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ScienceDirect
Powder Technology 177 (2007) 64–70
POWDER TECHNOLOGY
www.elsevier.com/locate/powtec

Micronization of cilostazol using supercritical antisolvent (SAS) process: Effect of process parameters

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Received 3 May 2006; received in revised form 8 February 2007; accepted 26 February 2007
Available online 3 March 2007

Abstract

The aim of this study was to improve dissolution rate of poorly water-soluble drug, cilostazol, using supercritical antisolvent (SAS) process. The effect of process variables, such as pressure, temperature, drug concentration, type of solvents, feed rate ratio of CO_2/drug solution, on drug particle formation during SAS process was investigated. Particles with mean particle size ranging between 0.90 and 4.52 μm were obtained by varying process parameters such as precipitation vessel pressure and temperature, drug solution concentration, solvent type, feed rate ratio of CO_2/drug solution. In particular, mean particle size and distribution were markedly influenced by drug solution concentration during SAS process. Moreover, the drug did not change its crystal form and the operating parameters might control the 'crystal texture' due to the change in crystallinity and preferred orientation during SAS process, as confirmed by differential scanning calorimetry and powder X-ray diffraction study. In addition, the dissolution rate of drug precipitated using SAS process was highly increased in comparison with unprocessed drug. Therefore, it is concluded that the dissolution rate of drug is significantly increased by micronization of cilostazol, leading to the reduction in particle size and increased specific surface area after SAS process.

Keywords: Cilostazol; Supercritical antisolvent; Micronization; Poorly water-soluble drug

1. Introduction

Micronization is an important procedure used in the pharmaceutical industry to reduce the particle size of active pharmaceutical ingredients, resulting in increase of their dissolution rate, and hence bioavailability [1–3]. However, conventional techniques like jet milling and spray drying neither produce very narrow and controlled size and distribution of particle nor prevent drug from thermal degradation. Therefore, several supercritical fluids based techniques have been proposed for the production of micronic and nanometric particles of pharmaceutical compounds [4].

Recently, particle formation processes based on the use of supercritical fluids as solvents or antisolvents, have been introduced as a viable means of controlling particle formation. The particle formation processes involving supercritical carbon dioxide (SC-CO_2) that are most often referred to be Rapid Expansion of Supercritical Solutions (RESS) [5–7] and Supercritical Antisolvent (SAS) System [8,9]. In general SAS process, an organic solution of solute is atomized through a nozzle into a high pressure vessel containing supercritical fluids, causing intimate mixing of the solution and the fluids, and resulting in solution expansion, supersaturation and particles precipitation. Many researchers have employed SAS process for micronization and for recrystallization of various active pharmaceutical ingredients [3,8,10,11]. The state of the art of SAS and other supercritical fluids-based micronization process has also been recently reviewed [3,12–14].

Cilostazol, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, and several of its metabolites, are known inhibitors of phosphodiesterse III and suppresses platelet aggregation and also acts as a direct arterial vasodilator [15–17]. Unfortunately, the use of cilostazol in pharmaceutical formulation

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doi:10.1016/j.powtec.2007.02.029

has been limited due to its low aqueous solubility and bioavailability, which impede its efficient therapeutic use [18].

In present study, poorly water-soluble cilostazol was used as a model drug and was micronized using SAS process with the aim to increase its dissolution rate, and hence bioavailability. The process variables such as precipitation vessel pressure and temperature, drug solution concentration, solvent type, feed rate ratio of CO_2/drug solution, which could affect particle size and distribution of cilostazol during particle formation, were also investigated.

2. Materials and methods

2.1. Materials

Cilostazol was obtained from Hwail Pharm Co. Ltd. (South Korea). Carbon dioxide (CO_2) with high purity of 99.99% was supplied from Myungsin General Gas Co. Ltd. (South Korea). All organic solvents were high performance liquid chromatography (HPLC) grade. All other chemicals were analytical grade, and double-distilled water was used throughout the study.

2.2. Micronization of cilostazol

The SAS process was performed using the experimental equipment as previously described [9,19,20]. Briefly, the SC-CO_2 was pumped to the top of the particle precipitation vessel through the outer capillary of the two-flow ultrasonic spray nozzle (Sonimist® HSS-600-1, Misonix Inc., NY, USA) by ISCO syringe pump (Model 260D, maximum operation pressure 80 MPa, maximum liquid flow rate 86 ml/min). The drug solution was introduced into the particle precipitation vessel by an HPLC liquid pump (NP-AX-15, Nihon Seimitsu Kagaku Co. Ltd, Japan, maximum operation pressure 80 MPa, liquid flow rate 0.01–9.99 ml/min) through the two flow ultrasonic spray nozzle. Meanwhile, the SC–CO_2 continued to flow through the vessel to maintain the steady state. The conditions of particle precipitation vessel were investigated at temperature ranging from 40 and 60 °C and pressure ranging from 8 and 15 MPa. The residual solvent (SC-CO_2 and organic solvent) was drained out of the particle precipitation vessel by the backpressure regulator (Tescom, model 26-1723-24-194). After the spraying of drug solution into the particle precipitation vessel was completed, an additional SC-CO_2 continued to flow into the vessel at same rate for further 120 min to remove residual solvent from precipitated particles and then slowly depressurized to atmospheric pressure. The precipitated particles were collected on the wall and bottom of the particle precipitation vessel and then stored in a desiccator at room temperature.

2.3. Analysis and characterization

The morphology of particles was examined by scanning electron microscopy (SEM; JSM-6300, Jeol Ltd., Japan). Samples were coated with gold and palladium using a vacuum evaporator and examined using a SEM at 20 kV accelerating voltage. Analysis of the residual solvents was carried out on a Shimadzu 2010 model gas chromatograph (Shimadzu, Japan) equipped with a flame ionization detection (FID) system. A DB-5 capillary column (30 m × 0.32 mm i.d.; film thickness 0.25 μm) was used. To prepare the GC samples, samples were dissolved in dimethylformamide. Butanol was used as an internal standard. Quantification was performed using a calibration curve. The particle size and particle size distribution of samples were determined by dynamic light scattering (DLS) using electrophoretic light scattering spectrophotometer (ELS-8000, Otsuka Electronics, Japan) at a fixed angle of 90° and at room temperature. The system was used in the auto-measuring mode. The samples were dispersed in water saturated with cilostazol (0.01 w/w polysorbate 80) and sonicated before measurement. The polydispersity index is a measure of the distribution of particle population.

DSC measurements were carried out by DSC S-650 (Scinco Co. Ltd., Korea). The samples of 3–4 mg were accurately weighed and sealed in aluminum. The measurements were performed under nitrogen purge over 40–180 °C at a heating rate of 5 °C/min. An empty pan was used for reference and DSC baseline, temperature, and enthalpy were calibrated with indium prior to each experiment at a heating rate of 5 °C/min. A nitrogen flow rate of 20 ml/min was used for each DSC run. Powder X-ray diffraction patterns were recorded on a Rigaku Powder X-ray diffraction system, Model D/MAX-2200 Ultima/PC (Japan) with Ni-filtered Cu-Kα radiation. The samples were run over the most informative range from 2° to 50° of 2θ. The step scan mode was performed with a step size of 0.02° at a rate of 3°/min. The current used was 45 mA and the voltage 45 kV. The specific surface area was determined using the gas adsorption method. Calculation is based on the BET equation. Surface Area Analyzer ASAP 2010 (Micromeritics Instrument Corporation, USA) was used. In vitro dissolution studies were performed according to the USP XXIV paddle method using VK 7000 dissolution testing station and VK 750d heater/circulator (Vankel, USA). The stirring speed used was 50 rpm, and the temperature was maintained at 37 ± 0.1 °C. Each test was carried out in 900 ml of the pH 1.2 simulated gastric fluids (without pepsin) with 0.3% w/v sodium laulyl sulfate. Accurately weighted samples containing the equivalent of 50 mg cilostazol were placed in the dissolution medium. Then, 2 ml of aliquot samples were withdrawn in certain time intervals and filtered using a 0.45 μm PTFE syringe filter. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted with methanol and assayed for drug concentration by HPLC. Chromatographic analyses were performed on a Waters HPLC system consisting of a pump (Model 600), an auto-sampler (Model 717 plus), UV detector (Model 486 Tunable Absorbance Detector). The C_{18} reverse phase column (Xterra, 5 μm, 4.6 mm × 250 mm, Waters) was used at room temperature. The mobile phase consisted of 60% acetonitrile delivered at 1.5 ml/min. The injection volume was 20 μl. The signal was monitored at 254 nm.

3. Results and discussion

In the SAS process, cilostazol was precipitated from dichloromethane and glacial acetic acid at various experimental conditions. The experimental conditions and mean particle sizes

of drug after SAS process are summarized in Table 1. The SEM images demonstrate that agglomerates of a very small submicron or micron particles were obtained from SAS process, as compared with unprocessed drug (Fig. 1). Fig. 2 shows the DSC thermograms of unprocessed and processed drug precipitated from dichloromethane and glacial acetic acid, respectively. Stowell et al. [21] reported three different polymorphs of cilostazol (Form A, B and C) with melting point of 159 °C, 136 °C and 146 °C, respectively. Fig. 2 demonstrates that the polymorph (Form A) of cilostazol was maintained during SAS process at all experimental conditions investigated. No chemical degradation of drug was also observed, as confirmed by HPLC analysis.

3.1. Effect of pressure, temperature and type of solvents

Cilostazol was precipitated from dichloromethane at various pressures in the range from 8 to 15 MPa (40 °C, R=40 and 100 mg/ml) and showed a small decrease in mean particle sizes ranging from 3.15 to 1.32 μm with increasing pressure from 8 to 15 MPa. Above 10 MPa, cilostazol was obtained as small crystals with a very expanded volume in a precipitation vessel due to the supersaturation of entire vapor phase [22] and electrostatic phenomena occurred by the laboratory-scale equipment [23]. Moreover, the mean particle sizes were somewhat increased with increasing temperature range from 40 to 60 °C (12 MPa, R=40 and 100 mg/ml). In the previous study, cilostazol was also precipitated from various organic solvents such as ethanol, methanol and glacial acetic acid due to their complete miscibility with supercritical CO_2 at the experimental conditions [24,25]. In addition, the solubility of drug in these organic solvents at 25 °C is ca. 3.86 mg/ml, 6.45 mg/ml and 211 mg/ml for ethanol, methanol and glacial acetic acid, respectively [26]. Glacial acetic acid as an organic solvent was selected for the further investigation on a basis of our previous study. The drug precipitated from glacial acetic acid showed a relatively small effect on mean particle sizes ranging from 2.31 to 0.95 μm with increasing pressures from 8 to 15 MPa (40 °C, R=40 and 100 mg/ml). However, glacial acetic acid was better than dichloromethane for micronization of drug during SAS process. The phase behavior in the particle formation mechanism with changing organic solvents is complicated because organic solvents possess multiple effects in the SAS process. However, this result can be explained by the nature of organic solvent that can alter the viscosity, vapor pressure, solubility and mass transfer in the system [10].

Table 1
Experimental conditions and results on the supercritical antisolvent micronization of drug

Run	Temperature (°C)	Pressure (MPa)	Solvent	Concentration (mg/ml)	Feed ratio (CO_2/liquid)	Mean particle size[a] (μm)
D1	40	8	CH_2Cl_2	100	40	3.15±0.42 (0.214)[b]
D2	40	10	CH_2Cl_2	100	40	1.84±0.20 (0.185)
D3	40	12	CH_2Cl_2	100	40	1.41±0.14 (0.148)
D4	40	15	CH_2Cl_2	100	40	1.32±0.13 (0.146)
D5	50	12	CH_2Cl_2	100	40	1.65±0.19 (0.096)
D6	60	12	CH_2Cl_2	100	40	2.58±0.22 (0.242)
D7	40	12	CH_2Cl_2	50	40	1.23±0.13 (0.109)
D8	40	12	CH_2Cl_2	150	40	4.52±0.68 (0.466)
D9	40	12	CH_2Cl_2	100	20	2.89±0.38 (0.212)
D10	40	12	CH_2Cl_2	100	60	1.33±0.14 (0.125)
G1	40	8	CH_3COOH	100	40	2.01±0.23 (0.122)
G2	40	12	CH_3COOH	100	40	1.05±0.14 (0.092)
G3	40	15	CH_3COOH	100	40	0.95±0.14 (0.065)
G4	60	12	CH_3COOH	100	40	1.35±0.21 (0.085)
G5	40	12	CH_3COOH	50	40	0.90±0.12 (0.075)
G6	40	12	CH_3COOH	150	40	1.63±0.21 (0.125)

[a] Mean particle size calculated by cumulant method using dynamic light scattering measurement (n=3, mean±S.D.).
[b] Polydispersity index.

Generally, the particle size and morphology are dominated by two possible mechanisms, evaporation of the solvent into the antisolvent phase and diffusion of the antisolvent into the droplets [27]. The mean particle sizes of drug precipitated from both dichloromethane and glacial acetic acid were decreased slightly with increasing pressure at constant temperature. It indicates that mean particle size is mainly determined by the diffusion of the SC-CO_2 into the droplets, strongly depending on precipitation pressure. In addition, the increased solubility of the solvent as the pressure increases at a fixed temperature is as a rule expressed in terms of the volumetric expansion of the liquid phase when increasing quantities of CO_2 are solubilized in it [3,28]. Therefore, the increases in diffusion driving force and solubility of solvent at higher pressure cause significant reduction in partial molar volume and cohesive energy density of the solvent, lowering its solvent power for the solid solute [29] and substantially causes higher degree of supersaturation, resulting in precipitation of particles with smaller mean particle size and narrower particle size distribution.

The density of carbon dioxide, which is influenced by pressure and temperature under supercritical conditions, plays an important role for mass transfer between organic solvents and CO_2 during particle formation. As shown in Fig. 3, the mean particle size of drug precipitated from dichloromethane and glacial acetic acid showed a good linear relation with the density of CO_2 generated by varying pressure and temperature.

3.2. Effect of drug concentration

The drug was also precipitated from dichloromethane and glacial acetic acid at various drug concentrations in the range from 50 to 150 mg/ml (40 °C, 12 MPa and R=40) to investigate

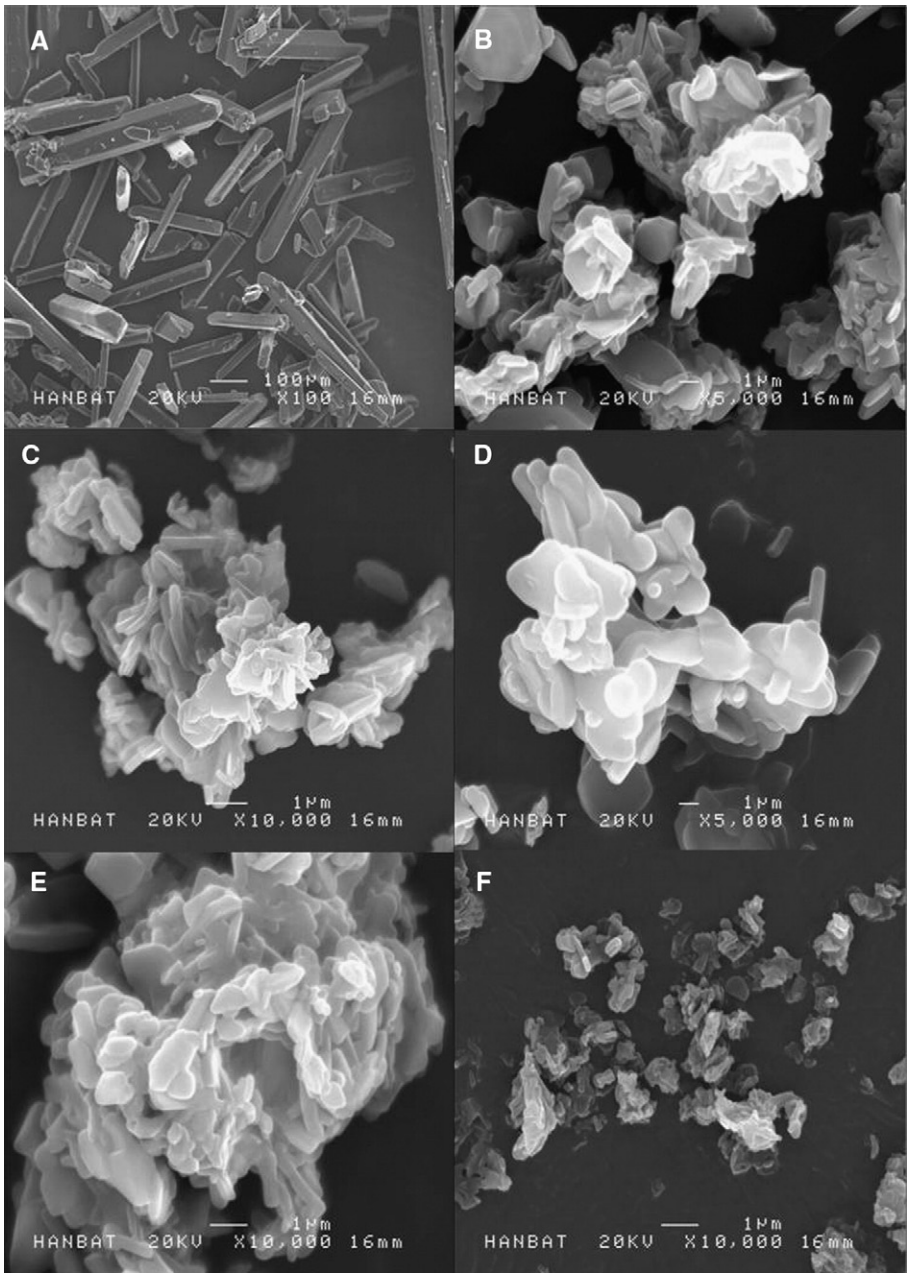

Fig. 1. SEM images of unprocessed cilostazol (A) and processed cilostazol precipitated by the SAS process: D1 (B), D3 (C), D8 (D), D9 (E) and G2 (F).

the effect of the drug concentration on the particle size of drug after SAS process. A remarkable influence of drug concentration on the particle size and distribution was observed. The mean particle size was increased with increasing drug concentration from 50 to 150 mg/ml. This tendency was also previously reported in the literature [10,30–32]. Especially, Reverchon et al. [31] suggested that the increase of mean particle size at various drug concentrations could be explained in terms of nucleation and growth processes. In case of low drug concentration, saturation and then precipitation of drug occurs very late during the droplet expansion process. Therefore, nucleation is the prevailing mechanism at these conditions and smaller particles are formed. On the other hand, solute precipitation is obtained earlier during the expansion process and the mechanism of particle growth intersects with nucleation, producing larger particles in case of high drug concentration. In addition, the polydispersity of particles was highly influenced by high drug solution concentration, as presented in Fig. 4 and Table 1.

Overall, the drug precipitated from glacial acetic acid showed small particle sizes and narrow particle size distribution, in comparison with dichloromethane. Especially, remarkable differences in particle size were observed at high concentration (150 mg/ml). As shown in Fig. 4A, the bimodal particle size distribution of drug precipitated from dichloromethane was observed at high concentration. In other to explain the bimodal nature of particle size distribution, the competition between nucleation and growth process of the SAS process needs to be considered [33]. This may be due to the two concurring mechanisms, nucleation and growth processes during particle

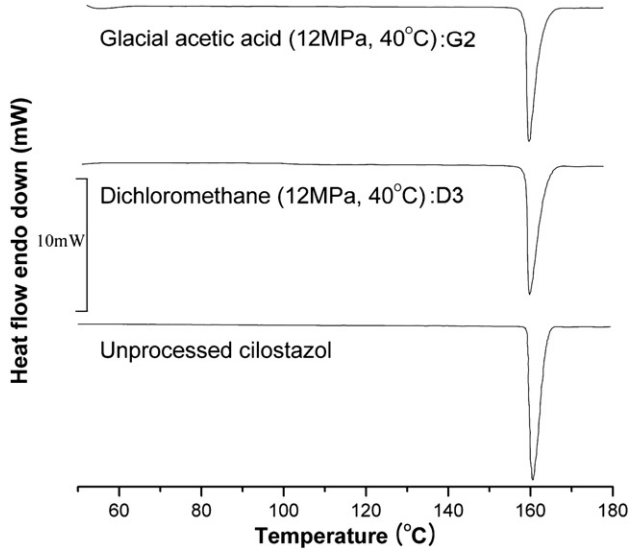

Fig. 2. DSC thermograms of the drug before/after processing with SAS process.

formation process. The particle size distributions of drug precipitated from glacial acetic acid showed narrower and monodisperse distribution than that precipitated from dichloromethane in terms of the distribution width given by the SPAN value and polydispersity index (Fig. 4 and Table 1). In addition, acetic acid as an organic solvent can take advantage of safety concerns because it is indeed listed as class 3 solvents while dichloromethane is class 2 solvents in the ICH guidelines [34]. In case of dichloromethane, the amount of residual solvent was severely limited, which is below 600 ppm. However, GC analysis revealed that residual solvent (dichloromethane) in the precipitated drugs has been routinely checked for all samples and found to be always below 50 ppm in our study.

3.3. Effect of feed rate ratio of CO_2/drug solution

The influence of the feed rate ratio on particle size of drug after SAS process at constant conditions (40 °C, 12 MPa and 100 mg/ml in dichloromethane) was studied. Experiments were performed at values of R ranging between 20 and 60 on a volume basis of drug solution and CO_2. As shown Fig. 5, the mean particle size and distribution of drug precipitated with feed rate ratios of 40 and 60 are very similar. However, the drug precipitated with high feed rate ratios of 20 showed a broader particle size distribution with mean particle sizes of 2.89 μm.

3.4. X-ray diffraction patterns

Fig. 6 represents the X-ray diffraction patterns of the cilostazol before/after SAS process. The diffraction pattern of unprocessed drug showed characteristic high-intensity diffraction peaks at 9.4, 10.3, 12.9, 15.3, 15.8, 18.8, 19.4, 20.4, 20.8, 22.0, 23.5, and 31.7° of 2θ that matched the known that of cilostazol Form A [18,21]. The characteristic diffraction peaks were observed at same position of 2θ, indicating that the crystallinity of drug was still remains after SAS process. As shown in Fig. 6, the characteristic diffraction peaks of drug after SAS process were the same as those of a starting material, while the relative integrated intensity of the peaks was reduced. The reduced relative integrated intensity of diffraction peaks can be explained by preferred orientation. Preferred orientation is a condition in which the distribution of crystal orientation is non-random and a specific crystalline frame may tend to cluster to a greater or lesser degree about some particular orientation [35]. These results show that the operating parameters may control the 'crystal texture' due to the change in crystallinity and preferred orientation [8].

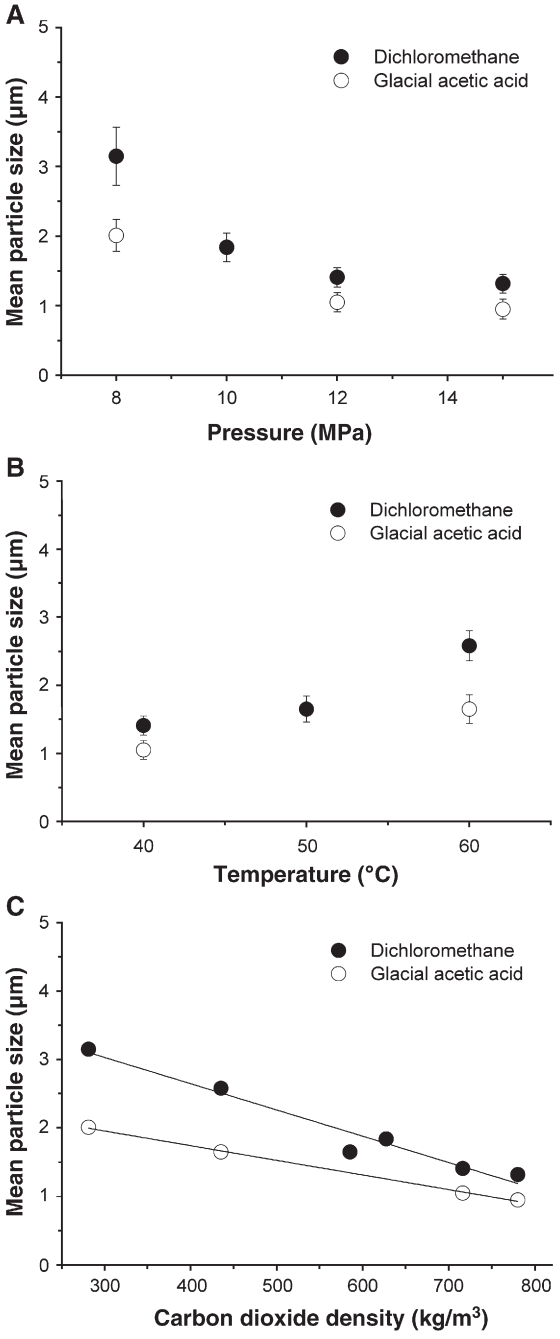

Fig. 3. Influence of pressure (A), temperature (B) and carbon dioxide density (C) on the mean particle size. Pure carbon dioxide density was calculated with the empirical Bender equation.

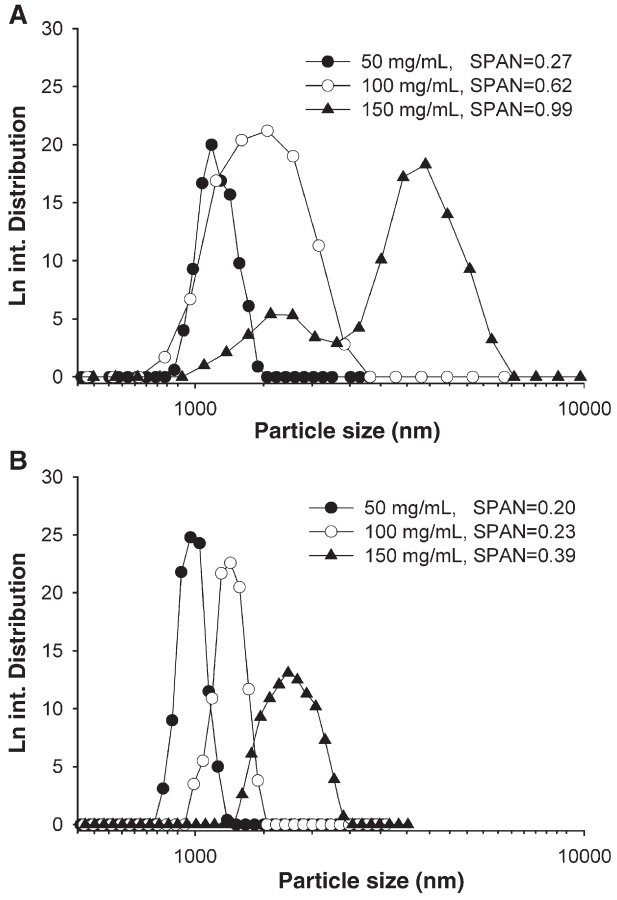

Fig. 4. Influence of drug solution concentration on the mean particle size/distribution during SAS process using dichloromethane (A) and glacial acetic acid (B). SPAN=$(d_{90}-d_{10})/d_{50}$, where d_{10}, d_{50} and d_{90} are the diameter sizes and the given percentage value is the percentage of particles smaller than that size.

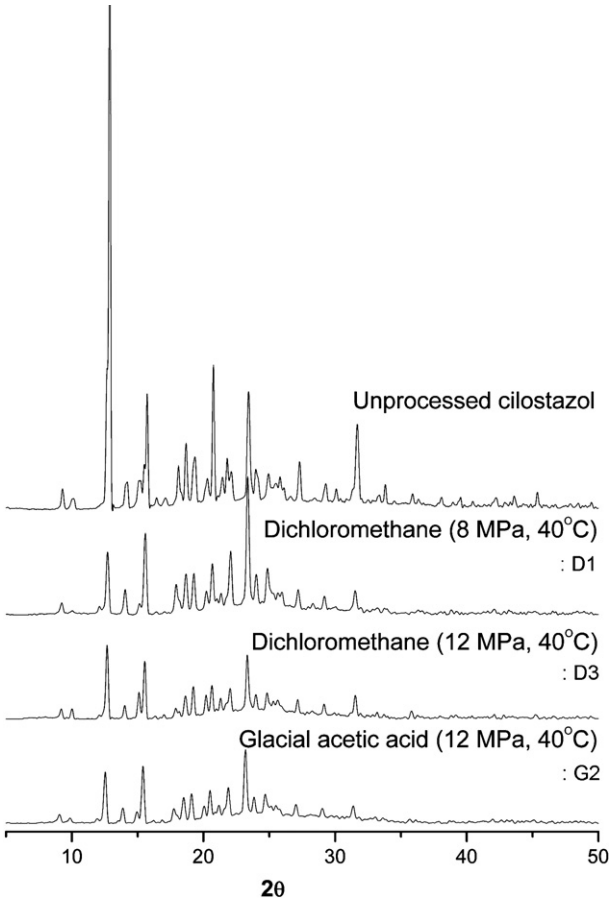

Fig. 6. Powder X-ray diffraction patterns of drug before/after SAS process.

3.5. Dissolution studies

Dissolution studies were carried out in sink condition ($C<0.2\ C_s$). Fig. 7 shows the dissolution profiles of unprocessed and processed drug precipitated from both dichloromethane and glacial acetic acid at 40 °C and 12 MPa, respectively. The dissolution rates of drug precipitated from both dichloromethane and glacial acetic acid are highly increased in comparison with unprocessed drug. The drug was approximately 95% dissolved for processed drug, while only 15% dissolved for unprocessed drug at 45 min. The dramatic increase in drug dissolution rate can be explained by the reduction of particle size resulting in an increased specific surface area. In fact, the processed cilostazol used in dissolution studies had a specific surface area of 4.09 m^2/g (dichloromethane) and 4.33 m^2/g (glacial acetic acid), respectively, which was significantly greater than that of the raw cilostazol (0.49 m^2/g).

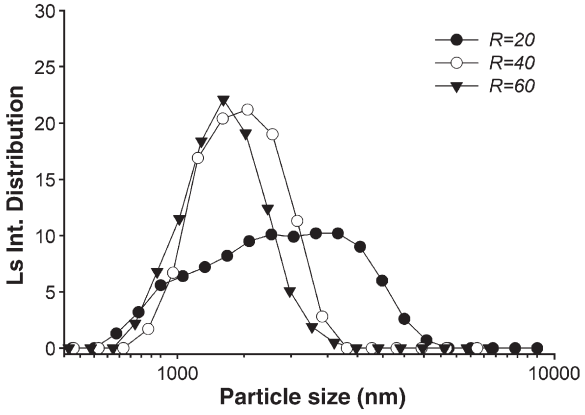

Fig. 5. Influence of the feed rate ratio between CO_2 and drug solution on the mean particle size and distribution during SAS process using dichloromethane.

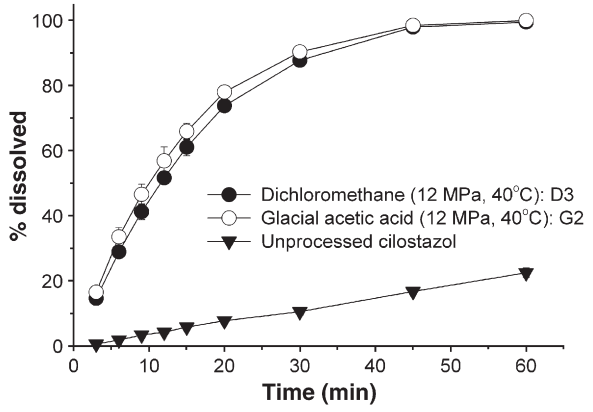

Fig. 7. Dissolution profiles of unprocessed/processed drug precipitated from both dichloromethane and glacial acetic acid.

In conclusion, micronization with supercritical antisolvent process resulted in a significant decrease in mean particle size, as compared to unprocessed drug. The mean particle size and distribution of drug could also be controlled by manipulating the precipitation pressure, temperature, types of solvents, drug concentration and feed rate ratio between drug solution and CO_2. In particular, the mean particle size of drug was strongly influenced by the drug concentration. In addition, the processed drug resulted in an enhancement in the dissolution rate respect to the unprocessed drug due to reduction in particle size and a higher surface to dissolution medium. The experiment results from SAS process used in our study could be a useful for micronization of poorly water-soluble drugs.

Acknowledgments

This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Lab. Program funded by the Ministry of Science and Technology (No. M10300000301-06J0000-30110).

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