# Preparation and Characterization of Solid Dispersion of Ipriflavone with Polyvinylpyrrolidone

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ABSTRACT–Solid dispersions of ipriflavone with PVP were prepared by a spray-drying method in order to improve the bioavailability. They were measured with scanning electron microscopy, differential scanning calorimetry, x-ray powder diffraction, and Fourier transform infrared spectroscopy to evaluate the physicochemical interaction between ipriflavone and PVP and study the correlation between these physicochemical characteristics and bioavailability. Ipriflavone exhibited crystallinity, whereas PVP was almost amorphous. The area of the endotherm (ΔH) of freezer milled ipriflavone, freezer milled ipriflavone physically mixed with freezer milled PVP, and physically mixed ipriflavone with PVP was almost the same, whereas ΔH of the solid dispersed ipriflavone with PVP was much smaller than that of the other preparation types. Also, the crystallinity and the crystal size of ipriflavone in the solid dispersed ipriflavone with PVP were much smaller than those of the other preparation types. From the in vivo test, the AUC of the solid dispersed ipriflavone with PVP was approximately 10 times higher than that of the physically mixed ipriflavone with PVP. The solid dispersion using the spray-drying method with a water-soluble polymer, PVP, may be effective for the improvement of the bioavailability.

Keywords–Solid dispersion, Bioavailability, Spray-drying, Crystallinity, Amorphous, X-ray powder diffraction

Up to the present, various methods to modify the dissolution characteristics of poorly water-soluble and crystalline drugs have been developed to achieve the enhancement of bioavailability.[1,2] One of these methods was a reduction of the particle size of drugs. Although the reduction of particle size can be easily and directly achieved by conventional grinding and ball milling, the resultant fine particles did not show the expected faster dissolution and better bioavailability due to aggregation and agglomeration.[3] As a result, various methods such as the use of surfactants, solvent deposition, inclusion complexation, and solid dispersion[4-7] have been developed to improve the bioavailability of drugs.

Solid dispersion, one of the various approaches to improve the dissolution of drugs, increases the surface area by reducing the particle size of the drug. Sekiguchi et al.[8] first introduced sulphathiazole-urea solid dispersion for the improvement of the bioavailability of sulphathiazole, and many drugs were then able to become fully or partially amorphous during preparation processing such as granulation, milling, or spray-drying.[3,9,10] Crystalline materials could be changed to

amorphous materials by various methods such as quenching of the melt, rapid precipitation from solution and condensation from the vapor state. Because the amorphous state is relatively metastable to the crystalline state, the co-presence of amorphous drugs and water-soluble polymers in a dispersed system can bring about reduced physical and chemical stability in pharmaceutical systems as a result of a greater degree of molecular mobility in the amorphous state than in the crystalline state.[11-14]

It has been widely applied that ipriflavone (3-phenyl-7-isopropyl-4H-1-benzopyran-4-one), which has been used in the treatment of osteoporosis, is a poorly water-soluble drug with an extremely low absorption rate in the body (below 1 μg/mL).[15] Also, poly-N-vinylpyrrolidone (PVP) is widely used to form solid dispersion and it has been reported that many drugs have been dispersed in this polymer.[16] It has been proposed that the extent of interaction between the drug and the polymer is related to crystallization inhibition.[11]

In our previous studies, the bioavailability of solid dispersions of ipriflavone in PVP with the various preparation methods such as freezer milled ipriflavone (FIP), FIP physically mixed with freezer milled PVP (FIP+FPVP), and solid dispersed ipriflavone with PVP (SIP) has been investigated.[15,17-19] Also, the effects of the molecular weight of PVP

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and hydrophilic polymers on *in vivo* absorption have been studied. Upon oral administration, SIP showed a significantly higher absorption and longer elimination half-lives and lag time than those of FIP and FIP+FPVP. Solid dispersed ipriflavone with PVP, with a molecular weight of 40,000 g/mol, showed the highest *in vivo* absorption in approximately molecular weights of 10,000, 40,000, 360,000, and 1,100,000 g/mol and solid dispersed ipriflavone using PVP showed the highest *in vivo* absorption among PVP, HPMC, and PEG.

The aims of this study were (1) to observe *in vivo* absorption for physically mixed ipriflavone with PVP (MIP), (2) to evaluate the physical and solid state interaction between ipriflavone and PVP using scanning electron microscopy (SEM), X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectro-scopy (FT-IR), and (3) to study the correlation between these physicochemical characteristics and bioavailability.

## Experimental

### Materials

Ipriflavone was purchased from Dongbang Chem. Co., Korea and PVP (K30) was purchased from Hongsung Pharm. Co., Korea with a weight-average molecular weight of 40,000 g/mol. All other chemicals were a reagent grade.

### Preparation of solid dispersions

FIP was prepared by freezer mill (SPEX 6700, Metuchen, USA) for 10 min in liquid nitrogen in order to reduce the particle size of ipriflavone. FIP+FPVP was prepared by FIP physically mixed with freezer milled PVP which reduced the particle size of PVP using the same technique of FIP preparation by pestle.

The MIP was prepared by physically mixing ipriflavone with PVP by pestle. The SIP was prepared by the spray-drying method. Briefly, twenty grams of each ratio of the two components were dissolved in appropriate volumes of ethanol and acetone at room temperature, and then spray-dried to disperse ipriflavone in PVP by fluidized bed coater (Uniglatt, Glatt Co., Germany) under the conditions of 12~20 mL/min pump speed, 40~70°C inlet air temperature, 40~45 outlet air temperature, and 20~40 psi spraying air pressure. In these preparations, the weight ratio of the drug to the water-soluble polymer was 5:5 (w/w).

After all the samples were prepared, they were stored for 12 hr at −20°C and subsequently freeze-dried for 24 hr in order to remove any residual solvents.

### *In vivo* test

The *in vivo* test was carried out on Sprague-Dawley rats (ca. 250~300 g body weight, Korea Research Institute of Chemical Technology, Toxicology Center Breeding Facility, Taejon, Korea) which were housed under specific pathogen free conditions. Whatever ipriflavone formulation, a single dose of 50 mg/kg was given orally to each rat. Blood samples (ca. 200 $\mu l$) were collected from the tail vein at 30 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr and 24 hr after administration and plasma was prepared by centrifugation at 12,000 rpm for 5 min. The plasma samples were stored at −20°C until further processing.

The drug concentrations in the plasma were determined by high performance liquid chromatography (HPLC). The HPLC system consisted of a UV detector (UV-2000, Thermo Separa-tion Products, USA), a pump (P-2000, Thermo Separation Products), and an autosampler (AS-3000, Thermo Separation Products). The analytical columns consisted of a C $_{18}$ Nova-pak cartilage (Waters, USA) and an Inertsil ODS (5 $\mu$m, 250×4.6 mm ID, GL Sci. Inc., Japan). The mobile phase was a mixture of acetonitrile and distilled water (70:30, v/v) and the flow rate was 1.0 mL/min. The UV wavelength selected for detection was 250 nm. Plasma proteins were precipitated using a triple volume of methanol, and aliquots (20 $\mu l$) of the supernatant were injected into the HPLC column.[15] The area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal rule.

### SEM

The solid dispersion and other preparation types were observed by SEM (S-2250N, Hitachi Co., Ltd., Japan) in order to examine the morphology and to estimate the particle size of ipriflavone. Samples for the SEM were mounted on a metal stub with double sided tape and coated with platinum for 30 sec under an argon atmosphere using a plasma sputter. The obtained photographs were examined at a magnification ratio of ×800.

### XRD

X-ray diffraction patterns of solid dispersion and other preparation types were analyzed by XRD (D8 discover with GADDS, Bruker, Germany). The radiation was generated by a copper Kα with monochrometer at 40 kV and 40 mA and collimated by a 0.5 mm pinhole, 120 s/step, and 0.02 degree step size. The samples were scanned over the 2θ range of 5~70°.

### DSC

Thermal characteristics such as the melting temperature (T$_m$) and the glass transition temperature (T$_g$) of ipriflavone, PVP alone, their physical mixture and the solid dispersion were

determined by DSC (2910, TA instruments, USA). The endo - thermic heats associated with the melting of the ipriflavone crystals were analyzed. The DSC was calibrated with an indium standard. Dry nitrogen was used as the purge gas. Samples (5~15 mg) were weighed in aluminum pans and DSC analyses were carried out at a nitrogen flow of 50 mL/min and a heating rate of 2°C/min from 30 to 200°C. The endothermic energy was derived by gravimetrically measuring the peak areas.

### FT-IR

The infrared spectra of ipriflavone, PVP alone, their physical mixture and the solid dispersion were obtained by an FT-IR (Magma IR$^{TM}$ 550, Nicolet, USA) equipped with a DTSG detector. Samples were prepared in KBr discs. A polystyrene filter was used to check the spectrophotometer calibration. 64 scans were collected for each sample at 4 cm$^{-1}$ resolution over the wavenumber range of 4000~400 cm$^{-1}$.

## Results and discussion

### Morphology of preparation types

SEM photographs of IP, PVP, and FIP and FIP+FPVP, MIP, and SIP clearing PVP with water were shown in Figure 1. It can be observed that most of the ipriflavone particles of FIP, FIP+FPVP, and MIP were aggregated and agglomerated, whereas those of SIP were not. Also, the ipriflavone particle sizes in SIP (1~10 μm) were smaller than those in FIP, FIP+FPVP, and MIP (20~50 μm).

### Changes of ipriflavone crystallinity with different types of preparation methods

To investigate the correlation between the crystalline state of ipriflavone and the bioavailability of the different preparation types, the samples were characterized with DSC, XRD, and FT-IR. Figures 2a and 3a show the typical DSC thermogram
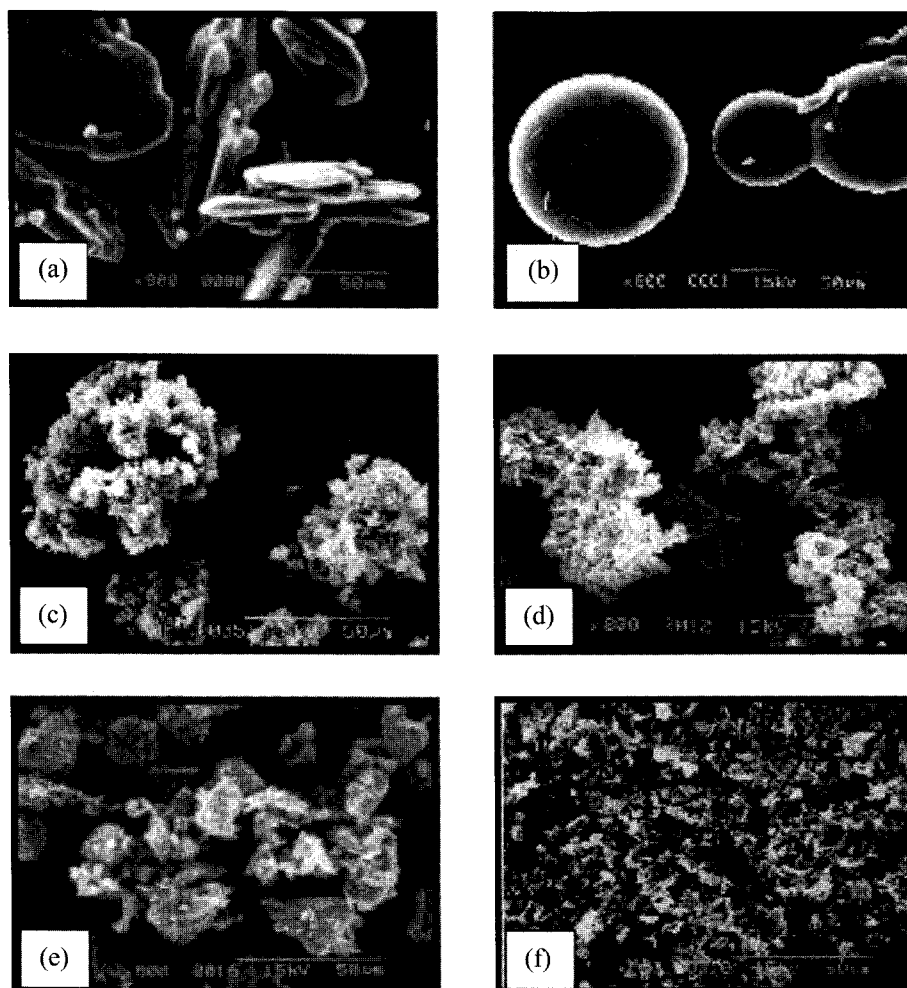


**Figure 1**–SEM photographs of (a) ipriflavone; (b) PVP; (c) FIP; and (d) FIP+FPVP; (e) MIP; (f) SIP clearing PVP with water (original magnifications; ×800).
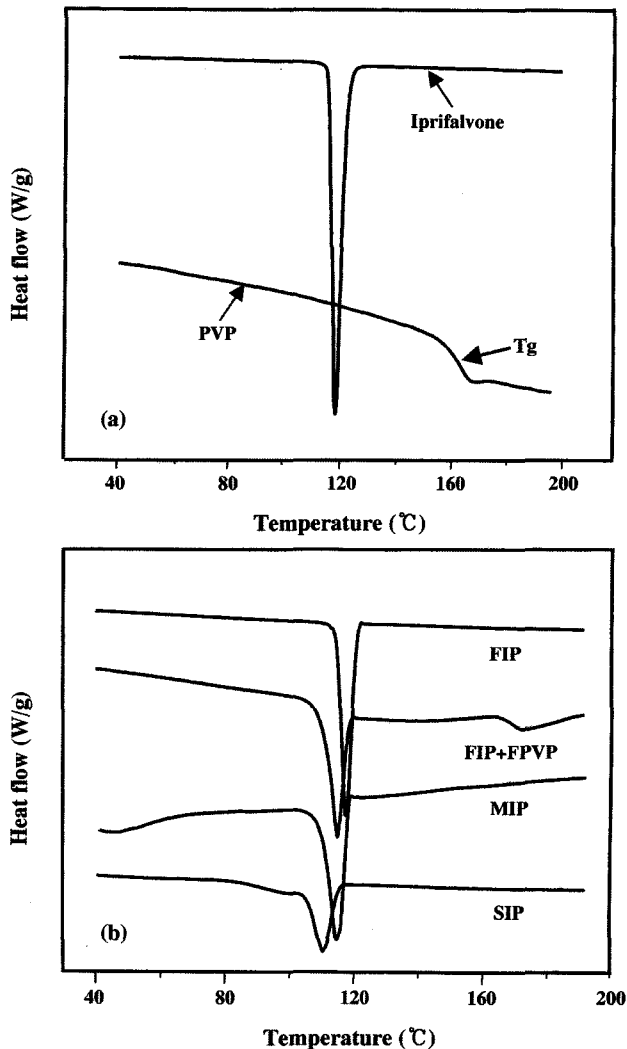
**Figure 2**–DSC thermograms of (a) ipriflavone and PVP; (b) MIP, FIP, FIP+FPVP, and SIP.



**Figure 3**–XRD spectra of (a) ipriflavone and PVP; (b) MIP, FIP, FIP+FPVP, and SIP.

and XRD spectrum of ipriflavone and PVP, respectively. In Figure 2a, $T_m$ and the area of the endotherm ($\Delta H$) of ipriflavone and $T_g$ of PVP were observed at 120°C, 118 J/g, and 164°C, respectively. In Figure 3a, it can be observed that the characteristic peaks of ipriflavone appeared at a diffraction angle of 2θ, at 5.9, 11.3, 15.1, 17.1, 21.5, 27.1, 41.2, and 46.5 ° and 5.9° of 2θ was larger than others, particularly, whereas PVP was almost amorphous.

Figure 2b shows DSC thermograms of FIP, FIP+FPVP, MIP and SIP. $\Delta H$ of FIP, FIP+FPVP, MIP, and SIP were observed at 114.7, 113.9, 113, and 60.7 J/g, respectively. It could be observed that $\Delta H$ of FIP, FIP+FPVP, and MIP was almost the same as $\Delta H$ of ipriflavone, whereas $\Delta H$ of SIP was much smaller than that of other preparation methods, that is to say, in the order of intact ipriflavone > FIP ≅ FIP+FPVP ≅ MIP > SIP.

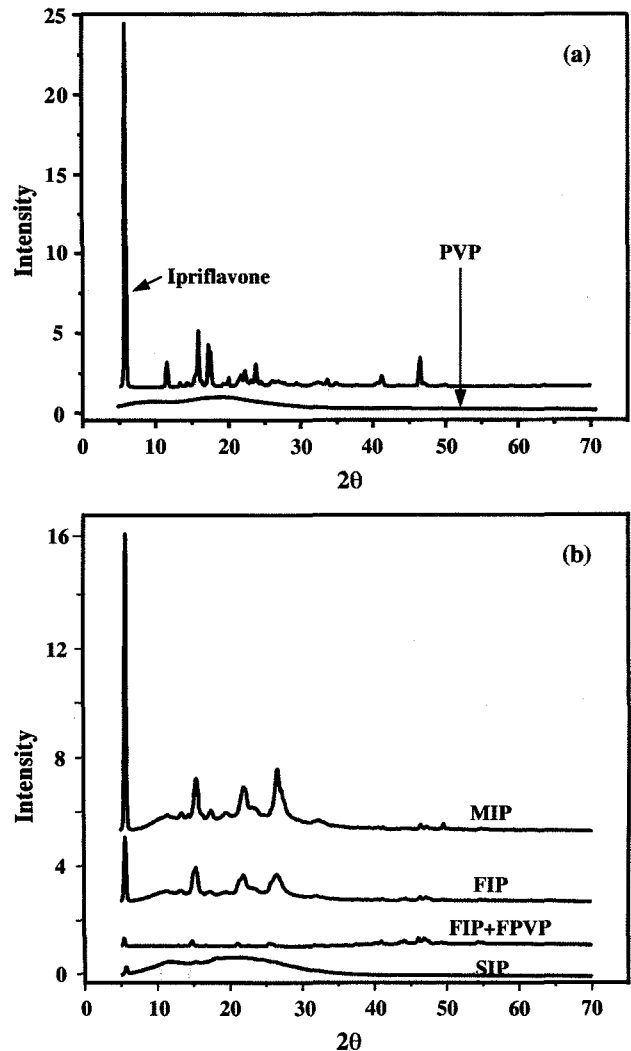Figure 3b shows the powder XRD patterns of FIP, FIP+FPVP, MIP and SIP. The characteristic peak of ipriflavone was observed in FIP and the ipriflavone-PVP physical mixtures, MIP and FIP+FPVP, although the peak intensity was reduced. However, it can be observed that the characteristic peak of ipriflavone appeared only at a diffraction angle of 2θ, at 5.9° for the solid dispersion of ipriflavone prepared by spray-drying with PVP.

On the assumptions that the crystal form of ipriflavone was a sphere and the characteristic peak of ipriflavone which commonly appeared at a diffraction angle of 2θ, at 5.9°, is looked upon as a standard peak, the results which calculate crystal size (or diameter) by the Scherrer equation and the crystallinity of ipriflavone in each type of preparation method is listed in Table I. The crystal size (or diameter) of ipriflavone

**Table I**-*Crystal size and crystallinity of ipriflavone, FIP, FIP+FPVP, MIP, and SIP*

|  | Crystal size (Å) | Crystallinity (%) |
|---|---|---|
| Ipriflavone | 435 | 78.8 |
| FIP | 294 | 42.6 |
| FIP+FPVP | 261 | 31.9 |
| MIP | 303 | 39.3 |
| SIP | 252 | 1.9 |
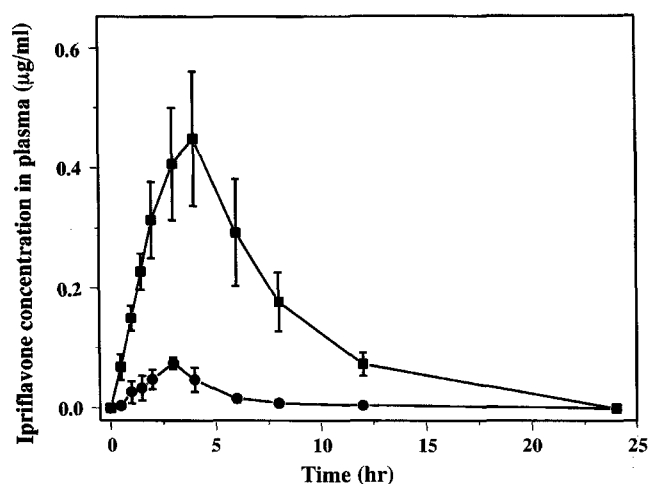


**Figure 4**-Plasma concentration-time curves of ipriflavone following oral administration of ipriflavone preparations in SD rats. Key: ■ ; SIP, ●; MIP. Values are mean±S.E.(n=3).
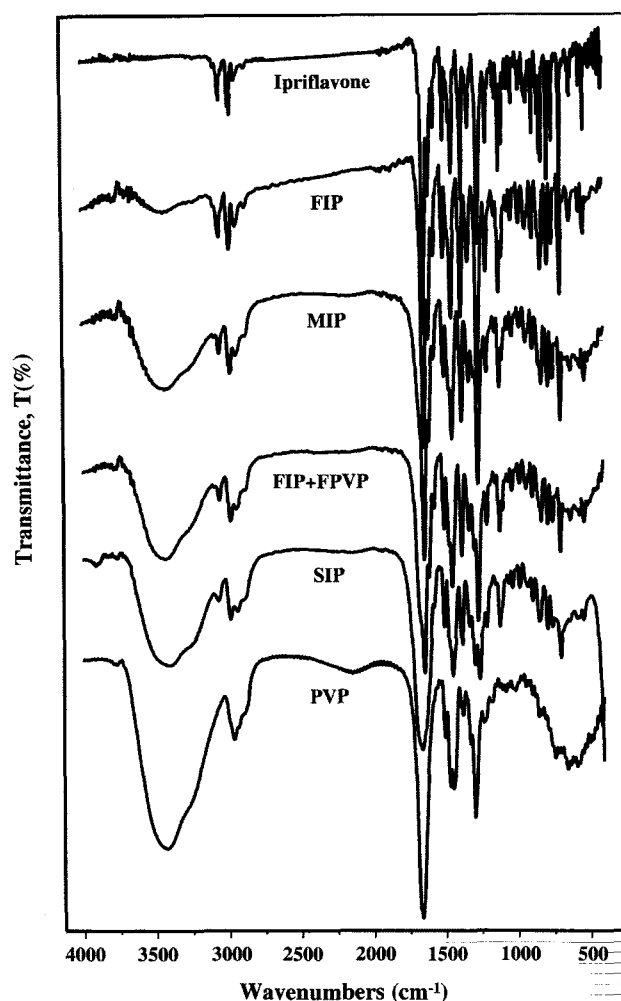
in SIP was much smaller than that in other preparation methods. Also, it could be observed that the crystallinity of ipriflavone in SIP was 1.9% and much smaller than that of other preparation methods, that is to say, in the order of intact ipriflavone > FIP ≅ MIP > FIP+FPVP > SIP. Compared with DSC data, the trends of these results were almost same as those of DSC works.

Ipriflavone concentration profiles in blood plasma of SIP and MIP are shown in Figure 4. The AUC of SIP (3.24 ±0.80 μg · hr/ml) was 10 times higher than that of MIP (0.31 ±0.14 μg · hr/ml). Also, the AUC of SIP was 6 and 60 times higher than those of FIP+FPVP (0.54±0.12 μg · hr/ml) and FIP (0.05± 0.05 μg · hr/ml), respectively.[15] That is to say, the bioavailability of each preparation type was in the order of intact ipriflavone < FIP < MIP ≅ FIP+FPVP < SIP. Concerning this point, we observed that the higher crystallinity of ipriflavone, the lesser the *in vivo* absorption. Similar investigations have been observed for itraconazole-Eudragit E 100, nifedipine-hydroxy- propylmethylcellulose, and piroxicam-PVP solid dispersions with significantly improved bioavailability. [10,20,21]

In general, the process of the crystallization of a highly crystalline drug during the processing of the solid dispersion is

largely divided into two processes; (a) the creation of the crystal nucleus and (b) the growth of the crystal. Sekikawa *et al.*[11] pointed out that PVP might inhibit the association of the drug molecule to form the crystal nucleus and inhibit the crystal growth; and the interaction between the drug and PVP should be the inhibitory and/or retardatory factor in the crystallization.

Figures 5 and 6 show the FT-IR spectra for ipriflavone, PVP, FIP, FIP+FPVP, MIP, and SIP. Typically the C=O stretch is observed over the region between 1750 and 1600 cm$^{-1}$. The C=O stretch of ipriflavone and PVP were observed at 1639 and 1658 cm$^{-1}$, respectively. In Figure 6b, it can be observed that the C=O stretch of ipriflavone and PVP are shown at 1639 and 1658 cm$^{-1}$ in FIP, FIP+FPVP, and MIP, whereas the C=O stretch of ipriflavone is not seen at 1639 cm$^{-1}$ and the C=O stretch of PVP is only seen at 1658 cm$^{-1}$ in SIP. This result suggests that there was some interaction between ipriflavone



**Figure 5**-FT-IR spectra of ipriflavone, PVP, FIP, MIP, FIP+FPVP, and SIP over the spectral range 4000–400 cm$^{-1}$.
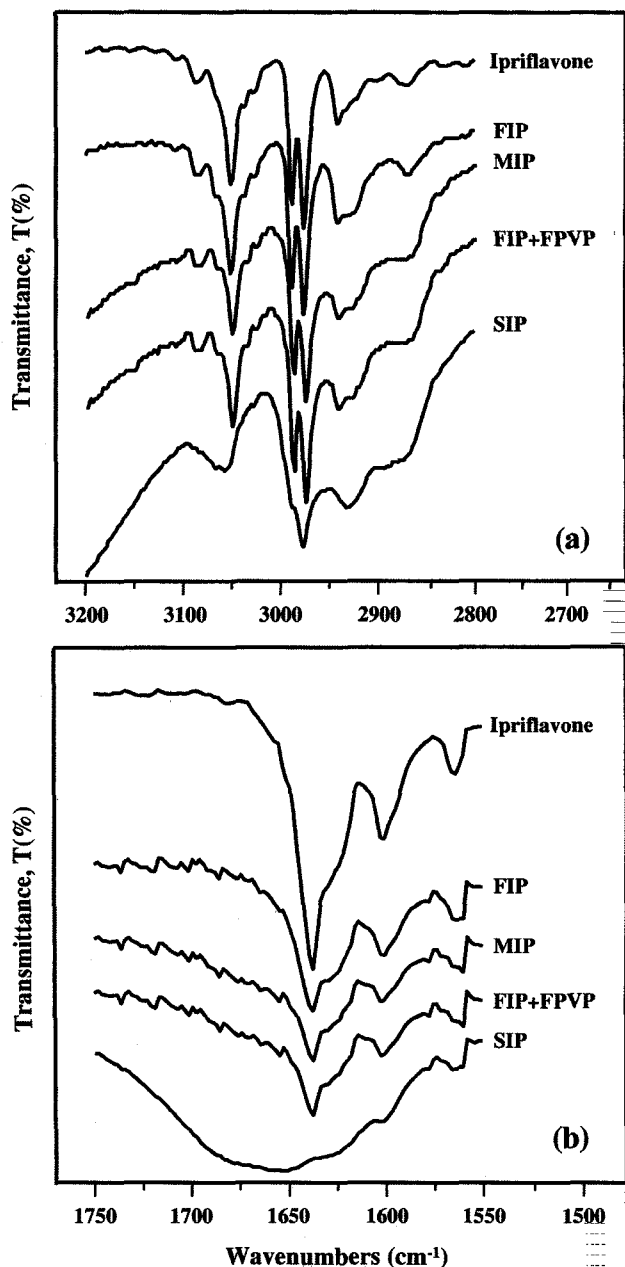
Figure 6–FT-IR spectra of ipriflavone, FIP, MIP, FIP+FPVP, and SIP over the spectral range (a) 3200–2800; (b) 1750–1550 cm⁻¹.
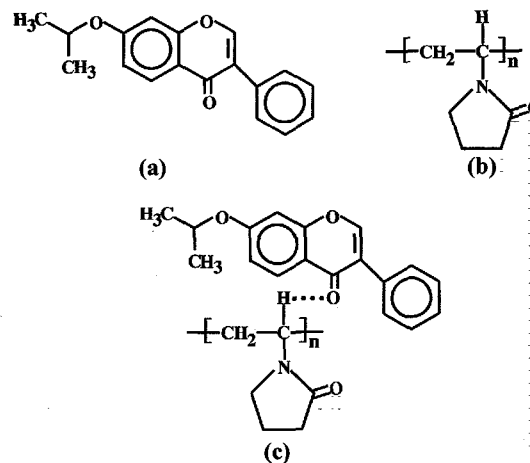


Figure 7–Structure of (a) ipriflavone; (b) PVP; (c) possible hydrogen bonding between ipriflavone and PVP.

in SIP was different than that of intact ipriflavone. This FT-IR pattern has been investigated for the amorphous solid dispersion of piroxicam-PVP and indomethacin-PVP. [21,22] At this point, some interaction such as intermolecular hydrogen bonds may exist between ipriflavone and PVP in solid dispersion.

Porubcan[23] demonstrated that new chemical bonds and strong complexations such as hydrogen bonding could change the crystalline structure of a drug resulting in a changed XRD pattern. Figure 7 shows the structures of ipriflavone and PVP and the possible hydrogen bond between them. PVP has two groups, =N- and C=O, and ipriflavone has one, C=O, that were capable of potential hydrogen bonding. Leonard et al.[24] discussed the C-H ------- O=C bonds in the Watson-Crick A-U and Hoogsteen A-T base pairing in the oligonucleotide. At this point, it can be suggested that the disappearance of the C=O peak of ipriflavone is attributable weak hydrogen bonding interaction between the C=O functional group in ipriflavone and the -H-C-N in PVP in the solid dispersions as shown in Figure 7.

## Conclusions

In order to investigate the correlation between the bioavailability and the physicochemical characteristics of ipriflavone, the various preparation types have been demon-strated. ΔH from DSC analysis of SIP was much smaller than that of the other preparation methods, that is to say, in the order of intact ipriflavone ≥ FIP ≅ FIP+FPVP ≅ MIP > SIP. Also, it can be observed that the crystallinity of ipriflavone in SIP was much smaller than in that of the other preparation methods in XRD analysis. From these results and the in vivo absorption

and PVP. Also, in Figure 6a, ipriflavone shows doublets at 3087 and 3079 cm⁻¹, and at 2986 and 2975 cm⁻¹. There were doublets at 3087 and 3079 cm⁻¹, and at 2986 and 2975 cm⁻¹, corresponding to those of ipriflavone in FIP, FIP+FPVP, and MIP. This indicates that there was no interaction between ipriflavone and PVP in FIP+FPVP and MIP. In SIP, however, the peak disappeared at 3087 and 2986 cm⁻¹, where it existed in ipriflavone, and singlets appeared at 3079 and 2975 cm⁻¹. This result suggests that the crystalline structure of ipriflavone

results, the lesser crystallinity there is, the higher the *in vivo* absorption that can be observed.

In conclusion, we have demonstrated that solid dispersion using the spray-drying method with a water-soluble polymer, PVP, is effective for the improvement of bioavailability. It seems that the crystallinity as well as the interaction with PVP of ipriflavone play important roles in *in vivo* absorption.

## Acknowledgements

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