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Increasing the dissolution rate and oral bioavailability of the poorly water-soluble drug valsartan using novel hierarchical porous carbon monoliths

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ABSTRACT

In the present study, a novel hierarchical porous carbon monolith (HPCM) with three-dimensionally (3D) ordered macropores (~400 nm) and uniform accessible mesopores (~5.2 nm) was synthesized via a facile dual-templating technique using colloidal silica nanospheres and Poloxamer 407 as templates. The feasibility of the prepared HPCM for oral drug delivery was studied. Valsartan (VAL) was chosen as a poorly water-soluble model drug and loaded into the HPCM matrix using the solvent evaporation method. Scanning electron microscopy (SEM) and specific surface area analysis were employed to characterize the drug-loaded HPCM-based formulation, confirming the successful inclusion of VAL into the nanopores of HPCM. Powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) demonstrated that the incorporated drug in the HPCM matrix was in an amorphous state and the VAL formulation exhibited good physical stability for up to 6 months. In vitro tests showed that the dissolution rate of HPCM-based formulation was increased significantly compared with that of crystalline VAL or VAL-loaded 3D ordered macroporous carbon monoliths (OMCMs). Furthermore, a pharmacokinetic study in rats demonstrated about 2.4-fold increase in oral bioavailability of VAL in the case of HPCM-based formulation compared with the commercially available VAL preparation (Valzaar®). These results therefore suggest that HPCM is a promising carrier able to improve the dissolution rate and oral bioavailability of the poorly water-soluble drug VAL.

1. Introduction

With the advent of combinatorial chemistry and high throughput in vitro pharmacology screening, the number of poorly water-soluble compounds has dramatically increased (Gardner et al., 2004; Lipinski, 2000). Active pharmaceutical ingredients (APIs) with poor aqueous solubility often demonstrate poor and erratic absorption when administrated orally due to the dissolution rate-limiting absorption in the gastrointestinal (GI) tract (Kawabata et al., 2011). It was reported that 70% of the potential drug candidates were discarded due to low bioavailability related with poor solubility in water before they ever reached the pharmaceutics department (Cooper, 2010). Hence, increasing the aqueous solubility and dissolution rate of poorly water-soluble APIs is a significant challenge to pharmaceutical scientists. Over recent decades, more and more strategies have been developed to overcome this obstacle for poorly water-soluble APIs, these strategies include reducing particle size to increase surface area (Gao et al., 2013; Merisko-Liversidge and Liversidge, 2011), enhancing the porosity (Hu et al., 2002), solubilization in surfactant systems (Chaubal, 2004), changing the drug crystalline state (Brough and Williams, 2013) and developing novel oral nano-drug delivery systems for immediate release (Nkansah et al., 2013; Zhang et al., 2012).

During the past several years, porous materials (mesoporous silica, carbon nanotube, microporous hydroxyapatite, macroporous polymer, etc.) have been widely used in drug delivery field (Prakash et al., 2011; Tang et al., 2012). For the development of an inorganic carrier-based formulation to control drug release in the GI tract where no systemic absorption of the particles is desired, microparticles are preferred to nanoparticles, since cellular uptake is significantly lower making them toxicologically

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less problematic (Sharma et al., 2012). Among the micrometer-sized porous materials, 3D ordered macroporous monoliths with well-defined surfaces, interconnected macroporous structures, and precisely controlled pore sizes in the sub-micrometer range have been proved to be useful as oral drug delivery platforms (Xie et al., 2012). Due to spatial confinement within the nanoscale pores, the encapsulated drug molecules are normally unable to form highly ordered crystals, instead remaining in microcrystalline or amorphous forms and leading to enhanced in vitro dissolution rate. However, 3D ordered macroporous monoliths generally lack mesopores in their matrices, which substantially limits their ability to highly disperse drugs down to the molecular level and the rate of mass transport (Wang et al., 2013). It is well known that mesoporous materials possess a larger inner surface area and pore volume to highly disperse the incorporated drug molecules, compared with ordered macroporous materials (Liang et al., 2008). Therefore, it is highly attractive to build up hierarchical porous architectures for 3D ordered macroporous monoliths by integrating small mesopore channels within interconnected macroporous matrices.

Notably, HPCM is an important class of new-generation porous carbon materials, which exhibit a continuously interconnected macroporous structure and accessible uniform mesoporous porosity as walls, low mass density, high surface area and large pore volume (Huang et al., 2008; Wu et al., 2012). In addition to its mesopore channels being able to change the crystalline state of a drug to an amorphous one, the interconnected macropore and mesopore channels of HPCM may allow the dissolution media to easily penetrate into the particles and facilitate drug dissolution, compared with either a solely mesoporous equivalent or macroporous equivalent. All these properties demonstrate the potential and advantages of using HPCM in oral drug delivery. However, until now, no study has explored their potential in improving the dissolution and bioavailability of poorly water-soluble drugs following oral administration.

In this study, a novel HPCM, with 3D ordered macropores (around 400 nm) and uniform accessible mesopores (around 5.2 nm), were successfully synthesized via a dual-templating approach and used as a potential carrier at first time. VAL (Fig. 1) is one of the angiotensin II receptor (AT1) antagonists recommended for treatment of hypertension, post-myocardial infarction or congestive heart failure (Chioléro and Burnier, 1998). It is a lipophilic compound (log P = 5.8) belongs to BCS class II drugs (low solubility and high permeability). The absolute bioavailability after oral administration of the solid dosage form of VAL is about 23% (Brookman et al., 1997). Therefore, improving the solubility and dissolution rate of such a drug is expected to enhance bioavailability and, hence, its therapeutic potency. The aim of this study was to develop a novel HPCM as an oral nano-drug carrier to improve the dissolution rate and increase the oral bioavailability of VAL. To achieve this goal, VAL-loaded HPCM was characterized in terms of morphology, macro-/mesoporous structures, specific surface area, physical state, solubility and in vitro dissolution. At the same time, the influence of the structural effect of the carbon matrix on the physicochemical properties of the VAL formulation was further studied by comparison with VAL-loaded OMCM. Finally, the in vivo pharmacokinetics of the VAL-loaded HPCM formulation was assessed in rats compared with the commercial VAL capsules.

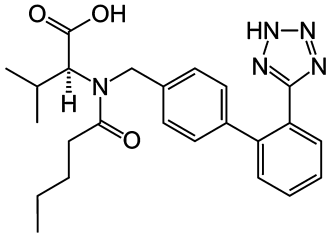

Fig. 1. Chemical structure of VAL.

2. Materials and methods

2.1. Materials

Coarse VAL (purity more than 99%) and telmisartan were obtained from Huahai Pharma (Zhejiang, China) and used as-received. Poloxamer 407 was kindly provided by BASF (Ludwigshafen, Germany). Tetramethyl orthosilicate, ammonium, furfuryl alcohol and oxalic acid were obtained from Kemiou Chemical Co. (Tianjin, China). HPLC-grade acetonitrile and methanol were purchased from Fisher Scientific (Pittsburgh, PA, USA). PrestoBlue® was purchased from Life Technologies (Carlsbad, CA, USA). Dulbecco's Modified Eagle Medium (DMEM) and fetal bovine serum (FBS) were purchased from Solarbio (Beijing, China). Distilled water purified using a DW 200 purification system (Hitech Instruments, Shanghai, China) was used in all experiments. Commercially available VAL preparation (Valzaar®, Torrent Pharma, India) was chosen as the reference in the bioavailability study.

2.2. Cell line

HT-29 human colon carcinoma cells were obtained from the American Type Culture Collection. The cells were cultured in DMEM medium, supplemented with 10% FBS, 100 U/ml penicillin, 1% (v/v) L-glutamine, 1% (v/v) non-essential amino acids and 0.1 mg/ml streptomycin at 37 °C in a 5% CO_2/95% air atmosphere.

2.3. Preparation of drug-loaded microparticles

2.3.1. Synthesis of spherical silica nanoparticles

Nearly monodisperse spherical silica nanoparticles were prepared using a sol–gel method (Rao et al., 2005). Typically, 7.5 ml tetramethyl orthosilicate was mixed with 200 ml ethanol and the mixture was stirred at room temperature. After 10 min, 19 ml ammonium was added as a catalyst for the hydrolysis and condensation of tetramethyl orthosilicate. The resulting mixture was vigorously stirred for 20 h at 25 °C. Finally, the obtained nanoparticles were collected by centrifugation, washed with ethanol, and dried in air to obtain the white silica powder.

2.3.2. Synthesis of HPCM and OMCM

HPCM was synthesized using furfuryl alcohol as a carbon source, oxalic acid as a polymerization catalyst, silica nanospheres as a hard macroporous template and Poloxamer 407 as a soft mesoporous template. In a typical procedure, 0.9 g Poloxamer 407 was dissolved in 30 ml furfuryl alcohol containing 0.5% oxalic acid to obtain the carbon precursor. The precursor was stirred for 20 min prior to addition of 16 g silica nanospheres. The resulting suspension was stirred at 25 °C for 30 min and then centrifuged at 4000 × g for 20 min. After removing excess precursor solution, the resulting precipitate was heated to 90 °C for 12 h to allow the polymerization of furfuryl alcohol. After polymerization, the polymer/silica composite was further heated to 400 °C for 4 h under a nitrogen purge and subsequently heated to 700 °C for 5 h to carbonize the polymer. Finally, the silica template in the carbon/silica composite was dissolved in 5 M potassium hydroxide solution for 10 h to form HPCM. In addition, 3D OMCM was also synthesized following the above-mentioned procedure in the absence of Poloxamer 407 as the mesoporous template.