Note

Photostable Solid Dispersion of Nifedipine by Porous Calcium Silicate

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Nifedipine (NIF) is a typical light-sensitive drug requiring protection from light during manufacture, storage, and handling of its dosage forms. The purpose of this study was to evaluate the utility of porous calcium silicate (PCS) for maintaining the photostability of NIF in a solid dispersion formulation. Adsorption solid dispersion (ASD) prepared using NIF and PCS as an amorphous formulation was more stable to light irradiation than a physical mixture of NIF and microcrystalline cellulose (a control physical mixture) as a crystalline formulation. In addition, PCS in physical mixtures with NIF adequately protected NIF from photodegradation, suggesting that this protective effect could be because of some screening effect by the porous structure of PCS blocking the passage of light reaching NIF in pores of PCS. These findings suggest that PCS is useful for improving the solubility and photostability of NIF in solid dispersion formulation.

Key words porous calcium silicate (PCS); nifedipine (NIF); photostability; solid dispersion; amorphous

Light-sensitive drugs are affected by ultraviolet irradiation or fluorescent light and are often susceptible to photodegradation.^{1,2)} The most important consequence of photodegradation is loss of potency. Nifedipine (NIF), a typical light-sensitive drug, requires protection from light during manufacturing, storage, and handling of its dosage forms. NIF is photochemically unstable, yielding the following two major photoproducts: nitroso and nitro derivatives.^{3–6)} These photodegraded products exert weak (approximately 10000 less potent than NIF) blocking action on voltage-dependent Ca^{2+} channels.⁷⁾ Thus, improvement of photostability is a key consideration in the development of potent NIF formulations. In addition, NIF is a poorly water-soluble drug, and for preparation of an oral formulation, it is necessary that the dissolution of the drug is improved.

Solid dispersion is one method for improving dissolution and has been investigated as a manufacturing method for solid preparations.⁸⁾ Solid dispersions are generally prepared with water-soluble polymers as carriers.^{9–12)} Recently, porous materials have been used as carriers of solid dispersions.^{13–17)} The amorphous state undergoes more rapid photodegradation than the corresponding crystalline state.^{11,12,18)} Researchers have used polymeric carriers, such as hydroxypropyl methylcellulose acetate succinate and hydroxypropyl cellulose, to prepare solid dispersions of NIF.^{11,12)}

Porous calcium silicate (PCS) has a characteristically porous structure with many pores (about 150 nm) and large individual pore volume (3.57 mL/g) and has been reported to be useful as a carrier of solid dispersions of poorly water-soluble drugs for improvement of solubility.^{13,16)} However, there are no reports on the photostability effects of porous materials as solid dispersion carriers. The aim of the present study was to evaluate the effect of PCS on the photostability of NIF in solid dispersion formulation.

Experimental

Materials NIF was purchased from Permchem Asia Ltd. (Tokyo, Japan; purity over 99.0% (w/w)). PCS (Fluorite® RE) was kindly provided by Tomita Pharmaceutical Co., Ltd.

(Tokushima, Japan). Silicified microcrystalline cellulose (Pro-solv SMCC90®) was obtained from Jrs Pharma GmbH & Co., Kg. (Rosenberg, Germany).

Preparation of Adsorption Solid Dispersion (ASD), Physical Mixture (PM), and Control Physical Mixture (Control PM) ASD was prepared as described below. NIF (2 g) was dissolved in ethanol (28 g) by heating at 60°C, then this solution was added to PCS (14 g) in the glass-stoppered Erlenmeyer flask and mixed for 30 min at 70 rpm with a rotation mixer. The mixture was dried for 12 h at 70°C.

PM and control PM were prepared by mixing NIF (2 g), silicified microcrystalline cellulose (SMCC) (14 g) and PCS (14 g) or NIF (2 g) in the glass-stoppered Erlenmeyer flask for 30 min at 70 rpm.

Irradiation Tests Powder samples of ASD, PM, and control PM were irradiated in a light-irradiation tester (LTL-200B3CJ-15, Nagano Science Co., Ltd., Osaka, Japan). Powder samples of 1 g were uniformly placed on a 10-cm-diameter dish. Illuminance and ultraviolet energy were set at 3600 lx and 0.6 W/m², respectively. Irradiation tests were performed at 25°C ± 0.5°C and 50% ± 1% RH.

HPLC Analysis Assays of residual NIF content in powder sample were performed by dispersing samples containing 10 mg of NIF in methanol (100 mL) followed by filtering and HPLC analysis of the solution using a Shimadzu LC-10ADvp pump (Shimadzu Corp., Kyoto, Japan), Shimadzu SPD-20A Detector (Shimadzu Corp.) set at 238 nm, and Inertsil ODS-3 column (GL Sciences Inc., Tokyo, Japan, 4.6 × 150 mm, 3 μm). The mobile phase comprised methanol–water in a 3:2 (v/v) ratio, and the flow rate was 0.5 mL/min. All analyses were performed at 40°C. Retention times of NIF and the nitroso and nitro derivatives were 14.9, 12.5, and 10.8 min, respectively.

Evaluation of Formulations Scanning electron microscopy (SEM; JCM-6000, JEOL Ltd., Tokyo, Japan) was employed to examine the morphology of NIF in powder samples with an accelerating voltage of 15 kV without coating.

Differential scanning calorimetry (DSC) analyses of powder samples were carried out on 1–10 mg samples using a DSC-60

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Plus (Shimadzu Corp.). The samples were heated to 200°C at a rate of 10°C/min.

Powder X-ray diffraction (PXRD) analysis was performed with Cu radiation, a voltage of 40kV and a current of 30mA (SmartLab, Rigaku Corporation, Tokyo, Japan). The scan rate was 40°/min over a 2θ range of 5–90° with a sampling interval of 0.02°.

Fourier transform infrared (FT-IR) spectra were obtained using a spectrophotometer (IRAffinity-1, Shimadzu Corp.) using the potassium bromide (KBr) pellet method. KBr disks were prepared by mixing several mg of sample with potassium bromide and compacting. The scan range was 4000 to 400 cm^{-1} .

Statistical Analysis All results are presented as the mean $\pm$ standard deviation (S.D.). All statistical analyses were performed using Statcel for Windows (OMS Ltd., Saitama, Japan). One-way ANOVA was followed by the Tukey–Kramer test for multiple comparisons. Differences were considered significant when the calculated p value was less than 0.05.

Results and Discussion

Figure 1 shows the percent of NIF remaining in powder samples under light irradiation. The percents of NIF remaining in control PM 1, 3, 7, and 14d after light irradiation were 36.6 ± 1.4 , 18.1 ± 0.9 , 8.1 ± 1.2 , and 4.5 ± 0.2 , respectively. Most of the NIF in control PM was decomposed by light irradiation. In contrast, the percents of NIF remaining in ASD and PM 3d after light irradiation were 50.9 ± 0.9 and 77.6 ± 0.4 , respectively, showing that the amounts of NIF remaining in ASD and PM after light irradiation were greater than those of control PM. Samples wrapped in aluminum laminate bags showed negligible differences in NIF content of samples over the test period (data not shown).

The photodegradation of solid NIF has been reported to follow first-order kinetics.^{4,5)} Degradation kinetics was calculated according to the following equation:

$$\ln A = \ln A_0 - kt,$$

where A is the percent of NIF remaining, t is time (in days), and k is the slope (degradation constant). The degradation rate

Fig. 1. Influence of PCS on Photodegradation of NIF Powder Samples

Values are expressed as the mean $\pm$ S.D. ($n=3$). * $p < 0.05$ versus control PM by Tukey–Kramer test. # $p < 0.05$ versus PM by Tukey–Kramer test.

constants of ASD, PM, and control PM are listed in Table 1. The rate constants of ASD and PM were significantly reduced compared with those of control PM, and the ratios of rate constants of ASD and PM to those of control PM were 0.42 and 0.13, respectively. These results indicate that the photolysis of NIF in ASD and PM was inhibited by PCS. The greater stability of crystalline chemicals than their amorphous forms^{11,12,18)} may be partly explained for the differences in photostability between ASD and PM. In added, these findings may be explained by the differences of NIF state in between crystalline and amorphous.¹⁹⁾ Therefore, we examined the state of NIF in ASD and PM to evaluate the effect of PCS on photostability of NIF.

Figure 2 shows SEM photographs of PCS, ASD, PM, SMCC, and control PM. Pure drug (Fig. 2A) showed irregular crystals of various sizes (about 0.5–180nm). Photograph of PCS (Fig. 2B) showed a rough surface due to the porous structure. Photograph of ASD was very similar to that of PCS, and no drug crystals were observed on the ASD surface (Fig. 2C). In PM, only a few microcrystals of NIF were observed on

Table 1. Degradation Rate Constant

Formulations	Degradation rate constant $k \pm \text{S.D.} (\times 10^{-2} \text{ per day})$	$k/k_{\text{control PM}}$
ASD	$25.4 \pm 0.09^{* \#}$	0.42
PM	$7.7 \pm 0.04^*$	0.13
Control PM	$61.0 \pm 0.16^{\#}$	1

k , degradation rate constant; $k_{\text{control PM}}$, degradation rate constant of control PM. Values are expressed as mean $\pm$ S.D. ($n=3$). * $p < 0.05$ versus control PM by Tukey–Kramer test. # $p < 0.05$ versus PM by Tukey–Kramer test.

Fig. 2. SEM Photographs of (A) NIF, (B) PCS, (C) ASD, (D) PM, (E) SMCC, and (F) Control PM

Fig. 3. DSC Plots of PCS, SMCC, ASD, PM, Control PM, and NIF

Fig. 4. PXRD Patterns of NIF, PCS, ASD, and PM

PCS particles (the arrow marks in Fig. 2D). The microcrystals of NIF were determined by comparing photographs of PCS and PM. This may result in a possible drug adsorption into the porous structure of PCS. However, both particles of NIF and SMCC were observed in control PM (Fig. 2F). The particles of NIF were determined by comparing photographs of SMCC and control PM in the same way (the arrow marks in Fig. 2F).

DSC analyses were employed to determine the crystalline of NIF in powder samples (Fig. 3). The DSC endothermic peaks derived from crystalline NIF were present in PM and control PM, whereas the DSC endothermic peaks were not present in ASD. A small endothermic peaks derived from crystalline NIF in PM may be suggested that part of NIF has entered in pores of PCS. Similarly, the PXRD pattern of the sample prepared from ASD did not show peaks derived from crystalline NIF (Fig. 4). These findings suggest that NIF is present in the amorphous state in ASD.^{11,13,14)}

FT-IR spectra were obtained to determine the interactions between NIF and PCS or SMCC (Fig. 5). The FT-IR spectra of pure NIF showed characteristic bands at 1678/1690 cm^{-1} (C=O stretching) (Fig. 5A) and 3327 cm^{-1} (secondary -NH) (Fig. 5B). These characteristic bands were observed in control PM, whereas these bands were hardly observed in ASD. There are several reports about the interaction between drug molecules and silanol group in silica.^{13,14,20)} Therefore, these results suggest that C=O and NH groups of NIF interacts with silanol group of PCS.

The above results suggest that NIF in ASD is present in the amorphous state by interactions between NIF and PCS. Furthermore, NIF in PM was present in the crystalline state,

Fig. 5. FT-IR Spectra of NIF, PCS, ASD, PM, Control PM, SMCC at (A) 1600–1800 cm^{-1} and (B) 3200–3500 cm^{-1}

and NIF particles were present on PCS particles and in pores of PCS. In irradiation test, the amounts of NIF remaining in ASD and PM using PCS were greater than those of control PM without PCS. Several researches^{11,12,18)} reported that the amorphous state undergoes more rapid photodegradation than the corresponding crystalline state. However, in this study, the photostability of amorphous NIF in ASD was markedly improved compared with that of crystalline NIF in control PM. These findings suggested that the photodegradation of NIF in solid dispersion was suppressed by PCS. In addition, it was clear that PCS in PMs with NIF adequately protects NIF from photodegradation. From this result, the protective effect could be because of some screening effect by the porous structure of PCS blocking the passage of light reaching NIF in pores of PCS.

Conclusion

NIF was present in the amorphous state in ASD, whereas NIF was mostly present in the crystalline state in PM and control PM. Furthermore, NIF particles in PM were present on PCS particles and in pores of PCS. In irradiation test, most of the NIF in control PM was decomposed, whereas the remaining amounts of NIF in ASD and PM were greater than those of control PM. Although in general, the amorphous state undergoes more rapid photodegradation than the corresponding crystalline state, ASD prepared with PCS as an amorphous formulation in this study was more stable to light irradiation than control PM as a crystalline formulation. In addition, PCS in PMs with NIF adequately protected NIF from photodegradation, suggesting that this protective effect could be because of a screening effect of the porous structure of PCS which limits the light reaching NIF in pores of PCS. These findings suggest that PCS is useful for improving the solubility and photostability of NIF.

Conflict of Interest The authors declare no conflict of interest.

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