Miscibility of Nifedipine and Hydrophilic Polymers as Measured by ^{1}H-NMR Spin–Lattice Relaxation

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The miscibility of a drug with excipients in solid dispersions is considered to be one of the most important factors for preparation of stable amorphous solid dispersions. The purpose of the present study was to elucidate the feasibility of ^{1}H-NMR spin–lattice relaxation measurements to assess the miscibility of a drug with excipients. Solid dispersions of nifedipine with the hydrophilic polymers poly(vinylpyrrolidone) (PVP), hydroxypropylmethylcellulose (HPMC) and α,β-poly(N-5-hydroxypentyl)-L-aspartamide (PHPA) with various weight ratios were prepared by spray drying, and the spin–lattice relaxation decay of the solid dispersions in a laboratory frame (T_1 decay) and in a rotating frame ($T_{1\rho}$ decay) were measured. $T_{1\rho}$ decay of nifedipine–PVP solid dispersions (3 : 7, 5 : 5 and 7 : 3) was describable with a mono-exponential equation, whereas $T_{1\rho}$ decay of nifedipine–PHPA solid dispersions (3 : 7, 4 : 6 and 5 : 5) was describable with a bi-exponential equation. Because a mono-exponential $T_{1\rho}$ decay indicates that the domain sizes of nifedipine and polymer in solid dispersion are less than several nm, it is speculated that nifedipine is miscible with PVP but not miscible with PHPA. All the nifedipine–PVP solid dispersions studied showed a single glass transition temperature (T_g), whereas two glass transitions were observed for the nifedipine–PHPA solid dispersion (3 : 7), thus supporting the above speculation. For nifedipine–HPMC solid dispersions (3 : 7 and 5 : 5), the miscibility of nifedipine and HPMC could not be determined by DSC measurements due to the lack of obviously evident T_g. In contrast, ^{1}H-NMR spin–lattice relaxation measurements showed that nifedipine and HPMC are miscible, since $T_{1\rho}$ decay of the solid dispersions (3 : 7, 5 : 5 and 7 : 3) was describable with a mono-exponential equation. These results indicate that ^{1}H-NMR spin–lattice relaxation measurements are useful for assessing the miscibility of a drug and an excipient in solid dispersions.

Key words miscibility; solid dispersion; spin diffusion; spin–lattice relaxation time; amorphous

Preparing solid dispersions of a poorly soluble drug with water-soluble polymers is a promising method for improving the dissolution characteristics and bioavailability of the drug. Miscibility between a drug and a polymer is considered to be one of the most important factors for obtaining stable solid dispersions.[1]

Miscibility of a drug with a polymer is usually evaluated by differential scanning calorimetry (DSC).[2—6] When a solid dispersion shows a single glass transition temperature (T_g) between the T_g values of the drug and the polymer, the drug and the polymer are considered to be miscible within the detection limit of DSC.[7] This method is applicable to a solid dispersion when T_g of the drug and the polymer can be detected clearly, and the temperature ranges of the base line shift due to glass transition do not overlap each other.

The interaction parameter χ of the Flory–Huggins equation provides a measure of miscibility.[8,9] Crowly and Zografi measured the water vapor sorption isotherm of indomethacin solid dispersions with PVP and reported that the estimated interaction parameter χ between indomethacin and PVP was greater than 0.5, indicating that indomethacin and PVP are immiscible in terms of χ value.[8] Although this method is excellent in being able to provide a quantitative measure of miscibility, it may be difficult to apply to unstable amorphous drugs, which crystallize during measurement of water vapor sorption.

A method that can be used as an alternative to DSC or measurement of the interaction parameter χ is analysis of the ^{1}H spin–lattice relaxation process of solid dispersions, which has been reported in the fields of polymer alloy and polymer blends. If two polymers are miscible, the relaxation decay of the mixture is describable by a mono-exponential equation, whereas if they are not miscible, relaxation decay is describable by a bi-exponential equation.[10,11]

In this paper, the feasibility of ^{1}H spin–lattice relaxation measurements for evaluating the miscibility of a drug and polymers in solid dispersions was studied. Nifedipine solid dispersions with PVP, HPMC and α,β-poly(N-5-hydroxypentyl)-L-aspartamide (PHPA) were used as model solid dispersions, and the miscibility measured by ^{1}H-NMR was compared with that measured by DSC. The dissolution profiles of nifedipine from PVP solid dispersions were compared with those from PHPA solid dispersions to discuss the effects of miscibility on the dissolution rate of nifedipine.

Theory ^{1}H spin–lattice relaxation rates of respective spins in a solid are usually averaged by a process called spin diffusion. Spin diffusion is the equilibration process of polarizations of spins at different local sites through mutual exchange of magnetization. [1]H spin–lattice relaxation decay for a single-phase solid is describable by a mono-exponential equation with a relaxation rate that is averaged by spin diffusion. When a solid consists of two phases, the spin–lattice relaxation decay is describable by a mono-exponential or a bi-exponential equation depending on both the domain size of each phase and the effective diffusion length (L). L is expressed as follows:

$$L=\sqrt{6Dt} \tag{1}$$

where D is the spin diffusion coefficient, and t is the diffusion time. D is a function of the distance between neighboring proton spins and spin–spin relaxation time (T_2), and is reported to be approximately $10^{-12} \text{ cm}^2 \text{ s}^{-1}$ for organic polymers. Typical spin–lattice relaxation time in a laboratory frame (T_1) and that in a rotating frame ($T_{1\rho}$) are of the order of 1 s and 10 ms, respectively. When these values for t were inserted in Eq. 1, effective diffusion lengths of approximately 50 nm and 5 nm were obtained for T_1 and $T_{1\rho}$, respectively. Depending on the domain size of each phase in a solid, the following 3 cases can be expected: (1) when the domain is smaller than about 5 nm, both the spin–lattice relaxation decay patterns in a laboratory frame (T_1 decay) and in a rotating frame ($T_{1\rho}$ decay) are describable by a mono-exponential equation; (2) when the domain size is about 5 to 50 nm, the $T_{1\rho}$ decay pattern is describable by a bi-exponential equation, whereas the T_1 decay pattern is describable by a mono-exponential equation; and (3) when the domain size is larger than about 50 nm, both the T_1 and $T_{1\rho}$ decay patterns are describable by a bi-exponential equation. When the $T_{1\rho}$ decay is describable by a mono-exponential equation, the solid can be considered as a single phase within the detection limit of NMR. T_1 and $T_{1\rho}$ decay thus provide information on miscibility of a drug and a polymer excipient.[11]

Experimental

Materials Nifedipine (N-7634), PVP (PVP-40) and HPMC (H-3785) were purchased from Sigma (Newcastle, DE, U.S.A.). PHPA was synthesized *via* polycondensation of L-aspartic acid.[12] Phenobarbital was obtained from sodium phenobarbital (Wako Pure Chemical Ind., Osaka) by neutralization and subsequent re-crystallization from acetone solutions as described previously.[13] Other chemicals used were of reagent grade. Nifedipine solid dispersions with PVP, HPMC and PHPA were prepared by a solvent evaporation method using a model GS-310 spray dryer (Yamato, Tokyo, Japan). Drying conditions are summarized in Table 1. The solid dispersions obtained were confirmed to be amorphous from microscopic observation under polarized light. Although the drying conditions were not optimized, 50 to 90% of the solid dispersions were obtained. Amorphous nifedipine was prepared by melting and subsequent rapid cooling as reported previously.[14]

DSC T_g of nifedipine–PVP and nifedipine–HPMC solid dispersions was measured by modulated temperature DSC using a model 2920 differential scanning calorimeter and a refrigerator cooling system (TA Instruments, Newcastle, DE, U.S.A.). The modulated temperature program used was a modulation amplitude of $\pm 0.5 \,^{\circ}\text{C}$, a modulation period of 100 s and an underlying heating rate of 1 °C/min. For nifedipine–PHPA solid dispersions, T_g was measured at a scanning rate of 20 °C/min using a conventional heating program. Temperature calibration of the instrument was carried out using indium.

NMR T_1 decay and $T_{1\rho}$ decay were measured using a model JNM-MU25 pulsed NMR spectrometer (JEOL DATUM, Tokyo, Japan). The inversion recovery pulse sequence was used to measure T_1 decay. $T_{1\rho}$ decay was measured in a spin locking field of 10 G. All measurements were carried out at 27 °C.

X-Ray Powder Diffraction X-Ray powder diffraction patterns of solid dispersions were obtained using a model RINT-TTR II X-ray diffractometer (Rigaku Denki, Tokyo) with Cu$K\alpha$ radiation (50 kV, 300 mA) at a scanning rate of 4 °C/min from $2\theta = 5°$ to $40°$.

Nifedipine Dissolution Profile Nifedipine–PVP (3 : 7) and nifedipine–PHPA (3 : 7) solid dispersions containing 100 mg of nifedipine were made into disks with a diameter of 2 cm at a pressure of 20 kN. Each disk was mounted on the rotor of the dissolution apparatus and the side surface of the disk was covered with a Teflon film. The sample was rotated at a rate of 100 rpm in 900 ml of distilled water at 37 °C. The amount of nifedipine dissolved was measured using a model DM-3100 solution monitor (Otsuka Electronics, Tokyo).

Results and Discussion

Figure 1 shows typical T_1 and $T_{1\rho}$ decay patterns for the

Table 1. Conditions of Spray Drying

Drug	Polymer	Solvent[a]	Outlet temperature (°C)	Atomizer gas (l/min)	Feeding rate (ml/min)
Nifedipine–PHPA					
0	10	A	68	7	5
3	7	A	68	7	3
4	6	A	68	7	3
5	5	A	68	7	3
Phenobarbital–PHPA					
3	7	A	68	7	3
Nifedipine–PVP					
0	10	A	90	9	10
3	7	A	90	9	10
5	5	A	90	9	10
7	3	A	68	7	3
Nifedipine–HPMC					
0	10	B	38	11	3
3	7	B	38	11	2
5	5	B	38	11	2
7	3	B	38	11	4

a) Solvent A, ethanol; solvent B, ethanol–CH$_2$Cl$_2$ (1 : 1). Flow rate of drying gas was adjusted to 0.5 m^3/min.
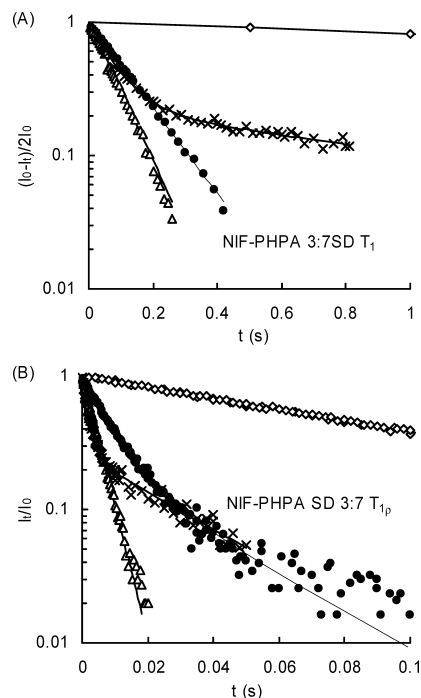

Fig. 1. T_1 (A) and $T_{1\rho}$ (B) Decay Patterns for Amorphous Nifedipine ($\diamond$), Amorphous PHPA ($\triangle$), Physical Mixture ($\times$) and Solid Dispersions ($\bullet$) of Nifedipine and PHPA

solid dispersion and the physical mixture of nifedipine and PHPA (3 : 7). T_1 and $T_{1\rho}$ decay patterns were mono-exponential for both amorphous nifedipine and PHPA. The T_1 and $T_{1\rho}$ values of nifedipine were 5.0 s and 104 ms, respectively, and those of PHPA were 0.084 s and 4.4 ms, respectively. The physical mixture of nifedipine and PHPA (3 : 7) exhibited bi-exponential T_1 and $T_{1\rho}$ decay with the relaxation time of each component, indicating that the particle sizes of nifedipine and PHPA in the physical mixture are much larger than the effective diffusion length (approximately 5 nm and 50 nm for $T_{1\rho}$ and T_1 decay, respectively). In contrast to the physical
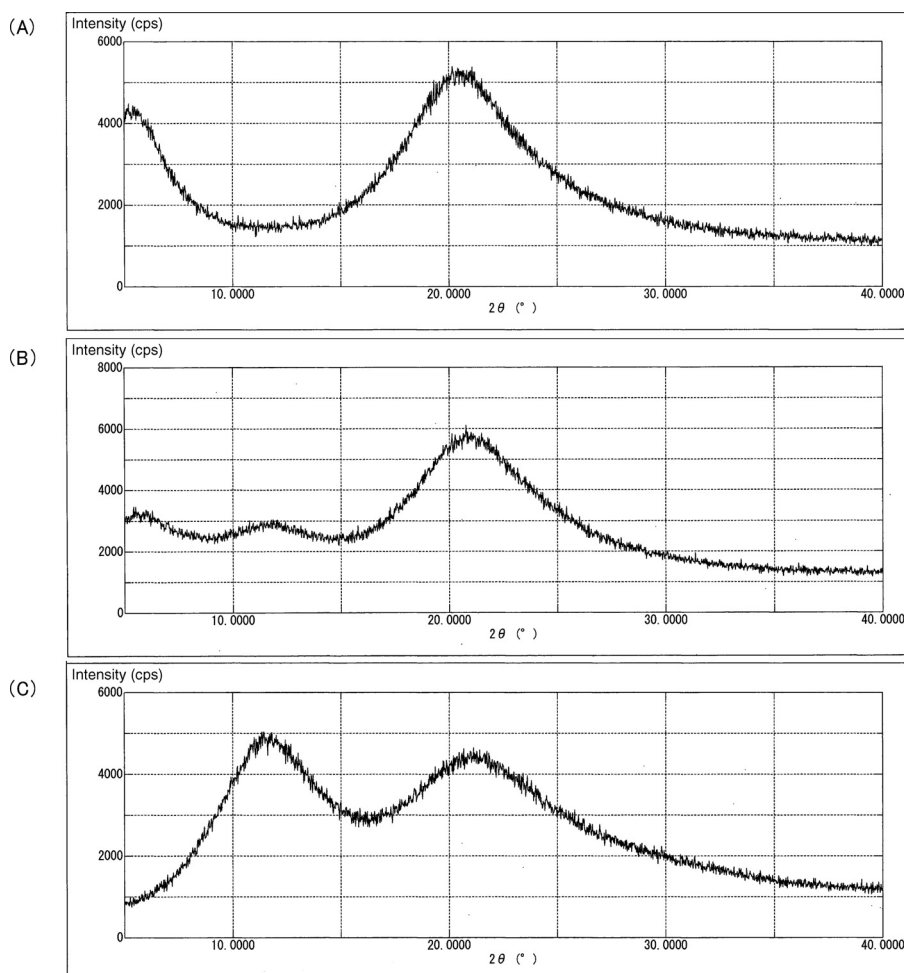
Fig. 2. Powder X-Ray Diffraction Patterns of PHPA (A), Nifedipine–PHPA (3 : 7) (B) and Nifedipine–PVP Solid Dispersions (3 : 7) (C)

mixture, the solid dispersion (3 : 7) showed mono-exponential T_1 decay, whereas bi-exponential $T_{1\rho}$ decay. These results indicate that nifedipine and PHPA are immiscible and that domains 5 to 50 nm in size are present in the solid dispersion. The nifedipine–PHPA solid dispersions (4 : 6 and 5 : 5) and the phenobarbital–PHPA solid dispersions (3 : 7) also exhibited bi-exponential $T_{1\rho}$ decay (data not shown). Figure 2 shows powder X-ray diffraction patterns of the nifedipine–PHPA and nifedipine–PVP solid dispersions. The observed halo pattern indicates that nifedipine in the PHPA dispersions is amorphous at the detection limit of powder X-ray diffractometry.

DSC data supported the contention that nifedipine and PHPA are immiscible. Figure 3 shows typical DSC traces for nifedipine–PHPA solid dispersions. The nifedipine–PHPA solid dispersion (3 : 7) showed glass transition at approximately 50 °C, corresponding to the T_g of amorphous nifedipine, and at approximately 75 °C, indicating that there are both an amorphous nifedipine phase and an amorphous nifedipine–PHPA phase in the solid dispersion. These DSC data indicate that amorphous nifedipine and PHPA are partially immiscible at this weight ratio. For the nifedipine–PHPA solid dispersion (5 : 5), T_g of the amorphous nifedipine–PHPA phase was not clearly observed because of the detection limit of DSC, suggesting that ^{1}H-NMR relaxation measurements can detect immiscibility of drugs and polymers more sensi-
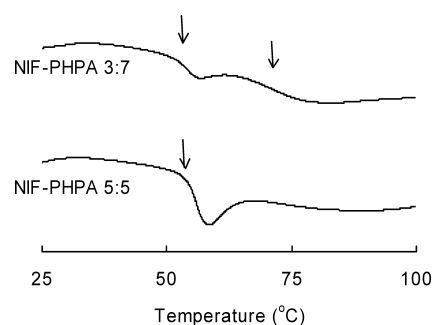

Fig. 3. DSC Traces for Nifedipine–PHPA Solid Dispersions
Arrows represent T_g.

tively than DSC. DSC data suggest that the nifedipine–PHPA solid dispersion (3 : 7) consists of pure amorphous nifedipine phase and amorphous nifedipine–PHPA phase. NMR data may support this speculation. As shown in Fig. 1B, initial $T_{1\rho}$ decay of the solid dispersion was slower than that of the physical mixture or pure PHPA. This slow relaxation rate of the solid dispersion may indicate that the relaxation rate of PHPA protons was decreased by spin diffusion with nifedipine protons existing near PHPA molecules; in other words, nifedipine–PHPA phase is considered to exist in the solid dispersion. The effect of weight ratios on the $T_{1\rho}$ decay of nifedipine–PHPA solid dispersions needs to examine in order
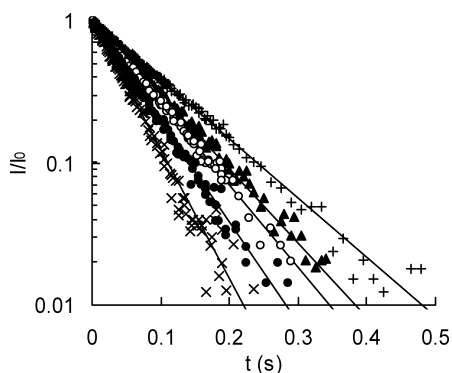
Fig. 4. $T_{1\rho}$ Decay Patterns for Nifedipine (+), PVP (×), and Nifedipine–PVP Solid Dispersions of 7 : 3 (▲), 5 : 5 (○), and 3 : 7 (●)
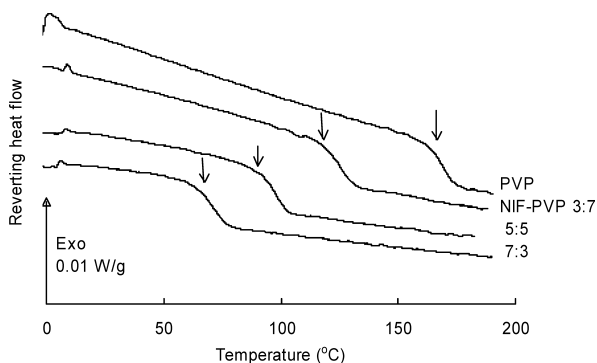

Fig. 6. DSC Traces for Nifedipine–HPMC Solid Dispersions

Arrows represent T_g.

Fig. 5. DSC Traces for Nifedipine–PVP Solid Dispersions

Arrows represent T_g.

Fig. 7. $T_{1\rho}$ Decay Patterns for Nifedipine (+), HPMC (×), and Nifedipine–HPMC Solid Dispersions of 7 : 3 (▲), 5 : 5 (○), and 3 : 7 (●)

Fig. 8. Dissolution Profiles of Nifedipine from Solid Dispersions with PVP and PHPA

to confirm the phase structure of the solid dispersion, since the molecular mobility of PHPA may different from that of pure PHPA.

In contrast to PHPA, PVP and nifedipine in the solid dispersions (3 : 7, 5 : 5 and 7 : 3) were considered to be miscible from $T_{1\rho}$ relaxation and DSC measurements. Figure 4 shows typical $T_{1\rho}$ decay of the solid dispersions. All the solid dispersions studied exhibited mono-exponential $T_{1\rho}$ decay, whereas physical mixtures of amorphous nifedipine and PVP (3 : 7, 5 : 5 and 7 : 3) exhibited bi-exponential decay (data not shown). Figure 5 shows DSC traces for the nifedipine–PVP solid dispersions. A single glass transition was observed for all of the solid dispersions studied. These data indicate that nifedipine and PVP are miscible at the detection limit of NMR and DSC.

For nifedipine–HPMC solid dispersions, the miscibility of nifedipine and HPMC could not be assessed from T_g measurements. As shown in Fig. 6, base line shift due to glass transition was not obvious for the nifedipine–HPMC solid dispersions (3 : 7 and 5 : 5). In contrast to DSC measurements, $T_{1\rho}$ relaxation measurements clearly indicated that nifedipine is miscible with HPMC in the solid dispersions. As shown in Fig. 7, all the nifedipine–HPMC solid dispersions studied showed mono-exponential $T_{1\rho}$ decay. In contrast to the solid dispersions, physical mixtures of amorphous nifedipine and HPMC (3 : 7, 5 : 5 and 7 : 3) exhibited bi-exponential decay (data not shown). These data indicate that NMR can detect miscibility of a drug and an excipient more sensitively than DSC.

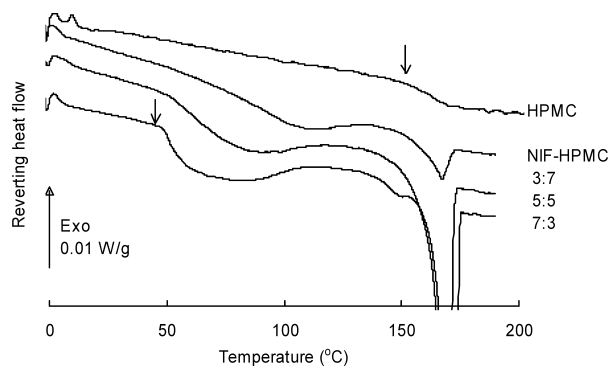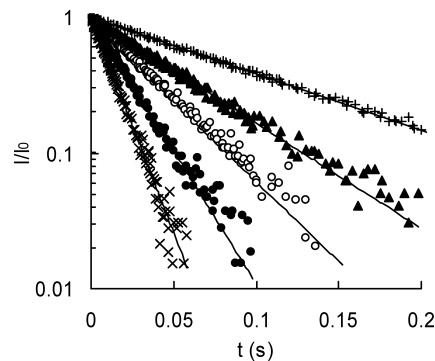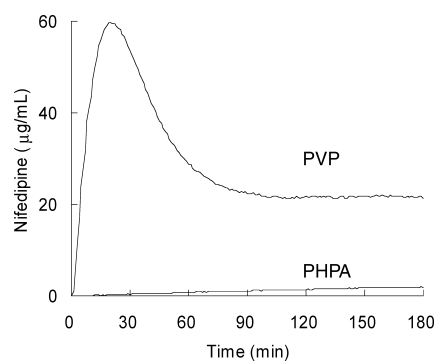Figure 8 shows the dissolution profile of nifedipine from solid dispersions with PVP and PHPA. The nifedipine–PVP solid dispersion exhibited rapid dissolition of nifedipine with super-saturation. In contrast, only a minimal amount of nifedipine was dissolved from the nifedipine–PHPA solid dispersion.

In conclusion, ^{1}H- NMR spin–lattice relaxation measurements were found to be useful for assessing the miscibility of a drug and excipients in solid dispersions, especially, when T_g is not clearly detected by DSC. The lower miscibility of PHPA than that of PVP and HPMC with hydrophobic drugs is considered due to the more hydrophilic nature of PHPA.

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