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The effect of a P123 template in mesopores of mesocellular foam on the controlled-release of venlafaxine

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ABSTRACT

A series of mesocellular foams (MCFs)-based mesoporous silica nanospheres (DH-MCF-P123-*n*, (*n* = 12, 2, 0.5)) were synthesized as controlled-release deliveries for a typical antidepressant drug, venlafaxine. The foams were 3-(2,3-dihydroxypropoxyl)propyl-grafted and the P123 template partially preserved. We studied the release profiles of venlafaxine-loaded DH-MCF-P123-*n* in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), respectively, as well as their corresponding venlafaxine loading capacities. Appropriate amounts of P123 template preserved in mesopores showed an efficient synergetic effect on increasing venlafaxine loading capacity and controlled-release property. Up to 90.87% (mass fraction) of venlafaxine could be loaded into DH-MCF-P123-2. For this carrier, 36% of venlafaxine was released after 1 h of incubation in SGF and 53% of venlafaxine was released after 12 h in SIF. The mechanisms of the loading and releasing processes were tentatively described based on the release behaviors.

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1. Introduction

Over the past few decades, there has been considerable interest in developing drug delivery nanotechnology for small molecules, proteins and DNA (Kim et al., 2009; Sahoo and Labhasetwar, 2003). Nanotechnology-based delivery systems, including polymeric biodegradable nanoparticles (Panyam and Labhasetwar, 2003; Panyam et al., 2002), ceramic nanoparticles (Jain et al., 1998; Roy et al., 2003), polymeric micelles (Hrubý et al., 2005; Lee et al., 2003, 2005), dendrimers (Gillies and Fréchet, 2005; Liu and Fréchet, 1999) and liposomes (Lasic et al., 1999; Park, 2002), have been introduced and designed to respond to specific stimuli, such as electric field (Murdan, 2003), magnetic field (Liu et al., 2008), pH (Gyenes et al., 2008; Yang et al., 2010; Zhu et al., 2005) and temperature (Zhang et al., 2009) to improve the drug efficacy, reduce the drug toxicity and meet the requirement of site-selective and targeted delivery (Sahoo and Labhasetwar, 2003). Polymeric micelles that possess the properties of a fairly narrow size distribution in the nanometer range and the unique core–shell architecture in aqueous solution are able to avoid renal exclusion, clearance by reticuloendothelial system (RES), and provide good endothelial cell permeability (Kataoka et al., 2001; Rosler et al., 2001). They are extensively used as the delivery for water-insoluble drugs, such as anti-tumor drugs (Gou et al., 2011; Matsumura et al., 2004; Nakanishi et al., 2001; Nasongkla et al., 2006; Torchilin et al., 2003; Yokoyama et al., 1998).

Mesoporous silica materials are a kind of ceramic nanoparticles with good biocompatibility, no toxicity, stability and adjustable pore size and structure. They have attracted considerable attention as supports for adsorption and immobilization of biologically relevant molecules (Horcajada et al., 2004; Mal et al., 2003; Pasqua et al., 2007; Slowing et al., 2008; Vivero-Escoto et al., 2010; Xu et al., 2008) since the first report of M41S materials as a drug delivery agent (Vallet-Regí et al., 2000) at the beginning of this century. Among various mesoporous materials, having large pore diameter and interconnected pore structure (Lettow et al., 2000; Schmidt-Winkel et al., 1999, 2000), mesocellular foams (MCFs) extend the delivery application for large biomacromolecules, and raise the drug loading capacity (Zhang et al., 2010, 2011). However, larger pores of MCFs also cause a problem of the drug burst release. The structural template of MCFs, Pluronic $EO_{20}PO_{70}EO_{20}$ (P123), is an amphiphilic poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) triblock copolymer that can self-associate to form micelles in aqueous solution and has relatively high biocompatibility (Kabanov et al., 2002). Recently, it was reported that a similar Pluronic triblock copolymer F127 showed positive effects on the controlled-release of cisplatin in a rabbit model (Sonoda et al., 2010). A P123/amorphous calcium phosphate (ACP) nanocomposition was reported as a successful carrier for ibuprofen (Cao et al., 2010). These successful cases aroused our interest in identifying the synergistic effect of the P123 template in

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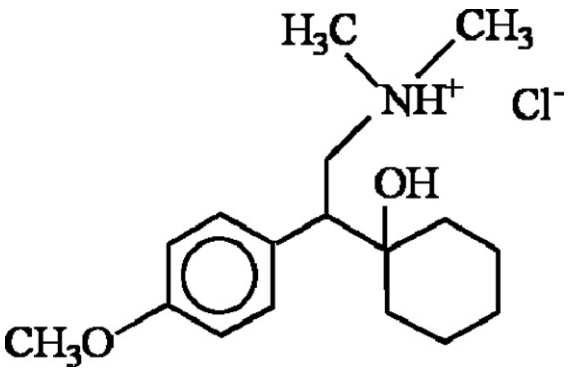

Fig. 1. Molecular structure of Venlafaxine hydrochloride (VenHCl).

mesoporous materials on the controlled-release of drugs. To the best of our knowledge, there are very few reports referring to this special delivery mesoporous material with template partially preserved, although it will be meaningful not only for the controlled-release methodology, but also for the future application and fabrication with the process of removing templates.

A large amount of antidepressants were produced because of the increasing prevalence of major depression worldwide (Gonzalez et al., 2010). Among them, as a bicyclic phenylethylamine derivative (Keltjens et al., 2003; Wellington and Perry, 2001) (Fig. 1), venlafaxine is a typical selective serotonin reuptake inhibitor (SSRI). Although a commercial extended release capsule (EFFEXOR XR®), one of the most commonly prescribed antidepressants on the US retail market in 2007 (Drug Topics, 2008), is already available, it still has some side effects, such as nausea, insomnia, weakness, drowsiness and constipation. Therefore, improving the controlled-release performance of venlafaxine is likely to be a good direction to increase patients' tolerance. In our previous work, poly(lactic acid) was introduced to coat the mesoporous silica nanoparticles (MSN) to improve the controlled-release of venlafaxine (Tang et al., 2011). However, the effect of the P123 template was not investigated.

Herein, MCFs with various amounts of P123 template preserved were synthesized and used as the drug delivery for venlafaxine. The loading capacity and in vitro release in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were investigated. The mechanism for the synergistic effect of P123 template on the loading and release processes was also described.

2. Materials and methods

2.1. Materials

Venlafaxine hydrochloride and Pluronic P123 were purchased from Sigma–Aldrich Company. Monobasic potassium phosphate, NaOH, tetraethyl orthosilicate (TEOS) and toluene were purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd. Ethanol (anhydrous), hydrochloric acid and 1,3,5-trimethylbenzene (TMB) were purchased from Sinopharm Chemical Reagent Co., Ltd. (3-Glycidoxypropyl)methyldiethoxysilane was provided by Shanghai Guipu Chemical Reagent Co., Ltd. All reagents were in analytical pure grade and used without further purification except for toluene, which was dehydrated before using.

2.2. Synthesis of MCFs

MCF was synthesized by modifying the conventional MCF synthesis method (Han et al., 2007), in which, Pluronic P123 (8.0 g) was dissolved in a hydrochloric acid solution (150 mL, 1.6 mol L^{-1}) at 40 °C by vigorous stirring. Then TMB (5.0 g) was added. After continuous stirring for 2 h, TEOS (18.4 mL) was added dropwise using a syringe with extra stirring for 5 min. The slurry was transferred into an autoclave and aged at 40 °C for 20 h under a static condition. Then the temperature was increased to 100 °C, and it was aged again for 24 h. The resulting precipitate was filtered, washed with water and ethanol, and dried. The product was denoted as MCF-as.

The above dry MCF-as (1.5 g) was refluxed in a hydrochloric acid ethanol solution (160 mL ethanol mixed with 1.3 mL concentrated HCl) for 12 h to remove the P123 template. Then it was filtered, washed with water and ethanol, and dried. The resulting material was denoted as MCF-P123-12.

2.3. Synthesis of 3-(2,3-dihydroxypropoxyl)propyl-grafted MCFs

The 3-(2,3-dihydroxypropoxyl)propyl-grafted spherical MCF materials were synthesized by the following process: The MCF-as powder (1.0 g), containing P123 template, was dispersed in dry toluene (80 mL), then, (3-glycidoxypropyl)methyldiethoxysilane (1.5 mmol) was injected. The mixture was refluxed overnight under a nitrogen atmosphere. The resulting 3-glycidoxypropyl-grafted MCF-as powder was filtered, washed with toluene and ethanol, and dried. The dry 3-glycidoxypropyl-grafted MCF-as powder (1.5 g) was refluxed in a HCl ethanol solution (160 mL ethanol mixed with 1.3 mL concentrated HCl) for n (n = 12, 2, 0.5) hours to remove (or partially remove) P123 template. The ring cleavage reaction of 3-(2,3-epoxypropoxy)propyl group took place in this HCl ethanol solution to yield 3-(2,3-dihydroxypropoxyl)propyl-grafted MCF materials. Finally, the resulting products (1.0 g) were treated with 80 mL of a 1:7 (v/v) water/ethanol solution of sodium bicarbonate (0.042 g) for 4 h at room temperature to remove any unreacted and physisorbed (3-glycidoxypropyl)methyldiethoxysilane. Then, they were filtered, washed with water and ethanol, and dried. The resulting materials were denoted as DH-MCF-P123-n (n = 12, 2, 0.5).

2.4. Loading venlafaxine

DH-MCF-P123-n (n = 12, 2, 0.5) powder (250 mg) was added into 10 mL venlafaxine (6.0 mg, 19.12 mmol) aqueous solution. The mixture was then sealed and stirred overnight at room temperature. After that, the precipitates were filtered, washed with a small amount of water and dried under vacuum at room temperature. The filtrates were diluted with H_2O to a final volume of 50 mL. The resulting materials were correspondingly denoted as VEN-DH-MCF-P123-n (n = 12, 2, 0.5).

The amounts of venlafaxine loaded in samples (wt) were calculated by Eq. (1) and the loading capacities of venlafaxine (mass fraction) were calculated by Eq. (2).

$$wt = \frac{m_1 - CV}{m_2 + (m_1 - CV)} 1000 \quad (1)$$

$$P\% = \frac{m_1 - CV}{m_1} \times 100 \quad (2)$$

where m_1 and m_2 are the initial mass of venlafaxine and DH-MCF-P123-n, respectively. C is the concentration of the filtrate diluted in 50 mL volumetric flask, and V is the volume of the diluted filtrate (here 50 mL).

2.5. In vitro release of venlafaxine

2.5.1. Preparation of SGF and SIF

Enzyme free SGF was prepared according to United States Pharmacopeia specification (USP-NF, 2005). 0.1 g sodium chloride was dissolved in 40 mL H_2O, and then, 0.35 mL condensed HCl was added, the pH value of this solution was approximately 1.2. Then, the solution was diluted with H_2O to a final volume of 50 mL.

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