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Improvement of Dispersion and Release Properties of Nifedipine in Suppositories by Complexation with 2-Hydroxypropyl-β-cyclodextrin

KATSUNORI NISHIMURA, RIE HIDAKA, FUMITOSHI HIRAYAMA, HIDETOSHI ARIMA and KANETO UEKAMA*
Graduate School of Pharmaceutical Sciences Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

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Abstract

An attempt was made to improve the release property of nifedipine (NP) from Witepsol® H-15, glycerin and polyethylene glycol (PEG) suppository bases by means of the complexation with 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD). The amorphous complexes of NP with HP-β-CyD in molar ratios of 1:1–1:10 (guest:host) were prepared by the spray-drying method. The NP/HP-β-CyD complex was homogeneously dispersed in Witepsol® H-15 suppository base, whereas the drug alone and the physical mixture of the guest and host were sedimented at the bottom of the base. The release rates of NP from Witepsol® H-15 and glycerin suppositories were significantly increased by the complexation with HP-β-CyD. On the other hand, HP-β-CyD gave negligible effect on the release rate of NP from PEG suppository base. The results indicated that Witepsol® H-15 suppository containing NP/HP-β-CyD complex is useful from a viewpoint of the release control and quality assurance.

Introduction

Nifedipine (NP), a calcium channel antagonist, has a short-elimination half-life with significant fluctuations in plasma drug concentrations [1, 2]. To attain a prolonged therapeutic effect and a reduced incidence of side-effects, many attempts have been made to maintain a suitable plasma level of NP for a long period of time with minimum frequency of administration, and many oral sustained release preparations of NP are on the market today, conferring a great benefit to patients [3, 4]. However, parenteral routes of administration may be more preferable for patients with swallowing problems such as dysphagia, vomiting and nausea. For such patients, rectal suppositories of NP have been prepared as home-made products (drug preparations in hospital pharmacy), using polyethylene glycol (PEG) bases and semi-synthetic hydrophobic bases such as Witepsol® [5]. However, PEG base sometimes irritates rectal membranes, because of the high water-absorbing properties. Witepsol® base is known to be chemically stable and to have less irritation to rectal membranes, but it is difficult to obtain sufficient plasma levels of drugs because of the slow release rate. Cyclodextrins (CyDs) are successfully used for improvement of physicochemical and biological properties of drugs such as the solubility, stability and bioavailability of drugs [6–8]. In this study, we investigated the release behavior of NP from Witepsol® H-15, glycerin and PEG suppositories containing NP/HP-β-CyD complexes, in anticipation of increased releases of the drug.

Experimental

Materials

Nifedipine was purchased from Wako Pure Chemicals Co. (Osaka, Japan), and β-CyD and HP-β-CyD (average degree of substitution: 4.8) were supplied by Nihon Shokuhin Kako Co. (Tokyo, Japan). Adalat® was donated by Bayer Yakuhin Ltd. (Osaka, Japan). Witepsol® H-15 was a gift from Mitsuba Boeki Co. (Tokyo, Japan). PEG 400, 1540 and 4000 and glycerin were purchased from Nacalai Tesque Co. (Kyoto, Japan). Other materials and solvents were of analytical reagent grade, and deionized, double-distilled water was used throughout the study.

Interaction studies

The solubility studies were carried out according to the method of Higuchi and Connors [9]. Excess amount

* Author for Correspondence. E-mail: uekama@gpo.kumamoto-u.ac.jp

(about 0.1 g) of NP in various concentrations of CyDs in water (1.5 mL) was shaken at 25 °C in the dark for 5 days. The concentrations of NP dissolved were measured by HPLC under the following conditions: a Hitachi L-7100 pump and a D-7500 UV detector (Tokyo, Japan), a GL Science Inertsil ODS column (5 μm, 4 mm × 150 mm, Tokyo, Japan), a mobile phase of methanol/water (3:1 v/v), a flow rate of 1.0 mL/min, and detection at 254 nm. Powder X-ray diffraction profiles were measured using a Rigaku RINT 2500 diffractometer (Tokyo, Japan) with Ni-filtered Cu-Kα radiation. Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer DSC-7 thermal analyzer (Norwalk, CT).

Preparation of NP/CyD complexes

Spray-drying method: NP and HP-β-CyD in molar ratios of 1:1, 1:3, 1:5 and 1:10 (guest:host) were dissolved in a mixed solvent of ethanol/methylenechloride (1:1 v/v), and spray-dried using a Yamato Pulvis GA32 spray-drier (Tokyo, Japan) under the following conditions: air flow rate 0.40 m^3/min, air pressure 1.0 kgf/cm^2, inlet and outlet temperatures 85 and 55 °C, respectively.

Preparation of suppositories

An aliquot of Witepsol® H-15, PEG 1540/4000 and glycerin bases was melted at 45, 80 and 45 °C, respectively, into which the powder sample of NP, its CyD complexes or its physical mixture (equivalent to 10 mg NP) were added and mixed homogeneously. The melt was poured into a metallic mold (volume 1.35 mL) and allowed to solidify at room temperature. The formulations were as follows: (1) the equivalent amount of 0.01 g NP and Witepsol® H-15 1.22 g for one suppository, (2) the equivalent amount to 0.0047 g NP, PEG 1540 0.05 g and PEG 4000 0.94 g for one suppository, and (3) the equivalent amount of 0.01 g NP, glycerin 0.54 g, gelatin 0.27 g and water 0.69 mL for one suppository. The amount of NP in Witepsol® H-15 suppository was determined by HPLC as follows: the suppository was put into a test tube containing water 4 mL and chloroform 4 mL, and the test tube was shaken for 30 min. After centrifugation (3000 rpm, 10 min), the organic phase (50 μL) was taken and diluted tenfold with methanol, and further centrifuged (3000 rpm, 10 min). The solution of 100 μL was diluted with methanol and analyzed for NP by HPLC as described above. The amounts of NP in PEG and glycerin suppositories were determined by dissolving in dimethylsulfoxide (DMSO) and the solution was appropriately diluted with DMSO and analyzed by HPLC as described above.

Release behavior of NP from suppositories

The *in vitro* release of NP from the suppositories was examined using a TMS-103 suppository release apparatus (Toyama Sangyo Co., Osaka, Japan) according to the method of Muranishi et al. [10]. Each suppository was placed in the cylindrical chamber, which was lined from the inside with a membrane filter (Millipore SSWP 04700, average pore size 3.0 μm, Bedford, MA) as a barrier for diffusion of the suppository base, and lowered into a flask containing a degassed saline (300 mL, 37 °C). The rotation rate of the steel rod in the suppository chamber was 25 rpm and that of the released phase was 100 rpm. At appropriate intervals, a 1.0 mL sample was withdrawn from the release phase and assayed for NP by HPLC method mentioned above.

Results and discussion

Complexation of NP with CyDs

As shown in Figure 1, phase solubility diagrams of β-CyD and HP-β-CyD with NP gave A_L type diagrams, where the solubility (St) of the guest increased linearly with CyD concentrations (Concn. of β-CyDs) up to at least 1.5×10^{-2} and 1.0×10^{-1} M for the former and latter CyDs, respectively. The increase of NP solubilities in Figure 1 obeyed the equations of $St = (9.4 \times 10^{-4}) \times$ (Concn. of β-CyDs) + (2.0×10^{-5}) for the β-CyD system and $St = (1.20 \times 10^{-3}) \times$ (Concn. of β-CyDs) + (2.0×10^{-5}) for the HP-β-CyD system, when expressed in mol/L unit, thus giving the stability constants of 47 ($\pm$1.7) M^{-1} and 60 ($\pm$1.5) M^{-1} for the β-CyD and HP-β-CyD complexes with NP, respectively, which were calculated by the equation of stability constant = slope/intercept (1-slope). The solid complexes of NP with HP-β-CyD in various molar ratios were prepared by the spray-drying method. The NP/HP-β-CyD complexes prepared by the spray-drying method in molar ratios of 1:1, 1:3, 1:5 and 1:10 showed only a halo-pattern in powder X-ray diffractogram and no endothermic peak at 172 °C in DSC curve, whereas the simple physical

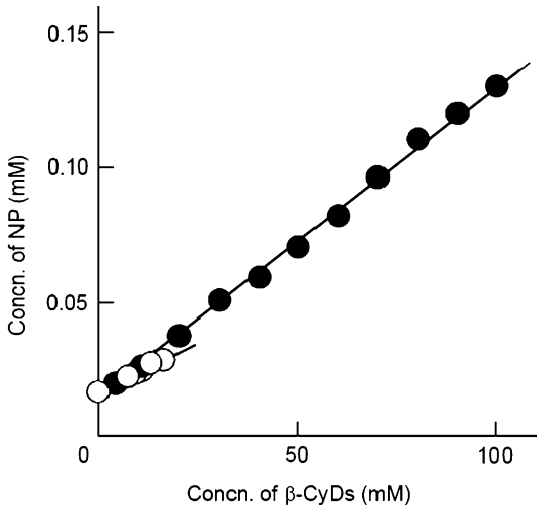

Figure 1. Phase solubility diagrams of NP/β-CyD system in water at 25 °C. (○) β-CyD system, (●) HP-β-CyD system.

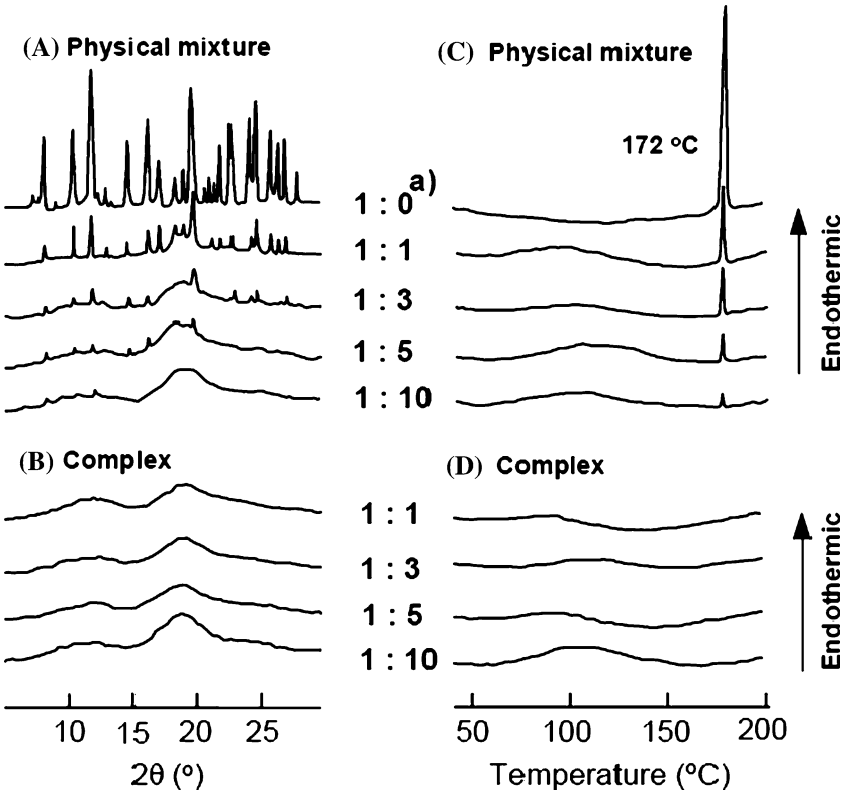

Figure 2. Powder X-ray diffraction patterns (A and B) and DSC thermograms (C and D) of NP/HP-β-CyD systems with different molar ratios. (A) and (C) physical mixture, (B) and (D) complex. (a) Molar ratio of NP/HP-β-CyD.

mixture of the guest and host gave sharp X-ray diffraction peaks and the endothermic peak at 172 °C due to the melting, as shown in Figure 2. These results indicate that NP forms an amorphous complex with HP-β-CyD when spray-dried with the host molecule.

Dispersion property of NP in Witepsol ® H-15 suppository base

The Witepsol® H-15, PEG and glycerin suppositories containing NP and its HP-β-CyD complexes with different molar ratios (1:1–1:10 guest:host) were prepared. The average contents of NP in the suppositories were within 99.0 ± 1.3–$100.6 \pm 2.6\%$ of the initially added amount of the drug. Figure 3 shows pictures of Witepsol® H-15 suppositories containing NP, its HP-β-CyD complexes and the physical mixtures. In the case of NP alone and the physical mixtures, an intense yellow color of NP was observed at the bottom of the suppository, indicating a heterogeneous distribution of the drug. On the other hand, the yellow color was uniformly spread over the suppository when NP was added as the HP-β-CyD complexes, indicating a homogeneous distribution of the drug. The distribution of NP in Witepsol® H-15 suppositories, where the suppository was divided into three parts, i.e., upper, middle and bottom parts, and the drug content of each part was determined by HPLC. It was apparent that NP is uniformly distributed in the suppository when it was added as the HP-β-CyD complexes, whereas about 70% of NP was sedimented at the bottom when added as the drug alone or the physical mixture. The different distribution behavior of NP crystals and the complex in the suppositories may be due to difference in specific gravity between them. However, the specific gravity of the HP-β-CyD complex (1.38 g/mL determined by the flotation method) was similar to that of NP crystals (1.31 g/mL). Therefore, other factors such as porosity, bulkiness and void volume etc. of the

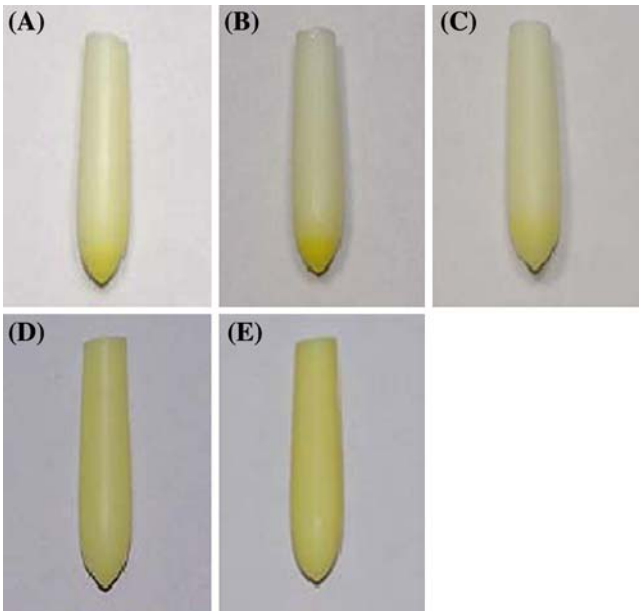

Figure 3. Distribution of NP in Witepsol® H-15 suppository bases containing NP alone, its HP-β-CyD complexes or physical mixtures, after solidification. (A) NP alone, (B) 1:1 physical mixture, (C) 1:5 physical mixture, (D) 1:1 complex, (E) 1:5 complex.

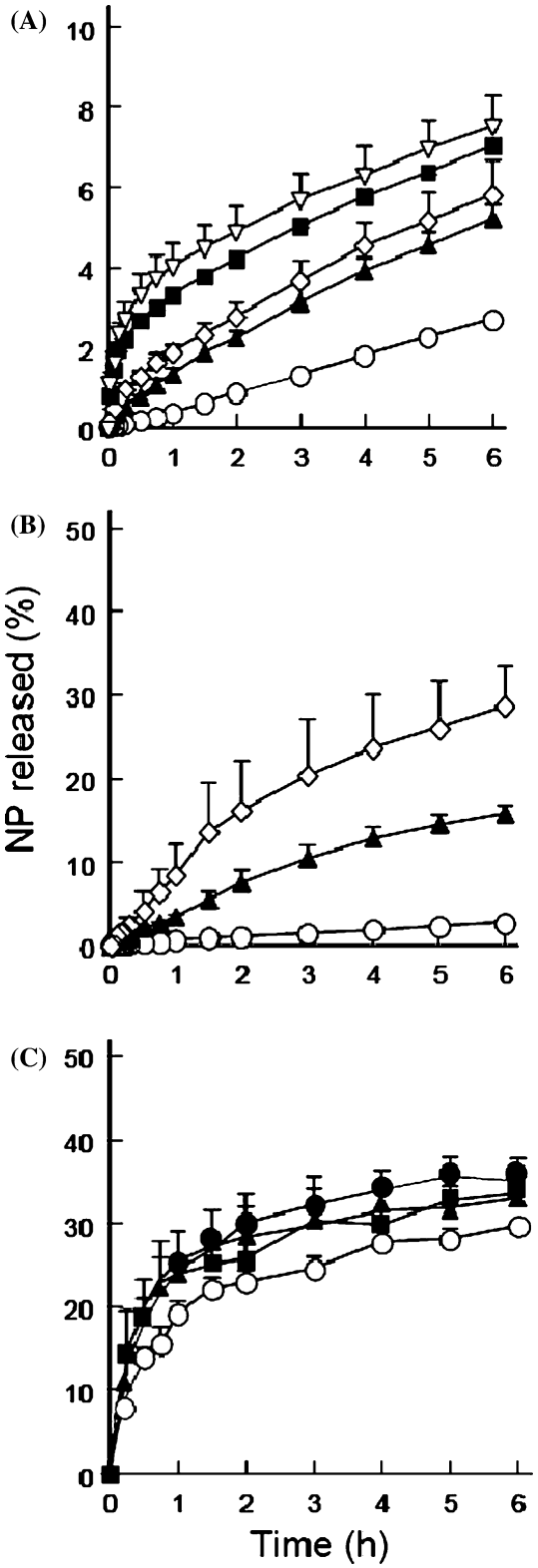

Figure 4. Release profiles of NP from Witepsol® H-15 (A), glycerin (B) and PEG (C) suppository bases containing NP alone or its HP-β-CyD complexes in saline at 37 °C. (○) NP alone, (▲) 1:1 complex, (◇) 1:3 complex, (■) 1:5 complex, (▽) 1:10 complex, (●) Adalat®. Each point represents the mean ± SE of three experiments.

complex may be responsible for the homogeneous distribution, although further studies should be done to elucidate the dispersion mechanism of the complex in Witepsol® H-15 base.

Release property of NP from suppositories

Figure 4 shows the release profiles of NP from Witepsol® H-15 (Figure 4A), glycerin (Figure 4B) and PEG (Figure 4C) suppositories containing NP and its HP-β-CyD complexes with different molar ratios. The releases of NP from Witepsol® H-15 and glycerin suppositories were very slow, probably because the drug is suspended as solid powder in these suppositories and is poorly soluble in the release medium (water). However, the release rate increased when the drug was formulated as the HP-β-CyD complex, and it increased as the molar ratio of the host augmented. The enhancing effect of HP-β-CyD was greater for the glycerin suppository than for the Witepsol® H-15 suppository, because of the water-soluble property of glycerin base. The release rate of NP from the PEG suppository (Figure 4C) was faster than those from Witepsol® H-15 and glycerin bases (Figures 4A, B), because both the drug and the HP-β-CyD were soluble in the former base, in contrast to the latter two bases. However, the release rate of NP from the PEG base was not changed by the addition of the HP-β-CyD complex, which may be due to the fact that the complex dissociates to free components in the base and/or the dissolution of the base is a rate-determining step in the release. In fact, the physical mixture of NP and HP-β-CyD showed negligible change in the release rate of the drug. A home-made product of NP suppository, i.e., the PEG suppository in which the content of Adalat® was added, also gave the similar release profile as those of NP alone and its HP-β-CyD complexes, as shown in Figure 4C.

The present results indicated that the NP/HP-β-CyD complex homogeneously distributes in Witepsol® H-15 suppository base and the NP/HP-β-CyD complex improves the release of NP from Witepsol® H-15 and glycerin suppositories. Therefore, Witepsol® H-15 suppositories containing NP/HP-β-CyD complex may be useful from a viewpoint of the release control and quality assurance.

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