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A combinational supercritical CO_2 system for nanoparticle preparation of indomethacin

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ABSTRACT

An improved system using both supercritical antisolvent precipitation and rapid expansion from supercritical to aqueous solution (RESAS) was proposed to overcome the problem of low solubility of medicinal substances in $scCO_2$. When the ethanol solution with IMC was sprayed into the vessel purged with $scCO_2$, no precipitation of IMC was observed if the CO_2 pressure was more than 15 MPa at 40 °C. This indicates that very small droplets of the ethanol solution with IMC could disperse in the high pressure CO_2. After expansion into distilled water using an RESAS device, this same solution, in CO_2 at high pressure, produced submicron particles of IMC. For the pharmaceutical application, the IMC suspension was freeze-dried and re-dispersed to the aqueous media. SEM images of freeze-dried sample showed that the suspension was composed of submicron particles with 300–500 nm. Although the average particle size of re-dispersed IMC related significantly to the pressure and temperature in the vessel on $scCO_2$ processing, the freeze-dried sample of the IMC suspension after the treatment shows good redispersibility as a nanosuspension. This apparatus is found to be a promising way to produce fine crystals of IMC with a high yield.

1. Introduction

The reduction of the particle size was considered as a way to increase the rate of dissolution, because the micronization of medicinal substances increases the effective surface area for dissolution according to the Noyes–Whitney equation. Micronization of pharmaceutical materials is often performed by means of a dry milling process (Wongmekiat et al., 2007; Wildfong et al., 2006; Chono et al., 2008; Inoue et al., 2007). However, the limitation of size reduction is known to be around several micrometers because of the aggregation between particles. Supercritical fluid technology has been used to manufacture fine particles of medicinal substances by a build-up process. Methods to produce microparticles or nanoparticles using $scCO_2$ have been investigated (Tong et al., 2006). $scCO_2$ is most widely used because of its low and easily accessible critical temperature (31.2 °C) and pressure (7.4 MPa), non-flammability, non-toxicity and inexpensiveness. For this purpose $scCO_2$ has been used in two different ways: as a solvent for drug substance, or as an antisolvent for the precipitation of materials dissolved in organic solvents. Because of the low solubility of active pharmaceutical ingredients (APIs) in $scCO_2$ (Shinozaki et al., 2006), the majority of methods investigated use $scCO_2$ as an antisolvent, i.e., gas antisolvent technique (GAS) (Yeo and Lee, 2004; Bakhbakhi et al., 2006; González et al., 2000), the supercritical antisolvent precipitation technique (SAS) (Reverchon et al., 1998), the aerosol solvent extraction system technique (ASES) (Kunastitchai et al., 2006), and the solution enhanced dispersion with supercritical fluid technique (SEDS) (Lobo et al., 2005; Tong et al., 2001; Schiavone et al., 2004). Antisolvent processes have been used to crystallize many types of solid compounds from their solutions. However, all methods which use $scCO_2$ as an antisolvent have to remove organic solvents on precipitation, since the desired solute was dissolved in an organic solvent before the injection into $scCO_2$ fluid.

Supercritical carbon dioxide techniques require few or no organic solvents if the $scCO_2$ is used for a 'good' solvent for the medicinal substances. The rapid expansion of supercritical solution (RESS) method, that uses $scCO_2$ as a good solvent for APIs, is useful for preparing drug fine particles (Huang and Moriyoshi, 2006; Türk et al., 2006). RESS method has two crucial problems: one is poor solubility of drug substances in the $scCO_2$, the other is a difficulty in the collection of particles. Some trials were reported for overcoming those problems: small amount of co-solvent was added as an entrainer to increase the drug solubility (Thakur and Gupta, 2006; Mishima et al., 1999), and supercritical fluid was sprayed into aqueous solvent (Pathak et al., 2004). However, nanoparticles of drug substances are still difficult to obtain using only the RESS method.

In this study, we used an in-house built apparatus as an advanced system using both the supercritical antisolvent precipitation technique and rapid expansion from supercritical to aqueous solution (RESAS) method. This system composed of a combinational

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unit of SEDS and RESAS device to overcome the solubility problem of APIs to $scCO_2$. The advantage of this system was that the powder can be produced continuously, and this system can be scaled-up. The aim of the present study was to prepare nanocrystals of a poorly water-soluble API by applying the improved method. Indomethacin (IMC) is a non-steroidal anti-inflammatory drug that has very low aqueous solubility (solubility in water: 5 μg/mL) which is often used as a model for practically insoluble drugs. The particle size of the dispersions obtained was characterized by dynamic light-scattering method, and then the suspensions were freeze-dried for further physicochemical characterization of the obtained powdered particles.

2. Materials and methods

2.1. Materials

Indomethacin (γ-form) was kindly supplied from Dainippon Sumitomo Pharma Co. Ltd. and used without further purification. 200 mg of IMC was dissolved into a 10 mL of ethanol before injection. Polyvinyl alcohol (POVAL® PVA-403: Kuraray America Inc.) was used as a dispersing agent towards particle size measurement. All other chemicals and solvents were of reagent grade.

2.2. An apparatus used for the study

A schematic procedure for the preparation of IMC suspensions is illustrated in Fig. 1. This apparatus consists of a reaction vessel and a precipitation unit. It is a supercritical fluid operating system based on the rapid expansion of supercritical solutions (RESSs) method. This device comprises of a CO_2 pump (max. 20 mL/min), a drug solution pump (10 mL/min), a reaction vessel (50 mL) and a back pressure regulator. The liquefied CO_2 is introduced into the vessel fixed at 14 mL/min, because the most appropriate performance was achieved in the pre-examination test of this apparatus.

First, the solvent CO_2 is introduced to a reaction vessel at a controlled temperature condition. Second, when the vessel reaches the desired pressure, both the drug solution (IMC concentration: 20 mg/mL) and CO_2 fluid are co-sprayed simultaneously via the coaxial nozzle (outer nozzle: a stainless steal tube of 1/16 in. od, 0.8 mm id (JASCO Co., Japan), inner nozzle; a J&W Scientific DB-23 capillary column of 0.25 mm od × 0.25 μm id (J&W Scientific Inc., USA)), fixed as shown in Fig. 1B. 200 mg of IMC was used per one batch study (20 mg/mL ethanol solution of 10 mL). The batch scale could be altered by changing the IMC concentration in ethanol or total amount of solution.

Immediately after the co-spraying, a CO_2 fluid containing IMC and ethanol is expanded from the reaction vessel into an aqueous media of 30 mL via the back pressure regulator. An upper limit pressure of this apparatus is 25 MPa. The temperature in the reaction vessel can be altered from 25 to 80 °C. The pressure in the vessel is maintained by a back pressure regulator.

After finishing the expansion, the suspension was dispersed by sonication. To obtain the particle for pharmaceutical formulation, the resultant dispersion of 30 mL was put in 200 mL of stainless steel container, and then subjected to freeze-drying at −120 °C for 72 h (FD-81TS, Tokyo Rikakikai Co. Ltd., Japan).

2.3. Analysis of physicochemical properties of suspensions

The particle size distribution of the IMC particles dispersed in an aqueous phase (either the dispersion prior to freeze-drying or after freeze-drying) was determined by the dynamic light-scattering method using FPAR-1000® (Otsuka Electronics Co. Ltd., Japan; measurement range, 0.003–5 μm). For the quantitative determination of IMC, recovered IMC was determined spectrophotometrically at a wavelength of 320 nm (UV-1700, Shimadzu, Japan). The ratio of drug obtained after the $scCO_2$ procedure to the total amount of drug loaded was calculated and expressed as yield percent. All experiments were triplicated to check the reproducibility of the $scCO_2$ procedure, and the mean values of the percentage yield were calculated.

2.4. Scanning electron microscopy (SEM)

The morphology of the commercial IMC powder and the freeze-dried samples was examined by SEM (JSM-330A, Nihon Denshi, Japan). Prior to examination, the samples were mounted onto metal stubs and were sputtered with a thin layer of gold under vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

2.5. Powder X-ray diffraction (PXRD)

PXRD analysis was performed with a Rigaku Geigerflex powder X-ray diffractometer (Rigaku Denki, Japan). The scanning rate was 4°/min over a 2θ range of 5–40°.

2.6. Differential scanning calorimetry (DSC)

Differential Scanning Calorimeter (DSC-6200, Seiko Instruments Inc., Japan), equipped with a liquid nitrogen cooling system, was used to measure the thermal behavior of the commercial IMC pow-

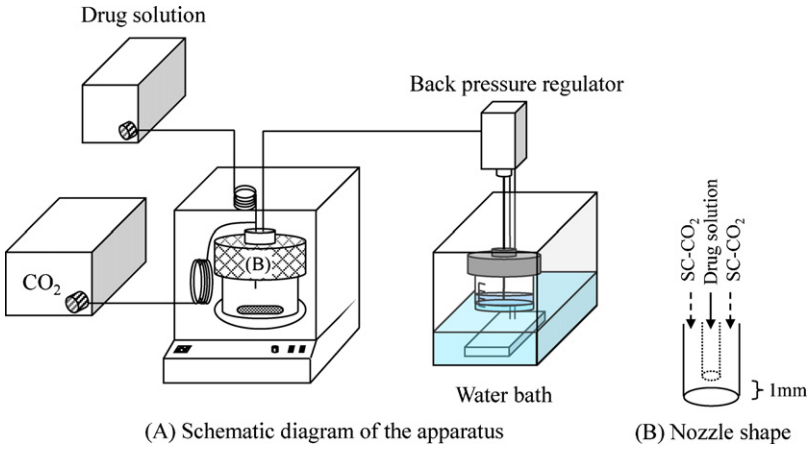

Fig. 1. Schematic diagram of the apparatus for the novel processing using supercritical carbon dioxide ($scCO_2$).

der and the freeze-dried samples. In the DSC analysis, 2–3 mg of sample powder was put in aluminum pan and examined at a scanning rate of 10 °C/min from 25 to 200 °C.

2.7. Dissolution study

A dissolution test for the commercial IMC powder and the freeze-dried samples was carried out according to the Japanese pharmacopoeia (XV). The prepared samples or the commercial IMC powder (20 mg) were added to 900 mL of JP 2nd fluid (phosphate buffer pH 6.8) at a temperature of 37 ± 0.5 °C and paddle stirring at a rotation speed of 50 rpm. Five milliliters of samples were withdrawn at specific time intervals, filtered through 0.2 μm filter, and the concentration of IMC was determined by UV-spectrophotometry.

3. Results and discussion

3.1. Fine particle formation of IMC

When a drug solution and $scCO_2$ was expanded via the coaxial nozzle into the $scCO_2$ purged high-pressure vessel, IMC crystals were precipitated, since $scCO_2$ in the vessel acts as an antisolvent (Lobo et al., 2005; Tong et al., 2001; Schiavone et al., 2004). If the reaction vessel was kept at pressures below 10 MPa, microparticles of IMC were obtained in the vessel, without forming IMC nanoparticles (data not shown). On the other hand, it should be noted that there were very small amount of IMC crystals in the vessel where the $scCO_2$ pressure was kept above 15 MPa. Density fluctuations could be observed through a sapphire glass window in all the cases where the pressure was above 15 MPa, suggesting that the IMC and ethanol was dispersed in $scCO_2$. However, it was found that IMC crystals were precipitated after preserving the fluid for several minutes even if the pressure was above 15 MPa. It was possible that very small droplets of ethanol were dispersed into the $scCO_2$ fluid creating a comparatively unstable state, rather than molecularly dispersed IMC dissolved in the $scCO_2$.

Interestingly, when the reaction vessel was kept at pressures above 15 MPa and immediately after the high-pressured CO_2 fluid including IMC and ethanol was expanded through the back pressure regulator into distilled water using RESAS unit, a suspension involving IMC fine particles were obtained as shown in Fig. 2. For the purpose of pharmaceutical use, the suspension was freeze-dried to obtain IMC particles. The size distribution patterns show two peaks, attributed to submicron-sized particles of 300–600 nm and their aggregated particles. Samples dispersed in the aqueous solution with 1.0% (w/v) polyvinyl alcohol exhibited a monodisperse particle size distribution in the nanosize range (Fig. 2C). This observation emphasizes that these microparticles are aggregations of the submicron particles. Freeze-dried samples of those suspensions reproduce submicron particles when the samples were dispersed in water. This indicates a good redispersibility of freeze-dried samples of $scCO_2$ processing products.

The average particle sizes and yields of IMC after dispersing freeze-dried samples are shown in Figs. 3 and 4. As shown in Table 1

Table 1
Effect of $scCO_2$ conditions on the particle properties of freeze-dried samples.

Pressure (MPa)	Temperature (°C)	Yield (%)	Mean particle size (nm)
10	40	1.6	2540.9
15	40	39.3	799.9
20	40	38.3	674.2
25	40	47.7	354.9
25	60	31.7	718.3
25	80	26.7	799.4

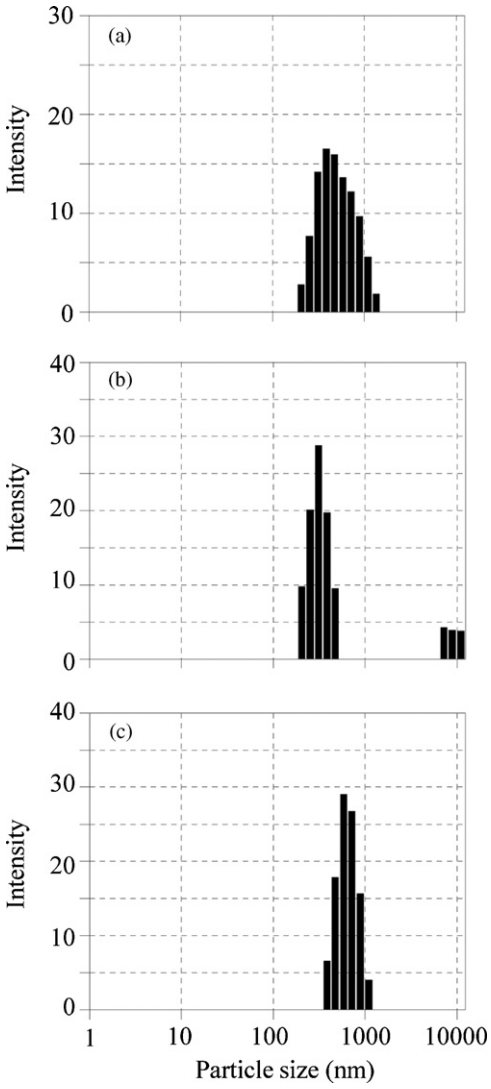

Fig. 2. Particles size distribution IMC suspension: (A) $scCO_2$ processed IMC suspension at 25 MPa·40 °C prior to freeze-drying; (B) freeze-dried sample of (A) was dispersed in distilled water; (C) freeze-dried sample of (A) was dispersed in 1.0% PVA-403 solution.

and Fig. 3, the average particle size decreased with an increase in the CO_2 pressure in the high-pressure vessel if the temperature was controlled at 40 °C. The sample prepared from $scCO_2$ fluid at 10 MPa shows a low yield of 1.6%, because most of the IMC particles were precipitated in the reaction vessel. In cases of samples processed at 15–25 MPa, freeze-dried samples of suspensions reproduce submicron particles when the samples were dispersed in water. This indicates a good redispersibility of freeze-dried samples of $scCO_2$ processing products. Fig. 4 shows the average particle size and yield of IMC after dispersing the freeze-dried samples, where the temperature of the $scCO_2$ in the vessel was varied from 40 to 80 °C. The average particle size increased with an increase in the temperature in the high-pressure vessel. These results are closely related to the pre-expansion condition of RESS method. It has been reported that the rapid expansion of a supercritical solution through a nozzle leads to a large cooling rate, resulting in high supersaturations with homogeneous nucleation and particle growth. Various process parameters influences the properties of the product such as temperature and pressure in the extraction unit, nozzle geometry and diameter, solubility, and the nature of solute–solvent interaction (Türk, 1999). The appropriate condition by use of the apparatus was found to be that the $scCO_2$ conditions were kept at 25 MPa·40 °C.

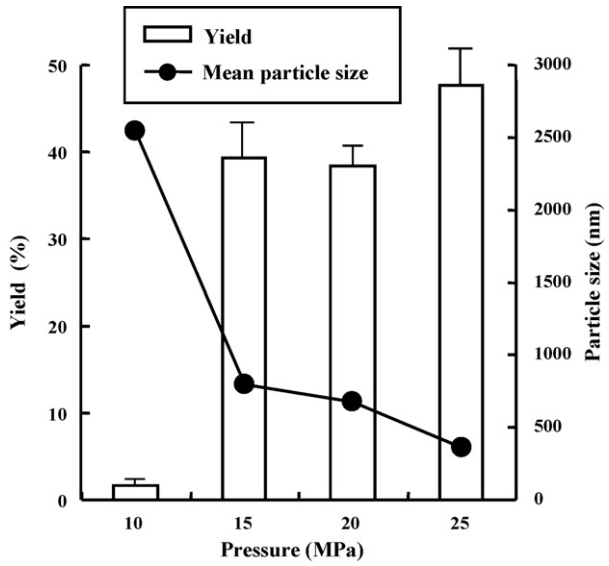

Fig. 3. Changes in the particle size and yield of IMC particle when the after freeze-dried sample of IMC suspension was dispersed into distilled water: $scCO_2$ processing was performed under various CO_2 pressures in the vessel (temperature: 40 °C).

With regards to the yield of the IMC, shown in Figs. 3 and 4, the values slightly increased with an increase in the pressure. The yield shows a relatively low value of about 50% if the one batch process of IMC solution was performed by this apparatus: the content of IMC was 200 mg for one batch. The residual IMC was left in the tube, vessel, and nozzle in the apparatus. The continuous manipulation of the experiment produces a high yield of IMC particles. The yield of IMC particles shows 76.7 ± 5.2% if the experiment was continuously performed with quadruplicate. Therefore, this apparatus produces fine crystals of IMC with a high yield. Harrison et al. reported that the relationship between a pre-expansion pressure and temperature of a benzoic acid–$scCO_2$ RESS expansion and particle size of those products. For benzoic acid, a decrease in particle size with increasing pre-expansion pressure, and an increase in particle size with increasing pre-expansion temperature was observed (Harrison et al., 2007). These results are consistent with our results

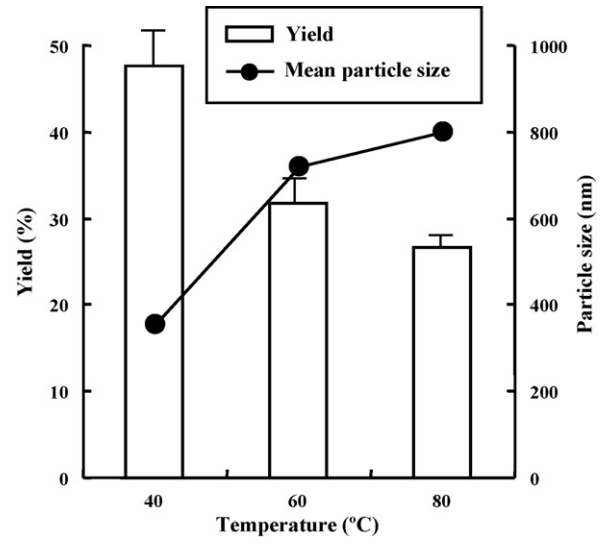

Fig. 4. Changes in the particle size and yield of IMC particle when the after freeze-dried sample of IMC suspension was dispersed into distilled water: $scCO_2$ processing was performed under various temperatures in the vessel (pressure: 25 MPa).

in terms of the particle size differences as shown in Figs. 3 and 4. Furthermore, a decrease in pre-expansion pressure or an increase in pre-expansion temperature is associated with a decrease in saturation, corresponding to an increase in the critical particle radius and a decrease in the nucleation rate (Helfgen et al., 2000).

3.2. Characterization of IMC prepared by $scCO_2$ processing

The particle size and morphology of freeze-dried samples of IMC particles as well as the commercial powder were characterized by the scanning electron microscopy. As shown in Fig. 5, the commercial IMC powder showed irregular-shaped particles with a relatively wide particle size distribution (mean particle size of several micrometers). SEM photographs of freeze-dried samples of IMC prepared in different $scCO_2$ pressures showed different shapes to commercial IMC powders. The SEM photograph shows rod-shaped and fibrous aggregates of submicron size IMC particles under the $scCO_2$ conditions were kept at 10 MPa·40 °C (Fig. 5B). In contrast, the spherical shaped submicron size IMC particles were observed in the cases of higher $scCO_2$ pressures. Most of the particles were spherical in the case of 25 MPa·40 °C (Fig. 5D). As shown in Fig. 5, the freeze-dried sample of suspension, which was treated at high pressure condition of $scCO_2$, involves spherical nanoparticle. Crystal properties were characterized by PXRD and DSC. The crystal property of commercial IMC powder and freeze-dried samples of $scCO_2$ treated IMC was evaluated by PXRD analysis (Fig. 6). The PXRD pattern of the commercial IMC crystals showed diffraction peaks at $2\theta = 11.7°$, 17.0°, 19.8°, 22.0°, and 26.8° which corresponds to the stable γ-form of IMC. The PXRD patterns of the freeze-dried sample of IMC treated at 10 MPa·40 °C showed diffraction peaks at $2\theta = 8.3°$, 11.8°, 14.4°, 18.0°, and 22°. This pattern is identical with that of the meta-stable α-form of IMC and is in a good agreement with previously published data (Takeuchi et al., 2005). The sample treated at 25 MPa·40 °C shows different diffraction patterns compared to those in α- and γ-forms. Most of diffractions were identical with that of the meta-stable α-form of IMC. Some of PXRD diffractions of this sample (indicated as arrows) might involve identical diffraction peaks of another crystal form of IMC reported by Lin (1992). Therefore, the sample treated at 25 MPa·40 °C might be considered to be a mixture of α-form and another form.

Further confirmation of the crystal properties was achieved by evaluation of the thermal behavior of the different samples using DSC (Fig. 7). As expected from PXRD, commercial IMC showed a sharp endothermic peak at 160 °C for the melting of the stable γ-form, while the melting peak of freeze-dried sample of IMC treated at 10 MPa·40 °C was observed at about 157 °C which corresponds to the meta-stable α-form. On the other hand, freeze-dried sample of IMC treated at 25 MPa·40 °C shows a small endothermic peak and an exothermic peak at around 148 °C followed by the fusion peak at 157 °C. The γ-form and α-form shows monotropic phase transition as reported by Legendre and Feutelais (2004). Although there was no strong evidence, the polymorphic transformations on DSC curve might indicate an existence of another form. If new form was contained in the sample of $scCO_2$ processing at 25 MPa·40 °C (Fig. 7B), this form might show enantiotropic as reported by Grunenberg et al. (1996). Results of DSC and PXRD studies show that IMC crystals prepared at 25 MPa would be a mixture of amorphous α-form, crystalline α-form, and an enantiotropic form which transforms to the α-form at high temperature. With respect to the DSC profiles, an endothermic peak at around 151 °C might indicate an existence of another form of IMC crystal or crystallization of amorphous IMC to α-form, since endothermic peaks at 151 °C were not reported in α-, β-, and γ-form (Lin, 1992). The new polymorphic form of IMC has rarely been reported; therefore, the $scCO_2$ processing of combina-

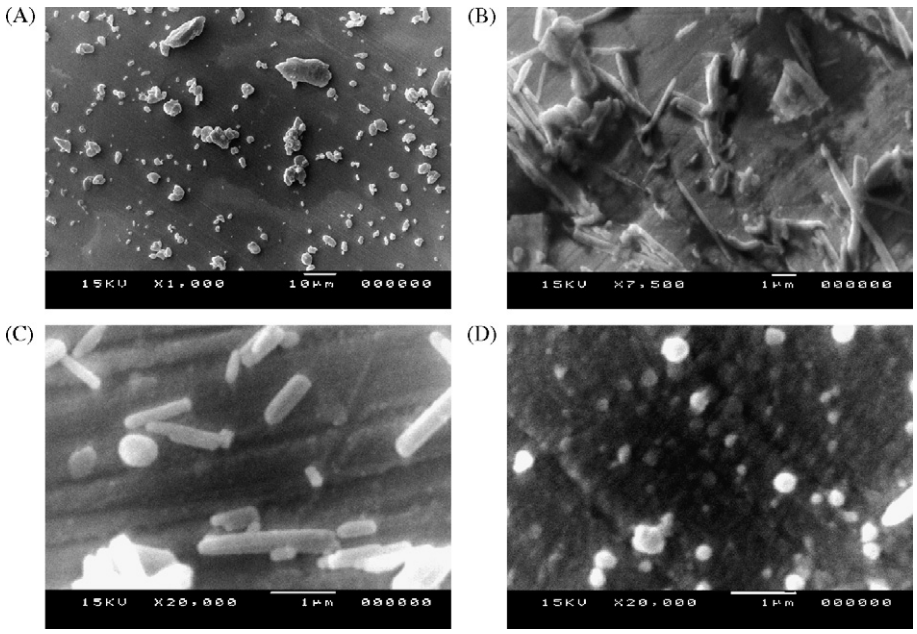

Fig. 5. SEM images of IMC after freeze-dried samples of $scCO_2$ processed suspension under various CO_2 pressures in the vessel (temperature: 40 °C). (A) Unprocessed IMC, (B) $scCO_2$ processing at 10 MPa·40 °C, (C) $scCO_2$ processing at 20 MPa·40 °C, and (D) $scCO_2$ processing at 25 MPa·40 °C.

tional system might be a possible way to produce IMC polymorph of another form.

3.3. Dissolution profiles of IMC nanoparticles

The dissolution profiles of commercial IMC powder and the freeze-dried samples prepared by the $scCO_2$ method are presented in Fig. 8. The dissolution of commercial IMC was slow and dissolved about 60% within 60 min. In the case of the $scCO_2$ treated samples, more than 90% of the IMC molecules dissolved within the first 3 min and complete dissolution was achieved within 10 min. The significant enhancement in the dissolution of IMC can be attributed to

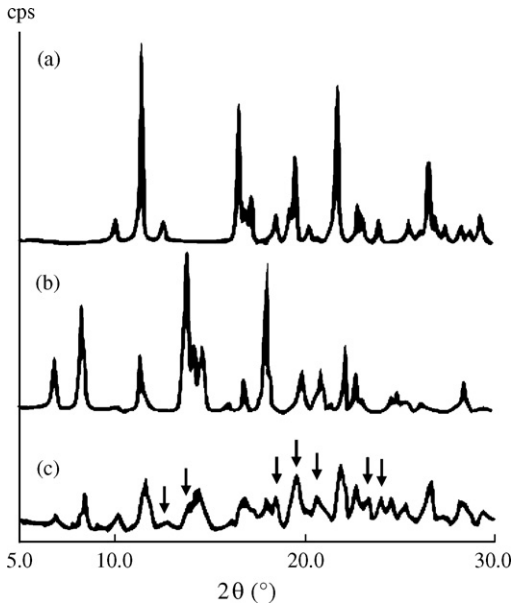

Fig. 6. PXRD patterns of IMC powder: (a) unprocessed IMC (γ-form), (b) $scCO_2$ processing at 10 MPa·40 °C, and (c) $scCO_2$ processing at 25 MPa·40 °C.

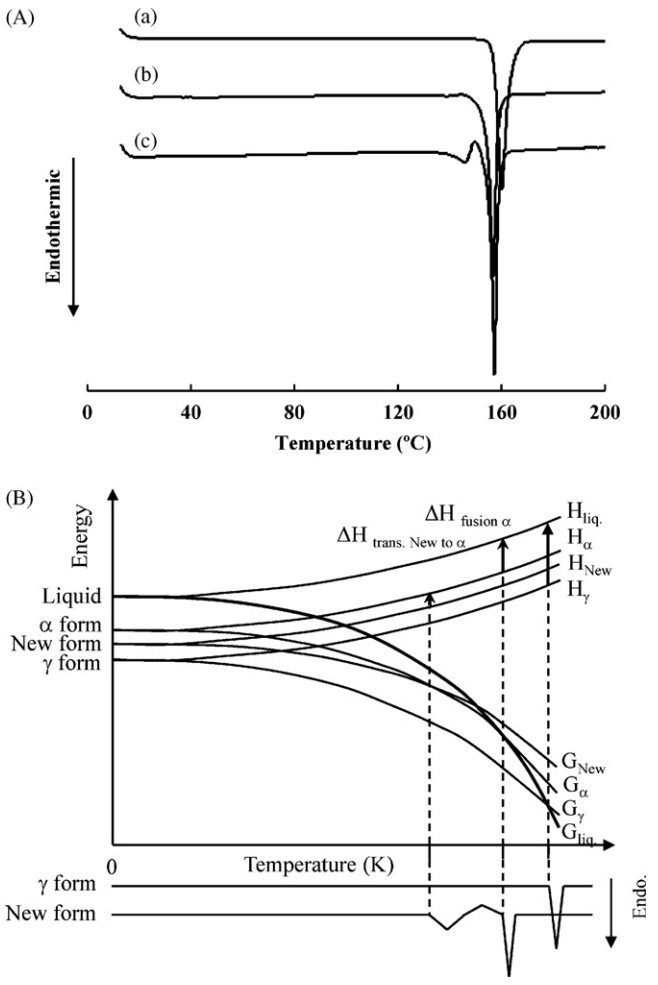

Fig. 7. DSC profiles (A) of IMC powder: (a) unprocessed IMC (γ-form), (b) $scCO_2$ processing at 10 MPa·40 °C, (c) $scCO_2$ processing at 25 MPa·40 °C, and (B) schematic energy–temperature diagram of the sample processing at 25 MPa·40 °C.

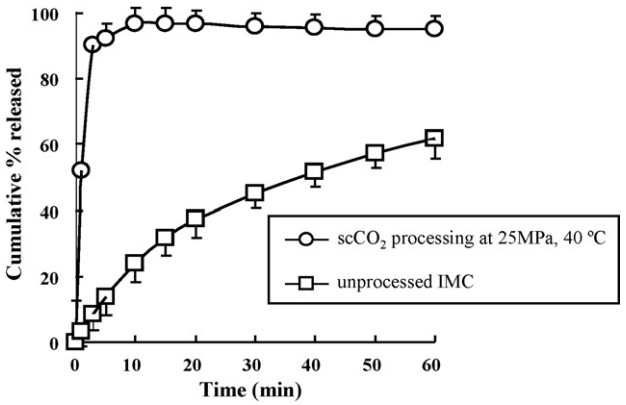

Fig. 8. Dissolution profiles of (—□—) unprocessed IMC powder and (—○—) freeze-dried sample of $scCO_2$ processed IMC at 25 MPa·40 °C ($n = 3$).

the particle size reduction to the nano-range with an increase in the surface area available for dissolution. Another factor that contributed to this enhancement is the polymorphic change to the meta-stable form which has higher solubility, since the formation of meta-stable polymorphs is well known to dramatically increase the apparent solubility and dissolution rate of poorly water-soluble drugs (Makhlof et al., 2008). Although the data is not shown here, the freeze-dried sample, after keeping for 6 months at 25 °C·75% relative humidity, shows almost same dissolution profile to the sample shown in Fig. 8.

Morphological studies reveal the formation of spherical submicron particles of IMC under 25 MPa·40 °C condition (Fig. 5). PXRD patterns of this sample indicate a decrease in the diffraction intensity for IMC under $scCO_2$ processing at 10 MPa·40 °C (α-form). The low crystallinity of IMC can be attributed to the amorphous component of IMC according to the high nozzle pressure of expansion. The amorphous component may contribute the improvement of dissolution profile in some part, as well as the size reduction of IMC to the nano-range.

4. Conclusions

The continuous system using $scCO_2$, a combinational method using antisolvent precipitation and RESAS methods, was successfully applied to produce IMC nanocrystals. This study highlighted the possible advantages of the continuous system to overcome the problem of low solubility of medicinal substances in $scCO_2$ in the RESS methods. Submicron particles of IMC having a highly spherical powder can be produced by this improved method. The powders obtained show a significant advantage for improving the dissolution profiles of IMC. Further, this apparatus does not require complicated and expensive collection devices. Our present study proposes a cost-efficient method using $scCO_2$ to produce submicron crystals of medicinal compounds.

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