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Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process

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Abstract

Solid dispersions of felodipine were formulated with HPMC and surfactants by the conventional solvent evaporation (CSE) and supercritical anti-solvent precipitation (SAS) methods. The solid dispersion particles were characterized by particle size, zeta potential, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (XRD), solubility and dissolution studies. The effects of the drug/polymer ratio and surfactants on the solubility of felodipine were also studied. The mean particle size of the solid dispersions was 200–250 nm; these had a relatively regular spherical shape with a narrow size distribution. The particle size of the solid dispersions from the CSE method increased at 1 h after dispersed in distilled water. However, the particle sizes of solid dispersions from the SAS process were maintained for 6 h due to the increased solubility of felodipine. The physical state of felodipine changed from crystalline to amorphous during the CSE and SAS processes, confirmed by DSC/XRD data. The equilibrium solubility of the felodipine solid dispersion prepared by the SAS process was 1.5–20 μg/ml, while the maximum solubility was 35–110 μg/ml. Moreover, the solubility of felodipine increased with decreasing drug/polymer ratio or increasing HCO-60 content. The solid dispersions from the SAS process showed a high dissolution rate of over 90% within 2 h. The SAS process system may be used to enhance solubility or to produce oral dosage forms with high dissolution rate.

Keywords: Felodipine; Solid dispersion; Supercritical anti-solvent precipitation

1. Introduction

Felodipine is a dihydropyridine calcium antagonist widely used as a potent antihypertensive drug (Saltiel et al., 1988). However, the oral bioavailability of felodipine is very low because of the first-pass effect. It is

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extensively metabolized in the gut and the liver, and is excreted almost entirely as metabolites. About 70% of each dose is excreted in the urine; the remainder appears in the feces (Dunselman and Edgar, 1991). Moreover, since felodipine is poorly water-soluble, the dissolution could be the rate-limiting process for the absorption of the drug. Many technological methods regarding the enhancement of dissolution characteristics of drugs with low water solubility have been reported, such as micronization, formation of solvates, adsorbate, complexes, microspheres, or more often, solid dispersions (Kim and Park, 2004).

The solid dispersion technique has been used widely to enhance the solubility and dissolution characteristics of drugs with low solubility (Leuner and Dressman, 2000). Solid dispersions are generally prepared by two methods: co-melting of a drug-carrier mixture or dissolution of the drug and carrier in a mutual solvent with subsequent solvent evaporation. The advantage of the conventional solvent evaporation (CSE) method is that the thermal decomposition of drugs or carriers can be prevented because of the low temperature at which organic solvent evaporation occurs. However, some disadvantages associated with this method include high preparation costs and difficulties in completely removing the liquid solvent (Chiou and Riegelman, 1971). Residual solvent in pharmaceutical preparations is a growing concern due to the associated toxicological risks. Solvents commonly used in solid dispersions from the CSE method may be retained in the solid dispersion as a residual organic volatile impurity (Chiou and Riegelman, 1971; Bitz and Doelker, 1995; Ruchatz et al., 1997).

Recently, the supercritical anti-solvent (SAS) process has been proposed as an alternative for formulating coprecipitates that may be smaller in particle size, lower in residual organic solvent, and have better flowability, therefore overcoming some of the problems which arise using the CSE method. In the SAS process, a supercritical fluid is used as the anti-solvent, causing the precipitation of the substrates initially dissolved in a liquid solvent. Certain aspects of this technology have attracted a number of scientists (Sencar-Bozic et al., 1997; Kerc et al., 1999; Sethia and Squillante, 2002; Kim et al., 2005).

Here, we prepared two solid dispersion formulations of felodipine in HPMC using the CSE and SAS methods, and evaluated the physicochemical properties of the dispersions using scanning electron microscopy (SEM), powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), particle size, zeta potential, water solubility, and dissolution. This study includes the effects of the drug/polymer ratio and the presence of surfactant on the solubility of felodipine.

2. Materials and methods

2.1. Materials

Felodipine (99.6%) was obtained from Mehta Pharmaceutical Industry (India). Hydroxypropylmethyl cellulose (HPMC) 2910 was purchased from Shinetsu Chemical Co., Ltd. (Japan). Poloxamer 188 (Lutrol® F68) and poloxamer 407 (Lutrol® F127) were purchased from BASF (Germany). Polyoxyethylene (60) hydrogenated castor oil (HCO-60) was purchased from Nikkol Chemicals Co., Ltd. (Japan). High purity carbon dioxide (99.99%) was supplied from Myungsin General Gas Co., Ltd. (Korea). All other chemicals were of reagent grade and were used without further purification.

2.2. Apparatus

The supercritical fluid system consisted of a stainless steel vessel with an observing lens which endures high pressure and temperature, a syringe pump (Isco, Model 260D Syringe pump), a high-pressure liquid pump (NP-AX-15, Nihon Semitsu Kagaku Co., Ltd., Japan), a pressure gauge, a refrigerating bath circulator (DTRC-620, Jeio Tech Co., Ltd., Korea), valves, and fittings. Two-fluid nozzle was used to produce a spray of liquid solution into the precipitation chamber (V = 847.8 cm^3, I.D. = 9 cm, H = 30 cm), which was equipped with a filter at the bottom to collect the precipitated powder.

2.3. Preparation of felodipine solid dispersion particles

2.3.1. Conventional solvent evaporation method

Felodipine and HPMC were dissolved or dispersed in ethanol. Next, various surfactants were added to the drug/polymer solution (Table 1). The ethanol

Table 1
Formulations of the solid dispersions

	Felodipine	HPMC	Poloxamer 188	Poloxamer 407	HCO-60
CSE method (mg)					
CSE1	50	500	–	–	–
CSE2	50	500	–	–	20
CSE3	50	500	50	–	20
CSE4	50	500	–	50	20
SAS process (mg)					
SAS1	100	1000	–	–	–
SAS2	100	1000	–	–	40
SAS3	100	1000	100	–	40
SAS4	100	1000	–	100	40
SAS5	100	1000	–	–	100
SAS6	200	1000	–	–	–
SAS7	500	1000	–	–	–

was removed using a rotary vacuum evaporator (KU-LNW, Sunil instrument Co., Ltd., Korea) set to 45 °C and 45 rpm for 12 h. The resulting solid dispersion was scraped out with a spatula and dried in a 37.5 °C-vacuum oven for 24 h. The dispersions were then pulverized using an IKA analysis mill and stored in desiccators at room temperature.

2.3.2. Supercritical anti-solvent precipitation process

First, felodipine, HPMC, and surfactants were dissolved or dispersed in a mixture of ethanol and methylene chloride (5.5:4.5, w/w). Then, CO_2 from a storage tank was delivered into the particle formation vessel at a constant rate using a syringe pump until the desired pressure was obtained. Once the pressure and temperature had equilibrated (100 bar, 45 °C), the drug/polymer solution was co-introduced into the vessel through the nozzle with CO_2. The supercritical CO_2 was fed into the vessel at a constant flow rate of 30 ml/min, while the drug/polymer solution was fed into the vessel at 0.5 ml/min. When the solution was sprayed through the nozzle, the solvent was rapidly extracted by the supercritical CO_2, resulting in the precipitation of solid dispersion particles on the wall and the bottom of the vessel. The mixture of solvent and supercritical CO_2 was drained out at the same rate as it was introduced; this could be controlled using a back pressure regulator (Tescom®, model 26-1723-24-194). Then, further washing process was performed to eliminate the solvent mixed in supercritical CO_2. After the washing process, the CO_2 was slowly drained off from the vessel. Once the CO_2 had been completely removed, the particles on the wall and the bottom of the vessel were collected.

2.4. Particle size and zeta potential analysis

The particle size and the zeta potential of the solid dispersion were analyzed using an electrophoretic light scattering spectrophotometer (ELS-8000, Otsuka Electronics Co., Japan). The samples were dispersed in water and sonicated for 10 min to create a homogenous dispersion. Changes in particle size were investigated for 7 h; particle precipitation and solubility were predicted from these data.

2.5. Scanning electron microscopy

Particle size and morphology of solid dispersions were observed using SEM (XL30SFEG, Philips, The Netherlands). The samples were coated with gold and palladium using a vacuum evaporator and were examined at a 10 kV accelerating voltage with a magnification of 5000–50,000.

2.6. Differential scanning calorimetry

DSC was performed on felodipine raw material and solid dispersions prepared from the two described methods using a differential scanning calorimeter (Rheometric Scientific model DLOS). Samples (2–4 mg) were sealed in aluminum pans. Next, DSC thermograms were recorded from 50 to 200 °C at a

heating rate of 10 °C/min. An empty pan was used as a reference. Prior to each experiment, the DSC baseline, temperature, and enthalpy were calibrated using indium and a heating rate of 5 °C/min. A nitrogen flow rate of 20 ml/min was used for each DSC run.

2.7. X-ray diffraction

The solid dispersion particles were evaluated by using an X-ray powder diffractometer (D/Max-IIIC, Rigaku, Japan) to assess the polymorphic state. Each diffractogram was recorded from 5 to 60° (2θ) at a scanning speed of 3°/min and a step size of 0.01°. Cu Kα radiation was used as the X-ray source; this was operated at a voltage of 40 kV and a current of 45 mA.

2.8. Solubility test

Excess amounts of felodipine solid dispersion were dissolved in 20 mL distilled water. The samples were sonicated for 20 min at room temperature, and then shaken in a water bath at 36.5 °C for 24 h. The suspensions were subsequently filtered through a 0.45 μm membrane filter, followed by dilution with ethanol (50:50, v/v). The filtered sample solutions were analyzed using a UV–vis spectrophotometer (UV mini-1240, Shimadzu, Japan) at wavelengths of 362 and 450 nm (Savolainen et al., 2002). Due to the presence of turbidity in the samples after filtration, a background correction to the absorbance (A) was made:

$$A(t) = A_{362}(t) - A_{450}(t)$$

2.9. Preparation of tablets

Of the formulations, two solid dispersion particles, such as CSE4 and SAS4, were compressed into tablets; these tablets had a theoretical felodipine content of 5 mg. Microcrystalline cellulose (Avicel® PH101) was added as a tablet diluent. The solid dispersions were blended with microcrystalline cellulose and magnesium stearate (1% of the total weight of the mixture) and compressed into tablets with a total weight of 200 mg on an ERWEKA® EKO (Germany). As a reference, tablets from a physical mixture (also containing 5 mg felodipine) were made for dissolution studies.

2.10. Dissolution studies

The in vitro release rates of the tablets containing solid dispersions were tested using a USP II apparatus (VK 7000, Vankel). The dissolution tests from each batch were performed in triplicate. Dissolution tests were performed in 500 ml phosphate buffer (pH 6.5) containing 2.0 g cetyl trimethylammonium bromide (Savolainen et al., 2002). The measurements were carried out at 37 °C; the paddle was rotated at 100 rpm. Each tablet was placed in a basket located about 1 cm above the paddle. Aliquots (10 ml) were withdrawn after 0.5, 1, 2, 4 and 7 h and filtered through a 1.2 μm filter.

3. Results and discussion

3.1. Particle size and zeta potential

The mean particle size was small for all of the particles prepared by the two methods, varying between 200 and 250 nm (Fig. 1). The particle size of felodipine tended to decrease compared to felodipine powder. This could enhance the solubility of felodipine because of an increase in surface area (Serajuddin, 1999).

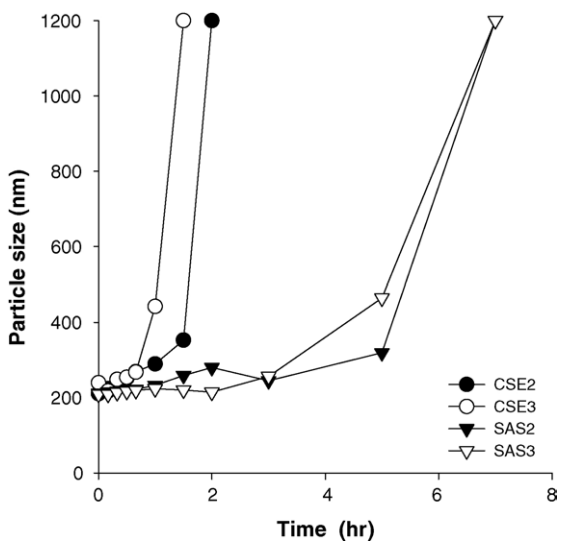

Fig. 1. Changes in particle size of felodipine solid dispersions processed by the CSE and SAS methods.

Table 2
Zeta potential values of solid dispersion particles ($n = 3$)

Formulation	Zeta-potential (mV)	
	CSE method	SAS process
Felodipine/HPMC	−18.61 ± 0.92	−17.07 ± 0.67
Felodipine/HPMC/HCO-60	−16.77 ± 0.65	−13.28 ± 1.41
Felodipine/HPMC/HCO-60/poloxamer 188	−15.26 ± 1.45	−17.36 ± 1.01
Felodipine/HPMC/HCO-60/poloxamer 407	−13.45 ± 0.53	−21.27 ± 0.56

The particle size greatly increased at a specific time, as shown in Fig. 1. It was believed that the supersaturation of the drugs was a result of reduced solubility. Therefore, to delay particle size increase, the formulation should enhance the solubility of felodipine. The particle size in the solid dispersions from the CSE and SAS methods greatly increased at about 1 and 6 h, respectively. It seems that the solid dispersion particles prepared by the SAS process would have higher solubility and stability than those produced by the CSE method. The addition of surfactants may contribute to the reduction in mean particle size because of the surface-active properties of surfactants (Park et al., 1999; Chen et al., 2002; Kawakami et al., 2002; Lim and Kim, 2002). However, in the SAS process, neither surfactant type nor content affected particle size.

The zeta potential is an index of the degree of precipitation of particles in a dispersed condition (Koppel, 1972). All of the particles were negatively charged in water, which could be attributed to presence of ionized carboxyl groups on the surface of the particles (Table 2). All of the solid dispersion particles prepared by the two methods had a good dispersion.

3.2. Particle morphology

The shape of the felodipine particles was irregular; particle size ranged from 2 to 10 μm (Fig. 2a). On the other hand, in the solid dispersions from the SAS process, the particles became more spherical with sizes ranging from 200 to 300 nm (Fig. 2b and c). The solid dispersions prepared by the CSE method were obtained as a film (Fig. 2d and e). This solid dispersion films were then pulverized into small fragments of about 1 mm. The surface of a section had many small holes and some big holes. It looks like a lump with many nanoparticles. The surface area of the particles increased greatly because of the reduction in particle size. Therefore, the preparation of solid dispersion particles by the CSE and SAS methods will contribute to solubility enhancement.

3.3. Differential scanning calorimetry

The DSC thermogram of felodipine is shown in Fig. 3. The thermogram of felodipine exhibited an endothermic peak at about 139 °C with an enthalpy of 20.61 J/g, corresponding to its melting point.

On the other hand, in the case of solid dispersion particles prepared by the CSE and SAS processes, the endothermic peak was not observed. DSC thermograms are shown in Fig. 4a and b. This means that the physical state of felodipine changed from crystalline to amorphous during the CSE and SAS processes. It has been known that transforming the physical state of the drug to the amorphous or partially amorphous state leads to a high-energy state and high disorder, resulting in enhanced solubility and faster dissolution.

3.4. X-ray diffraction

Many diffraction peaks with high intensity were observed on the diffraction pattern of felodipine raw material due to its crystallinity (Fig. 5). On the other hand, the particles prepared by the CSE and SAS processes showed a peak similar to the HPMC pattern in which none of diffraction peaks were observed. This result is comparable to that from the DSC thermogram of the felodipine raw material, indicating that the amorphous state of felodipine was formed by the two processing methods. Taken together, XRD of solid dispersion particles prepared by the CSE or SAS method showed peaks similar to the HPMC pattern in which none of diffraction peaks were observed. Therefore, the physical state of felodipine could contribute to enhanced solubility.

3.5. Drug solubility

The maximum solubility (S_{max}) was determined about 30 min after sonication, while the equilibrium solubility (S_{eq}) was determined after 24 h (Table 3). The solubility of felodipine in water is known to be

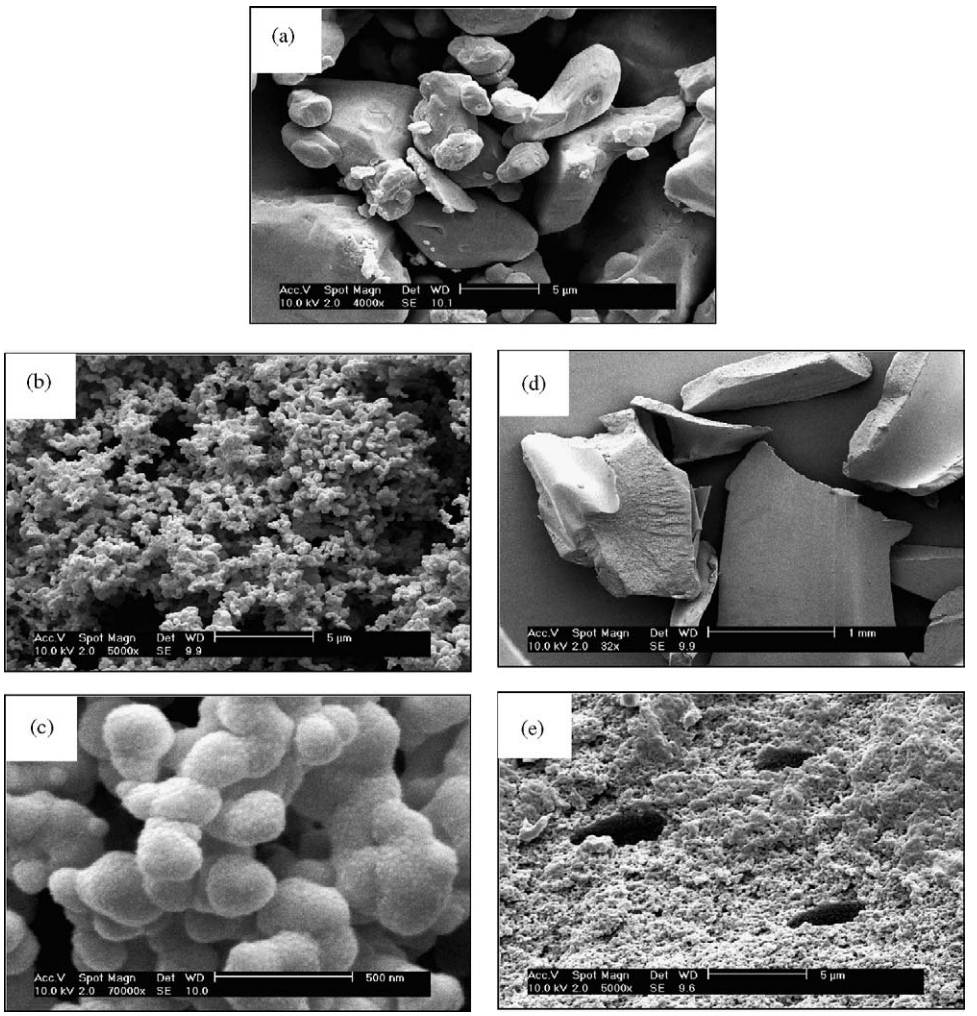

Fig. 2. Scanning electron micrographs of felodipine and solid dispersions. Felodipine raw material (a), felodipine/HPMC/HCO-60/P 188 solid dispersion particles from SAS 5000× (b), 70,000× (c), felodipine/HPMC/HCO-60/P 407 solid dispersion particles from CSE, 32× (d), 5000× (e).

0.5 μg/ml at ambient temperature (Kerc et al., 1992). In case of FDP/HPMC/HCO-60 and FDP/HPMC/HCO-60/P407 formulations, the maximum and equilibrium solubilities of felodipine were much higher than those of other formulations. Moreover, in these formulations, the maximum and equilibrium solubilities of felodipine from the SAS process were higher than those from the CSE method. Fig. 6 shows the effect of the formulation and preparation method of the solid dispersion on the kinetic solubility of felodipine. The equilibrium solubilities of particles prepared by the SAS process were 1.5–20 μg/ml and the maximum solubilities were 35–110 μg/ml.

Not only the equilibrium solubility of felodipine from the SAS process was not less than that from the CSE method, but also the solubilities of felodipine from the SAS process decreased more slowly than those from the CSE method. While the kinetic solubility of felodipine from the CSE method declined within 1–2 h, the kinetic solubility from the SAS process decreased slowly up to 6 h and subsequently lasted at higher concentration than aqueous solubility of felodipine. Taken

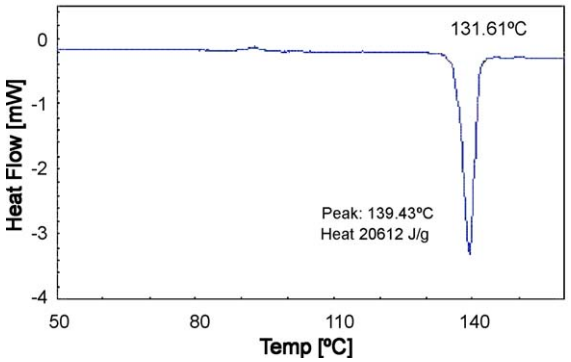

Fig. 3. DSC thermogram of felodipine raw material.

with the particle size from Fig. 2, the particle sizes of felodipine prepared by the CSE and SAS methods increased at 1 and 6 h, respectively. It is believed that the increased particle sizes of felodipine were attributed to the reduced solubility of felodipine. Moreover, particle size is an important factor in gastric emptying (Bruno et al., 1998). It could be possible to enhance gastric absorption by controlling particle size. Therefore, considering that gastrointestinal transit time is

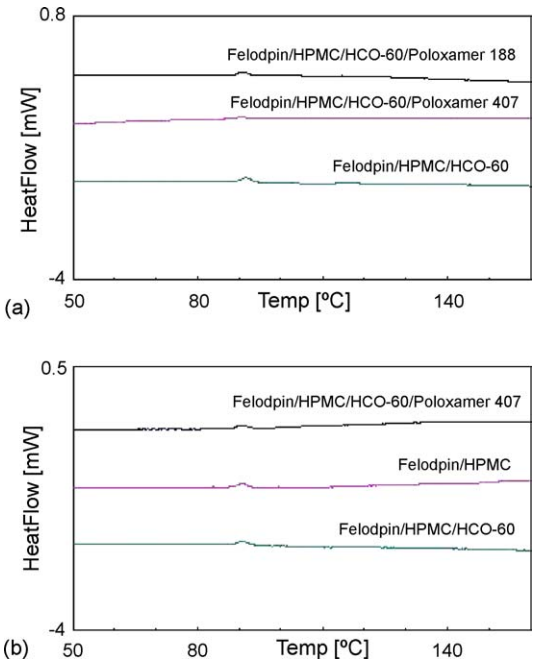

Fig. 4. DSC thermograms of solid dispersion particles from the SAS process (a) and from the CSE (b).

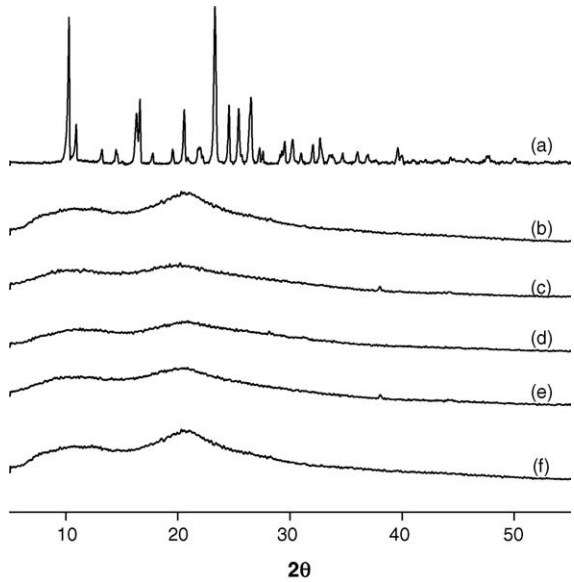

Fig. 5. X-ray diffraction patterns of felodipine (a), CSE-processed felodipine/HPMC/HCO60/P407 particles (b), SAS-processed felodipine/HPMC particles (c), CSE-processed felodipine/HPMC particles (d), SAS-processed felodipine/HPMC/HCO60/P407 particles (f) and HPMC (e).

4–5 h, the observation that the solubility of felodipine (which is poorly soluble) is decreased after 6 h is reasonable.

In addition, the solubility of drug increased with decreasing drug/polymer ratio and increasing HCO-60 content (Fig. 7a and b). Fig. 7a shows that the solubility of the drug increased as the drug/polymer

Table 3
Solubility of solid dispersion particles ($n = 3$)

Formulation	S_{max} (μg/ml)	S_{eq} (μg/ml)
CSE method		
Felodipine/HPMC	50.94	0.47
Felodipine/HPMC/HCO-60	56.77	7.15
Felodipine/HPMC/HCO-60/poloxmer 188	14.15	8.64
Felodipine/HPMC/HCO-60/poloxmer 407	40.55	16.38
SAS process		
Felodipine/HPMC	57.62	1.43
Felodipine/HPMC/HCO-60	70.87	13.51
Felodipine/HPMC/HCO-60/poloxmer 188	36.10	5.46
Felodipine/HPMC/HCO-60/poloxmer 407	107.24	17.01

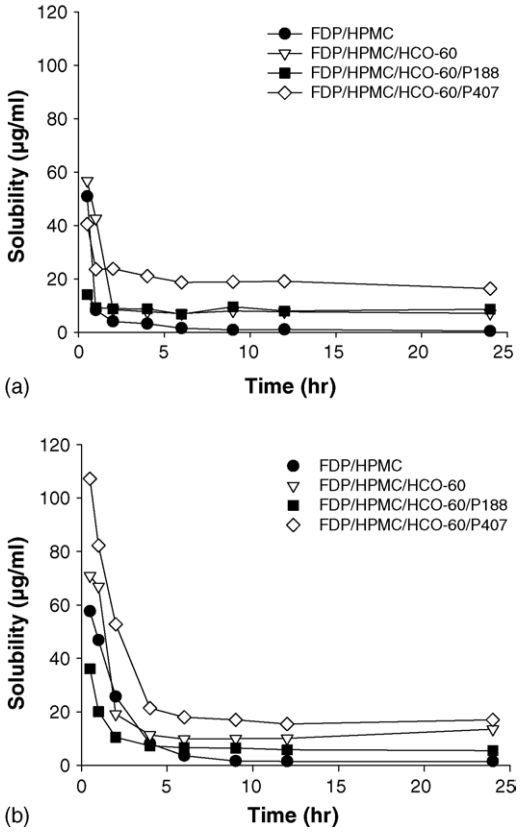

Fig. 6. Solubility profiles of felodipine particles from the CSE method (a) and the SAS process (b).

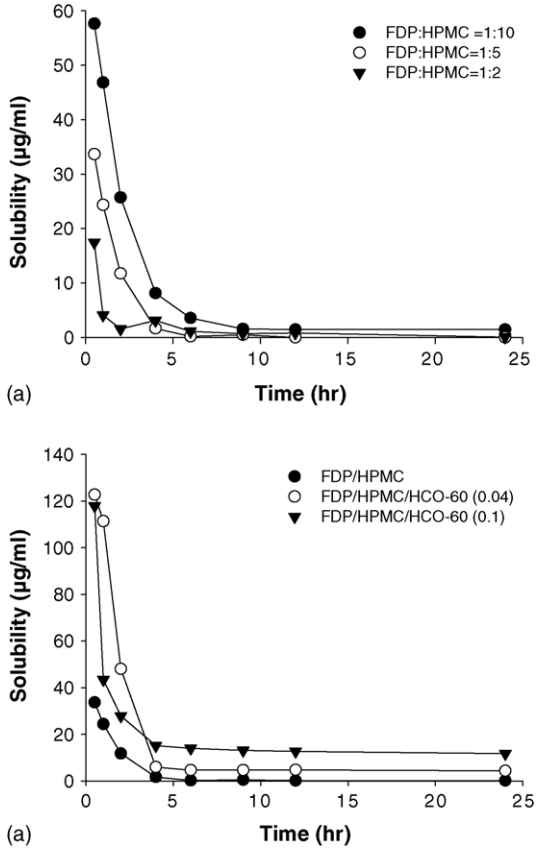

Fig. 7. Solubility profiles of felodipine particles from the SAS process; effect of drug/polymer ratio (a) and HCO-60 content (b).

ratio decreased. When the drug/polymer ratio was 1:10 (w/w), it had the highest solubility. The effect of the amount of HCO-60, a surfactant, on solubility is also shown in Fig. 7b. Drug solubility increased with increasing amounts of surfactant. In particular, the equilibrium solubility of felodipine increased more than 40 times by using a surfactant. When the supersaturated drugs were brought out, a decrease in drug solubility could be prevented by forming a micelle with the surfactant. From this result, it is thought that the SAS process and the use of a surfactant could maintain enhanced solubility.

3.6. In vitro dissolution studies

Dissolution profiles of felodipine from the tablets are shown in Fig. 8. The solid dispersion tablets showed a more rapid dissolution of felodipine than the physical mixture. After 2 h, the dissolution rate of the physical mixture was 52%, whereas the dissolution rate of the solid dispersion tablet was over 85%. The dissolution rate of poorly water-soluble drugs could be a rate-limiting process in drug absorption from a solid dosage form. The solid dispersion system could enhance solubility and would improve bioavailability of poorly water-soluble drug (van Nijlen et al., 2003).

A remarkable increase in the rate of felodipine dissolution was achieved by the SAS process compared to the physical mixture. In fact, the time necessary to dissolve 90% of the drug ($t_{90\%}$) was about 90 min, whereas the physical mixture showed a $t_{90\%}$ of about 4 h. These great differences in dissolution rates were attributed

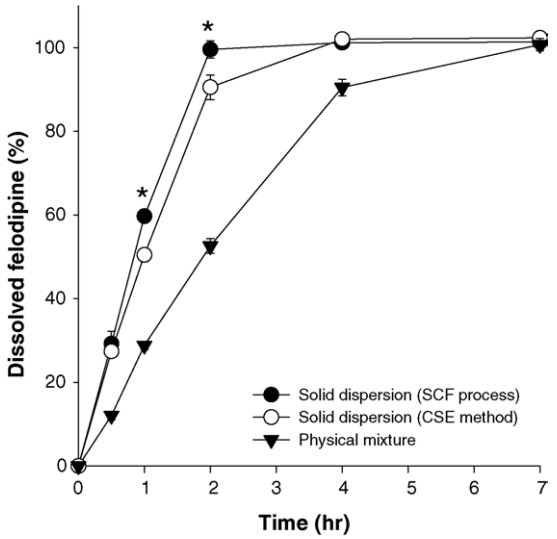

Fig. 8. Dissolution profiles of solid dispersions and a physical mixture (pH 6.5 phosphate buffer containing of 0.04% CTAB). *$P < 0.05$, significantly different compared to the dissolution of a solid dispersion prepared using the CSE method.

to changes from crystalline form to amorphous form.

4. Conclusion

Solid dispersion particles of poorly water-soluble felodipine were prepared by using the CSE and SAS methods. The SAS process would be useful in enhancing the solubility of poorly water-soluble felodipine with high dissolution rate and could be applicable to other poorly water-soluble drugs.

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