsions, and nanoparticles [2–4]. Among them, it has been demonstrated that polymer micelles in which the poorly soluble compounds are encapsulated in their cores, are an effective formulation strategy to improve solubility and oral absorption [5]. Nevertheless, one of the disadvantages of powdery polymer micelles in practical application is their insufficient physical stability. They are responsive to temperature and humidity, which leads to agglomeration, leakage, and recrystallization of the encapsulated drugs. Physical instability could potentially lead to variability in bioavailability [6]. In addition, the poor flowability of powdery polymer micelles due to the cohesion force also limits their dosage form design and manufacturing process.

Three-dimensional macroporous materials, act as volumetric reservoirs, and display many attractive advantages for supporting organic or inorganic nanoparticles, such as high porosity and large inner surface area to highly disperse the nanoparticles, precisely controlled pore sizes in sub-micrometer range, and interconnected porous structures to reduce the diffusion resistance of the encapsulated nanoparticles [7,8]. It has been demonstrated that several types of three-dimensional macroporous materials can greatly stabilize the entrapped compounds. Due to their rigid porous framework, three-dimensional macroporous materials can not only restrict the coalescence and growth of the entrapped

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drug particles but also can prevent or weaken protein degradation in the harsh environment [9,10]. Moreover, porous inorganic materials often have an excellent stability and flowability.

Herein, our design of three-dimensional macroporous matrix-supported polymer micelles may be a potential and simple approach to restrict agglomeration, leakage, and recrystallization of encapsulated drugs in polymer micelles. However, most of the three-dimensional macroporous materials reported to date (silica, carbon, and alumina) cannot soluble in gastrointestinal fluids, which hamper the fast release of the encapsulated polymer micelles.

In recent years, hydroxyapatite and chitosan have been studied for various biomedical applications. Hydroxyapatite, a natural mineral component of bone, has been widely used for bone regeneration [11,12]. Chitosan, a natural cationic polysaccharide, has been extensively used in drug delivery systems due to its excellent biodegradability and pH-responsiveness [13]. In addition, chitosan adheres to mucosal surfaces and also transiently opens tight junctions between epithelial cells [14]. More importantly, it is well known that both chitosan and hydroxyapatite are completely soluble in an acid environment such as gastric fluid [11,13]. Considering the potential advantages associated with previously reported three-dimensional macroporous materials, hydroxyapatite and chitosan, we developed a novel HA/CS foam with three dimensional macroporous structure for drug delivery. Furthermore, the HA/CS composite was used as a host matrix for supporting polymer micelles in order to improve the physical stability and flowability of powdery polymer micelles.

The major aim of this study was to develop a novel PM/HA/CS-based oral drug delivery system to enhance the solubility and oral bioavailability of poorly soluble drugs. Candesartan cilexetil (CC) was used as the poorly soluble model drug. CC is an angiotensin II receptor antagonist used for the treatment of hypertension; it is a lipophilic compound belonging to Biopharmaceutics Classification System (BCS) class II drugs. In healthy individuals, CC has a poor absolute bioavailability (15% or less) after administration of tablets. This low oral bioavailability is primarily due to its slow, variable, and incomplete absorption in the gastrointestinal tract [15]. Thus, improving the solubility and dissolution rate of such a drug is essential to enhance its onset of action, oral bioavailability and therapeutic potency. To achieve the goal of this study, the physicochemical properties and dissolution profile of CC-PM/HA/CS were systemically studied. Furthermore, the pharmacokinetics study of CC-PM/HA/CS was carried out in fasted Sprague-Dawley rats. We believe that the new information produced from our research will help promote the use of the three dimensional macroporous HA/CS foam and polymer micelles in pharmaceutical applications.

2. Materials and methods

2.1. Materials

Chitosan (mean Mw 141 kDa, deacetylation ≥75%), tetrahydrofuran, calcium chloride tetrahydrate, sodium phosphate monobasic dihydrate and d-alpha-tocopherol polyethylene glycol 1000 succinate (TPGS) were purchased from Aladdin (Shanghai, China). Pluronic F68 was provided by BASF (Ludwigshafen, Germany). Raw CC and candesartan (purity more than 99%) were provided by Huahai Pharma Ltd. (Zhejiang, China). Pluronic P123 was purchased from Sigma-Aldrich (Shanghai, China). CC tablets (Blopress®) were purchased from Tianjin Takeda Pharmaceutical Co., Ltd. (Tianjin, China). Distilled water was used throughout this study. All the other chemicals used were of analytical grade.

2.2. Preparation of drug-loaded particles

2.2.1. Preparation of colloidal crystals

Poly-(methyl methacrylate) (PMMA) spheres were first prepared using a soap-free polymerization method [16]. A typical preparation was described in the Supporting information.

2.2.2. Synthesis of three-dimensional macroporous HA/CS foam

The three-dimensional macroporous HA/CS foam was prepared using a wet chemical co-precipitation approach and PMMA colloidal crystals as a macropore template. In a typical preparation, chitosan (1.0 g) was dissolved in 100 ml aqueous acetic acid solution (2%) at room temperature to form a homogeneous chitosan solution. Next, calcium chloride tetrahydrate and sodium phosphate monobasic dihydrate (Ca/P molar ratio of 1.67) was dissolved in the chitosan solution to obtain the precursor sol. Successively, the prepared colloidal crystals (1.0 g) were impregnated with the precursor sol at 60 °C for 12 h to introduce chitosan, Ca^{2+} and PO_4^{3-} into the interstitial voids. After vacuum filtration, the impregnated colloidal crystals were vacuum dried at 40 °C for 3 h. The impregnation and drying process was repeated two-times. Subsequently, the dry composites were impregnated with 200 ml sodium hydroxide solution (5%) at 40 °C for 24 h. After filtration and titration of residual sodium hydroxide solution to neutral with distilled water, the obtained PMMA/HA/CS composite was separated by filtration and dried at 40 °C for 6 h. The dried PMMA/HA/CS powder was then soaked in tetrahydrofuran for 12 h to remove the template. Finally, the HA/CS foam was repeatedly washed with ethanol and vacuum dried at 40 °C for 3 h.

2.2.3. Fabrication of CC-PM/HA/CS complexes

The CC-PM/HA/CS complexes were prepared using the following two steps. Firstly, a thin-film hydration method was adopted to prepare CC-PM. In detail, 80 mg pluronic F68, 160 mg pluronic P123, and 12 mg TPGS were dissolved in 4 ml ethanol at ambient temperature under vigorous stirring. Next, 40 mg CC was dissolved in the above solution and then the solvent was evaporated using a rotary evaporator at 45 °C to obtain a CC/polymer film. After that, the dried film was hydrated with 3 ml distilled water under sonication for 5 min to obtain the CC-PM solution. Secondly, the CC-PM was incorporated into the macropores of the HA/CS foam and then freeze-dried to form CC-PM/HA/CS complexes. Briefly, HA/CS powder was added to the CC-PM solution (at drug-to-HA/CS ratios of 40:75, w/w) at room temperature. The resulting mixture was vortexed in a closed vial for 10 min and then brought to adsorption equilibrium under magnetic stirring for 6 h to achieve maximum CC-PM loading in the pore channels of the HA/CS foam. Next, the solvent was removed by freeze-drying using a freeze-dryer (−50 °C and 10 Pa). Finally, the resulting CC-PM/HA/CS powder was vacuum dried at 40 °C for 12 h and subsequently sieved through a 200-mesh sieve. For comparison, the freeze-dried CC-PM powder was also prepared as described above, without adding HA/CS foam.

2.3. Particle characterization

The porous structure and morphology of the CS/HA foam before and after incorporation of CC-PM were characterized using a VS-Tenoe scanning electron microscopy (SEM) instrument (FEI, USA). Prior to imaging, each sample was sputter-coated with gold under vacuum. The transmission electron microscopy (TEM) images of the prepared samples were recorded on a Tecnai G^2 Twin TEM instrument (FEI, The Netherlands). A Nicomp^{TM}380 partical sizer (PSS, USA) was used to determine the particle size distribution of the prepared CC-PM. The static angle of repose measurement was performed using a HMKFlow powder comprehensive characteristic tester (Huimeike, China). Prior to flowability measurement, the powdery CC-PM and CC-PM/HA/CS samples were dried in a desiccating chamber for 12 h.

2.4. Fourier transform infrared spectroscopy (FT-IR)

Each prepared sample was analyzed using a FT-IR spectrometer (Bruker IFS 55, Switzerland). Prior to measurement, each sample was

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