

Some Factors Influencing the Dissolution of Solid Dispersions with Nicotinamide and Hydroxypropylmethylcellulose as Combined Carriers

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The dissolution characteristics of solid dispersions with nicotinamide and hydroxypropylmethylcellulose (HPMC) as combined carriers were investigated in water, using nifedipine and nitrendipine as model drugs. The solid dispersions were obtained by the fusion method; after both drug and HPMC dissolved in the fused liquid of nicotinamide at 140 °C, the fused mixtures were cooled to solidify them. For nifedipine solid dispersions, the supersaturation behavior was enhanced with a decrease in the viscosity or an increase in the weight fraction of HPMC. Nifedipine was present as an amorphous state even in the solid dispersion with a 1:3:0.2 weight ratio of drug:nicotinamide:HPMC. Also, the more the weight fraction of nifedipine increased, the more the formation of amorphous drug in solid dispersions was suppressed, thereby lowering the drug supersaturation level. Moreover, the effect of humidity during storage on the dissolution profiles of nifedipine solid dispersions was examined. The humidity caused crystallization of amorphous nifedipine in solid dispersions, and decreased the drug supersaturation level. For nitrendipine solid dispersions, similarly to the nifedipine system, amorphous nitrendipine was obtained in solid dispersions, and this led to the supersaturation phenomenon. However, the inhibitory effect of HPMC on the crystallization of nitrendipine from supersaturated solution was less than that for nifedipine; this is attributable to the lower solubility of nitrendipine crystals. Therefore, the drug dissolution of this ternary dispersion system was influenced by the viscosity and weight fraction of HPMC, the solubility and weight fraction of the drug and the humidity during storage.

Key words nifedipine; nitrendipine; solid dispersion; combined water-soluble carrier; supersaturation; humidity

Since Sekiguchi and Obi¹⁾ first proposed the use of solid dispersions as a novel method for increasing the bioavailability of poorly water-soluble drugs by reducing particle size, many similar studies have been reported and reviewed.^{2,3)} The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion or solvent processes, and many substances have been recommended as carriers for binary and ternary solid dispersions. Ternary solid dispersion systems are based on a combination of carriers, which has the potential of combining desirable properties characteristic of binary solid dispersions. Combined water-soluble carriers have been examined including citric acid–succinic acid,⁴⁾ sugar mixtures,⁵⁾ polyethylene glycol (PEG)–sugars,⁶⁾ PEG–stearic acid,⁷⁾ and sterols–surfactants.⁸⁾

Nifedipine and nitrendipine, calcium-channel agents, are poorly water-soluble drugs.^{9,10)} Thus far nifedipine solid dispersions have been investigated; binary solid dispersions of nifedipine–polyvinylpyrrolidone (PVP) or –hydroxypropylmethylcellulose (HPMC)¹¹⁾ and ternary solid dispersions of nifedipine–PEG–phosphatidylcholine¹²⁾ have exhibited good dissolution and absorption of the drug. The present authors have developed a preparation of ternary solid dispersions of nifedipine–nicotinamide–HPMC by the fusion process.¹³⁾ This system was based on the fact that both nifedipine and HPMC dissolved in the fused liquid of nicotinamide at a lower temperature than the melting point of the drug. The incorporation of HPMC was effective for the formation of amorphous nifedipine, leading to the supersaturation phenomenon in dissolution studies. In addition, PVP and partially hydrolyzed polyvinyl alcohol were used instead of HPMC in this ternary system.¹⁴⁾ The use of a polymer with high

compatibility and adhesion with nifedipine provided a high supersaturation level of the drug in water. However, the effect of other factors, except for the polymer type, on drug dissolution of this ternary system has not been reported.

Hence, the purpose of this paper was to study the effect of the viscosity and weight fraction of HPMC, the solubility and weight fraction of drug, and the humidity during storage on the dissolution profiles of solid dispersions with nicotinamide and HPMC as combined carriers in water, using nifedipine and nitrendipine as model drugs.

Experimental

Materials Nifedipine, nitrendipine and nicotinamide, whose melting points (mp) were 173, 158 and 129 °C, respectively, were obtained from Wako Pure Chemical Industries Co., Ltd., Japan. Three grades of HPMC (Shin-Etsu Chemical Industries Co., Ltd., Japan) were used (TC-5E, TC-5R and TC-5S, with designated viscosities as 2% (w/v) aqueous solutions of 3, 6 and 15 mm²/s, respectively). All other chemicals were of reagent grade. All experiments were carried out under subdued light to prevent light degradation of nifedipine and nitrendipine.

Preparation of Solid Dispersion Systems The physical mixtures were prepared by lightly grinding together accurately weighed quantities of drug and excipients using a mortar and pestle for 1–2 min. Solid dispersions of nifedipine (0.5–2 g) or nitrendipine (1 g) and nicotinamide (3–5 g), with or without HPMC (0.2–3 g), were obtained by the fusion process, that is, by fusing the corresponding physical mixtures on a hot-plate at 140 ± 5 °C for 15 min. The surface temperature of six points on the hot-plate was measured by an infrared thermometer (COS Co., Ltd., Japan).

The fused samples were cooled and solidified at room temperature (slow cooling) or cooled in ice and solidified at 5 °C (rapid cooling) by placing them for 1–5 d in a desiccator over silica-gel before pulverizing them in a coffee mill. All dispersion samples used, except for the cooling temperature studies, were prepared by slow cooling. In all experiments, the fused dispersions were passed through a 42 mesh sieve and assayed for their drug content before use by HPLC at 237 nm.

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Drug Solubility Studies Excess amounts of nifedipine or nitrendipine were added to 5 ml distilled water. After shaking for 48 h at 37 °C, samples were withdrawn, filtered (0.2 μm), diluted with methanol and analyzed by HPLC at 237 nm. The chromatograph operating conditions were as follows: C18 reversed-phase column (YMC-Pack ODS-H80); 0.05 M phosphate buffer (pH 3.0):methanol:tetrahydrofuran (nifedipine, 60:32:8; nitrendipine, 50:42:8) eluant; flow rate of 1.3 ml/min; 237 nm detector (Shimadzu Seisakusho Co., Ltd., Japan).

Dissolution Studies Dissolution tests according to JP XIII (paddle method, 100 rpm) were carried out at 37 °C. A weighed quantity of physical mixture or solid dispersion containing 80 mg nifedipine or nitrendipine was placed in 900 ml distilled water. Samples were filtered (0.2 μm) and assayed by HPLC at 237 nm.

Storage Conditions Nifedipine solid dispersions were stored for 1 month in air-tight glass containers at 40 °C, or in three controlled-temperature and -humidity chambers: 25 °C/60% relative humidity (R.H.), 30 °C/60% R.H. and 40 °C/75% R.H. chambers (PR-2S, PR-1G and PR-1F, Tabai Espec Co., Ltd., Japan).

Differential Scanning Calorimetry (DSC) DSC analyses were carried out on samples of about 10 mg under a dry nitrogen purge using a DSC 220CU instrument (Seiko Denshi Kogyo Co., Ltd., Japan). The samples were heated at a rate of 10 °C/min to 200 °C. Melting point was characterized by the temperature at the point of intersection of the steepest slope line and the baseline.

Powder X-Ray Diffraction Analysis Powder X-ray diffraction analyses were performed with a Rigaku Geiger-Flex diffractometer (Rad-IIVC) using Ni-filtered, $\text{CuK}\alpha$ radiation, a voltage of 40 kV and a current of 20 mA. The scanning rate was 5°/min over a 2θ range of 2–50°, with a sampling interval of 0.02°.

Results and Discussion

Effect of Viscosity and Weight Fraction of HPMC

Figure 1 shows the effect of viscosity of HPMC used as a component of the combined carriers on the dissolution profiles of nifedipine solid dispersions (1:3:1 weight ratio of drug:nicotinamide:HPMC). The aqueous solubility of nifedipine at 37 °C was 9.3 $\mu\text{g}/\text{ml}$. The drug dissolution was enhanced with a decrease in viscosity, *i.e.*, the molecular weight of HPMC. Similar findings have been reported for dissolution studies of sulfathiazole¹⁵⁾ and ibuprofen¹⁶⁾ from PVP solid dispersions prepared by the solvent method. No X-ray diffraction peaks of 7.9, 10.3 and 11.7° 2θ in crystalline nifedipine were recognized from the samples shown in Fig. 1, suggesting that the amorphous formation of nifedipine in these dispersions led to the supersaturation phenomenon of the drug in water.

The effect of polymer molecular weight on the drug dissolution of solid dispersions is multi-factorial. A polymer with a low molecular weight has a greater dissolution rate than one with a high molecular weight, which would result in enhancing the drug dissolution rate of solid dispersions. It is also possible that for equal weights, the lower the polymer molecular weight, the greater the number of polymer molecules available for improving the dissolution rate of a drug. Since the fusion method in this study included no mechanical stirring of the fused mixture, it is also possible that when both nifedipine and HPMC dissolve in the fused nicotinamide, the viscosity of the fused mixture decreases with an decrease in the polymer molecular weight, thereby increasing the homogeneity of each component, especially, the dispersibility of the amorphous drug in the polymer matrix. This could contribute to the supersaturation level of the drug in water. Consequently, the lowest viscosity grade (3 mm^2/s) of HPMC was used for the following

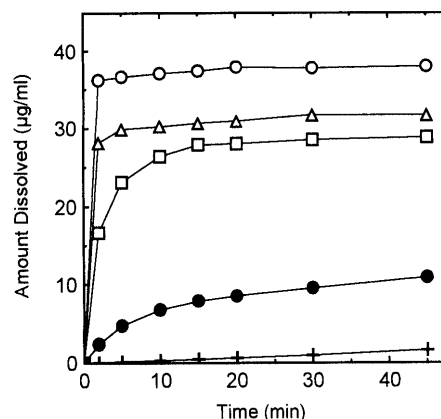


Fig. 1. Effect of HPMC Viscosity on the Dissolution of Nifedipine Solid Dispersions (Drug:Nicotinamide:HPMC=1:3:1)

+, nifedipine. HPMC viscosity: \circ , \bullet , 3 mm^2/s ; Δ , 6 mm^2/s ; \square , 15 mm^2/s . Open symbols, solid dispersions; closed symbol, physical mixture.

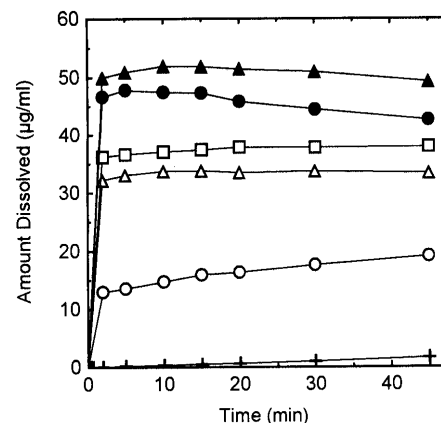


Fig. 2. Effect of HPMC Weight Fraction on the Dissolution of Nifedipine Solid Dispersions

+, nifedipine. Weight ratio of drug:nicotinamide:HPMC: \circ , 1:3:0.2; Δ , 1:3:0.5; \square , 1:3:1; \bullet , 1:3:2; \blacktriangle , 1:3:3. HPMC viscosity is 3 mm^2/s .

experiments.

The dissolution profiles of nifedipine solid dispersions containing different weight fractions of HPMC are shown in Fig. 2. In spite of the low solubilizing effect of HPMC on nifedipine,¹⁴⁾ the high ratio of the polymer increased the supersaturated concentration of the drug. From the X-ray diffraction analyses (Fig. 3), nifedipine was found to be present as an amorphous state even in the sample with a 1:3:0.2 weight ratio of drug:nicotinamide:HPMC. These results suggest that the good compatibility of HPMC, not only with nicotinamide but also with nifedipine,¹⁴⁾ is responsible for the formation of amorphous nifedipine in solid dispersions even with a low weight fraction of polymer. It can be assumed that as the HPMC ratio increases, the polymer coat thickness around the moleculars and/or colloidal particles of nifedipine, *i.e.*, the dispersibility of the amorphous drug in solid dispersions increases. This may encourage the inhibitory effect of HPMC on drug crystallization when solid dispersions dissolve in water, leading to a higher supersaturation level of the drug in water.

Save and Venkitachalam¹⁷⁾ demonstrated that a rapid cooling of the fused dispersion of nifedipine-PEG resulted in better dissolution properties than a slowly cooled

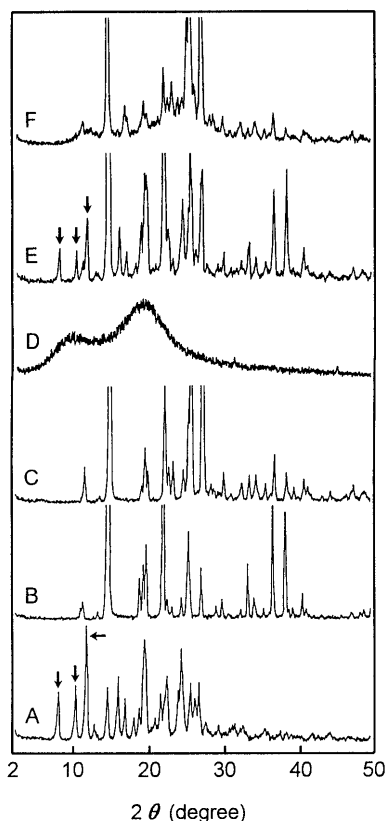


Fig. 3. Powder X-Ray Diffraction Patterns of Nifedipine Solid Dispersions (Drug: Nicotinamide: HPMC = 1:3:0.2)

A, nifedipine; B, nicotinamide; C, nicotinamide (fused sample); D, HPMC; E, physical mixture; F, solid dispersion. The arrows mark the positions for characteristic nifedipine lines. HPMC viscosity is 3 mm²/s.

dispersion. The effect of the cooling temperature on the dissolution profiles of nifedipine solid dispersions was thus confirmed using samples with a weight ratio from 1:3:0.2 to 1:3:1 for drug:nicotinamide:HPMC prepared by slow cooling at room temperature or rapid cooling in ice. However, there was no difference in the drug dissolution of the solid dispersions with the equal weight fraction of HPMC prepared under different cooling conditions. Considering that amorphous nifedipine formed even in the slowly cooled dispersion with the low weight fraction of the polymer, it seems probable that the rapid viscosity change in the fused mixture merely decreased the nicotinamide molecular ordering necessary for crystallization.

Effect of Solubility and Weight Fraction of Drug The effect of drug solubility on the dissolution profiles of solid dispersions was examined using nitrendipine as a dihydropyridine Ca-antagonist similar in chemical structure to nifedipine (Fig. 4). The aqueous solubility of nitrendipine at 37 °C was 1.8 µg/ml. Although the melting point of nitrendipine is higher than that of nicotinamide, it was soluble and miscible in liquid state nicotinamide at 140 °C; this permitted the preparation of nitrendipine solid dispersions with nicotinamide and HPMC. The dissolution profiles of nitrendipine solid dispersions were determined in water (Fig. 5). These solid dispersions produced a marked increase in the solubility of nitrendipine crystals; the drug concentration at 5 min was about 17-fold higher than the intrinsic drug solubility. Similarly to nifedipine,

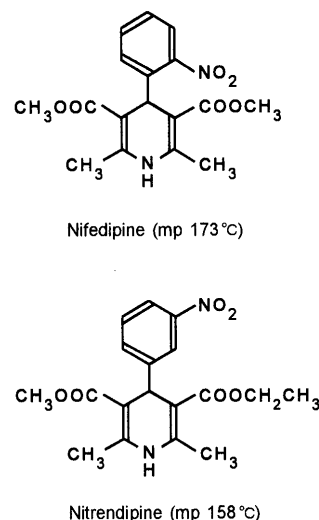


Fig. 4. Chemical Structures of Nifedipine and Nitrendipine
Melting points were measured by DSC.

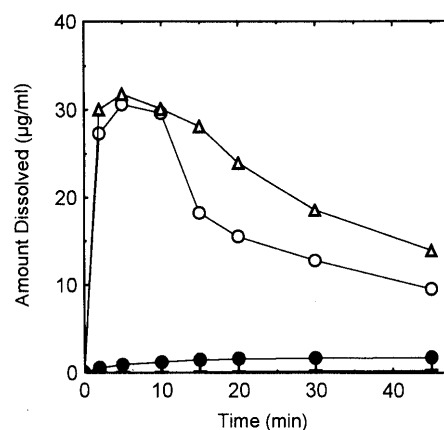


Fig. 5. Dissolution Profiles of Nitrendipine Solid Dispersions with Nicotinamide and HPMC

+, nitrendipine. Weight ratio of drug:nicotinamide:HPMC: ○, ●, 1:3:1; △, 1:3:3. Open symbols, solid dispersions; closed symbol, physical mixture. HPMC viscosity is 3 mm²/s.

the X-ray diffraction analyses proved that the supersaturation behavior of nitrendipine resulted from the formation of amorphous drug in solid dispersions. However, two dissolution characteristics of nifedipine solid dispersions (Fig. 2) were not noted: 1) an increase in the supersaturated concentration of the drug with increasing HPMC ratio, and 2) maintenance of the inhibitory effect of HPMC on the drug crystallization in water.

The precipitation rate of a solute from a supersaturated solution depends on two successive and largely independent processes, nucleation and growth of nuclei or crystallization. Once nuclei have formed, the second process, crystallization, begins. If C is the actual concentration of solute before crystallization has set in, and C_s is its solubility limit, $C - C_s$ is the supersaturation and $(C - C_s)/C_s$ is the relative supersaturation. The rates of nucleation and crystallization are said to be proportional to the relative supersaturation and the supersaturation, respectively.¹⁸⁾ In view of the solubility of drug crystals and the maximum supersaturated concentration of the drug (Figs. 2 and 5), the value of the relative supersaturation for nitrendipine is larger than

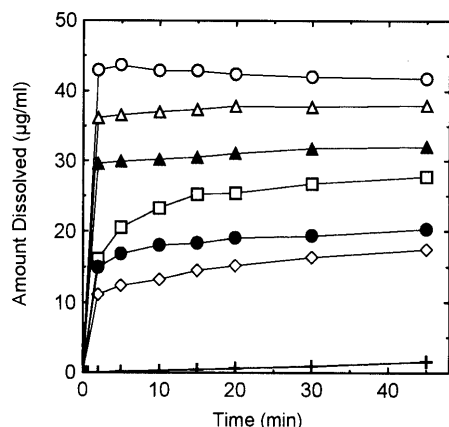


Fig. 6. Effect of Drug Weight Fraction on the Dissolution of Nifedipine Solid Dispersions

+, nifedipine. Weight ratio of drug:nicotinamide:HPMC: ○, 0.5:3:1; △, 1:3:1; □, 1.5:3:1; ◇, 2:3:1; ●, 2:3:2; ▲, 2:5:1. HPMC viscosity is 3 mm²/s.

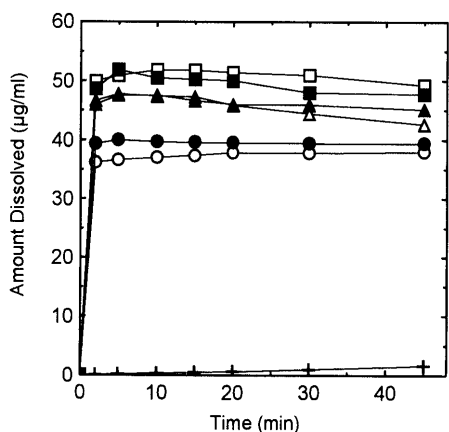


Fig. 7. Dissolution Profiles of Nifedipine Solid Dispersions Stored under 40 °C for 1 Month

+, nifedipine. Weight ratio of drug:nicotinamide:HPMC: ○, ●, 1:3:1; △, ▲, 1:3:2; □, ■, 1:3:3. Open symbols, initial; closed symbols, 40 °C. HPMC viscosity is 3 mm²/s.

that for nifedipine, suggesting that the nucleation rate of nitrendipine is higher than that of nifedipine.

Hasegawa *et al.*^{19,20} have shown that the inhibitory effect of non-ionic water-soluble cellulose polymers and anionic cellulose polymers (enteric-coating agents) on the crystallization of nifedipine from supersaturated solution was due to polymer adsorption on the solid-water interface at the stage when a hydrophobic drug-crystal surface was formed, and that the hydrophilic-hydrophobic property of the polymer affected the crystallization of nifedipine. The opposite situation, in which the hydrophobicity of a drug changes, will influence the inhibitory effect of a polymer on drug crystallization. Actually, compared with nifedipine, nitrendipine has a higher partition coefficient¹⁰ which is regarded as an indication of hydrophobicity and is related to drug solubility. Therefore, the dissolution properties of solid dispersions are affected by the aqueous solubility of the drug.

Figure 6 represents the dissolution profiles of nifedipine solid dispersions containing different weight fractions of drug. The supersaturated concentration of nifedipine decreased with increasing the drug ratio. The X-ray diffraction peak of 11.7° 2θ in crystalline nifedipine was

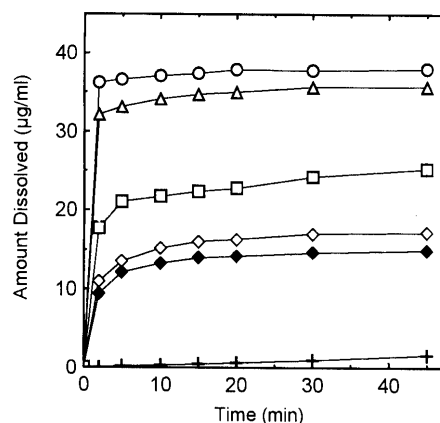


Fig. 8. Dissolution Profiles of Nifedipine Solid Dispersions Stored under 25 °C/60% R.H., 30 °C/60% R.H. or 40 °C/75% R.H. for 1 Month

+, nifedipine. Drug:nicotinamide:HPMC=1:3:1: ○, initial; △, 25 °C/60% R.H.; □, 30 °C/60% R.H.; ◇, 40 °C/75% R.H. Drug:nicotinamide:HPMC=1:3:3: ◆, 40 °C/75% R.H. HPMC viscosity is 3 mm²/s.

clearly observed for the sample with a 2:3:1 weight ratio of drug:nicotinamide:HPMC. Even during the preparation of this sample, all the drug dissolved in the fused nicotinamide, whereas the polymer did not. The higher the drug ratio, the less the polymer was soluble in the fused nicotinamide. This results from the higher compatibility of nicotinamide with nifedipine than HPMC.¹³ The decrease in the amount of HPMC dissolved in the fused nicotinamide might increase the drug crystallinity in solid dispersions, leading to a reduction in the drug supersaturation level. This is borne out by the finding that the increase in the ratio of nicotinamide but not HPMC was found to be fairly effective in improving drug dissolution (Fig. 6). Although an elevated heating temperature will increase the amount of HPMC which dissolves in the fused nicotinamide, this is closely linked to promoting the sublimation of nicotinamide and, thus, was not examined in this study.

Effect of Humidity during Storage Since molecules in an amorphous state are thermodynamically metastable compared with the crystalline state, the potential for the crystallization of amorphous drug in solid dispersions during storage is always present. The relative humidity is said to be an important factor influencing the solid state properties of amorphous systems. High humidities have induced changes resulting in a reduced dissolution for many solid dispersions.^{9,21}

The effect of humidity during storage on the dissolution profiles of nifedipine solid dispersions (a weight ratio from 1:3:1 to 1:3:3 for drug:nicotinamide:HPMC) was investigated. Figure 7 shows the dissolution profiles of the samples stored under 40 °C for 1 month. There was no difference in both the dissolution rate and the supersaturated concentration before and after storage. Figure 8 shows the dissolution profiles of the samples stored under 25 °C/60% R.H., 30 °C/60% R.H. or 40 °C/75% R.H. for 1 month. The supersaturated concentration of nifedipine for the solid dispersions (1:3:1 weight ratio of drug:nicotinamide:HPMC) were ranked as 25 °C/60% R.H. > 30 °C/60% R.H. > 40 °C/75% R.H. These results suggest that the presence of humidity played an impor-

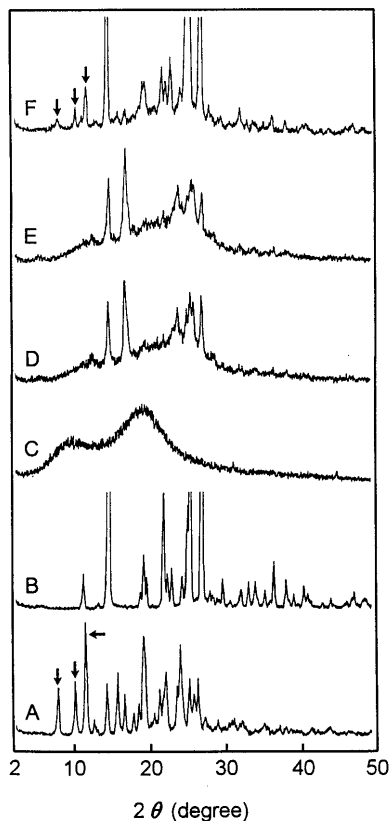


Fig. 9. Powder X-Ray Diffraction Patterns of Nifedipine Solid Dispersions Stored under 40°C or 40°C/75% R.H. for 1 Month (Drug : Nicotinamide : HPMC = 1 : 3 : 1)

A, nifedipine; B, nicotinamide (fused sample); C, HPMC. Solid dispersions: D, initial; E, 40°C; F, 40°C/75% R.H. The arrows mark the positions for characteristic nifedipine lines. HPMC viscosity is 3 mm²/s.

tant role in reducing the supersaturation level of drug. The reduced dissolution for the samples stored under 40°C/75% R.H. was not prevented by an increase in the HPMC ratio.

Figures 9 and 10 respectively show the X-ray diffraction patterns and the DSC thermograms of nifedipine solid dispersions (1:3:1 weight ratio of drug:nicotinamide:HPMC) stored under 40°C or 40°C/75% R.H. for 1 month. For the sample stored under 40°C (Fig. 9E), no major X-ray diffraction peaks in the crystalline nifedipine were detected, and the decreased peak intensity of nicotinamide was unchanged. For the sample stored under 40°C/75% R.H. (Fig. 9F), however, crystalline peaks of nifedipine and nicotinamide were apparent, indicating that both drug and nicotinamide were present as an almost crystalline state in this sample. On the DSC thermogram of the initial sample (Fig. 10D), two exothermic peaks attributable to the crystallization of amorphous nicotinamide (D-1) and the transformation from metastable crystals to stable ones (D-2) were observed.¹⁴⁾ These peaks were found in the sample stored under 40°C (Fig. 10E), whereas there was no exothermic peak for the sample stored under 40°C/75% R.H. (Fig. 10F). These findings suggest that absorbed moisture might induce the polymorphic transition of nicotinamide in solid dispersions.

The exothermic heat (ΔH_{exo}) on the DSC thermograms and the concentration of nifedipine released at 45 min in

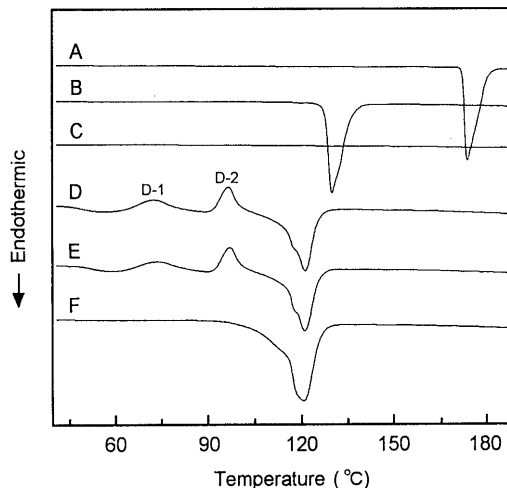


Fig. 10. The DSC Thermograms of Nifedipine Solid Dispersions Stored under 40°C or 40°C/75% R.H. for 1 Month (Drug : Nicotinamide : HPMC = 1 : 3 : 1)

A, nifedipine; B, nicotinamide; C, HPMC. Solid dispersions: D, initial; E, 40°C; F, 40°C/75% R.H. HPMC viscosity is 3 mm²/s.

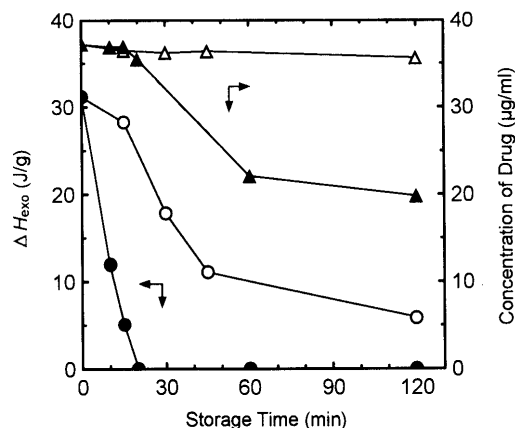


Fig. 11. Plots of the Exothermic Heat (ΔH_{exo}) on DSC Thermograms and the Concentration of Nifedipine Released from Solid Dispersions (Drug : Nicotinamide : HPMC = 1 : 3 : 1) against the Storage Time under 30°C/60% R.H. or 40°C/75% R.H.

○, ●, exothermic heat representing the total area of D-1 and D-2 peaks in Fig. 10; △, ▲, concentration of nifedipine released at 45 min in water. Open symbols, 30°C/60% R.H.; closed symbols, 40°C/75% R.H. HPMC viscosity is 3 mm²/s.

water were measured for the solid dispersions (1:3:1 weight ratio of drug : nicotinamide : HPMC) stored under 30°C/60% R.H. or 40°C/75% R.H. (Fig. 11). The ΔH_{exo} value gives the total area of the exothermic peaks (D-1 and D-2) shown in Fig. 10. This value decreased with storage time; after the D-1 peak disappeared, the D-2 peak decreased. Under 40°C/75% R.H., the ΔH_{exo} value decreased to zero by 20 min, and then the supersaturated concentration of the drug decreased with storage time. On the other hand, under 30°C/60% R.H., the ΔH_{exo} value was higher than that under 40°C/75% R.H., and the drug concentration hardly decrease for 2 h. These results suggest that, under humid conditions, the polymorphic transition of nicotinamide was more rapid than the decrease in the supersaturated concentration of nifedipine in water, i.e., the crystallization of amorphous drug in solid dispersions.

Studies by Sugimoto *et al.*¹¹⁾ show that, under humid conditions, amorphous nifedipine crystallizes in solid

dispersion granules using PVP, but is stable in granules using HPMC because HPMC is less hygroscopic than PVP. In this study, the use of HPMC together with nicotinamide as combined carriers, however, did not prevent amorphous nifedipine from crystallizing under humid conditions. It is well known that small amounts of absorbed moisture can plasticize amorphous solids, thereby leading to a decrease in the glass transition temperature (T_g) of amorphous solid and an increase in molecular mobility.²²⁾ Since the T_g value of nicotinamide is much lower than that of nifedipine (44 °C),¹⁴⁾ it is almost certain that an amorphous part of nicotinamide is liable to crystallize rather than amorphous drug under humid conditions. Assuming that nicotinamide is located close to amorphous nifedipine in the HPMC matrix because of its high compatibility with the drug, it is possible that the polymorphic transition of nicotinamide participates in an induction of the crystallization of amorphous nifedipine in solid dispersions.

In conclusion, for nifedipine solid dispersions, the low viscosity and high weight fraction of HPMC and the low weight fraction of nifedipine increased the supersaturated concentration of drug in water. The humidity during storage caused the crystallization of amorphous nifedipine in solid dispersions, thereby decreasing in the supersaturation level of drug. For nitrendipine solid dispersions, its lower aqueous solubility compared with nifedipine resulted in rapid drug crystallization from the supersaturated solution.

References

- 1) Sekiguchi K., Obi N., *Chem. Pharm. Bull.*, **9**, 866—872 (1961).
- 2) Chiou W. L., Riegelman S., *J. Pharm. Sci.*, **60**, 1281—1302 (1971).
- 3) Ford J. L., *Pharm. Acta Helv.*, **61**, 69—88 (1986).
- 4) Salama H. A., Ammar H. O., Kassem M. A., El-Ridy M. S., *Pharm. Ind.*, **39**, 290—293 (1977).
- 5) Geneidi A. S., Adel M. S., Shehata E., *Can. J. Pharm. Sci.*, **15**, 78—80 (1980).
- 6) Miralles M. J., McGinty J. W., Martin A., *J. Pharm. Sci.*, **71**, 302—304 (1982).
- 7) Fernandez J., Vila-Jato J. L., Blanco J., *Drug Dev. Ind. Pharm.*, **15**, 2491—2513 (1989).
- 8) Babar A., Jarowski C. I., *J. Pharm. Sci.*, **72**, 708—710 (1983).
- 9) Sugimoto I., Kuchiki A., Nakagawa H., Tohgo K., Kondo S., Iwane I., Takahashi K., *Drug Dev. Ind. Pharm.*, **6**, 137—160 (1980).
- 10) Diez I., Colom H., Moreno J., Obach R., Peraire C., Domenech J., *J. Pharm. Sci.*, **80**, 931—934 (1991).
- 11) Sugimoto I., Sasaki K., Kuchiki A., Ishihara T., Nakagawa H., *Chem. Pharm. Bull.*, **30**, 4479—4488 (1982).
- 12) Law S. L., Lo W. Y., Lin F. M., Chaing C. H., *Int. J. Pharm.*, **84**, 161—166 (1992).
- 13) Suzuki H., Sunada H., *Chem. Pharm. Bull.*, **45**, 1688—1693 (1997).
- 14) Suzuki H., Sunada H., *Chem. Pharm. Bull.*, **46**, 482—487 (1998).
- 15) Simonelli A. P., Mehta S. C., Higuchi W. I., *J. Pharm. Sci.*, **58**, 538—549 (1969).
- 16) Najib N. M., Suleiman M., Malakh A., *Int. J. Pharm.*, **32**, 229—236 (1986).
- 17) Save T., Venkitachalam P., *Drug Dev. Ind. Pharm.*, **18**, 1663—1679 (1992).
- 18) Gennaro A. R., "Remington's Pharmaceutical Sciences," 18th ed., Mack, Pennsylvania, 1990, pp. 275—276.
- 19) Hasegawa A., Kawamura R., Nakagawa H., Sugimoto I., *Yakugaku Zasshi*, **105**, 586—592 (1985).
- 20) Hasegawa A., Taguchi M., Suzuki R., Miyata T., Nakagawa H., Sugimoto I., *Chem. Pharm. Bull.*, **36**, 4941—4950 (1988).
- 21) Ford J. L., Rubinstein M. H., *Pharm. Acta Helv.*, **54**, 353—358 (1979).
- 22) Roos Y., Karel M., *J. Food Sci.*, **56**, 38—43 (1991).