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A two-step strategy to design high bioavailable controlled-release nimodipine tablets: The push–pull osmotic pump in combination with the micronization/solid dispersion techniques

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ABSTRACT

In order to decrease the fluctuation of blood concentration and to increase the oral bioavailability of nimodipine (NMD), a two-step strategy including the push–pull osmotic pump (PPOP) method in combination with micronization and solid dispersion techniques, was used to prepare the controlled-release high-bioavailability solid dosages. The optimization of formulation and process was conducted by comparing effects of different solubilization methods on release behavior of NMD. The in vitro dissolution studies indicated that both the two strategies were able to deliver NMD in the predetermined zero-order manner from 2 to 12 h, regardless of effects of release media and agitation rates. Although the C_{max} values of two PPOP tablets were lower than that of the reference formulation, both the T_{max} values were prolonged, demonstrating the prominent controlled release performance. In comparison with the commercial reference tables, the relative bioavailability of the two formulations was 67.0% and 121.1%, respectively, indicating the solid dispersion technique was more efficient than the micronization technique in terms of solubilization capability and absorption enhancement. In summary, the two-step strategy, combining the push–pull osmotic pump method with the solid dispersion technique, is a very effective method to prepare high bioavailable controlled-release formulations of the poorly soluble drugs, i.e. NMD, taking into account the therapeutical efficiency and safety.

1. Introduction

As a dihydropyridine calcium channel antagonists, nimodipine (NMD) can selectively dilate brain blood vessels and is widely used in the treatment of ischemic cerebrovascular disease (Manhold, 1985). In addition, it has been found some new clinical indications recently, such as the treatment of reversible cerebral vasoconstriction syndrome (Elstner et al., 2009), vascular dementia (Zhong et al., 2009) and acute effects on cerebral vasculature and brain metabolism (Choi et al., 2012). Nimodipine belongs to Class II of the Biopharmaceutical Classification System (BCS) with the typical characteristics of high permeability and poor solubility (Grunenberg et al., 1995). It has been reported that its oral bioavailability is about 5–13% (Langley and Sorkin, 1989). The poor dissolution behavior of nimodipine was considered as the substantial factor limiting its oral absorption.

Tablets are the most popular dosage form, because of convenience and patient compliance. However, for the poorly soluble nimodipine, it is difficult to acquire an effective and complete release in the gastrointestinal tract. Since the half-life of nimodipine is not long enough, multiple doses per day are required, which results in a significant peak-valley phenomenon of plasma concentration (Langley and Sorkin, 1989) and increases the risk of adverse reactions (Langer, 1998). In order to address the above problems, a two-step strategy is put forward in this study to enhance the dissolution performance and to maintain smooth plasma concentration, which is superior to that either just enhancing the water-solubility (Kopecky et al., 2003) or only controlling drug release behavior (Perez-Trepichio and Jones, 1996).

Micronization and solid dispersion techniques enhance water solubility via two distinct mechanisms. Micronization improves

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drug solubility by increasing the particle specific surface area (Sigfridsson et al., 2009). However, the micronized drug particles generally tend to agglomerate and exhibit poor flow ability (Han et al., 2011). To overcome this problem, the granulations (Ridgway and Williams, 1977) of the micronized particles with lactose were prepared to improve the stability and flowability. Solid dispersion (SD) disperses the drug in molecular, colloidal microcrystalline or amorphous form. Usually, water-soluble polymers, such as polyethylene glycol (PEG) (Dannenfelser et al., 2004) or polyvinylpyrrolidone (PVP) are applied to accelerate hydrophobic drugs dissolution along with the carrier's rapid wetting (Van Nijlen et al., 2003). Moreover, the presence of a carrier material could minimize the aggregation of drug particles (Van Nijlen et al., 2003). To avoid aging, application of surface-active agent (Chen et al., 2004; Jijun et al., 2011b) can also be taken into consideration.

Micronization and solid dispersion techniques are capable of increasing the saturable solubility and dissolution rate of the water-insoluble drugs, but the release behavior cannot be tailor-made. Therefore, it was necessary to take further measures to decrease the plasma concentration fluctuations. Among the controlled-release systems, the osmotic pump tablet (OPT) is a proper choice because of its distinct zero-order release behavior. Moreover, the release behavior is independent of the release medium pH, stirring speed and gastrointestinal peristalsis, but just dependent on the osmotic pressure of the release media (Verma and Garg, 2004). In the 1970s, the elementary osmotic pump (EOP) was first developed to deliver water-soluble drugs at a constant rate by the osmotic pressure generated from the saturated drug solution (Theeuwes, 1975). However, for insoluble nimodipine, micronization or solid dispersion techniques can enhance its solubility, but can hardly form a high osmotic pressure to obtain a smooth release (Zhang et al., 2011). Push–pull osmotic pump (PPOP) technology is a alternative choice, which drug and drug-containing layer polymer in the form of suspension was pushed out from the release hole by the boost layer polymer, to deliver insoluble or freely soluble drugs in a desired zero controlled-release manner (Malaterre et al., 2009).

This study exploited a two-step strategy to prepare the high bioavailable controlled-release formulations of poorly soluble NMD: step 1 is to improve the drug solubility by micronization or solid dispersion techniques; step 2 is to control the drug release behavior by push–pull osmotic pump technique. The pharmaceutical performances of the different combinational techniques were investigated by comparing the NMD dissolution behavior and in vivo pharmacokinetic performances.

2. Materials and methods

2.1. Materials

Nimodipine was provided by Wuhan Yuanchenggongchuang Tech. Co., Ltd. (Wuhan, China). Nitrendipine was purchased from Shanxi Sciphar Biotechnology Company (Shanxi, China). Nimodipine sustained-release tablets (Er Ping@) was obtained from Shandong Yunmen Pharmaceutical Co., Ltd. (Shandong, China). HPMC (different types) were kindly donated by Kangya of Ningxia Pharmaceuticals Co., Ltd. (Ningxia, China). Polyethylene oxide (PEO) (POLYOX™, different types) was supplied by Dow Chemical (Shanghai, China). Polyvinylpyrrolidone K30 (PVPK30) and poloxamer188 (Lutrol F68) were purchased from BASF Co., Ltd. (Ludwigshafen, Germany). PEG6000 and sodium chloride were purchased from Tianjin Kemiou Chemical Reagent Co., Ltd. (Tianjin, China). Cellulose acetate was obtained from Tianjin Bodi Chemical Co., Ltd. (Tianjin, China). Magnesium stearate was provided by Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (Anhui, China). Citric acid and disodium hydrogen phosphate were of analytical grade. All solvents used in this study were of high-performance liquid chromatography grade.

Table 1
The composition of core tablets (Formulation 1 and Formulation 2).

Ingredients	Formulation 1	Formulation 2
Drug layer		
Micronized NMD or NMD-SD	60 mg	240 mg
PEO (low molecular weight)	120 mg	240 mg
Lactose	20 mg	–
Magnesium stearate	q.s.	q.s.
Push layer		
PEO (high molecular weight)	80 mg	200 mg
HPMC	30 mg	–
Sodium chloride	30 mg	150 mg
Red iron oxide	0.5 mg	0.5 mg
Magnesium stearate	q.s.	q.s.

2.2. Methods

2.2.1. Preparation of micronized nimodipine push–pull osmotic pump tablets (Formulation 1)

2.2.1.1. Preparation of micronized nimodipine powder by different approaches. It was manipulated that the micronization of pure nimodipine through QM-1DW planetary ball mill (Nanjing University Instrument Plant, China) grinding for 5, 10 and 15 h, respectively, and mini-efficient pulverizer (Hunan Zhongcheng Pharmaceutical Machinery Plant, China) smashing for 5 min, 20 min, 30 min and 50 min, respectively. Then the particle size and size distribution of micronized NMD suspension and crude NMD suspension diluted with water were measured by LS-230 Beckman Coulter (Beckman Coulter, USA). Moreover, the dissolution tests of crude NMD and micronized powder were carried out in pH 6.8 citrate–phosphate buffer containing 0.5% sodium dodecyl sulfate (SDS) as described in Section 2.2.3 except that the sampling time was 5, 10, 20, 30, 45 and 60 min.

2.2.1.2. Preparation the core tablets. The core tablets composed of micronized drug layer and push layer were made by formula as shown in Table 1 (Formulation 1). Wet granulating technique was applied to prepare granules for the two layers under mentioned. The drug layer particles were prepared as follows: A uniform powder mixture of micronized drug, PEO (Mw 200,000–400,000) and lactose was wet by the addition of 95% ethanol as binder. Then obtained wet mass was pushed through a 20-mesh sieve to get the wet granulates and dried in a 101-1 drying oven (Pudong Electronic Instrument Factory, Shanghai, China) at 40 °C for 12 h. The drug layer granulates were ultimately obtained by passing the dried granulates through an 18-mesh sieve and mixed with q.s. magnesium stearate storing in a desiccator until further processing. The preparation of push layer particles was similar to that of drug layer particles except that the uniform powder mixture was consisting of PEO (Mw 4,000,000–6,000,000), HPMC (K4M, K15M, and K100M), sodium chloride and red iron oxide. Afterwards, the bilayered core tablets were obtained on a TDP single punch tablet-compressing machine (Shanghai First Pharmaceutical Machinery Factory, Shanghai, China) with an 8 mm concave punch by the following procedure. The drug layer particles were slightly prepresed, and the push layer particles were manually loaded over the drug layer, then the tablet was made by compression and the hardness of the core tablets was 6–8 kg cm^{-2}.

2.2.1.3. Coating and drilling hole. The core tablets were coated with cellulose acetate (CA) acetone solution containing PEG6000 and dibutyl phthalate (DBP) using TNW200-500 mini-sugar coating machine (Boji Jianhua Machinery Factory, Shanxi, China), with