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A physically stabilized amorphous solid dispersion of nisoldipine obtained by hot melt extrusion

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ABSTRACT

Nisoldipine is widely used clinically as an antihypertensive agent, however, its oral bioavailability and therapeutic effects are hindered by its very low solubility in water. The present study aimed to develop an amorphous solid dispersion (ASD) for nisoldipine, using hot melt extrusion, to increase or equilibrate with the *in vitro* dissolution and *in vivo* oral absorption of Nierxin, its commercial tablet formulation. The final preparation was prepared with Kollidon VA64 at a drug polymer weight ratio of 1:10. The amorphous state was confirmed by powder X-ray diffractometry, differential scanning calorimetry, and Fourier-transform infrared spectroscopy. This ASD exhibited a higher dissolution profile than Nierxin and its physical mixtures. It maintained an amorphous state when stored at 60 °C over 10 days, however, the hydrogen bonds between nisoldipine and Kollidon VA64 were disrupted and its dissolution slightly reduced when stored at RH 92.5% for 10 days. The pharmacokinetic study carried out in beagle dogs demonstrated that the ASD was bioequivalent to Nierxin. The results of this study suggest that ASD prepared by hot melt extrusion can be used as a suitable alternative to Nierxin in the future.

1. Introduction

Nisoldipine is a 1, 4-dihydropyridine calcium channel antagonist. It is primarily used for the treatment of hypertension by inhibiting the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle [1]. It can be used alone or in combination with other antihypertensive agents [2]. However, its oral bioavailability and clinical pharmacodynamics are limited due to its insolubility in water and extensive pre-systemic metabolism by CYP3A4 [3]. A nisoldipine immediate-release preparation with an increased dissolution rate would rapidly saturate the metabolic enzymes and, thus, reduce the total metabolism, and this is an important and fundamental way to improve the oral absorption of nisoldipine.

Amorphous solid dispersion (ASD) is an effective formulation strategy to improve the dissolution rate of poorly water-soluble compounds because it offers a high free energy [4]. Although ASDs can be prepared by a variety of methods, two techniques, spray drying [5,6] and hot melt extrusion (HME) [7,8], are most important for the research and development of ASD. Despite of its wide application for the preparation of ASD, spray drying technology has some potential problems, such as the safety and environmental issues associated with the use of an organic solvent, the low physical stability of the final preparation, as well as the high cost of the production process [9]. However, HME offers the advantages of solvent-free processing, improved product physical stability, a small manufacturing footprint, and low cost due to its continuous production [10]. Therefore, HME technology has attracted much more attention, and has been increasingly used for developing formulations of poorly water-soluble drugs.

In the present study, we attempted to develop a nisoldipine ASD using HME. The formulation optimization was carried out based on the dissolution results. The optimized nisoldipine ASD was characterized by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FT-IR). Dissolution testing was carried out on ASD, commercial tablets and physical mixtures in different media. The physical stability under storage at a controlled temperature and relative humidity was also studied systematically. Finally, the *in vivo* pharmacokinetics was investigated in beagle dogs.

2. Materials and methods

2.1. Materials

Nisoldipine was purchased from Dalian Meilun Biology Technology Co., Ltd. (Dalian, China). Soluplus and Kollidon VA64 (a co-polymer of polyvinylpyrrolidone-vinyl acetate in a mass ratio of 6:4) were kindly

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provided by BASF China Co., Ltd. (Shanghai, China). PEO (Polyox™ N80, $M_w = 2 \times 10^5$) was purchased from Shanghai Aoba Chemical Co., Ltd. (Shanghai, China). Sodium dodecyl sulphate (SDS) was purchased from Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin, China). Methanol was purchased from Concord Technology Co., Ltd. (Tianjin, China) and deionized-distilled water was used throughout this study. The commercial tablets, Nierxin, were purchased from Xincat Pharm. Co., Ltd. (Zibo, China).

2.2. Preparation of nisoldipine ASD by HME

HME was carried out using a Coperion Keyate-20 twin screw extruder (Nanjing KY Chemical Equipment Co., Ltd., Nanjing, China). Most importantly, the operations were carried out in the dark because of the chemical instability induced by photochemical degradation of nisoldipine [11]. The formulation was optimized based on *in vitro* dissolution (as described in Section 2.4) by varying the drug carriers (VA64, Soluplus, and PEO) and drug/carrier ratios (1:1, 1:3, 1:7, 1:10, and 1:15, w/w). The processing temperature and screw rate were set at 153 °C and 2.5 Hz, respectively. The raw materials were blended until homogeneous and then manually introduced into the extruder barrel. The extrudates were collected, cooled at room temperature, and ground using an FW100 grinder (Beijing Zhongxingweiye Instrument Co., Ltd., Beijing, China). Finally, the ground powders were passed through an 80-mesh sieve, and then filled into capsules, each containing 5 mg nisoldipine.

2.3. Characterization of nisoldipine ASD

2.3.1. DSC

The solid state of the final product was investigated using a DSC 1 STAR instrument (Mettler-Toledo Inc., Zurich, Switzerland). For the DSC measurements, the samples (about 5 mg) were weighed accurately and placed into standard aluminum pans, and then hermetically sealed with standard aluminum lids. An empty aluminum pan served as a reference. Heating curves were recorded at a heating rate of 10 °C/min from 40 to 170 °C under a dry nitrogen purge (50 mL/min).

2.3.2. PXRD

To confirm the DSC results, the PXRD was carried out using a D/Max-2400 X-ray diffractometer (Rigaku Corporation, Osaka, Japan). The samples were exposed to Cu Kα radiation (40 kV, 25 mA) over a 2θ range of 5 to 45°, with a step size of 0.04° and a step time of 0.5 s.

2.3.3. FT-IR

To explore the potential interactions between nisoldipine and the excipients in the ASD, FT-IR spectra were recorded using a Bruker IFS 55 instrument (Bruker Corporation, Switzerland). Each spectrum was recorded over the 4000 to 400 cm^{-1} range by averaging 16 scans at a resolution of 1 cm^{-1}.

2.4. Dissolution

The *in vitro* dissolution studies were carried out to optimize the formulation and to evaluate the physical stability of the ASD. The paddle method was used for the dissolution studies and the rotation speed was set at 50 rpm using a ZRS-8G dissolution apparatus (Tianda Tianfa Technology Co., Ltd., Tianjin, China). The medium was 900 mL degassed distilled water and the temperature was maintained at 37 °C. Ten milliliters of filtered samples were withdrawn at 5, 10, 20, 30, 45, and 60 min, and replaced each time with 10 mL of fresh medium. Then, the samples were subjected to HPLC analysis as described below.

The chromatographic system consisted of an L-2130 pump (Hitachi High-Technologies Co., Ltd., Tokyo, Japan) equipped with an L-2400 ultraviolet absorbance detector set at 237 nm. The separation was performed at 30 °C on a Cosmosil C18-PAQ column (5 μm, 250 mm × 4.6 mm, Nacalai Tesque Inc., Kyoto, Japan). The mobile phase consisted of methanol: water (80/20, *v*/*v*) and was delivered at 1 mL/min. The mobile phase was prepared freshly prior to each series of analyses. The retention time was 6 min and the total run of each sample was 7 min.

2.5. Stress test

When exposed to environments involving a high humidity or high temperature, the physiochemical properties of ASD may deteriorate [12]. Therefore, a stress test was conducted to evaluate the physical stability. The samples were placed in glass containers and stored in an HPX-16085H-III Temperature Humidity Incubator (Shanghai CIMO Medical Instrument Manufacturing Co., Ltd., Shanghai, China) under the following conditions: (1) 40 °C, RH 0%, (2) 60 °C, RH 0%, (3) 25 °C, RH 75%, and (4) 25 °C, RH 92.5%. On day 0, 5, and 10, samples were withdrawn and subjected to DSC, PXRD, FT-IR, and *in vitro* dissolution analysis. In addition, the weight gain was also determined for samples stored under high humidity conditions.

2.6. Pharmacokinetic study of a nisoldipine ASD

2.6.1. Animal studies

The pharmacokinetic study was approved by the Shenyang Pharmaceutical University Animal Management and Ethics Committee, and was carried out in accordance with the Guide for Care and Use of Laboratory Animals. Commercial tablets (Nierxin) served as controls. A randomized, two-period cross-over design was applied to study the pharmacokinetics in beagle dogs with a washout period of one week. Eight dogs, weighing between 10.0 and 12.0 kg, were enrolled in this study. The dogs were fasted for 12 h prior to dosing and were allowed to have a meal 6 h after administration. The locally prepared ASD and the commercial tablets were administered orally at a single dose of 5 mg. Blood samples (3 mL) were withdrawn from the fore foot vein at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 h after administration and transferred to heparinized tubes. The dogs had free access to water during the whole experimental period. All blood samples were centrifuged immediately at 3000 rpm for 10 min and the supernatant plasma was stored at −20 °C until analysis.

2.6.2. Analytical method

Nimodipine was used as an internal standard in the biological analysis. Plasma (400 μL), nimodipine (150 ng/mL, 20 μL), and methanol (20 μL) were sequentially added to disposable tubes and vortexed for 30 s. Then, methyltertiarybutyl ether (3 mL) was added and vortexed for another 3 min. Finally, the mixtures were centrifuged at 3000 rpm for 10 min, and the supernatant was transferred to a new tube and dried under a nitrogen purge. The residues were re-dissolved in 90% (*v*/*v*) acetonitrile and vortexed for 1 min and then, after centrifuging the re-dispersion at 13,000 rpm for 10 min, the supernatant was subjected to LC-MS-MS analysis as described below.

The chromatographic separation was conducted on an Acquity UPLC ™ system (Waters Corporation, Milford, MA, USA). A Kinetex 2.6u XB-C18 column (50 × 2.1 mm, 2.6 μm, Phenomenex) was used for separation, and the column was maintained at 30 °C with a flow rate of 0.2 mL/min. The mobile phase consisted of A (acetonitrile) and B (0.2% formic acid), and a gradient program was used for elution: in the initial stage (0–0.2 min), 40% of A was used; then it was linearly increased to 95% A within 0.1 min and this was maintained for 1.3 min (0.3–1.6 min); finally, it was reduced linearly to the initial condition within 0.1 min and maintained there until the run was completed. The retention time was 1.41 and 1.38 min for nisoldipine and nimodipine, respectively, during a run of 2.5 min. In addition, the autosampler was maintained at 4 °C, and aliquots of 5 μL were injected into the system.

An Acquity™ triplequadrupole tandem mass spectrometer (Waters Corporation, Milford, MA, USA) coupled with an electrospray ionization