Influence of Water-Soluble Polymers on the Dissolution of Nifedipine Solid Dispersions with Combined Carriers

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Received September 9, 1997; accepted November 7, 1997

The objective of this investigation was to clarify the influence of water-soluble polymers on the dissolution behavior of nifedipine from solid dispersions with combined carriers. All the solid dispersions of nifedipine were prepared by the fusion method using nicotinamide and 4 different water-soluble polymers, hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), partially hydrolyzed polyvinyl alcohol (PVA) and pullulan. HPMC, PVP or PVA dissolved in the fused liquid of nicotinamide and operated efficiently on the amorphous formation of nifedipine in solid dispersions. In dissolution studies, the drug concentration for these dispersions increased to more than twice intrinsic drug solubility. The rank order of the drug concentration was HPMC > PVP > PVA. However, since pullulan did not dissolve in the fused nicotinamide, nifedipine was present as a crystalline state in the solid dispersion; the supersaturation behavior of the drug was scarcely observed. The compatibility, namely, the solubility and miscibility, between nicotinamide or nifedipine and the polymers, was determined by differential scanning calorimetry using the mixtures treated with fusing and subsequent rapid cooling. Both HPMC and PVP exhibited high compatibility not only with nicotinamide but also with nifedipine. The crystallization behavior of nifedipine from a supersaturated solution containing nicotinamide or the polymers was studied. The inhibitory effect of HPMC or PVP for drug crystallization was evident, which would be related not to the solubilizing effect but to the adhesive force of the polymer for the drug. Therefore, it was understood that the use of a polymer with high compatibility and adhesion with nifedipine provides a high supersaturation level of the drug in dissolution. Further, the solubility parameter was found to be useful for selecting a suitable polymer as a component of combined carriers.

Key words nifedipine; solid dispersion; combined water-soluble carrier; compatibility; adhesion; solubility parameter

In the manufacture of pharmaceutical solids, common processes such as milling, spray drying and lyophilization can partially or completely transform crystalline drugs or excipients into metastable amorphous forms.[1] For drugs with low solubility in the crystalline state, the possibility of improving their solubility, dissolution rate and bioavailability based on the formation of an amorphous state is very attractive.[2] The rationale behind such a strategy is that a highly disordered amorphous material has a lower energetic barrier to overcome in order to enter a solution than a regularly structured crystalline solid. One way of producing amorphous pharmaceutical mixtures is to form solid dispersions by the use of polymers[3] and other glass-forming solids[4]; a widely reported technique is one in which the drug is dispersed within an inert carrier in the solid state by fusion or solvent processes.[5]

Nifedipine, a calcium-channel agent, is a poorly water-soluble drug, so that its bioavailability is low when it is orally administered in crystalline form.[6] Using nifedipine solid dispersions with non-ionic water-soluble polymers[7] or anionic polymers (enteric coating agents)[8] prepared by the solvent method, previous studies have shown that cellulosic polymers such as hydroxypropylmethylcellulose (HPMC) and HPMC phthalate act as good inhibitors of the drug crystallization from the amorphous state during the solvent removal process and the supersaturation behavior in dissolution studies. The authors have been developing a preparation of nifedipine solid dispersion with nicotinamide and HPMC as combined carriers by the fusion method.[9] Nicotinamide was important as a carrier because it dissolved both nifedipine and HPMC simultaneously at a lower temperature than the drug melting point. Furthermore, the presence of HPMC was efficient in forming the amorphous state of nifedipine in solid dispersion, leading to the supersaturation phenomenon in dissolution.

In this study, solid dispersions with nicotinamide and various water-soluble polymers as combined carriers were prepared by the fusion method, and their dissolution profiles were determined. Moreover, the compatibility between nicotinamide or nifedipine and the polymers under fusing and subsequent rapid cooling, as well as the drug crystallization from the supersaturated solution containing nicotinamide or the polymers, were investigated. The compatibility and adhesion between nifedipine and the polymers were also evaluated by the solubility parameter.

Experimental

Materials Nifedipine and nicotinamide, whose melting points (mp) are 173 and 129 °C, respectively,[9] were obtained from Wako Pure Chemical Industries Co., Ltd., Japan. HPMC (TC-5E, Shin-Etsu Chemical Industries Co., Ltd., Japan), polyvinylpyrrolidone (PVP K-30, BASF, Germany), partially hydrolyzed polyvinyl alcohol (PVA, 88% of saponification value, Nippon Synthetic Chemical Industry Co., Ltd., Japan) and pullulan (PI-20, Hayashibara Co., Ltd., Japan) were used. All other chemicals were of reagent grade. All experiments were carried out under subdued light to prevent light degradation of nifedipine.

Preparation of Solid Dispersion Systems The physical mixtures were prepared by grinding together accurately weighed quantities of nifedipine and the excipients, using a mortar and pestle, for 1—2 min. Solid dispersions of nifedipine (1 g) and nicotinamide (3—5 g) with or without a polymer (1 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 a hot-plate was measured by an infrared thermometer (COS Co., Ltd., Japan).

The fused samples were cooled at room temperature and solidified by placing them for 1—5 d in a desiccator over silica gel before pulverizing them in a coffee mill. In all experiments, the fused dispersions were sieved

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through 42 mesh and assayed for their drug content before use by HPLC at 237 nm.

Drug Solubility Studies Excess amounts of nifedipine were added to aqueous solutions (5 ml) containing various concentrations of nicotinamide, HPMC, PVP, PVA or pullulan. 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 (60 : 32: 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 solid dispersion containing 80 mg of nifedipine was placed in 900 ml of distilled water. Samples were filtered (0.2 μm) and assayed by HPLC at 237 nm.

Crystallization Studies Crystallization studies were performed using an apparatus for dissolution tests according to JP XIII (paddle method, 100 rpm) at 37 °C. A methanol solution (3 ml) containing 80 mg of nifedipine was added to an aqueous solution (900 ml) containing 240 mg of nicotinamide (0.027% w/v) or 80 mg of a polymer (0.009% w/v). Samples were filtered (0.2 μm) and assayed by HPLC at 237 nm.

Differential Scanning Calorimetry (DSC) DSC analyses were carried out on samples of about 10 mg under a dry nitrogen purge in a DSC 220CU (Seiko Denshi Kogyo Co., Ltd., Japan) fitted with an automated liquid nitrogen cooling accessory. The samples of solid dispersions were heated at a rate of 10 °C/min to 200 °C. Also, for examination of the compatibility between nicotinamide or nifedipine and the polymers, nicotinamide and nifedipine were heated at 10 °C/min to 160 and 200 °C, respectively, and the physical mixtures of nicotinamide–polymer and nifedipine–polymer (3 : 1 weight ratio of nicotinamide or nifedipine : polymer) were heated at 10 °C/min to 160 and 200 °C, respectively. These fused samples were subsequently cooled rapidly at 40 °C/min to −10 °C and then reheated at 10 °C/min to 200 °C.

Powder X-Ray Diffraction Analysis Powder X-ray diffraction analyses were performed with a Rigaku Geiger-Flex diffractometer (RadIIVC) using Ni-filtered, CuKα 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° and with a sampling interval of 0.02°.

Polymer Compatibility Studies The physical mixture of 3 : 1 weight ratio of nicotinamide : polymer was heated using a capillary melting point apparatus (B-530, Shibata Scientific Technology, Ltd., Japan) at a rate of 3 °C/min. Visual observations were made noting the temperature at which complete melting was accomplished, using a high-powered magnifying glass fixed on a mount over the sample. All determinations were made in triplicate.

Solubility Parameter Solubility parameters (δ) of nifedipine and polymers were calculated using Eq. 1, proposed by Fedors[10]:

$$\delta=(CED)^{1/2}=\left(\frac{\Delta E}{V}\right)^{1/2}=\left(\frac{\sum_i \Delta e_i}{\sum_i \Delta v_i}\right)^{1/2} \quad (1)$$

where CED, ΔE, V are the cohesive energy density, the energy of vaporization and the molar volume, respectively, and Δe_i, Δv_i are the additive atomic and group contributions for the energy of vaporization and the molar volume, respectively.

Results and Discussion

Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide and Various Polymers On the preparation of nifedipine solid dispersion with nicotinamide and HPMC as combined carriers, it is thought that the compatibility, that is, the solubility and miscibility, between nicotinamide and HPMC is important for producing the amorphous state of nifedipine in solid dispersion.[9] This means that if water-soluble polymers except for HPMC have good compatibility with the fused liquid of nicotinamide, they can be utilized as carriers for increasing the drug solubility.

In this study, PVP, PVA and pullulan were compared with HPMC as water-soluble polymers for combination with nicotinamide. HPMC, PVP and pullulan are essentially amorphous. The glass transition temperatures (T_g) for HPMC and PVP have been reported to be 156 and 185 °C, respectively.[11,12] PVA is semicrystalline; its values of T_g and melting point have been reported at 69 and 172 °C, respectively.[11] The compatibility of these polymers in the liquid state of nicotinamide was first confirmed by heating the physical mixtures of 3 : 1 weight ratio of nicotinamide : polymer (Table 1). The mixtures of nicotinamide–HPMC, –PVP or –PVA appeared to be soluble and miscible at about the melting point of nicotinamide. However, pullulan was hardly soluble in the fused liquid of nicotinamide even when heated up to about 180 °C. These results indicated that not only HPMC but also PVP and PVA might be available as components of combined carriers for the fused dispersions.

Table 1. Melting Points of Physical Mixtures of Nicotinamide and Polymer (Nicotinamide : Polymer = 3 : 1)

Polymer	mp (°C)
HPMC	130
PVP	125
PVA	133
Pullulan	—

The data were measured by a capillary melting point apparatus. —: Pullulan was hardly soluble.

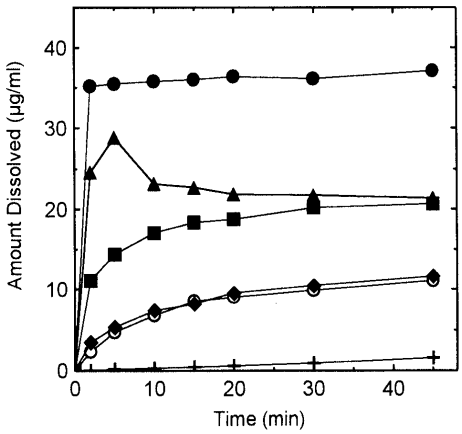

Fig. 1. Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide and Polymer (Drug : Nicotinamide : Polymer = 1 : 3 : 1)

+, nifedipine; ○, solid dispersions with nicotinamide (drug : nicotinamide = 1 : 5). Solid dispersions with nicotinamide and polymer: ●, HPMC; ▲, PVP; ■, PVA; ◆, pullulan.

Using these four types of polymers, nifedipine solid dispersions with combined carriers were prepared by the fusion method. When the physical mixtures of 1 : 3 : 1 weight ratio of drug : nicotinamide : HPMC, PVP, PVA or pullulan were heated at 140 °C, both the drug and HPMC, PVP or PVA were completely soluble in the liquid state of nicotinamide, as expected, whereas pullulan did not dissolve in the fused mixture of the drug and nicotinamide. Figure 1 shows the dissolution profiles of nifedipine from these solid dispersions in water. The concentration of nifedipine for solid dispersions including HPMC, PVP or PVA increased to more than twice intrinsic drug solubility (9.3 μg/ml in water at 37 °C). However, such super-

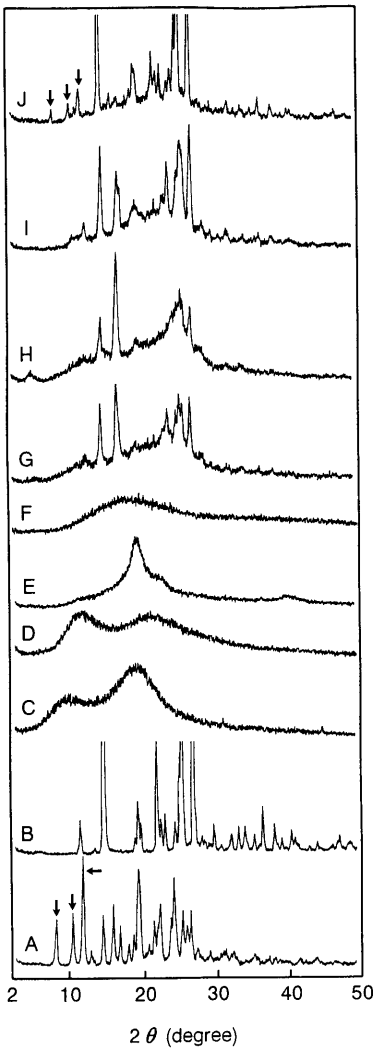

Fig. 2. Powder X-Ray Diffraction Patterns of Nifedipine Solid Dispersions with Nicotinamide and Polymer (Drug : Nicotinamide : Polymer = 1 : 3 : 1)

A, nifedipine; B, nicotinamide (fused sample); C, HPMC; D, PVP; E, PVA; F, pullulan. Solid dispersions with nicotinamide and polymer: G, HPMC; H, PVP; I, PVA; J, pullulan. The arrows mark the positions for characteristic nifedipine lines.

saturation of the drug was scarcely observed for the pullulan system. The observed rank order of the drug concentration was HPMC > PVP > PVA > pullulan. For the PVP system, the drug concentration decreased rapidly in the initial dissolution stage, then gradually attained a value that was nearly equal to the drug concentration of the PVA system. This finding is similar to the results reported by Sugimoto *et al.*,[6] who showed that the supersaturated concentration of nifedipine from coprecipitates with PVP prepared by the solvent method decreased gradually to the intrinsic solubility of the drug.

Figure 2 depicts the X-ray diffraction patterns of the solid dispersion samples. For the HPMC, PVP and PVA systems (Figs. 2G, H, I), peaks of 7.9, 10.3 and 11.7° 2θ in stable nifedipine crystals (Fig. 2A) and 7.1° 2θ in metastable nifedipine crystals reported by Hirayama *et al.*[13] were not detected. Moreover, the peak intensity of nicotinamide considerably decreased. These results suggested that the presence of these polymers in fused dispersions converted all crystalline nifedipine to an amorphous state and lowered the crystallinity of nicotinamide. However, major X-ray diffraction peaks of stable nifedipine crystals were recognized for the pullulan system (Fig. 2J). Therefore, the supersaturation behavior of nifedipine (Fig.1) evidently resulted from the formation of an amorphous drug in solid dispersions. It can be assumed that the polymer dissolved in the liquid state of nicotinamide causes an increase in viscosity by cooling, thereby inducing a corresponding reduction in the molecular motion of nifedipine and adequately acting as a very efficient steric barrier for the drug crystallization. It can be further expected that the supersaturation level of nifedipine is associated with the compatibility of the polymer with the drug in fused mixtures, the inhibitory effect of the polymer for drug crystallization in the dissolution medium, *etc.*

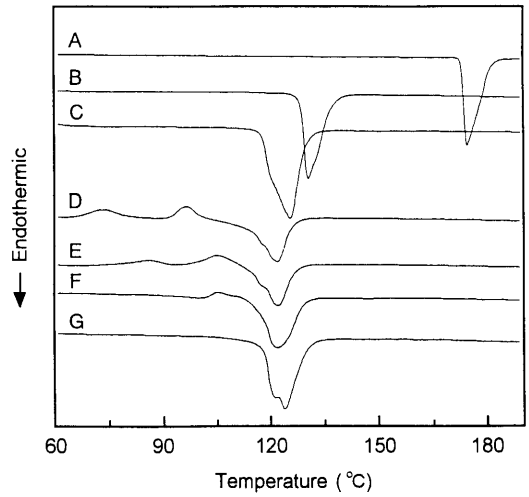

Fig. 3. The DSC Thermograms of Nifedipine Solid Dispersions with Nicotinamide and Polymer (Drug : Nicotinamide : Polymer = 1 : 3 : 1)

A, nifedipine; B, nicotinamide; C, solid dispersions with nicotinamide (drug : nicotinamide = 1 : 5). Solid dispersions with nicotinamide and polymer: D, HPMC; E, PVP; F, PVA; G, pullulan.

Figure 3 shows the DSC thermograms of solid dispersion samples. The pullulan system only gave an endothermic peak, similarly to the binary dispersion with nifedipine and nicotinamide. On the other hand, some exothermic peaks were observed for systems including the polymers other than pullulan. A reasonable explanation for these exothermic peaks is described hereafter.

Compatibility between Nicotinamide or Drug and Polymer under Fusing and Subsequent Rapid Cooling Since the crystallization of nifedipine was not entirely inhibited in fused dispersion with nicotinamide, as described in the previous paper,[9] the high compatibility between nifedipine and nicotinamide would not directly act to stabilize the disordered molecular state of the drug on the fusion method including a slow cooling at room temperature and a pulverization. In this study, the compatibility between nicotinamide or nifedipine and the polymers was assessed by DSC analyses of the physical mixture samples treated with fusing and subsequent rapid cooling (to −10 °C) processes.

Figure 4 shows the DSC thermograms for the treated mixtures of 3 : 1 weight ratio of nicotinamide : polymer. When heated to 160 °C, pullulan should be insoluble into

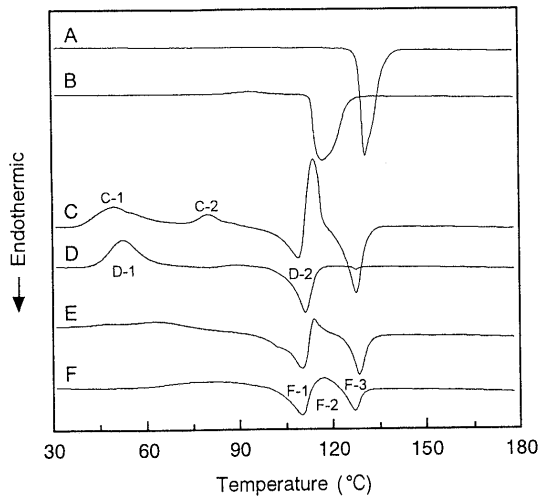

Fig. 4. The DSC Thermograms of Fused Mixtures of Nicotinamide and Polymer Obtained by Fusing and Subsequent Rapid Cooling (Nicotinamide : Polymer = 3 : 1)

A, nicotinamide; B, fused nicotinamide. Fused mixtures of nicotinamide and polymer: C, HPMC; D, PVP; E, PVA; F, pullulan.

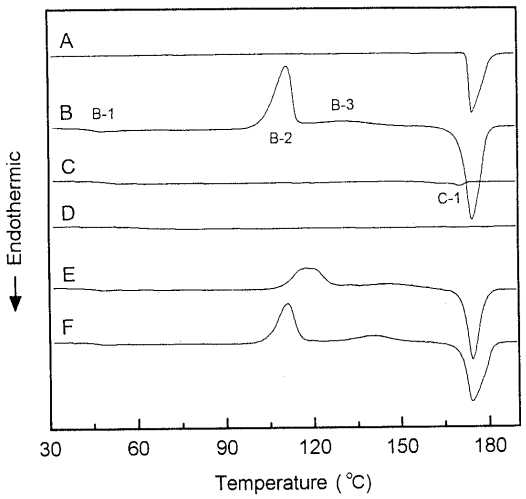

Fig. 5. The DSC Thermograms of Fused Mixtures of Nifedipine and Polymer Obtained by Fusing and Subsequent Rapid Cooling (Nifedipine : Polymer = 3 : 1)

A, nifedipine; B, fused nifedipine. Fused mixtures of nifedipine and polymer: C, HPMC; D, PVP; E, PVA; F, pullulan.

the liquid state of nicotinamide. Nevertheless, for the mixture treated with pullulan (Fig. 4F), the first endothermic (F-1), the exothermic (F-2) and the second endothermic (F-3) peaks were observed; these peaks might be due to the melting of a metastable crystalline form of nicotinamide, the crystallization of a stable crystalline form from the molten liquid of the metastable one, and the melting of the stable one, respectively. This finding implied that nicotinamide might be susceptible to polymorphic transition in an inner core or on the surface of polymer particles. For the mixture treated with HPMC (Fig. 4C), there were two evident exothermic peaks except for the peaks observed in the pullulan system; the first and second exothermic peaks (C-1, -2) would be due to the crystallization of amorphous nicotinamide and the transformation from a metastable crystalline form to a stable one, respectively. This proved that the two exothermic peaks detected in Fig. 3D might indicate the formation of amorphous and metastable crystalline nicotinamide in solid dispersions. For the mixture treated with PVP, only a pair of exothermic and endothermic peaks (Fig. 4D-1, -2) was observed; they would be based on the crystallization of amorphous nicotinamide and the melting of a metastable crystalline form, respectively. It was clear that PVP prevented nicotinamide from forming a stable crystalline form. The DSC thermogram for the mixture treated with PVA (Fig. 4E) was similar to that for the pullulan system. These results suggested that the compatibility of HPMC or PVP with nicotinamide was much higher than that of PVA.

The DSC thermograms for the treated mixtures of 3 : 1 weight ratio of nifedipine : polymer are exhibited in Fig. 5. Most of the treated nifedipine sample was amorphous (Fig. 5B). A break in the baseline at 44 °C (B-1) was ascribed to T_g of amorphous nifedipine. The exothermic peak at 112 °C (B-2) gave the heat of the crystallization of the amorphous form, which was very close, but opposite in sign, to the heat of fusion. A broadened exothermic peak at 130 °C (B-3) due to the transformation from a metastable crystalline form to a stable one[14] was slightly observed. As the treated nicotinamide sample was almost in a crystalline state (Fig. 4B), the T_g value of nicotinamide would be much lower than that of nifedipine. The peaks observed for the mixtures treated with PVA or pullulan (Figs. 5E, F) were analogous to those for the treated nifedipine sample, whereas such apparent peaks for the mixtures treated with HPMC or PVP (Figs. 5C, D) were almost not recognized. Also, when the physical mixtures were heated on a hot plate at about 200 °C, HPMC or PVP dissolved in the fused liquid of nifedipine, as did PVA to a certain extent, but pullulan was insoluble in it. These results demonstrated that the compatibility of HPMC or PVP with nifedipine was much higher than that of PVA. Considering the very slightly endothermic peak (C-1) observed for the mixture treated with HPMC, the rank order in the compatibility with nifedipine was PVP > HPMC > PVA > pullulan. It can be presumed that on the preparation of solid dispersions, the high compatibility of HPMC or PVP not only with nicotinamide but also with nifedipine enhances the homogeneity of each component in the fused mixture, that is, the dispersibility of the amorphous drug in the polymer matrix. Therefore, the amorphous drug in solid dispersions may be more strongly bound to HPMC or PVP than PVA, leading to a situation in which the amorphous drug is more subject to the inhibitory effect of HPMC or PVP on drug crystallization when the solid dispersions dissolve in water. This may be related to the higher supersaturation level of the drug in dissolution studies (Fig. 1).

Effect of Nicotinamide or Polymer on the Crystallization Behavior of Nifedipine from a Supersaturated Solution

The solubilizing effect of nicotinamide or the polymers for nifedipine was determined (Fig. 6). Nicotinamide, PVP and PVA were found to interact strongly with the equilibrium solubility of nifedipine in aqueous solution. Nicotinamide is well known as a hydrotropic agent, and the remarkable solubilizing effect of nicotinamide for nifedipine has been reported.[15] However, for HPMC and

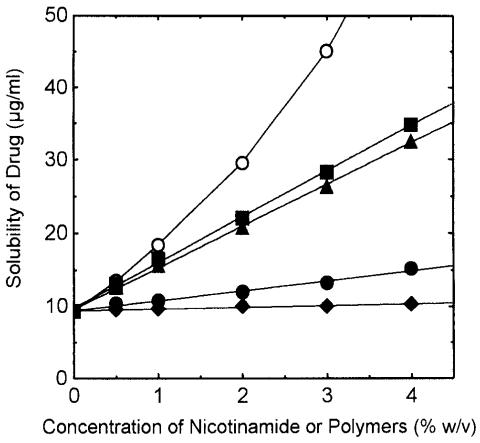

Fig. 6. Effect of Nicotinamide or Polymers on Aqueous Solubility of Nifedipine at 37 °C

○, nicotinamide; ●, HPMC; ▲, PVP; ■, PVA; ◆, pullulan.

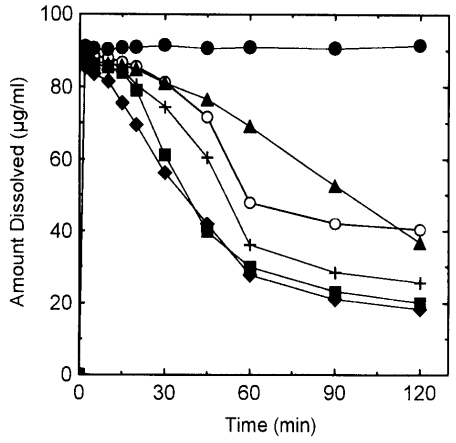

Fig. 7. Crystallization Behavior of Nifedipine in Nicotinamide or Polymer Aqueous Solutions at 37 °C

+, without additive; ○, nicotinamide; ●, HPMC; ▲, PVP; ■, PVA; ◆, pullulan.

pullulan, the increase in drug solubility was fairly low within the concentration range studied.

The crystallization behavior of nifedipine from a supersaturated solution containing nicotinamide or the polymers was investigated (Fig. 7). The crystallization of nifedipine was completely inhibited in the solution with HPMC. The inhibitory effect of PVP was also observed, but it was weaker than that of HPMC. On the other hand, PVA and pullulan did not entirely inhibit the drug crystallization. The concentration of nifedipine in the solution with PVA or pullulan decreased faster than that without the polymer until 60 min. Particularly, the presence of pullulan induced the drug crystallization most rapidly. The rank order of the inhibitory effect of the polymers for the drug crystallization was HPMC > PVP > PVA > pullulan. Also, nicotinamide exhibited a lower inhibitory effect than PVP. Therefore, it was supposed that the solubilizing effect for nifedipine was not closely related to the inhibitory effect for drug crystallization.

Simonelli *et al.*[16] proposed that the inhibition point of crystal growth of sulfathiazole depended on the relative rates of transport of the drug and PVP to the crystal surface from the bulk solution, and that the polymer formed a non-condensed net-like film over the crystal surface of the drug to inhibit the crystal growth. The crystallization behavior of nifedipine from the supersaturated solution with HPMC or PVP in Fig. 7 is consistent with the results revealed by Hasegawa *et al.*,[17] who concluded that the adsorption of more hydrophobic water-soluble cellulose polymers than PVP easily occurred at the solid-water interface at the stage in which a hydrophobic drug crystal surface was formed, indicating that it is a main factor in inhibiting drug crystallization. The polymer adsorption on a hydrophobic surface was well discussed in some studies on the stabilization of suspensions.[18,19] Consequently, it can be assumed that the hydrophilic–hydrophobic property of a polymer affects the crystallization of nifedipine through a physical interaction, namely, an adhesive force, between the drug and the polymer. This force should be necessary to obtain the higher supersaturation level of the drug in dissolution studies (Fig. 1).

Table 2. Solubility Parameters (δ) of Nifedipine and Polymers

No.	Substance	δ (MPa$^{1/2}$)	$\lvert\delta_1{}^{a)}-\delta_{2-5}\rvert$
1	Nifedipine	22.9	—
2	HPMC[b]	26.8	3.9
3	PVP	25.0	2.1
4	PVA[c]	31.3	8.4
5	Pullulan	34.1	11.2

Solubility parameters were estimated by the group contribution method of Fedors.[10] *a*) No. of substances. *b*) Calculated on the structure of a repeating unit given by Rowe.[22] *c*) Calculated as an 88 : 12 repeating unit ratio of $-CH_2CH(OH)-$: $-CH_2CH(OCOCH_3)-$.

Evaluation of the Interaction between Nifedipine and Polymer by the Solubility Parameter As noted above, it is contemplated that the high compatibility and adhesion between nifedipine and a polymer may give the high supersaturation level of the drug. So, attempts have been made to describe these properties between nifedipine and the polymers using solubility parameter techniques. The solubility parameter, δ, of the form of Eq. 1 suggests a link between the phenomena of "solubility" or "miscibility" and those of "cohesion" and "vaporization." The basis of the solubility parameter approach to interactions may be stated as follows. A material with a high δ value requires more energy on mutual dispersal than is gained by mixing it with a material of a low δ value, so immiscibility results. On the other hand, two materials with similar δ values gain sufficient energy on mutual dispersion to permit mixing. This concept is attractive for practical applications, *e.g.*, to explain the affinities of organic solvents in biological systems,[20] as well as the interactions between polymers and solvents.[21]

Table 2 displays the solubility parameters of nifedipine and the polymers estimated by the group contribution method of Fedors.[10] This method is generally applicable to polymers as well as to low molecular weight liquids, considering the smallest repeating unit of the polymer and the number of main chain skeletal atoms in it. Particularly, the δ value of HPMC was calculated based on the structure of a repeating unit given by Rowe,[22] and the δ value of PVA was calculated using a saponification value of 88%, that is, an 88 : 12 repeating unit ratio of $-CH_2CH(OH)-$:

$-CH_2CH(OCOCH_3)-$. From the difference in δ values, it was thought that the rank order in the interactions between nifedipine and the polymers was PVP > HPMC > PVA > pullulan.

The order of the compatibility level between nifedipine and the polymers under the rapid cooling process (Fig. 5) was PVP > HPMC > PVA > pullulan. This is consistent with that of the interaction level obtained from the δ values. For the crystallization of nifedipine from the supersaturated solution (Fig. 7), the order of the inhibitory effect was HPMC > PVP > PVA > pullulan. This is in agreement with that of the interaction level described above, except for HPMC > PVP. On the method of Fedors, the δ value is calculated using the group contributions applicable at a temperature of 25 °C. However, the temperature under the cooling process was not constant, and the crystallization studies were carried out at 37 °C in this study. Burrell[23] observed that in the case of substances having δ values ranging from 14.4 to 19.2 $MPa^{1/2}$, the average decrease in δ for an increase in temperature of 1 °C was 0.029 $MPa^{1/2}$. Although it is an average value for a limited number of compounds and may not be applicable to all types of compounds and experimental conditions, it certainly indicates that the change in δ with temperature is not very significant. In view of these considerations, it is suggested that the solubility parameter will be available as an indication to select polymers with high compatibility and adhesion with nifedipine.

In conclusion, when nicotinamide and either HPMC, PVP, PVA or pullulan were used as combined carriers, amorphous nifedipine was obtained in solid dispersions with HPMC, PVP or PVA, resulting in the supersaturation behavior of the drug in dissolution studies. Both HPMC and PVP exhibited higher compatibility not only with nicotinamide but also with nifedipine, in addition to higher inhibitory effect for the drug crystallization than PVA. Thus, a polymer with high compatibility and adhesion with nifedipine might lead to the high supersaturation level of the drug in dissolution. The solubility parameter was found to be useful for selecting a suitable polymer as a component of combined carriers.

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