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RESEARCH PAPER

Physicochemical Characterization and Drug Release Studies of Nilvadipine Solid Dispersions Using Water-Insoluble Polymer as a Carrier

Noriyuki Hirasawa,[1,*] Sayoko Ishise,[1] Hitomi Miyata,[1] and Kazumi Danjo[2]

[1]Medicinal Research Department, Nichiiko Pharmaceutical Co., Ltd.,
Namerikawa, Japan
[2]Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya, Japan

ABSTRACT

Nilvadipine solid dispersions were prepared by the solvent method using water-insoluble polymers, including low-substituted hydroxypropylcellulose, croscarmellose sodium, carmellose calcium, carmellose, and crospovidone. Differential scanning calorimetry and powder x-ray diffraction analysis showed that nilvadipine was present in an amorphous state in the solid dispersion obtained using crospovidone as a carrier. The degree of crystallinity of nilvadipine was dependent on the ratio of nilvadipine to crospovidone, and nilvadipine was present in an amorphous state when the ratio of nilvadipine to crospovidone was below one-half. Fourier transform infrared studies suggested the presence of hydrogen bonding between nilvadipine and crospovidone in the solid dispersion. Dissolution studies indicated that the maximum percentage of dissolution and dissolution rate constants were markedly increased in nilvadipine with crospovidone solid dispersion, compared with those of pure nilvadipine and physical mixtures. The dissolution rate of nilvadipine solid dispersion with crospovidone could be calculated by the Higuchi square root time equation.

INTRODUCTION

Poorly water-soluble drugs often show low absorption and weak bioavailability. Therefore, improvements in dissolution rate and/or solubility are important for development of drug preparations. The solid dispersion method for improving the dissolution rate of poorly water-soluble drugs was first proposed by Sekiguchi and Obi,[2] and the technique has been widely used to prepare both fast

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*Correspondence: Noriyuki Hirasawa, Medicinal Research Department, Nichiiko Pharmaceutical Co., Ltd., 205-1 Shimoumezawa, Namerikawa, 936-0857, Japan; Fax: +81-76-475-5530; E-mail: n-hirasawa@nichiiko.co.jp.

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release and sustained release drug preparations by melting, solvent, or melting-solvent methods.[3] In general, a carrier to disperse the drug and to increase the dissolution rate is chosen from among readily water-soluble materials.[4] For example, polyvinylpyrrolidone,[5] polyethylene glycol,[6] and hydroxypropylmethylcellulose[7] have often been used for fast-release preparations. Previously, we reported that lactose, which has a low molecular weight and is water-soluble, was useful as a dispersing carrier to improve dissolution of poorly water-soluble drugs, such as naproxen, ethenzamide, and carbamazepine.[8,9] In this study, nilvadipine was used as model of a poorly water-soluble drug. Nilvadipine (NIL) solid dispersions with water-insoluble polymer often used as disintegrants were prepared by the solvent method to improve the drug dissolution.

EXPERIMENTAL

Materials

Nilvadipine (Sagami Chemical Industry, Japan), low-substituted hydroxypropylcellulose (L-HPC, LH-22, Sin-Etsu Chemical, Japan), croscarmellose sodium (cl-CMC-Na, Ac-Di-Sol, Asahi Kasei, Japan), carmellose (CMC, NS-300, Gotoku Chemical, Japan), carmellose calcium (CMC-Ca, ECG-505, Gotoku Chemical, Japan), and crospovidone (cl-PVP, KollidonCL-M, BASF Japan, Japan) were used in this study. Other chemicals used were of reagent grade.

Preparation of Solid Dispersions

Solid dispersions at various weight ratios were prepared by the solvent method. One gram of NIL was dissolved in 100 g of ethanol, and then the required amount of carrier was suspended in this solution. The solvent was evaporated under reduced pressure at 45°C and then dried almost completely in a vacuum desiccator for 12 hr. The solid sample was ground gently with a mortar and pestle and passed through an 180-μm sieve.

Preparation of Physical Mixtures

Physical mixtures were prepared by mixing NIL and carrier with a test tube mixer (Vortex-Genie2, Scientific Industries, Japan) for 5 min. The samples were passed through an 180-μm sieve before use.

Thermal Analysis

Thermal analysis was carried out by differential scanning calorimetry (DSC) with a type DSC7 apparatus (Perkin-Elmer, Norwalk, CT, USA). Samples were placed in sealed aluminum pans and scanned at a heating rate of 10°C/min under a nitrogen atmosphere.

Powder X-Ray Diffraction

Powder x-ray diffraction analysis was performed with an x-ray diffractometer (RU-200BV, Rigaku, Japan). Operating conditions were as follows: target, CuKα; voltage, 40 kV; current, 80 mA; and scan speed, 5°/min.

Infrared Spectra

Fourier transform infrared (FT-IR) spectra were obtained with a System 2000 instrument (Perkin-Elmer, Corp., Norwalk, CT, USA) by the KBr disk method.

Dissolution Test

Dissolution tests were performed according to the JP14 paddle method. Sample powder, including 10 mg of NIL, was put into the dissolution medium (900 mL of purified water) at 37 ± 0.5°C, and the paddle was rotated at 50 rpm. The amount of dissolved NIL was determined with an ultraviolet spectrophotometer (UV-1600, Shimadzu, Tokyo, Japan) at 242 nm.

Scanning Electron Microscopy (SEM)

Morphology of solid dispersion particles was characterized by SEM using a JSM-T20 (JEOL, Japan). The sample was coated with gold by ion sputtering using a JFC-1100 (JEOL, Japan).

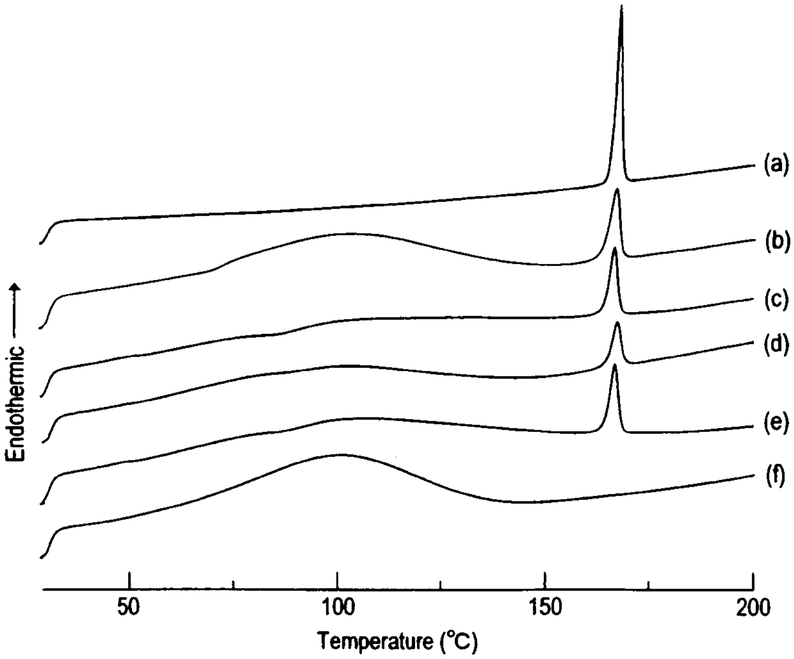

Figure 1. DSC thermograms of NIL/carrier (1/4) prepared by the solvent method. (a) NIL, NIL/carrier (1/4) prepared by the solvent method; (b) L-HPC; (c) cl-CMC-Na; (d) CMC; (e) CMC-Ca; (f) cl-PVP.

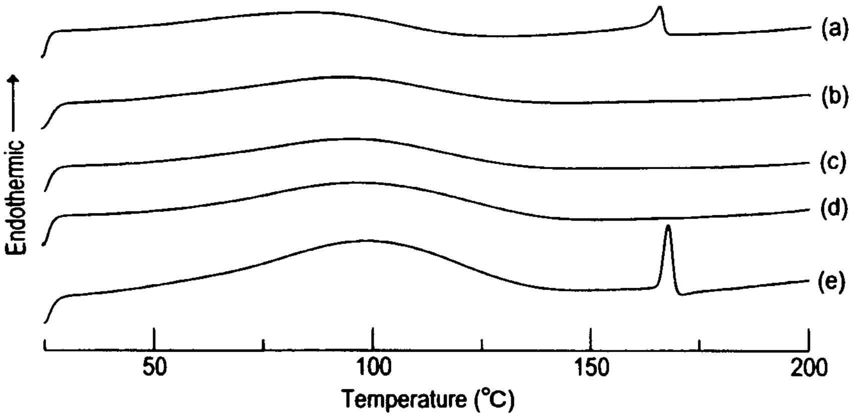

Figure 2. DSC thermograms of NIL/cl-PVP solid dispersion systems. Solid dispersion: (a) 1/1; (b) 1/2; (c) 1/3; (d) 1/5; (e) 1/4 physical mixture.

RESULTS AND DISCUSSION

Degree of Crystallinity of NIL in Solid Dispersion

DSC thermograms of NIL and NIL/carriers (1/4) prepared by the solvent method are shown in Fig. 1. NIL showed an endothermic peak at 169.2°C corresponding to its melting point. NIL/carriers (1/4) prepared by the solvent method with L-HPC, cl-CMC-Na, CMC, and CMC-Ca also showed endothermic peaks identical with NIL. On the other hand, the sample with cl-PVP showed no melting peak of NIL. These results indicated that only cl-PVP was able to alter NIL to an amorphous state in solid dispersion when used as a carrier. DSC thermograms of NIL/cl-PVP solid dispersions at various ratios and those of physical mixtures are shown in Fig. 2. NIL/cl-PVP (1/1) solid dispersion showed a melting peak of NIL at 165.9°C, which

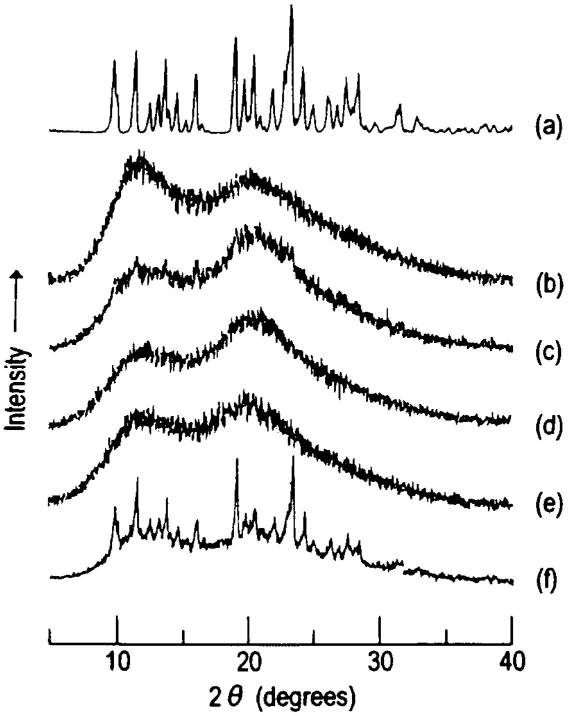

Figure 3. Powder x-ray diffraction patterns of NIL/cl-PVP solid dispersion systems. (a) NIL; (b) cl-PVP. Solid Dispersions: (c) 1/1; (d) 1/2; (e) 1/4; (f) 1/4 physical mixture.

was shifted toward lower temperature by 3.3°C and 2.3°C, compared with those of pure NIL and physical mixture, respectively. The melting peak of NIL was not observed when the ratio of NIL to cl-PVP was below 1/2. These observations indicated that NIL was present in an amorphous state in these solid dispersions. Powder x-ray diffraction patterns of NIL, cl-PVP, and NIL/cl-PVP solid dispersions at various ratios are shown in Fig. 3. Many sharp peaks were observed in the diffraction patterns of NIL, whereas a halo was observed in that of cl-PVP. The diffraction pattern of the physical mixture showed many sharp peaks identical to those of NIL, indicating that crystallinity of NIL did not change in the physical mixture. Diffraction peaks of NIL were observed in NIL/cl-PVP (1/1) solid dispersions, indicating the crystalline structure of NIL. No detectable diffraction peak of NIL was observed for NIL/cl-PVP (1/2, 1/4) solid dispersions, indicating the presence of NIL in an amorphous state. These DSC and powder x-ray diffraction studies indicated that the degree of crystallinity of NIL in the solid dispersions using cl-PVP as a carrier was dependent on the ratio of NIL to cl-PVP. When the ratio of NIL to cl-PVP was below 1/2, NIL was present in an amorphous state.

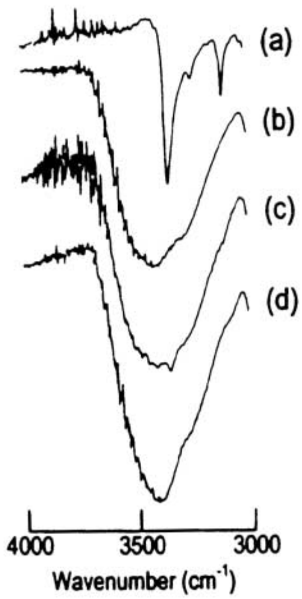

Figure 4. FT-IR spectra. (a) NIL; (b) cl-PVP; (c) NIL/cl-PVP (1/4) physical mixture; (d) NIL/cl-PVP (1/4) solid dispersion.

Interaction of NIL and cl-PVP in the Solid Dispersion

FT-IR spectra for NIL, cl-PVP, their physical mixture, and solid dispersion are shown in Fig. 4. NIL showed a band at 3,340 cm^{-1} caused by N—H stretching vibration in dihydropyridine. This band was similarly observed for the physical mixture, suggesting that there was no interaction between NIL and cl-PVP in the physical mixture. The band caused by the N—H stretching vibration of NIL was not observed in the solid dispersion. These results suggested the presence of intermolecular hydrogen bonding between NIL and cl-PVP in the solid dispersion.

Dissolution Profiles of NIL from Solid Dispersion

The dissolution profiles of NIL from the samples obtained by the solvent method with various water-insoluble polymers as carriers are shown in Fig. 5. As expected, the sample using cl-PVP as a carrier showed significant increases in the solubility and dissolution rate, compared with other samples, and the dissolution of NIL decreased around 180 min, most likely because of recrystallization of the NIL form supersaturate concentration. Figure 6 shows the dissolution of various ratios of NIL with cl-PVP

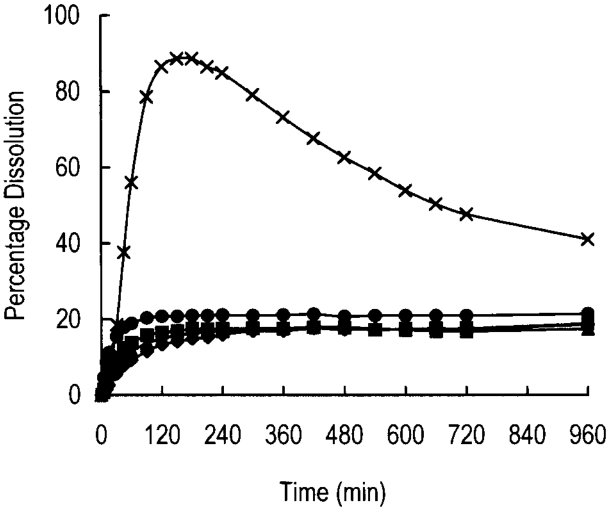

Figure 5. Dissolution profiles of samples of NIL/carrier (1/4) prepared by the solvent method with various water-insoluble polymers. ●, L-HPC; ▲, cl-CMC-Na; ■, CMC; ◆, CMC-Ca; ×, cl-PVP.

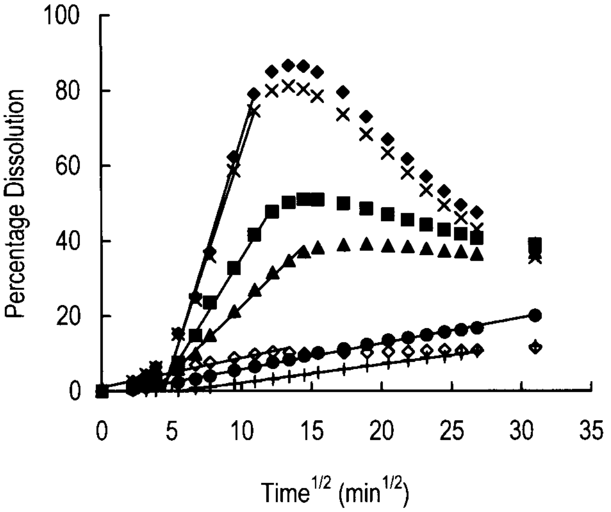

Figure 6. Dissolution profiles of NIL/cl-PVP systems. Solid dispersions: ●, 1/1; ▲, 1/2; ■, 1/3; ◆, 1/4; ×, 1/5; ◇, 1/4 physical mixture; +, NIL.

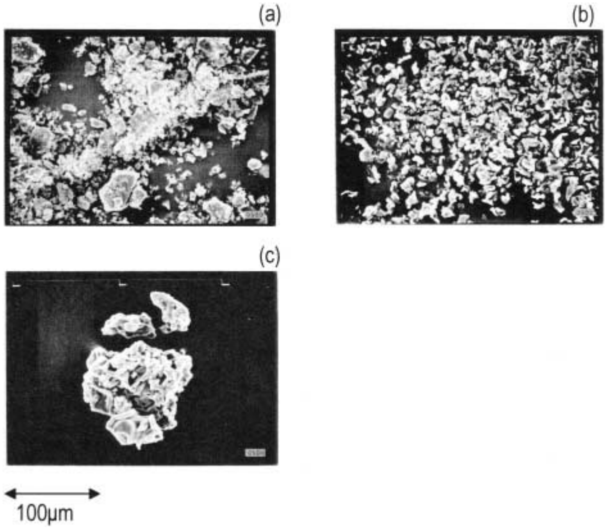

Figure 7. SEM of samples. (a) NIL; (b) cl-PVP; (c) NIL/cl-PVP (1/4) solid dispersion.

solid dispersions, physical mixture, and pure NIL. In the initial dissolution stage, there was a good correlation between the dissolution percentage of NIL and square root time. Dissolution of solid dispersions showed a lag time, because the hydrophobicity caused the powder to float on the surface of the dissolution medium and prevented its rapid contact. It was reported that release from an insoluble matrix could be determined from the Higuchi square root time equation.[1] This equation applied for tablets containing indomethacin with phosphatidylcholine solid dispersions[10] and nifedipine with Eudragit and Poloxamer solid dispersion particles.[11] Moreover, Carli et al.[12] reported that griseofulvin molecules were diffused inside cl-PVP particles in griseofulvin with cl-PVP solid dispersions. Figure 7 shows SEM of NIL, cl-PVP, and their solid dispersion. The solid dispersion looked like a matrix particle, which was agglomerated with NIL and cl-PVP, and NIL seemed to be present in cl-PVP in amorphous form. The maximum percentage of dissolution ($C_{\max}$) and apparent dissolution rate constants (K), calculated from the slope of the straight line, are listed in Table 1. $C_{\max}$ and K of NIL/cl-PVP (1/4) solid dispersion were about 8-fold and 25-fold higher than those of pure NIL, respectively. This was because of formation of the high-energy amorphous form.

CONCLUSIONS

DSC and powder x-ray diffraction studies indicated that the NIL present in an amorphous state in the solid dispersions using cl-PVP as a carrier, and when the ratio of NIL to cl-PVP was below 1/2 NIL, was present in an amorphous state. FT-IR analysis suggested hydrogen bonding between NIL and cl-PVP in the solid dispersion. The dissolution of NIL, which is poorly soluble in water, was markedly improved in the amorphous form in solid dispersions

Table 1. Maximum percentage dissolution (C_{max}) and dissolution rate constants (K).

Sample	C_{max} (%)	K (%/min$^{1/2}$)	r^2
NIL/cl-PVP (1/1) solid dispersion	20.1	0.7	0.997
NIL/cl-PVP (1/2) solid dispersion	39.2	3.6	0.994
NIL/cl-PVP (1/3) solid dispersion	51.0	6.0	0.995
NIL/cl-PVP (1/4) solid dispersion	86.7	12.1	0.992
NIL/cl-PVP (1/5) solid dispersion	81.2	11.2	0.993
NIL	10.6	0.5	0.999
NIL/cl-PVP (1/1) physical mixture	11.5	0.8	0.967

using cl-PVP as a carrier. The dissolution profile of the solid dispersion fitted a diffusion equation for a matrix system.

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