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Nanoparticle formation from probucol/PVP/sodium alkyl sulfate co-ground mixture

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ABSTRACT

Nanoparticles of a poorly water-soluble drug, probucol, have been obtained by co-grinding with PVP and SDS. The purpose of this study was to investigate the effect of the alkyl chain length of sodium alkyl sulfates (C*n*S, *n* = 6, 8, 12, 16 and 18) on probucol nanoparticle formation. From the results of particle size determination and quantitative measurement of nanoparticle fraction of probucol by HPLC, it was found that the alkyl chain length of the sodium alkyl sulfate affected the probucol nanoparticle formation. The efficiency, based on the quantitative determination of nanoparticles, was in the order: C18S > C16S > C12S > C8S > C6S. Probucol nanoparticles of less than 800 nm were effectively produced (more than 95%) with the increase of the amount of surfactants. ^{13}C solid-state NMR of co-ground mixtures showed a new peak originating from the probucol interaction with PVP together with the existence of probucol crystal peaks. Excess amounts of surfactants were expected to play an important role for stabilizing the probucol nanoparticles in the suspension via the electrostatic repulsive effect.

1. Introduction

Among the orally administered solid pharmaceutical dosage forms, the dissolution of drug molecule is the key determinant in the amount of drug, which can be absorbed. However, as reported by Takagi et al. (2006), 30–40% of drugs on each list of the top 200 immediate-release drug products from the United States, Great Britain, Spain and Japan are categorized as practically insoluble drugs. The enhancement of drug solubility has been studied for many decades, and many techniques such as the complex formation with cyclodextrin (Leuner and Dressman, 2000; Brewster and Loftsson, 2002; Uekama, 2004), the solid dispersion of the drug with additives (Khan et al., 2000; Craig, 2002; Valizadeh et al., 2004), water-soluble prodrug formation (Hamada et al., 2004; Mántylá et al., 2004) and water-soluble salt formation (Zu et al., 2004; Nielsen et al., 2005) have been employed to increase the solubility of drugs. Additionally, according to the Noyes–Whitney equation, the particle size reduction, i.e., the increase of the particle surface area is the effective method to increase the dissolution rate.

The grinding method is a simple way to reduce the size of particles. However, the grinding of the drug substance alone is not effective enough to reduce the particle size and to obtain a physically stable drug formulation (Parrott, 1974). Addition of a water-soluble polymer and/or a surfactant as one of the components could resolve this problem and show satisfactory results. Several studies revealed that the co-grinding of a drug with additives induces the particle size reduction and enhances the dissolution rate (Suzuki et al., 2001; Vergote et al., 2002; Merisko-Liversidge et al., 2003). Mura et al. (2002) reported that co-grinding of glisentide with polyvinylpyrrolidone (PVP) evidently shows a better dissolution profile due to the size reduction, polymorphic transformation and amorphization. Mechanical stress during the grinding process induces distortion of particles, amorphization and molecular interaction between the drug and the additives (Saleki-Gerhardt et al., 1994; Juhász, 1998; Brittain, 2002).

From our previous study, it has been revealed that co-grinding of several poorly water-soluble drugs, such as griseofulvin, phenytoin and probucol, with PVP and sodium dodecyl sulfate (SDS) is an effective method to produce aqueous nanosuspensions (Pongpeerapat et al., 2004). The average size of the drug nanoparticles measured in water was less than 200 nm, and stable at least for 2 weeks. Polyvinylpyrrolidone is regarded as an essentially nontoxic water-soluble polymer, which can improve the solubility profile of a number of poorly water-soluble drugs (Walking, 1994). Sodium dodecyl sulfate is an anionic surfactant that has been employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics (Behn, 1994).

It has been reported that intermolecular interactions among the components, drug/polymer/surfactant, were hypothesized as the key factor of drug nanoparticle formation (Pongpeerapat et al., 2006; Moribe et al., 2006). The effect of molecular weight of PVP on drug nanoparticle formation has been investigated by

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Pongpeerapat et al. (2006). These authors reported that, from the ^{13}C solid-state NMR results, the lower molecular weight PVP interacted with probucol and SDS more strongly than the high molecular weight PVP when the ternary mixture was ground. As a result, the smaller probucol nanoparticles were obtained using low molecular weight of PVP. The effect of species of polymer on drug nanoparticle formation from the drug/polymer/SDS ternary ground system has also been reported by Moribe et al. (2006). They found that hydroxypropylmethylcellulose (HPMC) or methylcellulose (MC) instead of PVP could produce flurbiprofen nanoparticles.

The solubility of probucol in water was estimated to be around 2–5 ng/mL at 25 °C (Yagi et al., 1996). Probucol also showed a low absorption profile when orally administered. The maximum blood plasma concentration after oral administration of 1 g probucol tablet to male patients was only 0.0002% (Zaitseva et al., 1995). Thus probucol is classified as class 2 drugs according to the biopharmaceutical classification system (Amidon et al., 1995). Nanoparticle formation of probucol by the co-grinding method appeared to be a promising approach to improve its bioavailability when orally administered (Shudo et al., 2008). Understanding the role of drug and additives on the solid-state formation of nanoparticles will provide crucial benefits in selecting appropriate additives and ratio of the components for producing drug nanoparticles. The objective of this study was to investigate the role of surfactants on probucol nanoparticle formation from ternary co-grinding of probucol/PVP/surfactant. We focused on the alkyl chain length of sodium alkyl sulfate and the weight ratio of the ternary ground system. The particle size distribution of the ternary ground mixture (GM) was determined by the dynamic light scattering technique. Physicochemical properties of ground mixture were investigated by ^{13}C solid-state NMR measurements. Quantitative determination of probucol in aqueous suspension was determined by HPLC. The stability of probucol nanoparticle suspended in water at 25 °C was also investigated by monitoring the change of the mean particle size.

2. Materials and methods

2.1. Materials

Probucol (form I) was provided by Daiichi-Sankyo Pharmaceutical Co., Ltd. (Tokyo, Japan). PVP K17 (Plasdone® C15, $M_w \sim 10{,}000$) was obtained from ISP Technologies Inc. (Wayne, NJ). Anionic surfactants, the sodium hexyl sulfate (C6S, purity 99%) was purchased from ChemPur Feinchemikalien and Forschungsbedarf GmbH (Karlsruhe, Germany), sodium octyl sulfate (C8S, purity 95%) and sodium octadecyl sulfate (C18S, purity 93%) were purchased from Sigma–Aldrich, Inc. (St. Louis, MO). Sodium dodecyl sulfate (C12S, SDS, purity 95%) and sodium hexadecyl sulfate (C16S, purity 98%) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All chemicals were used as received.

2.2. Methods

2.2.1. Preparation of physical mixture (PM) and ground mixture (GM)

The weight ratio of probucol/PVP was fixed at 1/3. The weight ratio of probucol, PVP and surfactant was presented as 1/3/*x*, where *x* was the weight ratio of surfactant. The value of *x* varied from 0.1 to 1. The physical mixture (PM) was prepared by mixing probucol and additives in a glass vial for 5 min using vortex mixture. For the preparation of the ternary ground mixture (GM), 3.0 g of physical mixture was ground in a vibrational rod mill (TI-500ET, CMT Co., Ltd., Tokyo, Japan) for 30 min. Temperature of the grinding process was controlled and maintained at 10 ± 5 °C using a nitrogen-gas flow cooling device. The grinding cell and the rod were made of stainless steel.

2.2.2. Particle size analysis and stability study of probucol nanoparticles in water

The volumetric particle size distribution for each suspension was determined at 25 °C by the dynamic light scattering method using Microtrac UPA® or Microtrac FRA® (Nikkiso, Tokyo, Japan). The detection range of UPA was 0.003–6 μm, and that of FRA was 0.1–700 μm. The ground mixture powder was dispersed into distilled water at the drug concentration of 0.5 mg/mL and then sonicated for 2 min. Stability study was conducted at 25 °C for 21 days. The particle size distribution was measured at a predetermined period of time, i.e. 0 and 4 h then 1, 3, 7, 14 and 21 days.

2.2.3. Quantitative determination of the probucol as nanoparticles

To determine the quantity of probucol in suspensions, 0.50 mg/mL of probucol suspensions were prepared. The suspension was passed through a 0.8 μm membrane filter (nitrocellulose filter, Millipore®, Billerica, MA) to exclude the large particles. The filtrates obtained were diluted with the HPLC mobile phase solution (acetonitrile/distilled water 92.5/7.5, v/v). The drug concentration in nanoparticle fractions was determined using HPLC (LC-6A, Shimadzu Co., Kyoto, Japan). The mobile phase was delivered at a flow rate of 1.0 mL/min through a C-18 Inertsil® ODS-2 (4.6 mm I.D. × 150 mm; GL Sciences Inc., Tokyo, Japan) at 40 °C with the detection wavelength of 254 nm.

2.2.4. Solid-state nuclear magnetic resonance (NMR) spectroscopy

All ^{13}C solid-state NMR spectra were acquired using a JNM-ECA600 NMR spectrometer that has a magnetic field of 14.09 T (JEOL, Tokyo, Japan) and operates at 150 MHz for ^{13}C. Samples (ca. 100 mg) were placed as powders into 4 mm silicon nitride (Si_3N_4) rotors. All spectra were acquired using variable amplitude cross-polarization (CP) together with magic angle spinning (MAS) at 15 kHz and a high-power two-pulse phase-modulation ^1H decoupling. For each spectrum, a total numbers of accumulations (7000 for ternary systems and 3000 for an unprocessed sample) were obtained depending on the signal-to-noise ratio required. Pertinent acquisition parameters include relaxation delays of 3 s for all experiments, a cross-polarization (CP) contact time of 5 ms and a ^1H 90° pulse of 2.7 μs. The total of data points was 2048 in each experiment and zero-filled to 8192 points. All spectra were externally referenced to tetramethylsilane by setting the methine peak of adamantane to 29.5 ppm. The wave separation of ^{13}C solid-state NMR spectra was performed with computer-fitted curves using the Delta™ NMR Data Processing Software (JEOL, Tokyo, Japan).

3. Results and discussion

3.1. Stability of ground mixtures in water and quantitative analysis of probucol nanoparticle formation

From our preliminary study, the binary grinding of probucol was not enough to reduce the particle size of probucol to the nano-range. The mean particle sizes of probucol in the binary ground mixture of probucol/PVP (1/3, w/w) and probucol/C12S (1/1, w/w) were 23.0 and 23.8 μm, respectively. On the other hand, the mean particle size of ternary ground mixture of probucol/PVP/C12S (1/3/1, w/w/w) was successfully reduced to 90 nm (Pongpeerapat et al., 2008). Particle size analysis of the suspension of the ternary ground mixture composed of probucol, PVP and various kinds of sodium alkyl sulfate with different chain lengths was performed. The results are summarized in Table 1. The scanning electron micrograph of similar co-ground mixture, probucol/PVP K12/C12S, showed aggregates of 15–25 nm of spherical nanoparticles (Pongpeerapat et al.,

Table 1
Mean particle size of ternary ground mixtures of probucol/PVP/sodium alkyl sulfate at various weight ratios in distilled water.

Weight ratio	Mean particle size[a] (μm) ± S.D.				
	PBC[b]/PVP/C6S	PBC/PVP/C8S	PBC/PVP/C12S	PBC/PVP/C16S	PBC/PVP/C18S
1/3/0.1	19.2 ± 0.1	18.5 ± 0.2	14.6 ± 0.1	17.8 ± 0.0	11.4 ± 0.0
1/3/0.2	15.6 ± 0.4	14.6 ± 0.0	15.8 ± 0.6	10.2 ± 0.2	0.237 ± 0.043
1/3/0.3	15.1 ± 0.1	0.283 ± 0.066	0.079 ± 0.001	0.090 ± 0.002	0.132 ± 0.005
1/3/0.5	10.2 ± 0.0	0.065 ± 0.002	0.053 ± 0.003	0.091 ± 0.001	0.114 ± 0.003
1/3/1	0.083 ± 0.003	0.068 ± 0.002	0.086 ± 0.005	0.093 ± 0.003	0.090 ± 0.004

[a] Results are expressed as mean ± S.D. (n = 3).
[b] Abbreviation for probucol

2006). Polyvinylpyrrolidone and sodium alkyl sulfate were soluble in water at the concentration used in the experiment. Thus, the mean particle size obtained was assumed to be attributable to probucol nanocrystals. The mean particle size of probucol became smaller consistently with the increase of the surfactant ratio. A single and sharp particle size distribution at nano-range was observed when the optimum weight ratio of surfactant was reached in each co-ground system. At this optimum weight ratio, the mean particle size of probucol drastically decreased, and resulted in a percentage of nanoparticle (smaller than 800 nm) of more than 80%. For sodium octyl sulfate (C8S), the optimum weight ratio for the nanoparticle formation was evaluated between 1/3/0.3 and 1/3/0.5, while for C12S and C16S the weight ratio was between 1/3/0.2 and 1/3/0.3.

The percentage of probucol nanoparticle smaller than 800 nm was quantified by using HPLC and the results are shown in Fig. 1. At the same weight ratio, a more effective probucol nanoparticle formation was observed using the sodium alkyl sulfate with a longer alkyl chain. Percentage of probucol nanoparticles increased with the increase of the weight ratio of the surfactant. When the amount of surfactant exceeded the optimum weight ratio in each system, the excess amount of the surfactant did not affect the percentage of probucol nanoparticles obtained.

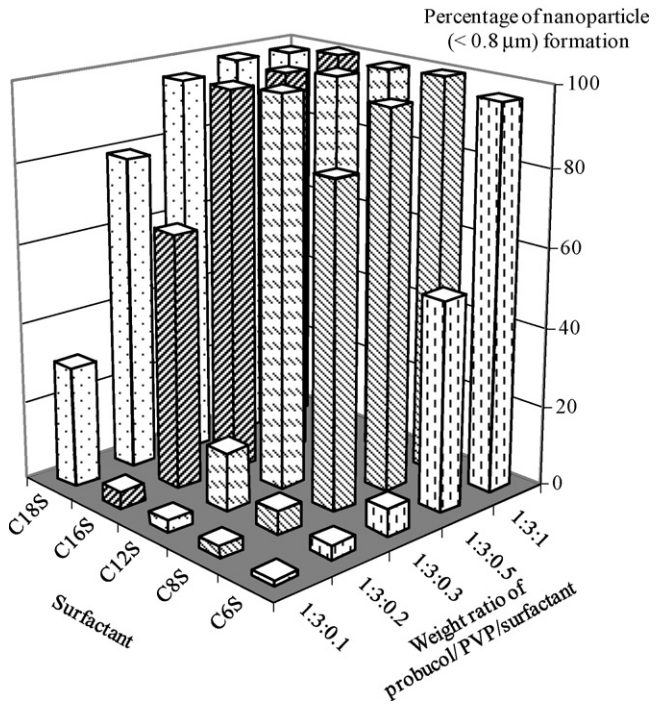

Fig. 1. Percentage of probucol nanoparticle (<0.8 μm) formation from ternary ground mixtures with various species and ratios of sodium alkyl sulfate surfactant determined by HPLC. For each measurement, the standard deviation (S.D.) was less than 2.0 (n = 3).

The optimal amount, the amount of surfactant required for the effective nanoparticle formation, was altered depending on the alkyl chain length of the surfactant used. For instance, when the surfactant with 6-carbon alkyl chain (C6S) was used, the percentage of nanoparticles formed was 1.3% at the weight ratio of 1/3/0.1 then increased up to ca. 100% when the weight ratio became 1/3/1. On the other hand, when the surfactant with a longer alkyl chain (C18S) was used, the percentage of nanoparticles was around 30% at the weight ratio of 1/3/0.1 then increased up to 96–99% at the weight ratio of 1/3/0.3.

A stability study of the nanoparticle in an aqueous phase was conducted from the particle size changes of the suspension (Fig. 2). Nanoparticles of probucol instantly formed after dispersing the ground mixture into water. The mean particle size was still less than 200 nm and was steadily suspended in water without occurrence of precipitation up to 21 days at 25 °C. Pongpeerapat et al. (2008) suggested that PVP K17 and SDS formed a necklace–structure complex in the suspension of ternary ground mixtures of probucol/PVP K17/SDS at the weight ratio of 1/3/1 (w/w/w). Surface covering of PVP–SDS complexes on probucol nanoparticles would result in stabilization of the probucol nanoparticles in the suspension.

Tadeschi et al. (2006) investigated the interaction between PVP and sodium alkyl sulfate in the solution state by electron paramagnetic resonance spectroscopy. They found that, at the surfactant concentration which was higher than the critical micelle concentration (CMC), the charge density of the surface of micelles increased in the order of C12S > C10S > C8S > C6S. They also reported about the strength of polymer–surfactant association when PVP (M_w 24,000; 1%, w/w) was introduced into the surfactant solution. The strength of the association increased with the increase of the alkyl chain length. Assuming from the interaction between PVP and sodium alkyl sulfate in the solution state, in solid state, sodium alkyl sulfate with a longer alkyl chain length was more favorable to interact with the nitrogen atom on the pyrrolidone ring of PVP through its negatively charged head groups. For smaller amounts, the surfactant with a longer alkyl chain could induce PVP to properly interact with probucol and produce the nanoparticles.

3.2. Solid-state nuclear magnetic resonance (NMR) spectroscopy

We have been investigating the physicochemical properties of ternary physical mixtures and ground mixtures by powder X-ray diffractometry. However, it was difficult to identify the molecular state of probucol and additives because most of ground mixtures exhibited the X-ray halo patterns. In PXRD patterns of ground mixtures, only surfactants showed sharp diffraction peaks regardless of the surfactants used. Thus, ^{13}C solid-state NMR was performed to investigate the molecular state of ternary components in the ground mixtures. The numbering of carbon atoms and ^{13}C solid-state NMR spectra of probucol, PVP, sodium hexyl sulfate and sodium dodecyl sulfate are presented in Fig. 3.

The molecular interaction among ternary components was expected to play an important role in particle size reduction. A

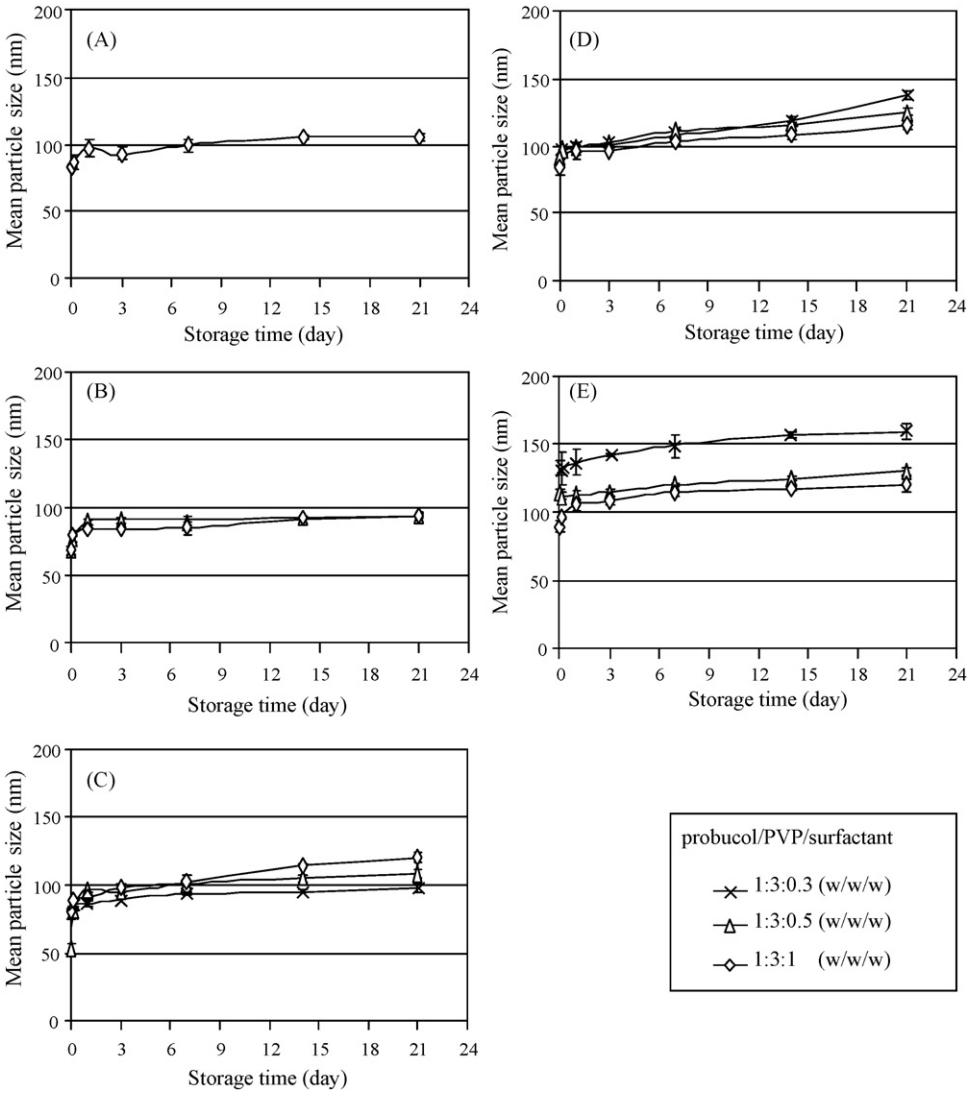

Fig. 2. Mean particle size of probucol/PVP/surfactant ternary ground mixtures in distilled water after storage at 25 °C for 21 days. (A) Probucol/PVP/C6S, (B) probucol/PVP/C8S, (C) probucol/PVP/C12S, (D) probucol/PVP/C16S and (E) probucol/PVP/C18S. Each point represents the mean ± S.D. ($n = 3$).

possible intermolecular interaction was proposed among probucol, PVP and C12S (Pongpeerapat et al., 2006). Probucol interacted with PVP through hydrogen bonding between the hydroxyl group at carbon 6 of probucol and the carbonyl group of PVP. An electrostatic interaction should exist between the negatively charged sulfate group of SDS and the comparatively positive nitrogen atom on the pyrrolidone ring of PVP. The intermolecular interaction among the components results in the change of the electromagnetic environment of particular carbon atoms which are connected to the interacting functional group. This electromagnetic change could be observed by ^{13}C solid-state NMR measurement.

Two regions of NMR spectra were the focus. The interaction between probucol and PVP could be observed at around 170–112 ppm, which represented the NMR signal of the hydroxyl carbon (C6) and the aromatic carbon (C3–C5) of probucol. The interaction between probucol and sodium alkyl sulfate was observed at around 72–65 ppm where the NMR signal of carbon 1″ connecting to the sulfate group of surfactant could be observed. Figs. 4 and 5 show the ^{13}C solid-state NMR spectra of probucol/PVP/C6S and probucol/PVP/C12S ternary components, respectively. In NMR spectra of both ternary ground mixtures, peaks of probucol (C3–C6) at 170–112 ppm became broad, independently of the surfactant content, compared with the peaks of the physical mixture. Moreover, a new peak due to the interaction between probucol and PVP was observed around 143 ppm (marked by ♦). Similar broad peaks and a new peak were observed in the NMR spectrum of binary ground mixture of probucol/PVP (1/3, w/w) (Pongpeerapat et al., 2006). However, no significant change of C3–C6 of probucol due to the interaction between binary ground mixture of probucol/SDS (1/1, w/w) was observed in the NMR results. Thus, the broad peaks reflected the molecular state change of probucol when PVP was present in the co-ground mixture.

In probucol/PVP/C6S ternary ground mixtures, the peak of carbon 1″ of C6S shifted from 69.1 to 67.4 ppm at the weight ratio of 1/3/0.3 (Fig. 4B) and to 67.6 ppm at that of 1/3/0.5 (Fig. 4C). At the higher weight ratio of 1/3/1 (Fig. 4D), two peaks of carbon 1″ of C6S were observed. The high-field shift would be due to the molecular interaction between the nitrogen atom on the pyrrolidone ring of PVP and sulfate group of and C6S. The peak of 70.2 ppm was belonging to the excess amount of crystalline C6S.

In probucol/PVP/C12S system, peak of carbon 1″ of C12S shifted from 69.1 to 67.0 ppm at the weight ratio of 1/3/0.1 (Fig. 5B) and to 67.4 ppm at that of 1/3/0.2 (Fig. 5C). At the weight ratio of 1/3/0.3 (Fig. 5D), not only the chemical shift due to the interaction between PVP and C12S, but also the small peak at 69.1 ppm (indicated by arrow) were observed. The latter peak originated from the excess

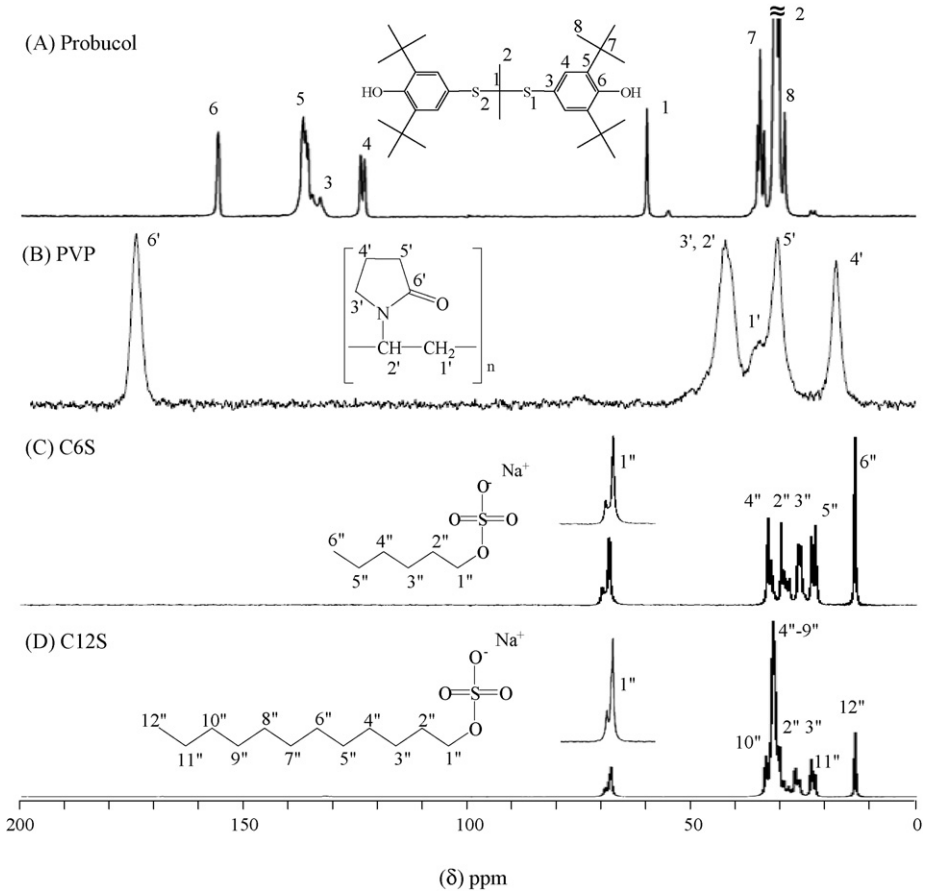

Fig. 3. ^{13}C solid-state NMR spectra of probucol (A), PVP (B), sodium hexyl sulfate (C) and sodium dodecyl sulfate (D).

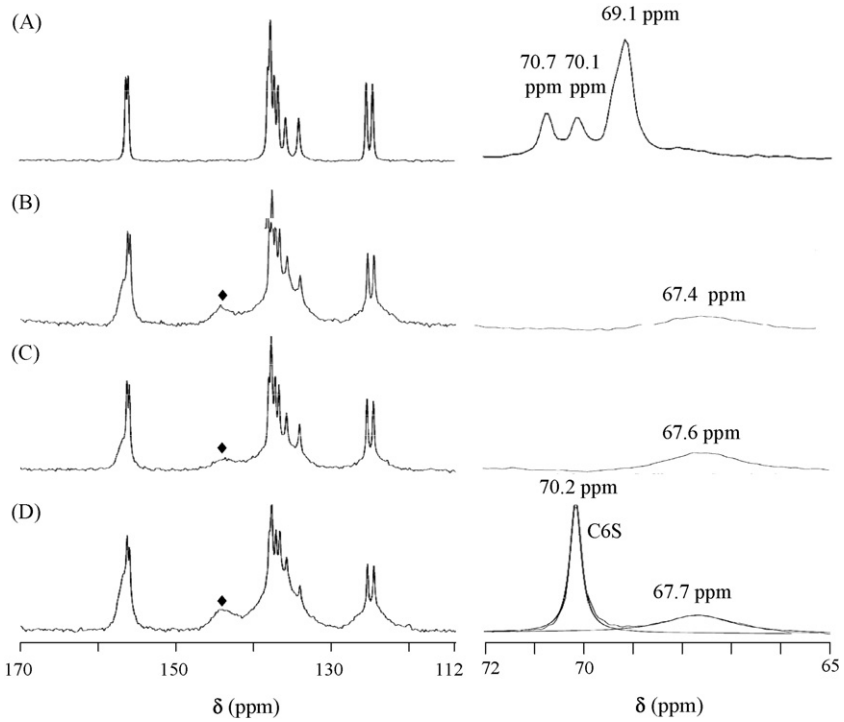

Fig. 4. ^{13}C solid-state NMR spectra of the ternary mixture of probucol/PVP/C6S. (A) Physical mixture of probucol/PVP/C6S at the weight ratio of 1/3/1. The weight ratio of the ground mixture of probucol/PVP/C6S is 1/3/0.3 (B), 1/3/0.5 (C) and 1/3/1 (D).

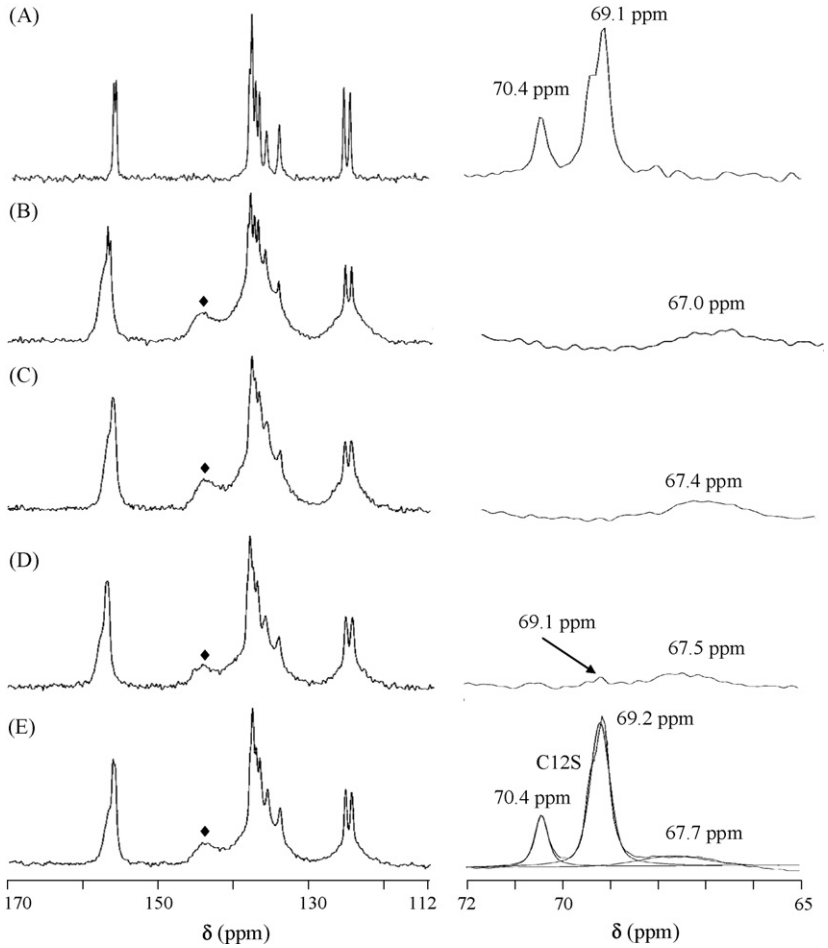

Fig. 5. ^{13}C solid-state NMR spectra of ternary mixture of probucol/PVP/C12S. (A) Physical mixture of probucol/PVP/C12S at the weight ratio of 1/3/1. The weight ratio of the ground mixture of probucol/PVP/C12S is 1/3/0.1 (B), 1/3/0.2 (C), 1/3/0.3 (D) and 1/3/1 (E).

amount of crystalline C12S. The ^{13}C solid-state NMR spectrum at the weight ratio of 1/3/1 (Fig. 5E) showed three peaks at 70.4, 69.2 and 67.7 ppm within the range 70–65 ppm. The first two peaks originated from carbon 1″ of crystalline C12S. The peak at 67.7 ppm was the high-field shift from 69.1 ppm due to the molecular interaction between PVP and C12S.

In the probucol/PVP/C12S system, although the obtained particles were in the micro-range at the weight ratio of 1/3/0.1 and 1/3/0.2, all ground mixture exhibited similar spectral changes in NMR regardless of the C12S content. Similar results were also observed in the ternary ground mixture using C6S. The possible explanation for this phenomenon is that probucol nanoparticles already existed in the ternary ground mixture even at the weight ratio of 1/3/0.1 and 1/3/0.2. However, nanoparticles could not be dispersed properly in water without the excess amount of surfactant. To prove this assertion, a particle size analysis of probucol/PVP/C12S (weight ratio 1/3/0.1 and 1/3/0.2) in C12S solution (concentration: twofold above the CMC) was performed and data are presented in Table 2. Interestingly, the micro-range particles were not observed in the ground mixture of both samples. The observed particle sizes were reduced from around 15 μm to 95 nm in both weight ratios. These results emphasized the importance of a grinding-induced intimate interaction among ternary components to obtain a stabilized ground mixture suspension.

As described in the section, determination of probucol nanoparticles (Table 1 and Fig. 2), probucol nanoparticles were produced when the weight ratio of C12S was 1/3/0.3 or higher. Taking the results into account, the weight ratio of 1/3/0.3 was the appropriate ratio for probucol nanoparticle formation when C12S was used as a surfactant in the ternary system. The optimum weight ratio is dependent on the species of surfactant used. The interaction among three components as revealed by ^{13}C solid-state NMR measurements indicated the importance of molecular interaction to the formation of probucol nanoparticles.

Producing drug nanoparticles by the co-grinding method could be an appropriate choice in the industrial production. However, the important parameter in producing the drug nanosuspension by the co-grinding method is the amount of surfactants. This study revealed that both the alkyl chain length and the appropriate amount of surfactants in ternary ground mixtures were the key factor in producing probucol nanoparticles with high yield.

Table 2
Mean particle size of ternary ground mixtures of probucol/PVP/sodium dodecyl sulfate (C12S) at weight ratios of 1/3/0.1 and 1/3/0.2 in distilled water and in C12S solution.

PBC[a]/PVP/C12S	Mean particle size[b] (μm) ± S.D.	
Weight ratio	In distilled water	In C12S solution[c]
1/3/0.1	14.6 ± 0.1	0.095 ± 0.005
1/3/0.2	15.8 ± 0.6	0.095 ± 0.003

[a] Abbreviation for probucol.
[b] Results are expressed as mean ± S.D. (n = 3).
[c] Twofold above the critical micelle concentration.

4. Conclusions

The effect of the alkyl chain length of sodium alkyl sulfates on probucol nanoparticle formation was investigated using a ternary ground mixture. Particle size distribution and quantitative determination by HPLC indicated that the sodium alkyl sulfate with a longer alkyl chain contributed more effectively to produce the probucol nanoparticles when the weight ratio of the ternary components was the same. The amount of probucol nanoparticles increased with the increase of that of the surfactant. More than 99% of probucol changed to nanoparticles at the mixing weight ratio 1/3/1 of the probucol/PVP/surfactant. It was postulated that, the excess amount of surfactant affects the stability of nanoparticles when the ternary ground mixture was suspended in the aqueous solution. It was suggested that PVP–surfactant complexes formed in the aqueous solution entirely covered the surface of probucol nanoparticles thus, preventing the rapid agglomeration of particles. The surfactant content-dependent intermolecular interaction among the ternary components was recognized by ^{13}C solid-state NMR spectrometry. These findings brought about important aspects of the formulation optimization of the drug/polymer/surfactant ternary co-grinding system.

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