Journal of Drug Delivery Science and Technology 37 (2017) 28–37

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Controlled-release oral dosage forms containing nimodipine solid dispersion and hydrophilic carriers

Hyo-Jung Lee [a], Ju-Young Kim [b], Sung-Hoon Park [c], Yun-Seok Rhee [d], Chun-Woong Park [a, **], Eun-Seok Park [c, *]

[a] College of Pharmacy, Chungbuk National University, Republic of Korea
[b] College of Pharmacy, Woosuk University, Republic of Korea
[c] School of Pharmacy, Sungkyunkwan University, Republic of Korea
[d] College of Pharmacy and Research Institute of Pharmaceutical Sciences, Gyeongsang National University, Republic of Korea

ARTICLE INFO

Article history:
Received 2 August 2016
Received in revised form
30 October 2016
Accepted 2 November 2016
Available online 5 November 2016

Keywords:
Nimodipine
Solid dispersion
Polyvinylpyrrolidone
Poloxamer
Controlled-release

ABSTRACT

The aim of this study was to prepare solid dispersion of nimodipine (NMD) by solvent evaporation method to overcome the poor water solubility of NMD, and to formulate controlled-release (CR) tablets containing the NMD solid dispersion. NMD is a dihydropyridine calcium-channel antagonist that is practically insoluble in water. Owing to the short half-life of the drug in the plasma, NMD immediate-release tablets should be administered frequently for the treatment and prevention of ischemic disorders following aneurysmal subarachnoid hemorrhage. In this study, solid dispersion technique was applied to increase the low solubility of NMD. Carriers for solid dispersions were prepared with different kinds of hydrophilic polymers. Kinetic solubility studies were performed for the prepared solid dispersions, using sodium acetate buffer (pH 4.5). Solid dispersions were then characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared spectrometry (FT-IR). CR tablets containing the NMD-PVP K30 solid dispersions were designed to reduce the dosing interval and increase patient compliance. Hydroxypropyl methylcelluloses (HPMC) were used as release-modifiers, and lactose anhydrous as a diluent.

1. Introduction

Nimodipine (NMD; Fig. 1) has been shown to selectively dilate cerebral arteries and increase cerebral blood flow [1]. NMD is the only available therapy proven to reduce the morbidity and mortality associated with delayed ischemic deficits following aneurysmal subarachnoid hemorrhage (SAH) [2]. It has been also used in the treatment of ischemic stroke, vascular dementia, and migraine [3,4]. NMD is a yellow crystalline powder and practically insoluble in water [5]. Its intrinsic solubility is reported as 2.3 μg/mL [6,7]. In a biopharmaceutical classification system (BCS), NMD is classified as class 2, which represents low water solubility and high gastrointestinal permeability. Therefore, dissolution could be the rate-limiting step in its absorption [8].

Solid dispersions are one of the most successful strategies to improve the solubility of poorly water-soluble drugs [9]. Solid dispersions can be defined as molecular mixtures in which drug molecules are dispersed within carrier molecules. In this study, solvent evaporation method was applied for the preparation of solid dispersion systems.

NMD immediate-release formulation was first developed by Bayer AG, by the commercial name of Nimotop®. In clinical practice, the dosing regimen calls for a 60-mg oral dose of NMD to be given every 4 h [10]. Prophylactic administration should begin within 4 days after the onset of SAH and should be continued up to 21 days. In the surgical intervention, administration of Nimotop® tablets must be continued to complete the 21 days of treatment.

Oral administration of NMD is associated with problems such as short elimination half-life (1–2 h), which leads to frequent dosing and fluctuation in concentrations in the plasma. For the achievement of controlled release formulation containing NMD, various strategies such as floating tablets, gelatin capsules, and matrix tablets have been investigated [11–14].

* Corresponding author. School of Pharmacy, Sungkyunkwan University, 300 Cheoncheon-dong, Jangan-gu, Suwon, Gyeonggi-do 440-746, Republic of Korea.
** Corresponding author. College of Pharmacy, Chungbuk National University, 194-41 Osong-eup, Heungdeok-gu, Cheongju, Chungcheongbuk-do 28160, Republic of Korea.
E-mail addresses: cwpark@cbnu.ac.kr (C.-W. Park), espark@skku.edu (E.-S. Park).

http://dx.doi.org/10.1016/j.jddst.2016.11.001
1773-2247/

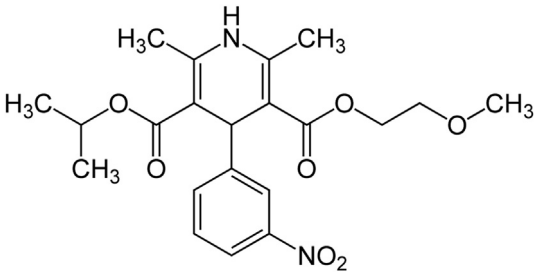

Fig. 1. Chemical structure of NMD.

In this study, NMD solid dispersions with PVP and poloxamer were prepared by solvent evaporation methods, and physicochemical properties and solid-state of the NMD solid dispersions were investigated. Furthermore, controlled-release (CR) tablets containing the NMD solid dispersions were prepared using hydrophilic polymeric matrices for the release control, and the effects of type and amount of polymers were evaluated.

2. Materials and methods

2.1. Materials

NMD was purchased from Lusochimica (Lomagna, Italy). Poloxamer 188 (Lutrol® F68), Polyvinylpyrrolidone (PVP) K17 (Kollidon® 17), K25 (Kollidon® 25), and K30 (Kollidon® 30) were supplied from BASF (Wuerzburg, Germany). Glyceryl behenate (Compritol® 888 ATO) and glyceryl palmitostearate (Precirol® ATO 5) were purchased from Gattefossé (Lyon, France). Polyethylene glycol 4000 (PEG 4000) was supplied from Yakuri Pure Chemicals (Tokyo, Japan). Polyethylene oxide (PEO) 7,000,000 (Polyox® WSR 303) (Colorcon, Harleysville, PA, USA), hydroxypropyl methylcellulose (HPMC) 15,000 cP (Metolose® 90SH 15000SR) (Shin-Etsu, Tokyo, Japan) were used as release-modifiers for the NMD controlled release tablets. Lactose anhydrous (DMV International Pharma, Veghel, Netherlands) was used as a diluent, and magnesium stearate (Acros Organics, Geel, Belgium) as a lubricant. All other reagents were either of analytical or HPLC chromatographic grade.

2.2. Preparation methods

2.2.1. Preparation of NMD solid dispersions

NMD solid dispersion with poloxamer 188 was prepared by hot-melt method [15,16]. After the drug and poloxamer 188 were added into a glass test tube, it was heated and maintained at 150 °C for 20 min for the drug and carrier to completely melt. After silicon dioxide was added, the melted mixture was further agitated for 10 min. After cooling at room temperature, the solidified mixture was then milled and sieved through the mesh #35 to produce solid dispersion powders. The ratios of drug and the carrier in the prepared solid dispersions were 1:1, 1:2, and 1:3 $_{w/w}$.

The simple solvent evaporation method was applied to prepare NMD solid dispersions with PVPs. Three grams of NMD and 3–9 g of PVP were added to about 12 g of acetone. This mixture was stirred and sonicated to completely dissolve the drug and PVP in the solvent. The acetone was then evaporated at 60 °C in vacuo, and the solid mass was obtained. The mass was milled and sieved through the mesh #35. Similar to the solid dispersions prepared by hot-melt method, the solid dispersions with PVPs were also prepared in drug:carrier ratios of 1:1, 1:2, and 1:3 $_{w/w}$.

2.2.2. Determination of equilibrium solubility of NMD

Solubility test was performed to determine the equilibrium solubility of NMD. An excess amount of NMD (20 mg) was added to 10 mL of 0.1 M HCl (pH 1.2), acetate buffer (pH 4.5), and phosphate buffers (pH 6.8 and 7.4), respectively. Samples were then shaken at 100 rpm in a thermostatic water bath (Model SWB-03, Jeio Tech, Seoul, Korea). The temperature was maintained at 37 ± 0.5 °C. Samples were withdrawn after 48 h, passed through 0.45-μm cellulose acetate membrane filter (Advantec, Inc., Dublin, CA, USA), and assayed by HPLC.

2.2.3. Kinetic solubility studies of NMD solid dispersions

USP XXV apparatus 2 (paddle method) was modified for the kinetic solubility studies, using an excess amount of NMD solid dispersions (approximately 30 mg of NMD). Nine hundred milliliter of pH 4.5 acetate buffer was used as a medium, without addition of any surfactant because the solubilizing effect of surfactants must be avoided. The temperature of the medium was 37 ± 0.5 °C and the paddle rotation was 75 rpm. After the NMD solid dispersions were added into the medium, samples were withdrawn at 5-, 10-, 15-, 30-, 45-, and 60-min intervals. At each sampling time, 5 mL of the sample was withdrawn, and then, 5 mL of the supplementary medium was added to the dissolution vessel immediately after each sampling. The samples were diluted with the mobile phase, and the drug concentration in the medium was measured by HPLC immediately.

2.2.4. Differential scanning calorimetry (DSC)

DSC studies were conducted on raw NMD powders, carrier powders, physical mixtures of NMD and carriers, and prepared solid dispersions. The physical mixture consisted of NMD and a carrier at 1:1 ratio, prepared by simple blending of both components. Pyris 1 DSC (PerkinElmer, Waltham, MA, USA) was used for the DSC analysis. Samples (around 10 mg) were placed in aluminum pans and sealed with lids. From 30 to 150 °C, each sample was heated at the scanning rate of 10 °C/min.

2.2.5. Powder X-ray diffraction (PXRD)

To investigate the crystallinity of NMD in the prepared solid dispersions, PXRD studies were employed. The D8 Focus (Bruker AXS, Karlsruhe, Germany) XRD system was used. PXRD data were obtained at room temperature over the 2 θ range from 5° to 45°, at a scanning rate of 2°/min.

2.2.6. Fourier transform infrared spectroscopy (FT-IR)

FT-IR studies were conducted to identify possible physicochemical interactions between the drug and carrier. FT-IR spectra were obtained on a Bruker IFS-66/S spectrometer (Bruker, Karlsruhe, Germany). The scanning range was 400–4000 cm^{-1}.

2.2.7. Preparation of NMD CR tablets

CR tablets containing NMD solid dispersions were prepared by direct compression. The prepared solid dispersions, release modifiers, and lactose anhydrous were measured following Table 1, and mixed homogeneously. Next, magnesium stearate was added as a lubricant, and the mixture was then directly compressed into 8 mm round tablets, using a hydraulic presser (Model #3912, Summit, NJ, USA). The tableting pressure was fixed to 2 tons, and the hardness was between 30 and 70 N when measured by a hardness tester (Model 6D, Dr. Schleuniger, USA).

2.2.8. Dissolution studies of NMD CR tablets

USP XXV apparatus 2 (paddle method) was used in the dissolution tests of NMD CR tablets. As a dissolution medium, 900 mL of pH 6.8 phosphate buffer or pH 1.2 hydrochloric acid buffer was used