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Note

Comparison between polyvinylpyrrolidone and silica nanoparticles as carriers for indomethacin in a solid state dispersion

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Abstract

States of interaction between indomethacin (IM) and polyvinylpyrrolidone (PVP) in an amorphous solid dispersion prepared by co-grinding were compared with those between IM and silica nanoparticles. Changes in the carbon chemical states of the solid dispersions were evaluated based on the chemical shift in the ^{13}C-CP/MAS-NMR. Hydrogen bonds between the amide carbonyl of PVP particles and the carboxyl groups of IM molecules were formed by co-grinding. Despite the wide difference in carrier properties, the apparent equilibrium solubility (AES) of IM in the ground IM–PVP mixture was predicted by solid state NMR on the basis of the relationship previously established for IM with SiO_2. This indicates that AES is affected solely by the state of IM, irrespective of the carrier species, and despite carrier-dependent chemical interactions.

Keywords: Indomethacin; Interaction; Polyvinylpyrrolidone; Co-grinding; Solid state NMR

Co-grinding is one of the effective methods to prepare a solid dispersion in order to enhance the dissolution rate (Shakhtshneider et al., 1996; Sugimoto et al., 1998). Water soluble polymers serve as carriers of solid dispersions, from which drugs are released quickly (Chiou and Riegelman, 1971). Polyvinylpyrrolidone (PVP) is water soluble and widely used as a carrier of solid dispersions to increase the dissolution rate while suppressing recrystallization (Taylor and Zografi, 1997). We previously employed SiO_2 nanoparticles as a drug carrier and found that a ground indomethacin (IM)–SiO_2 mixture brought about a specific chemical interaction. The interaction with SiO_2 at the interface immobilized the IM molecules and suppressed recrystallization (Watanabe et al., 2001). In addition, the short range order of IM estimated by solid state NMR was changed and the apparent equilibrium solubility (AES) of IM

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was increased as an IM–SiO_2 system (Watanabe et al., 2002a, accepted). In this note, we examined the interaction between amorphous IM and PVP in the solid state. We also studied the differences due to the carrier, i.e. between PVP and SiO_2 based on the ^{13}C-CP/MAS-NMR spectra and the AES of amorphous IM.

A commercial reagent (Sigma Chemical Co., USA) was used as the source of IM (γ-indomethacin: 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid). As a carrier for co-grinding, PVP (Kollidon 90F, BASF A.G., Germany) was used. IM and PVP were mixed in a monomer molar ratio of 1:1 to obtain a physical mixture. In the solvent evaporation method, this ratio was proposed as it produced suitable hydrogen-bonded IM–PVP complexes (Taylor and Zografi, 1997). Grinding of the mixtures was carried out using a laboratory size vibration mill (Hi-speed Vibrating Sample Mill Model TI-100, CMT MFG Co., Japan). X-ray powder diffraction (XRPD) patterns for all the samples were obtained by a Geiger Flex Rint-2200 (Rigaku Co., Japan) diffractometer. Detailed grinding and XRPD measurement conditions for the mixture are given elsewhere (Watanabe et al., 2001). Cross polarization magic-angle-spinning (CP/MAS) NMR spectra for ^{13}C were obtained using a 300 MHz spectrometer (CMX-300, Chemagnetics Inc., USA). The experimental settings, which may affect the ^{13}C line broadening in an organic solid (Vanderhart et al., 1981), were kept constant and were the same as those used in our previous IM–SiO_2 system study (Watanabe et al., 2002a, accepted). The AES in water was determined at 37.0 ± 0.5 °C. A net amount of 10 mg of IM was added to 100 ml of water in a beaker. The suspension was vigorously agitated with a stirrer. About 2 h after dissolution, the drug concentration attained eventually the constant value at least up to 48 h. This may be regarded as the apparent solubility of the drug in equilibrium. From the time span mentioned above and the reproducibility, we defined in this paper the value of the concentration 24 h after dissolution as AES (Watanabe et al., 2002a, accepted). After 24 h, aliquots were prepared and filtered through a 0.45-μm membrane filter. The drug concentration ($n=6$) was analyzed with a UV spectrometer (UV-3100, Shimadzu Co., Japan) to determine the AES.

As shown in Fig. 1, the XRPD peaks for IM disappeared after co-grinding for 180 min. We reported that after grinding IM without PVP for 180 min, diffraction peaks of IM still remained although in lower intensity (Watanabe et al., 2001). This indicates that rapid amorphization of IM by co-grinding occurred as a result of the interaction with PVP. Changes in the carbon chemical states in the solid dispersion are visualized by the changes in chemical shifts of the ^{13}C-CP/MAS-NMR spectrum shown in Fig. 2. The structural groups of PVP and corresponding NMR peaks (Zheng et al., 1999) are inscribed in Fig. 2. By using PVP as a carrier, the NMR peaks from IM became much broader after grinding as it was the case with SiO_2 (Watanabe et al., 2001). The peak intensity of the carbonyl carbon of PVP (peak No. 6 in Fig. 2) decreased or disappeared after co-grinding. Such a decrease in intensity was not detected for the other carbon atoms of PVP. By comparing with an amorphous solid dispersion prepared by solvent evaporation, where IM and PVP were replaced by acetic acid and methylpyrrolidone, respectively, Taylor and Zografi (1997) found that hydrogen bonds were formed between the PVP amide carbonyl and IM carboxylic acid hydroxyl groups. In general, formation of hydrogen bonds brings about a higher chemical shift in the NMR spectra due to a delocalization of

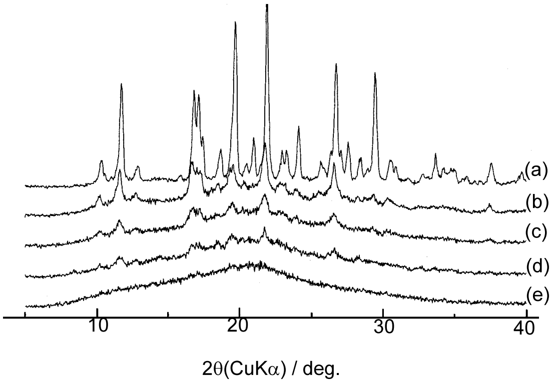
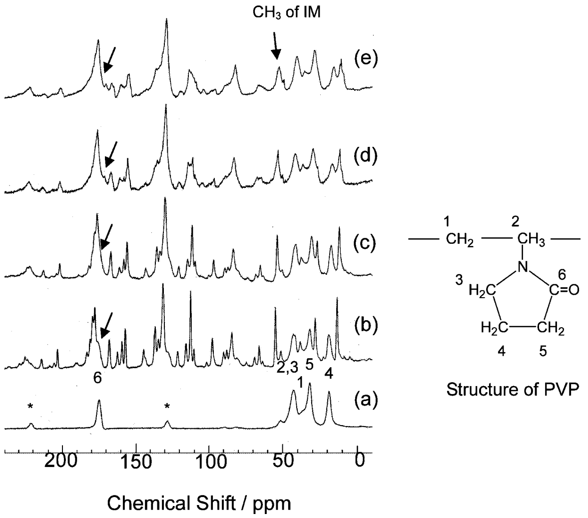


Fig. 1. XRPD profiles of physically mixed and ground IM–PVP: (a) physical mixture; (b) mixture ground for 30; (c) 60; (d) 120; and (e) 180 min.



Structure of PVP

Fig. 2. ^{13}C-CP/MAS-NMR spectra of physically mixed and ground IM–PVP: (a) PVP; (b) physical mixture; (c) mixture ground for 30; (d) 60; and (e) 180 min.

electrons. Therefore, a decrease in the peak of carbonyl group of PVP would indicate hydrogen bond formation between the amide carbonyl group at the surface of PVP particles and the carboxyl group of IM molecules by co-grinding. We therefore conclude that hydrogen bonds can be formed between the drug and the water-soluble carrier not only by the solvent evaporation technique but also by co-grinding.

As mentioned in our previous report (Watanabe et al., 2002a, accepted), changes in the standardized full width at half maximum (SFWHM) of the NMR peak at around 60 ppm are closely related to the disordering of the IM molecular structure and to the AES of IM. Therefore, we estimated the AES of IM in the IM–PVP mixtures ground for 30 and 180 min, on the basis of the NMR spectra. Since no peak interference for the peak assigned to $-CH_3$ of IM in Fig. 2 was observed by peaks from PVP, the full width at half maximum (FWHM) of this peak was estimated. The SFWHM correlated linearly with the logarithm of AES for the IM–SiO_2 system (Watanabe et al., 2002a, accepted), and the correlation coefficient was 0.995. The predicted AES of ground IM with PVP for 30 and 180 min were 41.1 and 78.3 μg/ml, respectively, based on the relationship established between the logarithm of AES and the SFWHM for the IM–SiO_2 system. The predicted values of AES were in agreement with the observed values, 42.9 ± 0.9 and 77.1 ± 1.6 μg/ml (the mean ± S.D., $n = 6$). Thus, the AES of IM in the IM–PVP mixture could be predicted by the relationship between the AES and the SFWHM obtained from the IM–SiO_2 system.

The comparison between SiO_2 and PVP as carriers is summarized in Table 1. Employing PVP or SiO_2 employed as carriers for co-grinding accelerated the amorphization of crystalline IM. The mechanism of interaction between PVP and IM is by the hydrogen bond, while that between SiO_2 and IM is by a hetero Si–O–C bond (Watanabe et al., 2001, 2002b). Judging from the applicability of the relationship established between the AES and the SFWHM in the IM–SiO_2 system, we conclude that AES can be determined solely by the state of IM, in other words,

Table 1
Comparison of PVP and SiO_2 as carriers

Carrier	PVP	SiO_2		
Organic/inorganic	Organic polymer	Inorganic		
Solubility in water	Water soluble	Water insoluble		
Mechanism of interaction between the carrier and IM	Hydrogen bond	Hetero Si–O–C bridging bond		
Preparation method of solid dispersions	Co-grinding for 30 min	Co-grinding for 180 min	Melt-quenching	Co-grinding for 180 min
Observed AES of IM (the mean ± S.D., $n = 6$)	42.9 ± 0.9 μg/ml	77.1 ± 1.6 μg/ml	89.3 ± 1.8 μg/ml	87.2 ± 2.1 μg/ml
Predicted AES of IM	41.1 μg/ml	78.3 μg/ml	87.2 μg/ml	86.3 μg/ml

disordering of the IM structure, irrespective of the carrier species and despite the carrier-dependent chemical interaction.

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