Solid-State Interaction of Ibuprofen with Polyvinylpyrrolidone

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We found that ibuprofen (IPF) became amorphous when the crystalline powder was merely mixed with polyvinylpyrrolidone (PVP), using a test tube mixer, and allowed to stand at appropriate temperatures. The crystallinity of the mixture was evaluated from the X-ray diffraction spectra by Ruland's method. The degree of decrease in crystallinity (A), defined as the ratio of the decrease in crystallinity to the value calculated by assuming additivity of crystallinity, increased gradually with time for the IPF–PVP system. We found that the higher the storage temperature, the higher the weight ratio of PVP in the mixture and the lower the molecular weight of PVP, the greater was the degree of decrease in crystallinity. The effect of PVP particle size was observed in 1 : 1 and 1 : 3 IPF/PVP mixtures.

The interaction of IPF with PVP in the solid state was investigated by IR and ^{13}C-NMR analyses, and the molecular geometry of 1-ethyl-2-pyrrolidone (EtP, a model compound for PVP) was calculated by the molecular orbital method (PM3). Our findings suggested that EtP undergoes O-protonation, forming a hydrogen bond at the carbonyl oxygen, in preference to N-protonation.

Key words ibuprofen; polyvinylpyrrolidone; amorphous; solid-state interaction; solid dispersion

A number of different polymers have been used in pharmaceutical formulations as diluents, binders, and disintegrating agents for tablets and capsules. However, the active drug sometimes interacts with the polymer in the solid state, resulting in changes of appearance and/or chemical stability of the product. Recently, in a series of compatibility studies, Botha and Lotter[2)] found that ketoprofen interacted with polyvinylpyrrolidone (PVP) and some other polymers. On the other hand, solid dispersions with PVP can enhance the *in vitro* dissolution rate of poorly water-soluble drugs containing a carboxyl group within the molecule; for example ketoprofen,[3)] indomethacin,[4-6)] ibuprofen (IPF),[7)] furosemide[8)] and mefenamic acid.[9)] Most of these solid dispersions were prepared by coprecipitation, melting, or spray-drying methods. A variety of mechanisms have been proposed[10,11)] to explain the increase in drug dissolution, but little is known about the nature of the interaction between carboxylic acids and PVP.

In the present study, we examined the solid-state interaction between an acidic drug, IPF, and PVP mixed without grinding or shaking at temperatures below the melting point of the drug.

Materials and Methods

Materials IPF was purchased from Wako Pure Chemical Industries Ltd., PVP (PVP K-12, K-30, K-90) was a gift from BASF Japan. The mean molecular weight and mean particle diameter of PVP are shown in Table 1. The diameter of at least 500 particles was determined with an image analyzer (Nireco, Luzex 500).

Preparation of Physical Mixture The drug and PVP, in various proportions, were mixed with a test tube mixer (Taiyo Automatic Mixer Type s-10) for 10 min at constant amplitude and rate (500 rpm).

X-Ray Powder Diffraction Analysis Powder X-ray diffraction analyses were performed with a Rigaku Geiger-Flex diffractometer (Rad-IIVC) using Ni-filtered, CuK_α radiation, a voltage of 40 kV, and a current of 20 mA. The scanning rate was 2°/min over a 2θ range of 2—140° and with a sampling interval of 0.02°.

Measurement of Crystallinity The crystallinity of the drug was measured using an X-ray diffractometer (Rigaku Denki Rad-IIVC) and was calculated by Ruland's method under the following conditions: lower limit (due to the constant of normalization), 1.21; smoothing level, 5; FWHM (corresponding to half-width at low value of s, $s=2\sin\theta/\lambda$), 5; loop number, 15; point (correction factor of FWHM for small peaks), 0.4; loop number, 15; FWHM (corresponding to half-width at high values of s), 5; range (region of s value), 0.3—1.21; k (coefficient of lattic imperfections) was selected as the value of minimum deviation. Crystallinity is shown as the average value of three measurements; the standard deviation is not shown, as the values were under 1.0% for all samples.

Thermal Analysis Differential scanning calorimetry (DSC) was carried out with a type 3100 instrument (MAC Science Co., Ltd.). The operating conditions in the open pan system were: sample weight, 5 mg; heating rate, 10 °C/min.

Infrared (IR) Spectra IR spectra were obtained on a Fourier-transform IR (FTIR) spectrophotometer (Type 8100, Shimadzu Co., Ltd.).

Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) Spectroscopy ^{13}C-NMR spectra were recorded on JEOL FX-90Q and EX-400 spectrometers. Molecular orbital calculations by the PM3[12)] method were performed with MOPAC ver. 5.0 software (QCPE No. 445) and ver. 5.1 (JCPE program, #Po28) software on a personal computer (PC-9801 RA, NEC).[13)]

Results and Discussion

Confirmation of Interaction of Solid Dispersion of IPF and PVP Figure 1 shows the powder X-ray diffraction patterns of IPF and PVP at 25 °C. The diffraction pattern of IPF had many peaks (Fig. 1 (1)), but no sharp peaks were observed for PVP, due to its amorphous nature (Fig. 1 (2)). The intensity of the X-ray diffraction of the physical

Table 1. Heywood's Diameter and Mean Molecular Weight of PVP

PVP	Heywood's diameter (μm)	M_w[a)]	M_n[b)]
K-12	88	2.9×10^3	1.3×10^3
K-30	67	4.5×10^5	1.0×10^5
K-90	122	1.1×10^6	3.6×10^5

a) Weight-average molecular weight. *b*) Number-average molecular weight.

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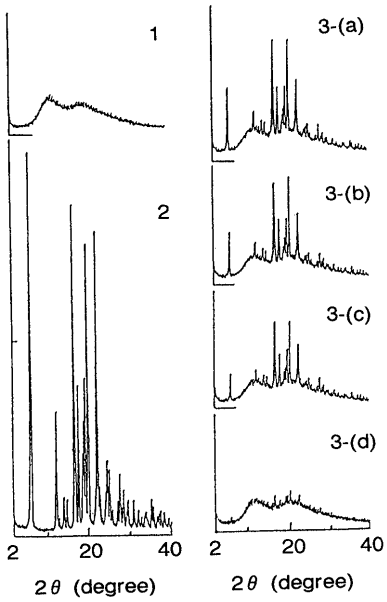

Fig. 1. X-Ray Diffraction Patterns for the IPF–PVP System at 25 °C

1, PVP; 2, IPF; 3, physical mixture IPF : PVP = 1 : 3, (a), immediately after mixing; (b), after 1 d; (c), after 2 d; (d), after 14 d.

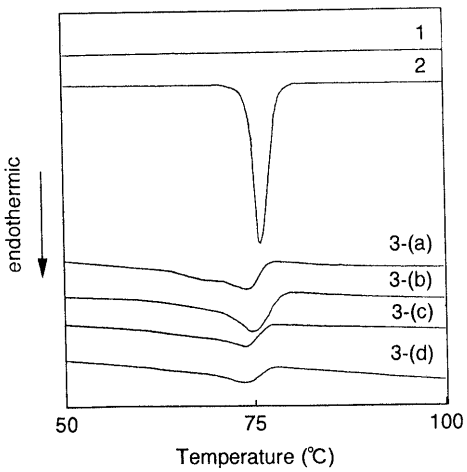

Fig. 2. DSC Curves for the IPF–PVP System at 25 °C

1, PVP; 2, IPF; 3, physical mixture IPF : PVP = 1 : 3; (a), immediately after mixing; (b), after 1 d; (c), after 2 d; (d), after 14 d.

mixture decreased with standing time when stored in a desiccator with phosphorus pentoxide; the peaks almost disappeared after 14 d (Fig. 1 (3)).

Figure 2 shows changes in the DSC curves with standing time for IPF, PVP, and their physical mixture. The DSC curves of crystalline IPF showed a sharp endothermic peak at 76 °C (349 K), but the peaks of the physical mixture as well as the X-ray diffraction intensity decreased with standing time due to the creation of a solid dispersion. We investigated the effects of various factors as detailed below on the interaction between IPF and PVP.

Effect of the Ratio of the Mixture on the Interaction of IPF and PVP: We used three different ratios of IPF and PVP in the mixture, all with a particle size of 112 μm. Each mixture was allowed to stand in a desiccator containing phosphorus pentoxide at 25 °C. Figure 3 shows the changes in the crystallinity of IPF with standing time. The crystallinity of IPF decreased with increasing ratio of

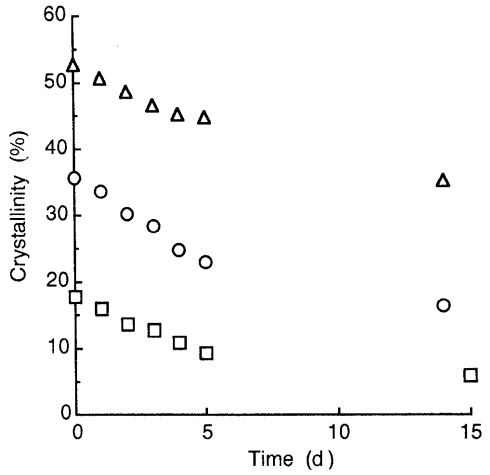

Fig. 3. Changes in Crystallinity in the IPF–PVP System at 25 °C

□, IPF : PVP = 1 : 3; ○, IPF : PVP = 1 : 1; △, IPF : PVP = 3 : 1.

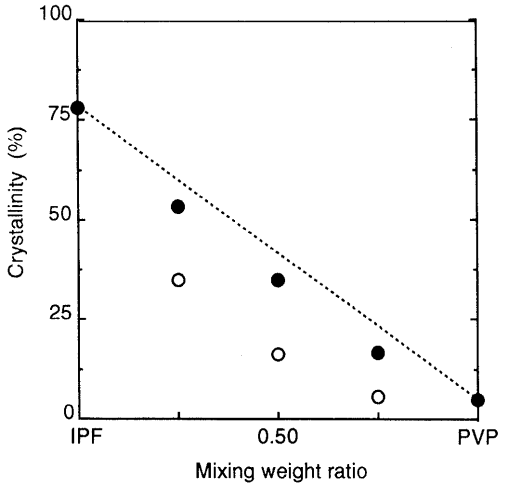

Fig. 4. Changes in Crystallinity in the IPF–PVP System at 25 °C in Relation to Mixing Weight Ratio

----, calculated value of crystallinity; ●, immediately after mixing; ○, after 14 d.

PVP for all standing times examined.

If there is no interaction between IPF and PVP, the crystallinity of IPF decreases with increasing PVP content of the mixture, as shown in Fig. 4. The dotted line shows the calculated value for the crystallinity assuming no interaction. The crystallinity of IPF decreased immediately after mixing and decreased still further with time. We defined the degree of decrease in crystallinity, A, by the following equation.

$$A=(C-M)/C \quad (1)$$

where C is the calculated value of crystallinity, shown by the dotted line in Fig. 4, and M is the observed crystallinity value.

Figure 5 shows the relationship between the degree of decrease in crystallinity, A, and the mixing weight ratio for the IPF–PVP system. The value of A increased with increasing PVP content and standing time.

Effect of Moisture Content on Crystallinity: The effect of the moisture content in PVP on the crystallinity was studied in a 1 : 1 IPF/PVP mixture. Before mixing, PVP was allowed to stand in a desiccator containing phos-

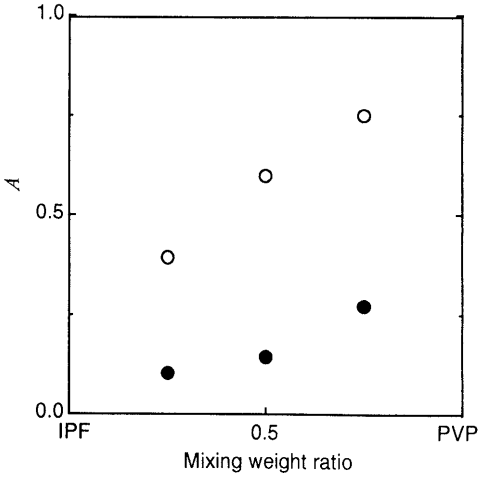

Fig. 5. Relationship between Degree of Decrease in Crystallinity (A) and Mixing Weight Ratio in the IPF–PVP System

●, immediately after mixing; ○, after 14 d.

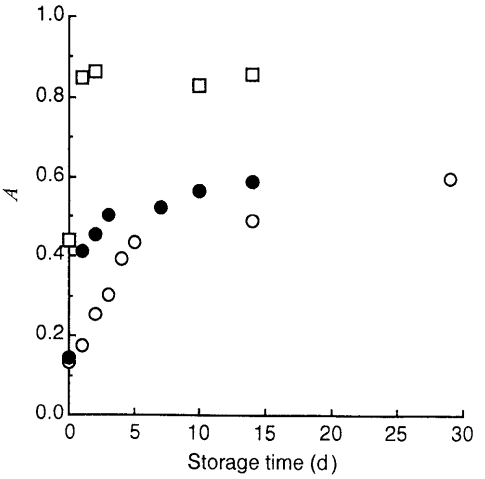

Fig. 6. Changes in Degree of Decrease in Crystallinity (A) in the IPF–PVP System (1 : 1) with Storage Time

○, PVP (dried sample) 25 °C; ●, PVP (moist sample) 25 °C; □, PVP (dried sample) 50 °C.

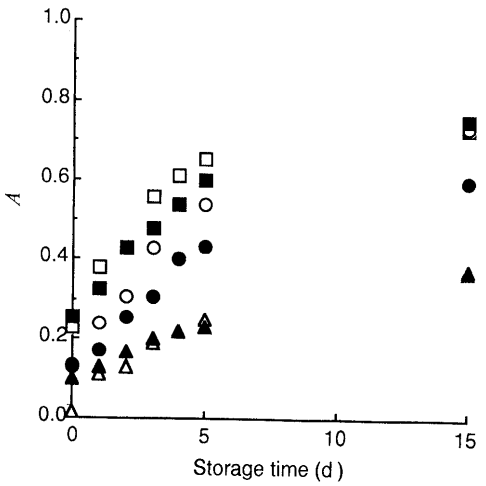

Fig. 7. Effect of Particle Size on the Degree of Decrease in Crystallinity (A) in IPF–PVP System

PVP 67 μm: □, IPF : PVP = 1 : 3; ○, IPF: PVP = 1 : 1; △, IPF : PVP = 3 : 1; PVP 112 μm: ■, IPF : PVP = 1 : 3; ●, IPF: PVP = 1 : 1; ▲, IPF : PVP = 3 : 1.

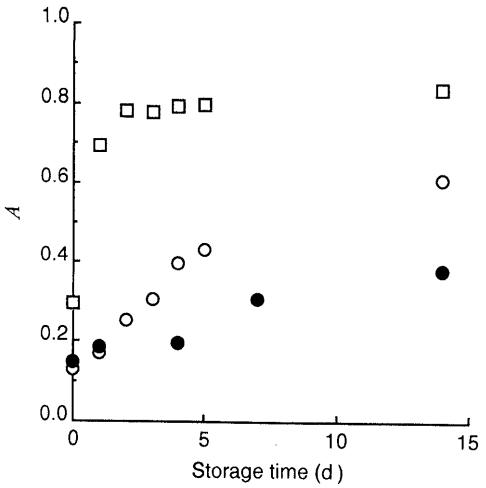

Fig. 8. Effect of Molecular Weight on the Degree of Decrease in Crystallinity (A) in the IPF–PVP System

□, PVP K-12 (88 μm); ○, PVP K-30 (112 μm); ●, PVP K-90 (122 μm).

phorus pentoxide (for dried samples) or a saturated solution of NaBr·2 aq. at 25 °C (relative humidity 57.3%, for moist samples) which included 22% (dry base) moisture. Moist PVP showed more activity than the dried form, as shown in Fig. 6. It has been reported[14] that the glass transition temperature (T_g) of PVP decreases with increasing moisture content. It is thought that the adsorbed water molecules interfere with hydrogen bonding of the chain, thus increasing motility and facilitating interaction between IPF and PVP.

Effect of Temperature on Crystallinity: It is well known that the rate of reaction between a drug and a polymer increases with increasing temperature. We examined the changes in degree of decrease in crystallinity, A, for the IPF–PVP system at 50 °C using dried PVP. The degree of decrease in crystallinity, A, of the system standing at 50 °C increased more quickly than in the system standing at 25 °C and quickly reached equilibrium, as shown in Fig. 6. We considered that IPF molecules bound easily with PVP molecules due to the activation of molecular movement by the increased temperature.

Effect of Particle Size on Crystallinity: The interaction between particles in the solid state is affected by the coordination number of the particles, and probably also by the ratio of the particle sizes of drug and polymer.

Figure 7 shows the effect of particle size on the degree of decrease in crystallinity, A, for constant PVP particle size. There was a slight increase with decreasing particle size.

Effect of Molecular Weight of PVP on Crystallinity: The effect of the molecular weight of PVP on the degree of decrease in crystallinity, A, was investigated using PVP of three different molecular weight in a 1 : 1 ratio of IPF to PVP standing in a desiccator containing phosphorus pentoxide at 25 °C. The value of A increased with decreasing molecular weight of PVP; the change took place quickly and reached an equilibrium (Fig. 8). In this case, the number of monomers per unit weight is independent of molecular weight; however, the number of terminal groups is in inverse proportion to the molecular weight, and therefore interaction between the drug and the

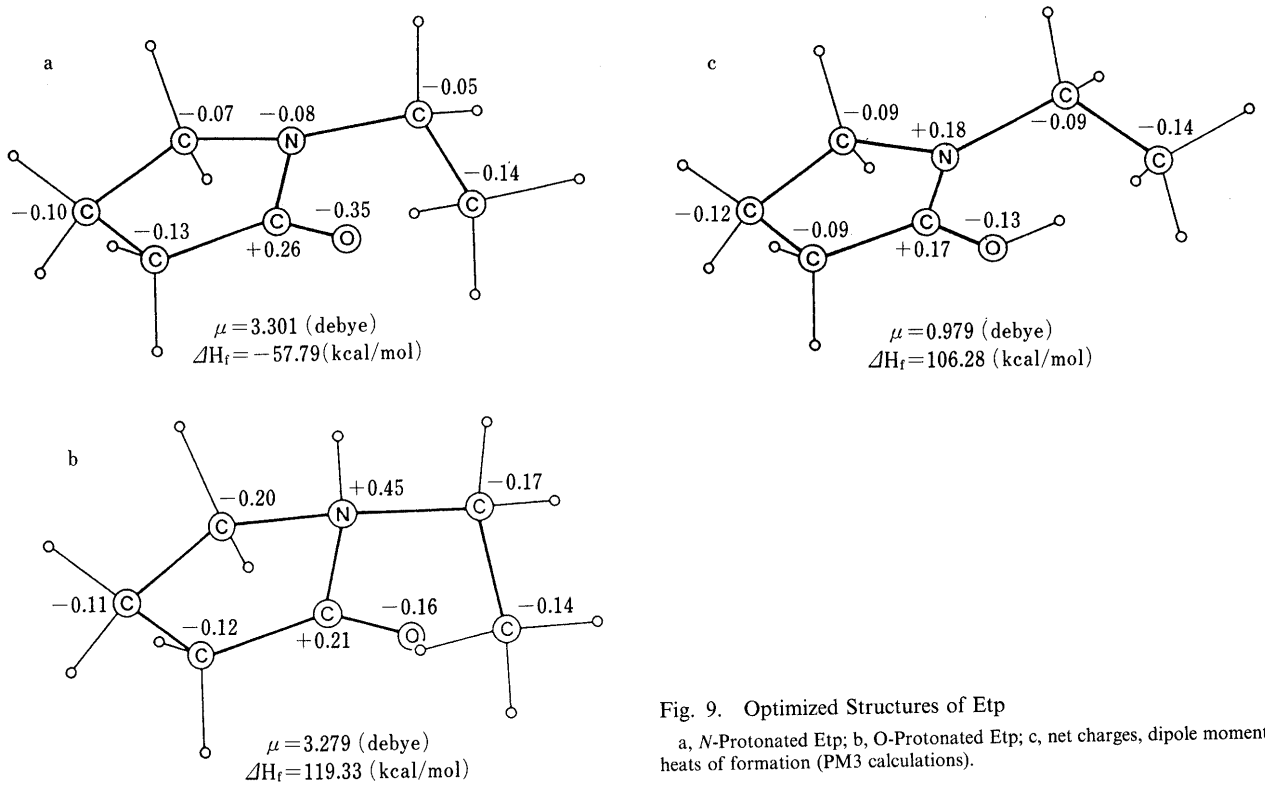

Fig. 9. Optimized Structures of Etp

a, *N*-Protonated Etp; b, O-Protonated Etp; c, net charges, dipole moments, and heats of formation (PM3 calculations).

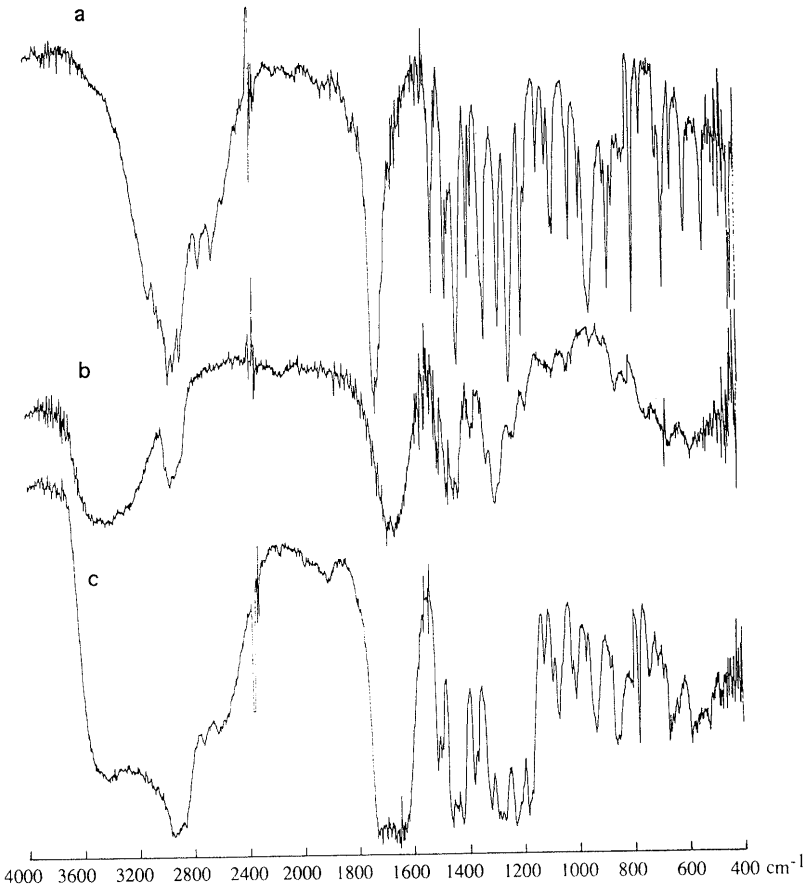

Fig. 10. IR Spectra of Solid Dispersions and Related Materials

a, IPF; b, PVP; c, IPF–PVP (IPF : PVP = 1 : 1, after 14 d).

terminal group of PVP is increased when the molecular weight of the polymer is low. Interaction between chains decreases with decreasing molecular weight, due to the easy diffusion of the drug within the polymer.

Conformation of IPF in PVP To examine the nature of the interaction of IPF with PVP, PM3 calculations were

performed on protonation at the nitrogen atom or the carbonyl oxygen atom of the amido group in PVP. In this study, we selected 1-ethyl-2-pyrrolidone (EtP) as a model compound. The molecular geometries of EtP, N-protonated EtP and O-protonated EtP were calculated by PM3, which is based on optimized structures, until the heat of formation of the system was minimized. The minimum energy structures are shown in Fig. 9. The relative energies for these compounds obtained from the PM3 calculation are shown in Fig. 9. The findings suggested that the EtP is preferentially O-protonated, forming a hydrogen bond at the carbonyl oxygen atom, and this is more stable than N-protonation due to the low final heat of formation (13 kcal). The net charges and dipole contributions to EtP, N-protonated EtP, and O-protonated EtP calculated by PM3 are shown in Fig. 9. This figure indicates that the electrons were strongly localized on the carbonyl carbon in O-protonated EtP, and that some electrons may be transferred from IPF to EtP. The degree of electron localization influences both the IR and ^{13}C-NMR spectra, as described below.

Confirmation with IR Spectra The IR spectra of solid dispersions (1% $CHCl_3$ solution) were compared with those of PVP, EtP, and IPF in 1% $CHCl_3$ solution (Fig. 10). The spectrum of the drug and polymer solution (1% $CHCl_3$) showed a single peak due to C–H stretching for IPF and PVP at 2940—2960 cm^{-1} with a very broad baseline covering the range of 2400—3500 cm^{-1}, indicating the presence of pronounced hydrogen bonding between IPF and PVP in solution. In the carbonyl frequency region, the drug showed a narrow strong band at 1709 cm^{-1} due to carboxylic C=O stretching. The polymer gave a broad strong band at 1670 cm^{-1} due to the cyclic amide C=O stretching. On the other hand, in the solid dispersion of IPF and PVP both C=O stretchings were seen as a broad band at 1620—1740 cm^{-1}.

For the physical mixture, in which there was no hydrogen-bonding interaction, the carbonyl band of the drug appeared as a narrow band separated from the broad C=O stretching band of the polymer, while in the solid dispersion both appeared as a strong broad band, presumably due to complex formation, most likely through hydrogen bonding. In the low-frequency region of 500—1600 cm^{-1}, the bands observed in the mixture were almost the same for both IPF and PVP. This might indicate that although the drug molecule is hydrogen-bonded with the polymer through the carboxylic acid OH group, the overall symmetry of the molecule is not significantly affected.

Confirmation with ^{13}C-NMR Spectra The signal of the carboxylic acid carbon in IPF appeared at δ 181.2 ppm, which is typical of a free carboxylic acid (Fig. 11a). On the other hand, the signal of the carbonyl carbon in PVP appeared at δ 175.4 ppm as shown in Fig. 11b. The spectrum of the solid dispersion is shown in Fig. 11c. The carboxylic acid carbon signal appeared at δ 178.3 ppm and the carbonyl carbon signal at δ 176.0 ppm. These results suggested that the carboxylic acid group of IPF interacts with PVP through hydrogen bonding. EI-Hinnawi and Najib[15] reported that the carboxylic acid group of IPF hydrogen bonds at the nitrogen atom of the pyrrolidone ring of the polymer. Our results indicated that the carboxylic acid moiety of IPF interacts with PVP through hydrogen bonding at oxygen, as illustrated in Fig. 12. This structure seems more likely than hydrogen bonding at the nitrogen atom, since the nitrogen milieu, which is the bridge-head of PVP, is affected by steric hindrance.

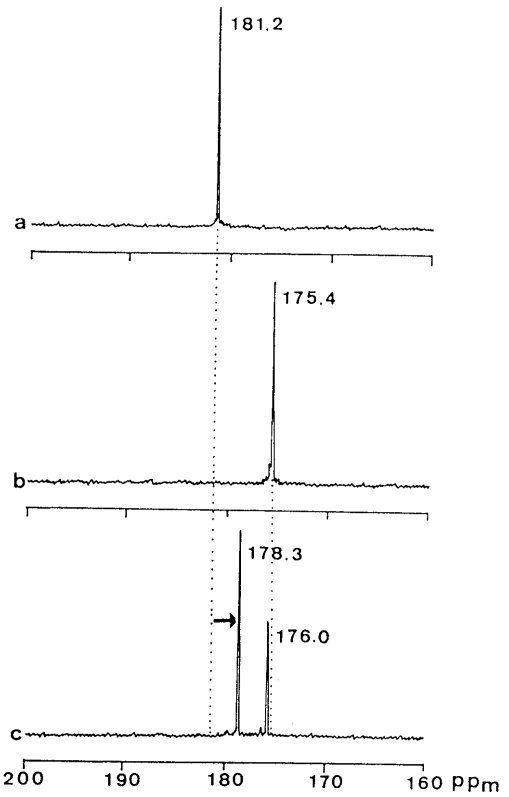

Fig. 11. ^{13}C-NMR Spectra of Solid Dispersions and Related Materials
a, IPF; b, PVP; c, IPF–PVP (IPF : PVP = 1 : 1, after 14 d).

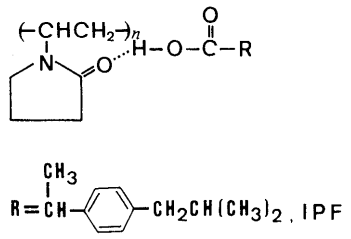

Fig. 12. Possible Structure of Solid Dispersions

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