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Hollow mesoporous silica as a high drug loading carrier for regulation insoluble drug release

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ABSTRACT

The purpose of this study was to develop a high drug loading hollow mesoporous silica nanoparticles (HMS) and apply for regulation insoluble drug release. HMS was synthesized using hard template phenolic resin nanoparticles with the aid of cetyltrimethyl ammonium bromide (CTAB), which was simple and inexpensive. To compare the difference between normal mesoporous silica (NMS) and hollow mesoporous silica in drug loading efficiency, drug release behavior and solid state, NMS was also prepared by soft template method. Transmission electron microscopy (TEM), specific surface area analysis, FT-IR and zeta potential were employed to characterize the morphology structure and physicochemical property of these carriers. The insoluble drugs, carvedilol and fenofibrate(Car and Fen), were chosen as the model drug to be loaded into HMS and NMS. We also chose methylene blue (MB) as a basic dye to estimate the adsorption ability of these carriers from macroscopic and microscopic view, and the drug-loaded carriers were systematically studied by differential scanning calorimetry (DSC), X-ray diffraction (XRD) and UV-vis spectrophotometry. What' more, the in vivo process of HMS was also study by confocal microscopy and in vivo fluorescence imaging. In order to confirm the gastrointestinal safety of HMS, the pathological examination of stomach and intestine also be evaluated. HMS allowed a higher drug loading than NMS and exhibited a relative sustained release curve, while NMS was immediate-release. And the effect of preventing drugs crystallization was weaker than NMS. As for in vivo process, HMS was cleared relatively rapidly from the mouse gastrointestinal and barely uptake by intestinal epithelial cell in this study due to its large particle size. And the damage of HMS to gastrointestinal could be ignored. This study provided a simple method to obtain high drug loading and regulation insoluble drug release, expanded the application of inorganic carriers in drug delivery system and pharmaceutic adjuvant.

1. Introduction

The application of a large number of novel materials is used in pharmaceutical research on account of their remarkable physical and chemical properties (Doane and Burda, 2012; Taratula and Kuzmov, 2013; Master et al., 2013; Wicki and Witzigmann, 2015). Among them, inorganic porous materials have attracted the attention of researchers owing to their outstanding properties, such as adjustable pore size, high specific surface area and good biocompatibility (Huang et al., 2011; Monty Liong et al., 2008; Xu et al., 2013; Zhu et al., 2014). In particular, silica-based porous materials have been regarded as significant potential drug excipients, which have attracted increasing attention of pharmaceutical researchers (Zhang et al., 2010; Hu et al., 2011a; Wang et al., 2015; Zhao et al., 2014; Wu et al., 2012; Xie et al., 2013). There is no doubt that oral administration is the most convenient and preferred route for drug administration system due to its simplicity and safety, which have encouraged many research to develop more oral preparations in order to conform daily application. However, considerable amount of marketed drugs and many new drug candidates are water-insoluble, which cannot be absorbed completely though the gastrointestinal tract. In the Bio-pharmaceutic Classification System (BCS), these low solubility but high permeability drugs are belong to the BCS Class II. Hence, the key to increase the bioavailability is located in improving the solubility and dissolution rate of this class of drugs. Accordingly, it has become a great challenge for formulation researchers to tackle the poor dissolution rate and oral bioavailability of new medicines.

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Various approaches could be employed to improve the disadvantage of poorly water-soluble drugs, such as nanocrystal, solid dispersions, lipid-based formulation and so on (Carriere, 2015; Chen et al., 2016; Jahangiri et al., 2016; Maniruzzaman et al., 2015; Pestieau et al., 2015). Meanwhile, it has been a preferred approach to loaded water-insoluble drugs into mesoporous silica. All the above properties allow mesoporous silica to be applied as excellent carrier to improve drug bioavailability. The nano-scale channel could efficiently disperse the drug molecules, which change crystalline form into amorphous state, explaining the increased solubility and dissolution. At the same time, the rigid and inert structure inhibits the aggregation of drug molecule, which could improve the drug stability. Moreover, sustained or controlled drug delivery systems are often desirable, the regulation of the drug release rate is another challenge for formulation researchers to improve patient compliance, drug efficacy and decrease the side effect. Commonly, to achieve sustained drug release, polymers were encapsulated onto the surface of mesoporous silica nanospheres. These processes were always complex and time consuming (Hu et al., 2015; Sun et al., 2013). In order to prevent burst release, the drug loaded on the surface need to be removed, the drug loading capacity was relatively low, so that these normal mesoporous silica materials are unsuitable for the clinical use.

In order to improve the drug loading efficiency and achieve sustained release, we focused on the recently developed hollow mesoporous silica. Hollow mesoporous silica, which has a hollow core and a shell with mesopores, combines the characteristics of both macroporous and mesoporous structures in one single unit. The hollow core can act as a storage reservoir or a micro-reactor, whereas the mesoporous shell provides pathways for encapsulated substances or substantial surface area for reactions. Hollow mesoporous silica has shown great potential in many fields, for example, as drug carrier, sorbent, or sensor in biotechnology, catalysis, and separation (Chen et al., 2013; Sasidharan and Zenibana, 2013). Regarding the sphere structure of the hollow core, we have considered nonporous phenolic resin nanoparticles, which were fabricated easily, dispersed well in later reaction solution and removed by calcining. In order to encapsulate phenolic resin with silica, the assist of hexadecyl trimethyl ammonium bromide (CTAB) is necessary. Moreover, these surfactants will form mesoporous structure after calcining, thus the hollow mesoporous silica nanoparticles were fabricated. In order to compare the drug loading efficiency, solid state and release behavior between hollow mesoporous silica (HMS) and normal mesoporous silica (NMS), NMS was also prepared by soft template method. The physicochemical properties of HMS and NMS were systematically analyzed by TEM, nitrogen adsorption and FT-IR characterization. Car and fen were selected as BCS II model drug, which were loaded into different carriers using two methods (solvent evaporation method and adsorption equilibrium method). In order to compare the drug loading ability between HMS and NMS intuitively, methylene blue (MB) was also used as model dye. The physicochemical properties the drug-loaded samples were systematically analyzed by nitrogen adsorption, DSC, XRD, UV spectrometry and so on. What' more, confocal microscopy and in vivo fluorescence imaging were also used to monitor of the biodistribution in gastrointestinal tract and uptake properties by intestinal epithelial cell. In order to confirm the gastrointestinal safety of HMS, the pathological examination of stomach and intestine also be evaluated. Thus HMS could achieve high drug loading and regulation drug release, but the solid state is a significant factor to be considered. Due to its large particle size, HMS was barely uptake by intestinal epithelial cell and cleared relatively rapidly from the gastrointestinal in this study. And the damage of HMS to gastrointestinal could be ignored. This study could provide a simple and feasible approach to obtain high drug loading and regulation insoluble drug release, expanded the application of inorganic carriers in drug delivery system and pharmaceutic adjuvant.

2. Materials and methods

2.1. Materials

Resorcinol, cetyltrimethyl ammonium bromide (CTAB), tetraethyl orthosilicate (TEOS), formaldehyde solution (5 wt%), ammonia aqueous solution (25 wt%), absolute ethanol, absolute methanol, dichloromethane, N,N-dimethylformamide (DMF), butanedioic anhydride, hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide, sodium dodecyl sulfate (SDS), methylene blue(MB), saline, glycerol were received from Tianjin Bodi Chemical Holding Co. Ltd. Paraformaldehyde, 4′,6-diamidino-2-phenylindole (DAPI) and 3-aminopropyltriethoxysilane (APTS) were purchased from Sigma-Aldrich. Cryoembedding media (OCT) and Triton × 100 were purchased from Shenyang Baoxin Co., Ltd. Cyanine5.5 hydrazide (Cy5.5) was purchased from HyperCyte Biomedical CO., Ltd. All chemicals were analytical grade and used as purchased without further purification. Raw carvedilol (purity > 99.0%) was obtained from Shenyang Funing Pharmaceutical Company (Shenyang, China). Fenofibrate was denoted by Yinhe Pharmaceutical Factory (Wuhan, China). Deionized water was prepared by ion exchange.

2.2. Samples preparations

2.2.1. Preparation of PR template

Nonporous phenolic resin template was prepared according to the procedure reported by a self-assemble method (Qiao et al., 2013; Liu et al., 2011). Typically, 300 mL deionized water, 105 mL absolute ethanol and 1.5 mL ammonia aqueous solution (25 wt%) were added into a 500 mL conical flask, then stirred for a while. Subsequently, 3 g resorcinol was added and continually stirred for 30 min. Then, 4.2 mL formaldehyde solution was added to the reaction solution and stirred for 24 h at 30 °C. The reaction mixture was hydro-thermal treated for 24 h at 100 °C under a static condition in a Teflon-lined autoclave. Finally, the solid product was recovered by centrifugation and dried overnight.

2.2.2. Preparations of HMS, HMS-NH_2 and HMS-COOH

In order to prepare hollow mesoporous silica, 0.1 g phenolic resin particles, 0.6 g CTAB, 160 mL deionized water, 120 mL absolute ethanol and 2 mL ammonia aqueous solution (25 wt%) were put into the reaction vessel, and stirred for 30 min. Then 0.86 mL TEOS was dropt into the mixture, and stirred for 6 h. Finally, the solid product was recovered by filtration, dried proper and calcined in air at 600 °C for 5 h (Liu and Wang, 2015; Lu et al., 2011).

The HMS was aminated by the alkylating agent and carboxylation by butanedioic anhydride to obtain carboxyl group of the carrier. For a typical treatment, 0.6 g HMS was dispersed with 120 mL ethanol in a round bottom flask. With inflating 10 min nitrogen, 0.6 mL APTS was dropped by pipette under stirring. The mixture was heated to 80 °C and refluxed overnight to react completely. Finally the HMS-NH_2 was centrifuged and washed with ethanol and dried overnight. For further carboxylation, 0.4 g HMS-NH_2 and 0.39 g succinic anhydride were dispersed into 45 mL and 35 mL DMF respectively. Then the succinic anhydride solution was dropt into the HMS-NH_2 suspension to react for 24 h. Finally the HMS-COOH was centrifuged, washed with ethanol and dried overnight.

2.2.3. Preparation of HMS-Cy5.5

The hollow mesoporous silica nanospheres were labeled by Cy5.5 hydrazide through the condensation between the hydrazide