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Preparation of a push–pull osmotic pump of felodipine solubilized by mesoporous silica nanoparticles with a core–shell structure

Chao Wu [a], Zongzhe Zhao [a], Ying Zhao [a], Yanna Hao [a], Ying Liu [a], Chang Liu [b,*]

[a] Pharmacy School, Liaoning Medical University, Jinzhou,Liaoning 121001, China
[b] Department of Endocrinology, First Affiliated Hospital of Liaoning Medical University, Jinzhou, Liaoning 121001, China

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ABSTRACT

The purpose of this study was to use mesoporous silica nanoparticles to improve drug dissolution after releasing from a push–pull osmotic pump. Felodipine was selected as the model drug and it was first incorporated into mesoporous silica nanoparticles prepared previously by the solvent evaporation method after we had examined a series of drug–silica ratios to load the drug into the mesoporous silica nanoparticles in order to find the optimum ratio for drug loading. Then, the drug–carrier was added to the drug-layer of the push–pull osmotic pump. PEO (Mw 100,000) was used as a suspending agent and PEO (Mw 6,000,000) was used as an expanding agent. The core tablets were coated with cellulose acetate (CA) as a semipermeable membrane containing polyethylene glycol (PEG) 6000 to control the membrane permeability. In vitro dissolution studies showed that the self-made osmotic pump tablets were able to deliver felodipine in an approximately zero-order manner in 12 h. A pharmacokinetic study was carried out to compare the new system with reference sustained-release tablets. It was found that the half-life of felodipine in the push–pull osmotic pump tablets was prolonged 1.8-fold, the bioavailability was increased 18% and the maximum plasma concentration reduced by 25%. In conclusion, using the self-made push–pull osmotic pump in combination with mesoporous silica nanoparticles was able to effectively increase the bioavailability of felodipine and reduce fluctuations in its plasma concentration.

1. Introduction

The osmotic pump, first described in the literature in 1955, was designed by Rose and Nelson (Rose and Nelson, 1955) to deliver drugs to animals and then, in 1975, Theeuwes (Theeuwes, 1975) prepared an the elementary osmotic pump (EOP) and put forward a basic theory to describe its action. The EOP was designed to control the release of water-soluble drugs. It consists of three parts, namely, the core tablets, the semipermeable membrane, and the release hole. Firstly, the water in the environment penetrates into the interior of the EOP through the semipermeable membrane, and then the components of the core tablets dissolve and release through the hole. The force driving the release comes from the high osmolality generated by the dissolved osmotic agent. It is difficult to control the release rate of poorly water-soluble drugs, since they cannot form homogeneous solutions (Zhang et al., 2011). The Push–Pull osmotic pump (PPOP) was designed to solve this problem. Compared with EOP, the core tablets of the PPOP consist of drug-layer and the push-layer. The expanding agent in the push-layer swells after absorbing water and pushes the drug in the drug-layer out through the release hole in a zero controlled-release manner as desired (Malaterre et al., 2009). Although the drug is released from the osmotic pump at a constant rate, due to poor water solubility, the dissolution rate is not improved which means that the released drug cannot be absorbed rapidly into the blood and, consequently, the bioavailability is low.

To our knowledge, investigations into PPOP have mainly focused on how to control the drug release, while ignoring the subsequent problem of drug dissolution. Liu et al. (Liu et al., 2014) prepared a nimodipine PPOP in combination with solid dispersion techniques. The in vitro dissolution studies showed that nimodipine was delivered in a zero-order manner and the relative bioavailability was 121.1% in comparison with the commercial reference tablets. We used a new technique to overcome the dissolution problem: mesoporous silica nanoparticles (MSN).

Mesoporous silica material (MSM) was first discovered by the Mobil Corporation (Kresge et al., 1992) and it has attracted substantial attention from researchers involved in many fields such as nonlinear optics, catalysis, and molecular adsorption. MSM have many excellent properties including good biocompatibility

* Corresponding author. Tel.: +86 0416 4673439.
E-mail address: chaoyu0118@163.com (C. Wu).

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(Hudson et al., 2008), low toxicity (Park et al., 2009), and excellent chemical stability (Verlooy et al., 2009). In particular, it has a large pore volume and large surface area (Liou, 2010), which makes it an excellent candidate for drug delivery. Vallet-Regi et al. were the first to use MSM as a drug carrier for ibuprofen loaded into MCM-41 (Vallet-Regi et al., 2000). Since then, there has been an exponential growth in research related to using MSM as a drug carrier (Hu et al., 2012; Lu et al., 2007; Salonen et al., 2005). In 2004, Charnay et al. used MSM as a dissolution enhancer for poorly water-soluble drugs (Charnay et al., 2004). The nanoscale pores in MSM played an important role in improving the dissolution of poorly water-soluble drugs. The pore diameter of MSM is only 2–50 nm which means that the drug crystallization is limited and it exists in an amorphous state (Sliwinska-Bartkowiak et al., 2001). The drug in this form exhibits an increased dissolution rate in comparison with the crystalline form. According to published reports, approximately 40% of drugs have low oral bioavailability because they are poorly water-soluble (Kennedy, 1997; Zhao et al., 2012). MSM provides a new and effective method to overcome this obstacle and improve the therapeutic effects of drugs.

Felodipine (FDP), the selected model drug, was developed by AstraZeneca Company to treat primary hypertension and chronic stable angina pectoris. It belongs to BCS (Biopharmaceutical Classification System) II which means that it is poorly soluble and highly permeable which results in a low dissolution rate and oral bioavailability (Shah et al., 2014; Todd and Faulds, 1992). After oral administration of FDP in the form of commercially available sustained-release tablets, a clear peak appeared in the plasma concentration–time curves and, so, we decided to develop a controlled release FDP preparation. In our study, we initially loaded FDP into the prepared MSN to increase the dissolution and then PPOP was prepared to control its release. The pharmaceutical performance of PPOP was evaluated by comparing it with the commercially available FDP sustained-release tablets in a series of in vitro dissolution experiments and an in vivo pharmacokinetic study.

2. Methods

2.1. Materials

FDP with purity >99% was provided by Wuhan Dahuaweiye Pharmaceutical Chemical Co., Ltd. (Wuhan, China). Tetraethyl orthosilicate (TEOS) and hexadecyl trimethyl ammonium bromide (CTAB) were obtained from Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin China). FDP sustained-release tablets® were supplied by Hefei Cubic Pharmaceutical Co., Ltd. (Hefei, China). PEO was obtained from Dow Chemical (Shanghai, China), cellulose acetate (CA) and PEG 6000 were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China) and all other chemicals used in this study were of analytical/HPLC grade.

2.2. Preparation of MSN and drug loading

Step 1: 180 mL ethanol, 65 mL deionized water, and 4.5 mL ammonia were placed in a glass container and stirred until uniformly mixed. Then, 15 mL TEOS was dripped into the mixture. After stirring for 4 h at room temperature, the supernatant was removed by centrifugation at 9500 rpm/min for 10 min. The obtained precipitate was washed twice with ethanol and water, and then dried at 40 °C for 12 h in a vacuum oven (DZF6050, Shanghaiboyuan, China) to obtain silica nanoparticles (SN).

Step 2: 13 mL ethanol and 30 mL deionized water were placed in a glass container, followed with 150 mg CTAB and 100 mg SN obtained from Step 1. After stirring for 30 min, 0.45 mL ammonia and 0.3 mL TEOS were added. The system was stirred for 6 h at room temperature and then centrifuged at 9500 rpm/min for 10 min. The obtained precipitate was washed twice with ethanol and water, and then dried at 40 °C for 12 h in a vacuum oven. Finally, the sample was calcined at 600 °C for 6 h to obtain MSN.

FDP was incorporated into MSN using the solvent evaporation method. This involved dissolving a certain amount of FDP in acetone and then different amounts of MSN were added to obtain samples with different drug–carrier ratios (1:1, 1:2, and 1:3). This system was stirred for 3 h in a closed container and then the solvent was evaporated. Finally, the samples were dried in a vacuum oven.

2.3. Characterization of FDP–MSN

2.3.1. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

The surface topography of the samples was examined by SEM (JSM-7001F, JEOL, Japan) operated at 20 kV, and the fine details of the mesoporous structure were studied by TEM (Tecnai G2F30, FEI, USA), operated at 200 kV.

2.3.2. N_2 adsorption–desorption analysis

The nitrogen adsorption/desorption isotherms were measured using a surface area instrument (SA3100, Beckman Coulter, USA). In order to eliminate the effect of moisture on the results, samples were degassed at 40 °C for 12 h before analysis. The surface area was calculated using the BET method, the pore size distribution was analyzed using the Barett–Joyner–Halenda (BJH) model and the total volume of the pores was determined by the amount of nitrogen adsorption.

2.3.3. Solid state characterization by differential scanning calorimeter (DSC) and powder X-ray diffractometer (PXRD)

A crystalline drug could produce thermal effects during the crystal transition or melting and this change could be monitored by DSC (DSC-60, Shimadzu, Japan). However, the amorphous drug would not exhibit this change and, therefore, DSC could be used to identify the drug state in the samples. Standard indium was used to calibrate the instrument, and samples were heated at a constant rate of 10 °C/min over the range 50–300 °C and the system was maintained under a nitrogen flow of 150 mL/min to provide an inert atmosphere.

PXRD (Rigaku Ultima IV, Rigaku, Japan) was used to further confirm the solid state of FDP in MSN. Samples were exposed to Cu–Kα radiation under 30 kV and 30 mA. The step size was 0.02°, the scan speed was 4°/min and the range (2θ) was from 5° to 60°.

2.3.4. Fourier-transform infrared spectroscopy (FT-IR spectroscopy)

An FT-IR spectrometer (IRAffinity-1, Shimadzu, Japan) was used to carry out FT-IR spectroscopy over the range 4000–400 cm^{-1} using KBr as a background.

2.4. Preparation of PPOP

2.4.1. Preparation of the core tablets

The core tablets were prepared by powder direct compression technology. Table 1 lists the composition of the drug layer and the push layer. All components of the drug layer and the push layer were ground in a mortar then passed through an 80-mesh sieve, Afterwards, the core tablets were obtained using a TDP single punch tabletting machine (TDP-1.5, Shanghai Wangqun, China). Initially, the drug layer granules were slightly compressed, and then the push layer granules were manually loaded. Finally, the core tablets were prepared by compression and the hardness was 6–8 kg/cm^2.