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Research Paper

Molecular Interaction among Probucol/PVP/SDS Multicomponent System Investigated by Solid-State NMR

Adchara Pongpeerapat,[1] Kenjirou Higashi,[1] Yuichi Tozuka,[1] Kunikazu Moribe,[1] and Keiji Yamamoto[1,2]

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Purpose. Effects of polyvinylpyrrolidone (PVP) molecular weight on the solid-state intermolecular interactions among probucol/PVP/sodium dodecyl sulfate (SDS) ternary ground mixtures (GM) and the formation of nanoparticles were investigated by solid-state NMR spectroscopy.
Materials and Methods. Ternary GMs of probucol were prepared with PVP (K12, K17, K30 or K90) and SDS at a weight ratio of 1:3:1 and were ground for 15, 30 and 60 min. Solid-state interactions were evaluated using powder X-ray diffraction (PXRD) and solid-state cross polarization/magic angle spinning (CP/MAS) ^{13}C NMR spectroscopy. A high resolution scanning electron microscopy (SEM) was employed to observe nanoparticles of probucol in the GM.
Results. The solid-state ^{13}C CP/MAS NMR results indicate that the low molecular weight PVP interacts with probucol and SDS more strongly than the high molecular weight PVP in the ternary GM. This finding was consistent with the result that smaller drug nanoparticles were obtained using low molecular weight of PVP. SEM images of probucol/PVP K12/SDS confirmed the presence of nanoparticles (15–25 nm) in the GM.
Conclusions. Grinding-induced solid-state interactions among drug, PVP and SDS could be detected using solid state ^{13}C NMR. The interactions in both probucol-PVP and PVP-SDS should occur simultaneously to generate nanometer-sized particles of probucol.

KEY WORDS: grinding; nanoparticle; polyvinylpyrrolidone; sodium dodecyl sulfate; solid-state NMR.

INTRODUCTION

Particle size reduction has been an effective method to improve the bioavailability of poorly water-soluble drugs. A mechanochemical method such as co-grinding, whereby pharmaceutical active ingredients are ground together with excipients, is a promising way to obtain a dispersed system (1–3). The mechanical stress brings about distortion of particles, amorphization, polymorphic transformation and molecular interaction between a drug and the additives (4). Several studies have revealed the grinding-induced particle size reduction and the enhanced dissolution rate (1–3). The co-grinding technique has some advantages for size reduction of solid active pharmaceutical ingredients due to the simple, organic solvent free, preparation process. However, conventional grinding commonly results in particle sizes greater than 1 μm due to aggregation. For the effective size reduction of drug particles, water-soluble polymers and surfactants have been used as additives to inhibit particle agglomeration and improve the dissolution properties of the drug (1–3). Polyvinylpyrrolidone (PVP), a water soluble polymer, is commonly used in a variety of pharmaceutical formulations due to its low toxicity and chemical stability. The improved stability and dissolution properties of hydrophobic drugs prepared with PVP has been demonstrated (5–8). Sodium dodecyl sulfate (SDS) has been used as an emulsifying agent in pharmaceutical formulations. Because of intrinsic toxicity problems, SDS is often used in combination with other excipients to obtain enhanced solubility and dispersion stability of drug particles (9,10). Combined use of SDS and PVP can be also applicable to prepare stable drug nanosuspension as in the case of drug/PEG/SDS system (10). There are many studies, which have demonstrated the PVP-SDS interactions in aqueous solutions (11–13). However, detailed information of PVP-SDS interactions in the solid state is not readily available.

Solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopy has been recognized as a powerful method for the study of pharmaceutical materials in solid state. The combined techniques of cross polarization (CP) and magic angle spinning (MAS) give high-resolution ^{13}C spectra, and molecular level information. The application of solid-state NMR spectrometry to the characterization of solids is particularly attractive due to the sensitivity of the chemical shift to molecular conformation, and the chemical environment in the crystal structure (14). Solid-state ^{13}C spectroscopy has been used for the analysis of the amorphous content, polymorphs, mixed crystals and mixtures of drugs in the presence of excipients (14–18). The technique also can be used for the investigation of intermolecular interactions in

[1] Department of Pharmaceutical Technology, Graduate School of Pharmaceutical Sciences, Chiba University, 1–33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan.
[2] To whom correspondence should be addressed. (e-mail: yamamotk@p.chiba-u.ac.jp)

drug-excipient binary formulation, though it has been rarely applied to multi-component systems.

The ternary system of a poorly water soluble drug with polymer and surfactant should be a potential candidate for the formation and stabilization of drug nanoparticles. Our previous study demonstrated that drug/polymer/surfactant ternary grinding was a promising method to prepare drug nanoparticles (19–21). Drug/PVP K17/SDS at a weight ratio of 1:3:1 was a representative composition applied to hydrophobic drugs (19,20) and the drug nanosuspension prepared from the ternary ground mixture (GM) was stable for at least for 1 month (20). The study of molecular interactions among components of the drug/PVP/SDS ternary system should provide crucial information concerning the role of PVP and SDS in drug nanoparticle formation. Further investigations of drug-additive interactions at the molecular level would be an attractive approach to get better insight into the possible mechanisms for nanoparticle formation. The aim of this study is to investigate the effects of PVP molecular weight on the solid-state intermolecular interactions among components of probucol/PVP/SDS ternary system and the resulting nanoparticle formation by solid-state NMR spectroscopy. Probucol, which is one of the cholesterol-lowering agents used in the treatment of hypercholesterolemia, was used as a model drug.

MATERIALS AND METHODS

Materials

Probucol (Form I) was supplied by Daiichi Pharmaceutical Co., Ltd. (Japan). Probucol has two crystalline forms (Forms I and II) and is practically insoluble in water (5 ng/ml at 25°C). Melting point of probucol Form I and II are 126 and 116°C, respectively. PVP K12 (Kollidon® 12 PF, M_w ~2,500) was obtained from BASF Japan Ltd. PVP K17 (Plasdone® C15, M_w ~10,000), PVP K30 (Plasdone® K29/32, M_w ~50,000) and PVP K90 (Plasdone® K90, M_w ~1,000,000) were obtained from ISP Technologies, Inc. (USA). SDS was purchased from Wako Pure Chemical Industries Ltd. (Japan). All other chemicals used were of reagent grade.

Preparation of GM

Probucol (0.500 g), PVP (1.500 g) and SDS (0.500 g) (weight ratio of 1:3:1) were physically mixed in a glass vial using a vortex mixer (physical mixture, PM). For the preparation of ternary GMs, the PM was ground in a vibrational rod mill (TI-200, Heiko Seisakusho, Japan) for 30 min. The grinding was performed under ambient room conditions, with no temperature control or monitoring. The grinding cell was made of aluminium oxide. For the binary system, probucol (0.625 g) and PVP (1.875 g) or probucol (1.250 g) and SDS (1.250 g) were ground by the same method as described above.

Preparation of Freeze-Dried PVP K90/SDS 3:1

PVP K90 (3.00 g) and SDS (1.00 g) were dissolved in 8.00 ml of distilled water. The sample was frozen at −196°C in a liquid nitrogen. Then, the sample was freeze-dried under 8 Pa, with a trap temperature of −45°C for 48 h, using EYELA freeze dryer FD-1000 (Tokyo Rikakikai Co., Ltd., Japan).

Powder X-ray Diffraction (PXRD) Measurement

PXRD measurements were performed in triplicate on a Rigaku Miniflex diffractometer (Tokyo, Japan), at a voltage of 30 kV, a current of 15 mA, a scanning speed of 4° min^{-1}, and a CuKα radiation source.

Particle Size Analysis

The GM was dispersed into distilled water and then sonicated for 2 min to make the suspension. The drug amount in the suspension was fixed as 0.50 mg/ml. Particle size was determined by the dynamic light scattering method using Microtrac UPA® (Nikkiso, Japan; measurement range: 0.003–6 μm) and by the light scattering method using Microtrac FRA® (Nikkiso, Japan; measurement range: 0.1–700 μm).

Solid-State NMR Spectroscopy

^{13}C-NMR spectra were measured in triplicate on a JNM-LA400 NMR spectrometer (JEOL, Japan) operating at 100.4 MHz with a CP/MAS (cross-polarization/magic angle spinning) probe. The sample (*ca*. 200 mg) was placed in a cylindrical rotor made of ceramic materials, and spun at 5,000 Hz. The contact time and the repetition time were fixed at 5 ms and 5 s, respectively. The spectral width and number of data points were 40 kHz and 16,384, respectively. To achieve an appropriate signal-to-noise ratio, the number of accumulations was 10,000 for ternary systems and 2,260 for intact and binary systems. Experimental conditions were as follows: temperature at 25.0°C, a ^{1}H decoupling field amplitude of 50 kHz, and a rf field amplitude for cross polarization of 50 kHz. The wave separation of ^{13}C-NMR spectra was estimated with computer-fitted curves using ALICE2 software (JEOL, Japan).

High Resolution Scanning Electron Microscopy (SEM) Analysis

High resolution SEM was performed using a Nova 200 NanoLab (FEI Company, Japan) operated at 3 kV. A sample was fixed to a SEM stage using a carbon paste then coated with a platinum sputter.

RESULTS AND DISCUSSION

Particle Size Analysis

We have been previously performed particle size analysis for the suspensions of poorly water-soluble drug /PVP K17/SDS ternary GM at a weight ratio of 1:3:1, and shown good stability and high recovery of the drug nanoparticles (19,20). Since the physicochemical properties of additives affected the recovery and the particle size of the obtained drug nanoparticle, the effect of the PVP molecular weight on nanoparticle formation was investigated. Four kinds of PVP with different molecular weight were used to prepare the

Table I. Mean Particle Size of Probucol Nanoparticles Obtained from Ternary Ground Mixtures of Probucol/PVP/SDS 1:3:1 After Dispersing into Distilled Water

Ternary Ground Mixture	Mean Particle size (nm)		
	Ground for 15 min	Ground for 30 min	Ground for 60 min
Probucol/PVP K12/SDS	79 ± 9.2	16 ± 1.3	14 ± 1.7
Probucol/PVP K17/SDS	125 ± 1.8	90 ± 1.5	64 ± 4.7
Probucol/PVP K30/SDS	763 ± 7.4	150 ± 6.6	65 ± 6.2
Probucol/PVP K90/SDS	9706 ± 16.7	5279 ± 11.9 (181 ± 3.8*)	3934 ± 71.6

Data represent mean ± SD of three trials.
* Samples were prepared by grinding probucol with freeze-dried PVP K90/SDS.

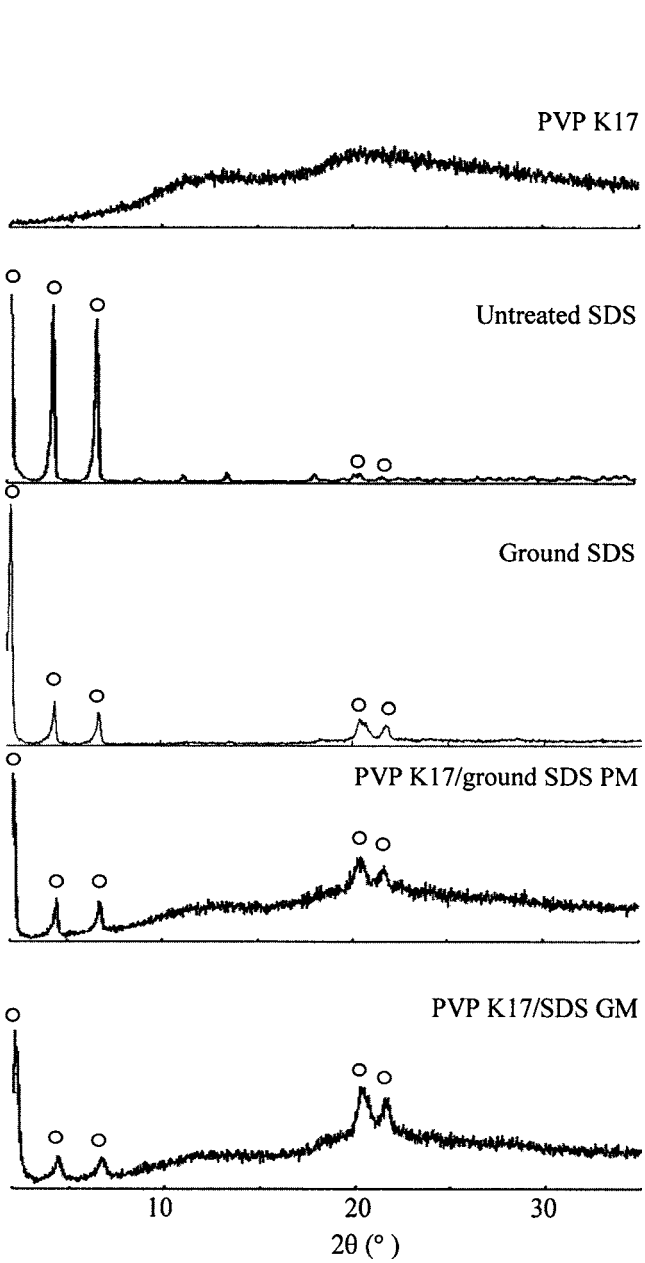

Fig. 1. PXRD patterns of PVPK17, untreated SDS, ground SDS, the physical mixture (PM) of PVP K17 and ground SDS, and a ground mixture (GM) of PVP K17 and SDS. The binary mixtures of PVPK17 and SDS were prepared at a weight ratio of 3:1. *Unfilled circles* represent the characteristic peaks of SDS.

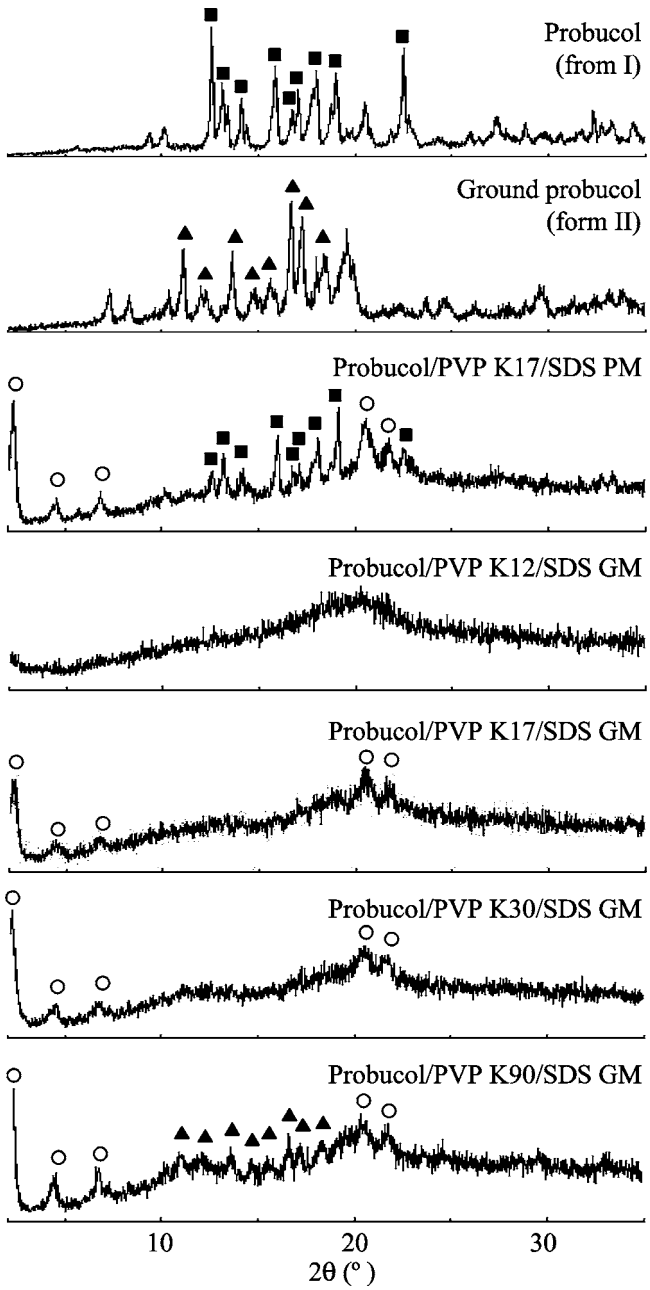

Fig. 2. PXRD patterns of ternary PM and GM of probucol/PVP/SDS. *Filled squares* and *triangles* represent the characteristic peaks of probucol form I and form II, respectively. *Unfilled circles* represent the characteristic peaks of SDS.

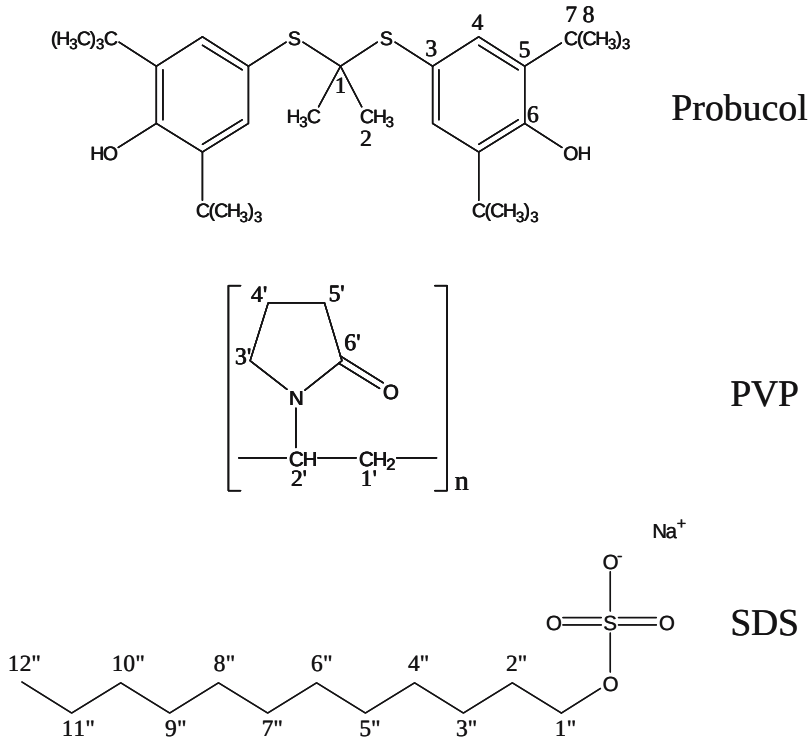

Fig. 3. The chemical structure of probucol, PVP and SDS. The numbering of the carbon atoms in the above structures corresponds to that in Figs. 4, 5, 6 and 8 for the ^{13}C CP/MAS NMR spectra.

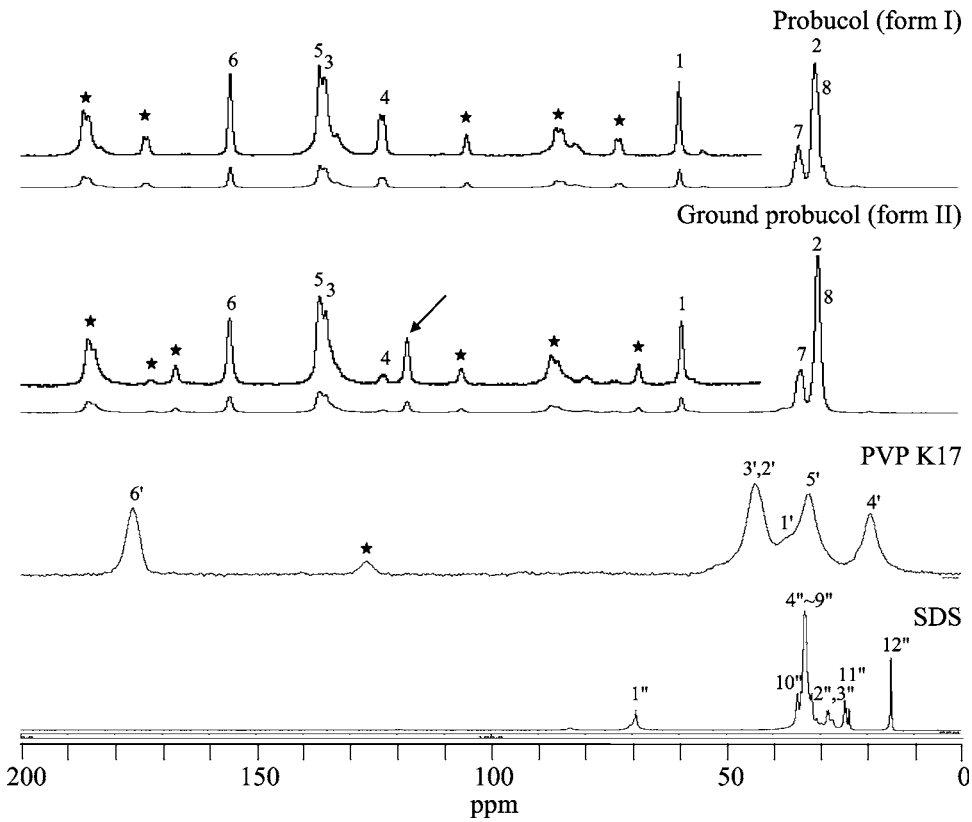

Fig. 4. ^{13}C CP/MAS NMR spectra of the materials used in this study. The *left sides* of probucol (form I) and ground probucol (form II) spectra were magnified and reproduced on top of each spectrum. The *arrow* indicates the characteristic resonance peak of probucol form II. *Stars* indicate the spinning sidebands.

ternary GMs. The mean particle size of GMs, after their dispersion into distilled water, is shown in Table I. Probucol nanoparticles could be obtained when the low molecular weight PVP (PVP K12, PVP K17, and PVP K30) was used as co-grinding additives, while PVP K90 did not show nanoparticle formation. Particle size reduction correlated with a decrease in the molecular weight of PVP. Moreover, the required grinding time for nanoparticle formation depends on the molecular weight of PVP. These results reflect the magnitude of interactions of the drug with additives, since the bulky PVP K90 showed no nanoparticle formation. For further understanding of interaction and mechanism of the drug nanoparticle formation, the physicochemical properties of the ground mixtures were characterized by PXRD, and solid-state CP/MAS ^{13}C-NMR spectroscopy.

Solid State Characterization by PXRD

The PXRD patterns of PVPK17, untreated SDS, ground SDS, the PM of PVP K17 and ground SDS, and the GM of PVP K17 and SDS are shown in Fig. 1. The positions of characteristic diffraction peaks observed in the binary GM of PVP K17 and SDS at 2θ = 2.2, 4.4, 6.7, 20.4 and 21.7, were the same as the PXRD pattern of the PVP/ground SDS PM. This indicated that the characteristic diffraction peaks observed in the PVP K17/SDS GM resulted from SDS.

Figure 2 shows X-ray diffraction patterns of probucol/PVP/SDS systems. Probucol intact (stable form I) transformed into metastable form II after grinding. The ternary PM shows characteristic X-ray diffraction peaks of both probucol crystals and SDS crystals. No diffraction peak of probucol was observed in the ternary GMs of probucol with PVP and SDS, except for the GM prepared with PVP K90. Co-grinding of probucol with a low molecular weight PVP seemed to promote the interaction between probucol and PVP through hydrogen bonding interaction between the drug hydroxyl group and carbonyl function of PVP as has been reported by Broman *et al.* (8). Generally, grinding causes extremely small sizes of crystallite or micro-assemblies of molecules. These small particles, surrounded by additives, do

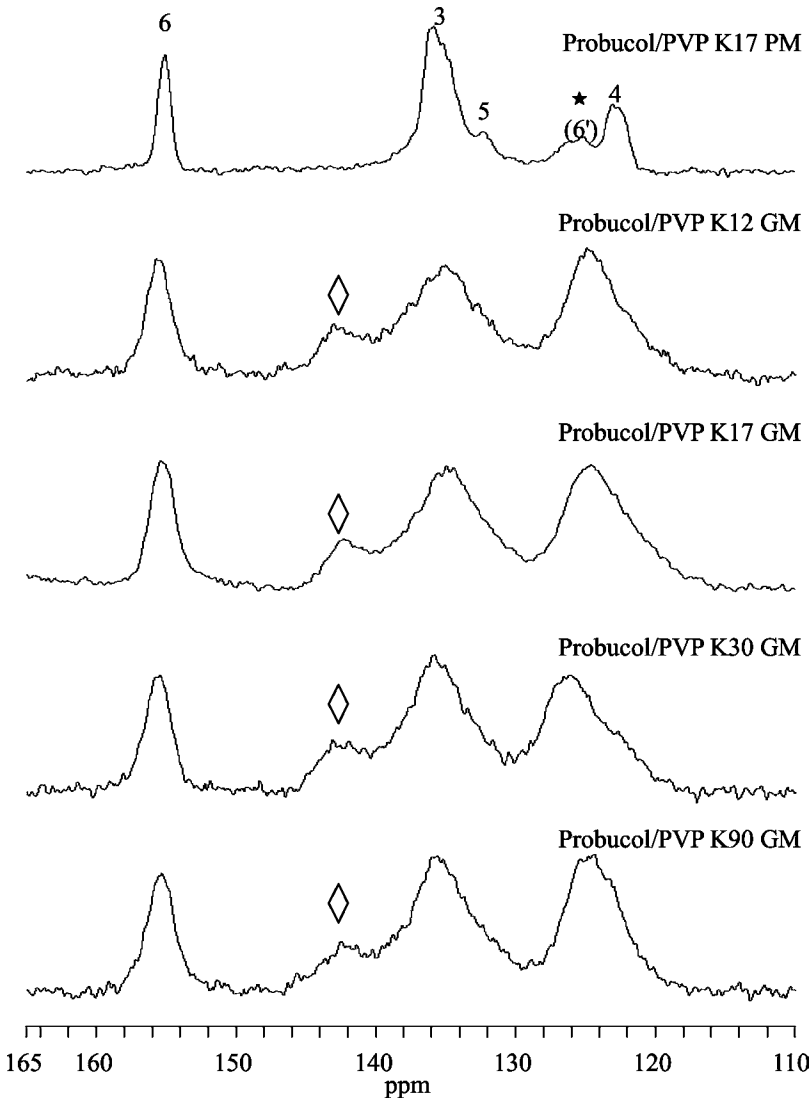

Fig. 5. ^{13}C CP/MAS NMR spectra of binary PM and GMs of probucol/PVP. *Diamonds* represent the new peaks. The *spinning sideband* of the resonance peak of the carbonyl carbon (C-6′) of PVP is depicted as a star with the corresponding carbon number.

not shown any clear diffraction peaks in the X-ray diffractogram. It was speculated that the probucol molecules existed in an amorphous state and/or as very small crystallite. On the other hand, ternary GMs with a high molecular weight PVP K90 exhibit the diffraction peaks of probucol of polymorphic form II, which are similar to that of simple grinding of probucol. Molecular interaction between probucol and PVP K90 appeared to be difficult to form during grinding process.

Solid-State ^{13}C CP/MAS NMR Study

^{13}C CP/MAS NMR Spectra of Probucol, Ground Probucol, PVP and SDS

The chemical structures and ^{13}C CP/MAS NMR spectra of probucol, PVP and SDS are shown in Figs. 3 and 4, respectively. The solid-state ^{13}C spectrum of each component was assigned on the basis of the solution ^{13}C NMR spectra and literature data for similar systems (11,23,24). The untreated probucol exhibited the resonance peak of the hydroxyl-substituted carbon in the phenolic ring (C-6) at 154.9 ppm. Probucol polymorphs of forms I and II can be distinguished using ^{13}C CP/MAS NMR spectra. A characteristic resonance peak of probucol form II was found at 117.4 ppm. This resonance in NMR spectra arises from conformational changes, since the chain of C–S–C–S–C at the center of the probucol molecules extends and forms a symmetric structure in form I, but the symmetry is lost in form II (22).

Solid-State Interactions in the Binary Ground Mixture of Probucol/PVP

Molecular interactions between probucol and PVP were investigated by solid-state NMR (Fig. 5). The NMR spectrum of the binary PM was identical to the superposition of the spectra of probucol and PVP. All GMs exhibited the same changes in NMR spectra regardless of the PVP molecular weight. The NMR spectra of probucol in all binary GMs show a peak broadening and the downfield shift of the hydroxyl carbon, together with the new broad NMR peak at around 143 ppm. No resonance of probucol polymorph form II was observed.

Solid-State Interaction in the Ternary Ground Mixture of Probucol/PVP/SDS

Figure 6 shows ^{13}C spectra of the ternary PM and GMs with four kinds of PVP. The ^{13}C spectra are especially focused on two regions: hydroxyl carbon (C-6) and aromatic carbon of probucol (C-3 to C-5) in the range 110–165 ppm, and sulfate carbon of SDS (C-1′) in the range 60–80 ppm.

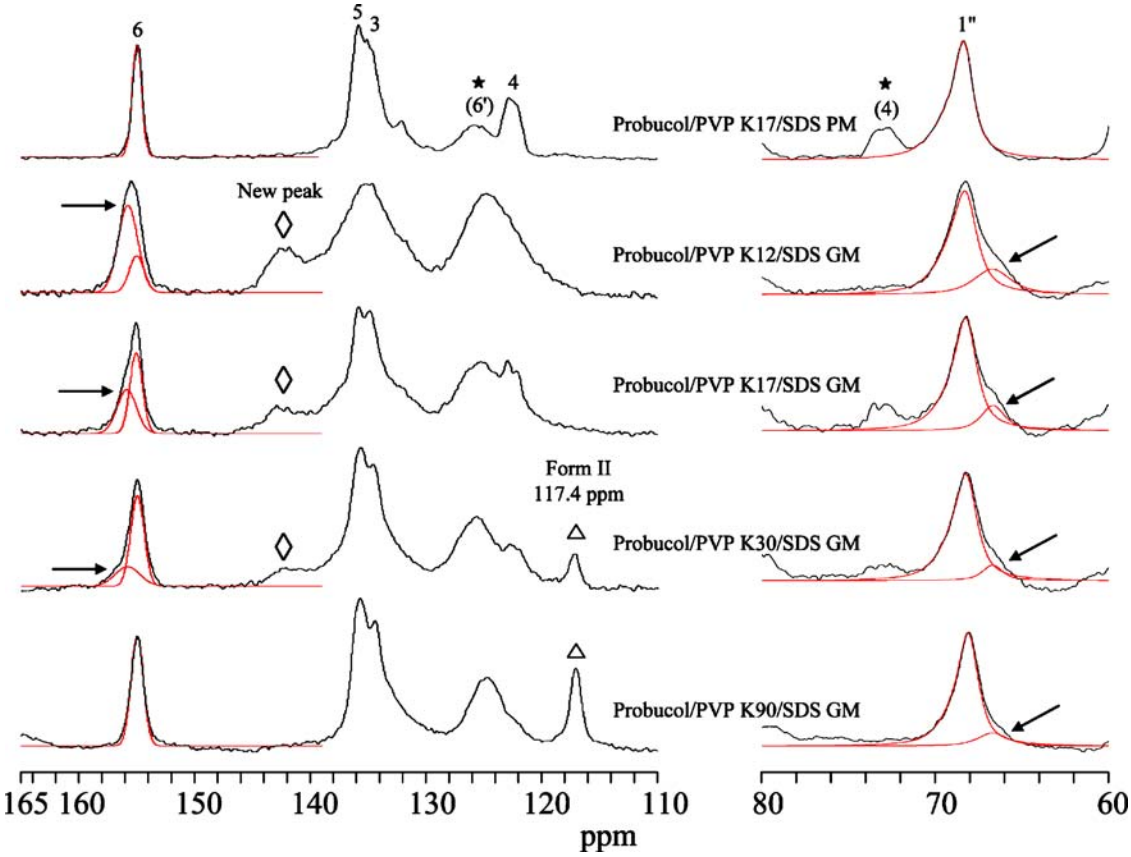

Fig. 6. Effect of PVP molecular weight on ^{13}C CP/MAS NMR spectra of ternary GMs of probucol/PVP/SDS. *Arrows* indicated changes in chemical shift of probucol and SDS. *Diamonds* and *triangles* represent the new peaks and characteristic resonance peak of probucol form II, respectively. The *spinning sidebands* of the resonance peak of the aromatic carbon (C-4) of probucol and the carbonyl carbon (C-6′) of PVP are depicted as *stars* with the corresponding carbon numbers.

The spinning sidebands of the resonance peak of the aromatic carbon (C-4) of probucol and the carbonyl carbon (C-6′) of PVP were depicted as stars with the corresponding carbon numbers. The spectrum of the ternary PM shows no significant interaction among probucol, PVP and SDS. The C-6 resonance of probucol (around 155 ppm) in the ternary GM with PVP K12, 17 or 30 exhibited some peak broadening. When peak separation was performed using computer-fitted curves (ALICE2 software, JEOL, Japan), it was found that the signal consisted of two components: the downfield shifted peak resulted from the probucol-PVP interaction (155.7 ppm) and the original peak of probucol crystals (154.9 ppm). This shift was consistent with the formation of a hydrogen bonding interaction between the drug hydroxyl group and carbonyl group of PVP (8,24). The intensity of the resonance from probucol-PVP interaction increased in the order of PVP K30< K17< K12, whereas the downfield shift was not observed in the ternary GM with PVP K90. A new broad peak around 143 ppm (◊), arising from changes in the resonance of aromatic carbon of probucol, was observed in the GMs with PVP K12, K17, and K30. On the contrary, the ternary GM prepared with PVP K90 did not show a new broad peak around 143 ppm, whereas it exhibited a new characteristic peak of probucol form II at 117.3 ppm. Interestingly, the ternary GM with PVP K30 obviously shows the form II peak that could not be detected in PXRD patterns. These results showed that solid-state NMR spectroscopy has an advantage in the detection of the polymorphic transition of probucol crystals in the microenvironment.

With respect to the NMR resonance from SDS carbons, the ternary PM exhibited the characteristic signals from the C-1′ carbon of SDS at 68.3 ppm. The ternary GMs showed a shoulder peak at around 66.7 ppm. The curve fitting revealed that the shoulder peak was caused by the upfield shift from 68.3 to 66.7 ppm resulting from the PVP-SDS interaction. Complexation of PVP and SDS both through electrostatic and hydrophobic interactions in aqueous solutions was reported by several studies (11–13). An electrostatic interaction should exist between the negatively charged SDS head group and the nitrogen atom on the pyrrolidone ring of PVP (11). Roscigno *et al.* also reported that the electrostatic interaction was assisted by the attractive interaction between the negatively charged PVP oxygen ($N^+ = C-O^-$) and the electron poor C-1′ of sodium decyl sulfate (23). The highfield shift of the resonance of SDS increased with the decrease of molecular weight of PVP. This result is consistent with the fact that the low molecular weight PVP had greater effects on interactions of ibuprofen or piroxicam with PVP (5,7).

The results from the solid-state ^{13}C NMR spectra indicated that the interactions of both probucol-PVP and PVP-SDS increased with the decrease of PVP molecular weight (PVP K90< PVP K30< PVP K17< PVP K12). It was suggested that grinding-induced interactions brought about the achievement of molecular dispersion. As the greatest extent of interactions was found in the ternary GM prepared with PVP K12, the smallest nanoparticles would be obtained. Particle size analysis demonstrated that the size of probucol nanoparticles obtained from the probucol/PVP K12/SDS GM was significantly reduced to 16 nm. As reported in our previous study (20), zeta-potential measurements indicated that PVP and SDS were on the surface of the drug nanoparticles. Smaller nanoparticles were obtained from the ternary GM of PVP K17 and PVP K30 when the experiments were conducted at the optimum conditions such as ternary composition and grinding time. As shown in Table I, when the grinding time was increased to 60 min, an effective particle size reduction to approximately 65 nm could be achieved from the ternary ground mixtures with PVP K17 and K30.

It should be pointed out that a color change induced by mechanical stress was observed. The ternary GMs prepared from PVP K12, PVP K17 and PVP K30 and also all the binary GMs of probucol/PVP produced a pink colored powder after grinding. These phenomena would be related to the appearance of a new broad resonance peak at around 143 ppm. No color change was observed for the ternary GM prepared from PVP K90, which did not show the new NMR peak at around 143 ppm and nanoparticle formation. HPLC quantitative analysis confirmed that this kind of change did not derive from a chemical decomposition of probucol. After GMs were dispersed into distilled water, suspensions did not display a pink color, indicating a reversible color change. Sheth *et al.* reported that, under mechanical stress, the colorless crystal piroxicam became yellow at the amorphous state due to charged piroxicam molecules formed by the intermolecular proton transfer (25). Although it is difficult to clarify the reason for pink coloration, the color change under

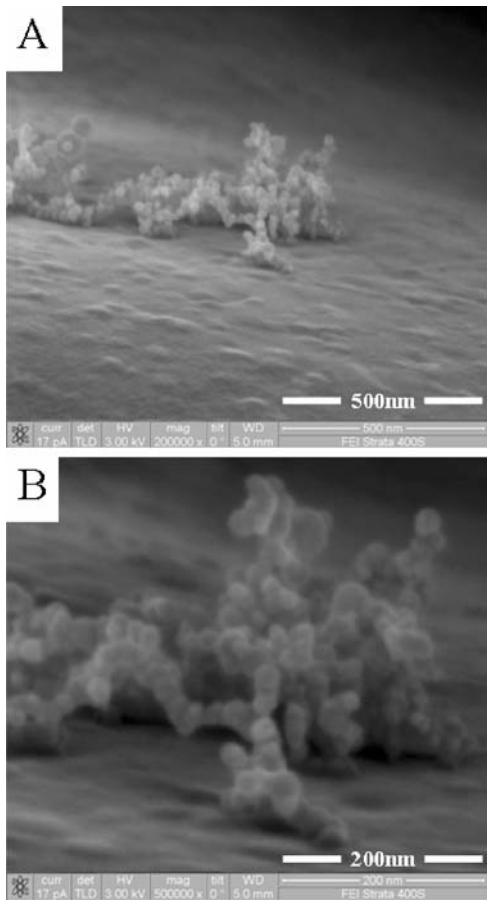

Fig. 7. SEM micrographs of probucol nanoparticles prepared from the ternary GM of probucol/PVP K12/SDS.

Table II. Mean Particle Size of the Probucol Nanoparticles Obtained from Ternary GMs* of Probucol/PVP K12/SDS 1:3:Y after Dispersing into Distilled Water

SDS Weight Ratio (Y) in the Ternary GM of Probucol/PVP K12/SDS 1:3:Y	Mean Particle Size (nm)
0.3	> 1 μm
0.4	> 500 nm
0.5	25 ± 9.1
1.0	16 ± 1.3
1.5	68 ± 3.0
2.0	126 ± 3.6
3.0	131 ± 2.8

Data represent mean ± SD of three trials.
* Grinding time 30 min.

mechanical stress might be associated with the solid-state disorder of probucol molecules at the particle surface, as a consequence of a solid-state interaction between the hydroxyl of probucol and the carbonyl of PVP induced by grinding.

Nanoparticle Morphology

SEM micrographs of the ternary GM of probucol/PVP K12/SDS are represented in Fig. 7. It is interesting to note that the agglomerates are composed of spherical nanoparticles with extremely small size of 15–25 nm for ternary GM prepared with PVP K12. In agreement with PXRD results, the halo pattern of probucol in the ternary GM could be due to the existence of the small crystallite of probucol. The SEM micrographs obviously show the formation of assemblies of drug nanocrystals in the ternary GM, induced by grinding. The mean particle size of probucol in the suspension was 16 nm (Table I), suggesting that the agglomeration of the dispersed probucol nanocrystals was inhibited, probably due to the adsorption of PVP and SDS onto the particle surface.

Effect of Ternary Compositions on Drug Nanoparticle Formation

The results of the binary system indicate that probucol interacts with PVP regardless of its molecular weight, whereas the interaction between PVP and SDS increases with decreasing molecular weight of PVP, suggesting that SDS may have a greater affinity for the end groups of the PVP chain. PXRD patterns demonstrated that the binary GM of SDS with PVP K12 was transformed into an amorphous state, while that with PVP K17 and K30 showed diffraction peaks of SDS (data not shown). Table II shows the mean particle size of probucol nanoparticles when the ternary PMs of probucol/PVP K12/SDS are ground at various SDS weight ratios: 1:3:0.3, 1:3:0.4, 1:3:0.5, 1:3:1, 1:3:2 and 1:3:3. A SDS ratio of at least 0.4 (1:3:0.4) was necessary to produce nanometer-sized particles. Ratios of 1:3:0.5 to 1:3:1 were the most appropriate at achieving a reduction of the particle size to 20 nm. The halo pattern of SDS was observed in the PXRD of these systems. In the GMs 1:3:2 and 1:3:3, the mean particle size of probucol increased when an excess amount of SDS crystals remained in the system. The characteristic X-ray diffraction of SDS crystals was observed in the PXRD of these systems. The solid-state interaction between PVP and SDS definitely played a key role in the formation of nanoparticles; however, excess amounts of SDS crystals, which does not interact with PVP, could obstruct the interaction between drug and polymer during the grinding process.

The accessibility of SDS into the polymer matrix in the solid-state was more difficult for the high molecular weight PVP, as shown in the GM with PVPK90. In order to solve this problem, a PVP K90/SDS solid dispersion prepared by freeze-drying method was used. PVP K90 and SDS (3:1) were dissolved into small amounts of water, and then freeze-dried before the grinding with probucol. NMR spectra of the ternary GM of probucol with freeze-dried PVP K90/SDS showed different results from that shown in Fig. 5. As illustrated in Fig. 8, the resonance of SDS in the ternary GM clearly moves upfield from 68.3 to 66.7 ppm due to PVP-SDS interactions, showing that a higher accessibility of SDS into PVP K90 was achieved by freeze-drying. The resonance of probucol in the ternary GM also moves downfield from 154.9 to 155.7 ppm, indicating a significant interaction between probucol and PVP K90. Moreover, the formation of 181 nm probucol nanoparticles was observed from a ternary GM of probucol with the freeze-dried PVP K90/SDS (Table I). These results indicated that the increase in the

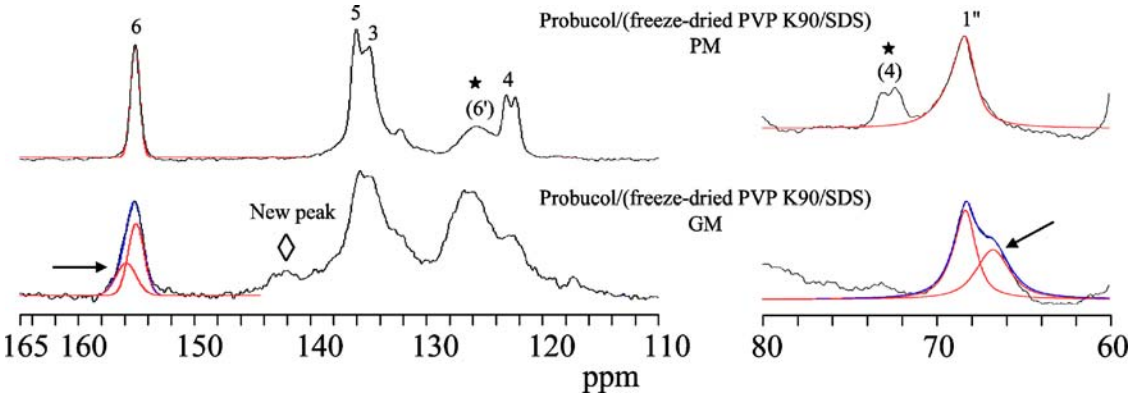

Fig. 8. ^{13}C CP/MAS NMR spectra of ternary PM and GM of probucol with freeze-dried PVP K90/SDS (3:1) at a weight ratio of 1:(3:1) ground for 30 min. *Arrows* indicate changes in chemical shift of probucol and SDS. The *diamond* represents the new peak. The *spinning sidebands* of the resonance peak of the aromatic carbon (C-4) of probucol and the carbonyl carbon (C-6′) of PVP are depicted as *stars* with the corresponding carbon numbers.

accessibility of SDS to the PVP polymer by freeze-drying could enhance the interactions between them.

CONCLUSION

The ^{13}C NMR studies reveal that the solid-state interactions of probucol/PVP and PVP/SDS on grinding play a key role for probucol nanoparticle formation. In the ternary GM, simultaneous grinding-induced interactions of probucol-PVP and PVP-SDS are enhanced by a decrease of the PVP molecular weight, leading to a size reduction of probucol crystallites. Binary mixtures of probucol and PVP show an interaction with PVP, regardless of its molecular weight, whereas the interaction in binary mixtures of PVP and SDS is significantly affected by the molecular weight of PVP. Consequently, the interactions of both probucol-PVP and PVP-SDS are required for nanoparticle particle formation of probucol. Solid-state NMR is a promising tool for revealing the molecular states of multicomponents in solid dosage forms.

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