Production of Nanoparticles of *RS*-(±)-Ibuprofen Using Rapid Expansion of Supercritical Solutions (RESS)

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Supercritical carbon dioxide has currently received a lot of attention as attractive media for the production of small and solvent-free particles. Rapid expansion of supercritical solutions (RESS) technique has been paid much attention and has been expected as an effective and environmentally friendly nanoparticle design method. In this study, the production of nanoparticles of *RS*-(±)-ibuprofen by RESS technique using supercritical carbon dioxide is presented. The experimental temperature and pressure are 308.2 and 313.2 K, and 13.5–20.0 MPa, respectively. We have successfully produced nano-sized particles (mean particle size: about 200 nm) with the narrow particle size distribution. Moreover, the properties of the nanoparticles produced have been strongly influenced by the supersaturation defined as the difference between the chemical potential of the solute at the section of preparing the supercritical solution saturated with the solute and that at the section of the collection of the particles produced.

INTRODUCTION

Nanoparticles exhibit unique size-dependent properties compared to bulk counterparts and would enhance a variety of technologies including pharmaceutical, coating, environmental, chemical processing, electronic, and sensing applications. In the pharmaceutical industry, there is the need for micronization of drugs into nanometer-sized particles to improve solubility and dissolution rates of drugs into the living body. The development of methods for the preparation of nanoparticles has received a great deal of attention. Generally, micronization is mostly carried out in industrial production by two commonly techniques used, recrystallization from liquid solutions and comminution. However, these two methods have some drawbacks such as wide particle size distribution, high thermal and mechanical stress, impurity contamination from a comminution device and environmental pollution problems associated with the use of large amounts of organic solvents. Therefore, it is desirable to explore alternative methods, which at least partially overcome those problems. As an alternative to the traditional techniques, various crystallization techniques using supercritical fluids have recently been proposed [1]. The characteristics of supercritical fluids allow to vary the morphology of solid particles in a wide range. Supercritical fluids have been thought to be new-type attractive solvents and have been applied in various fields of industries such as separations, reactions and material processing because their solvent power is moderate, and their transport properties are favorable in mass transfer rates. In particular, recently new crystallization techniques using supercritical fluids such as rapid expansion of supercritical solutions (RESS), supercritical antisolvent recrystallization (SAS), and particles from gas

saturated solutions (PGSS) processes have been proposed and the techniques have been paid much attention and have been expected as effective and environmentally friendly particle design methods [1]. The most well-known crystallization technique based on supercritical technique would be RESS technique. A solute is dissolved in a supercritical fluid and the solution expands rapidly through a nozzle. Due to this strong and rapid pressure, and temperature drop, the solute dissolved becomes insoluble in a low-pressure gas and thus a high supersaturation is created in the spray jet. Fast nucleation and growth of crystalline particles occur. Consequently, micro- or nano-sized particles can be produced because of the very high supersaturation and a very small growth time. After the process, the solvent is in the gaseous phase so that solvent free and dry products can be achieved and an additional wash and drying process is not necessary. RESS technique has been paid much attention and has been expected as an effective and environmentally friendly particle design method. The properties of fine particles formed by RESS technique depend on several operating conditions, as well as on the geometry of the expansion device [1]. This study has aimed to examine the effect of the temperature and pressure of preparing a supercritical solution saturated with a solute on the particle production by RESS technique using carbon dioxide as a supercritical solvent. In this study, the production of nanoparticles of *RS*-(±)-ibuprofen as a model compound has been performed. Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a nonstereoidal anti-inflammatory drug (NSAID) that is available in a variety of prescription and nonprescription drug products. An ibuprofen molecule has one chiral center, there are therefore two enantiomers of *S*-(+)- and *R*-(–)-form. Racemic ibuprofen; *RS*-(±)-ibuprofen, contains both *S*-(+)-ibuprofen and *R*-(–)-ibuprofen molecules, generally in equal amounts and this is a racemic compound. The racemate is used clinically although only the *S*-(+)-enantiomer is effective.

MATERIALS AND METHODS

Materials. *RS*-(±)-ibuprofen (supplied by Shasun Chemicals And Drugs Co., Ltd.; its purity is more than 99.94%) were used as solutes. High-purity carbon dioxide (more than 99.990%, supplied by Showa Tansan Co.) was used as received.

Apparatus and Procedures. The apparatus is basically a flow-type and consists of a section of preparing a supercritical solution saturated with a solute, that of the production of solid particles, and that of the collection of particles produced. The apparatus is shown schematically in Figures 1 and 2. From the gas cylinder (1), carbon dioxide was supplied and was liquefied through the cooling unit (6). The liquefied carbon dioxide was sent to the preheater (8) by the feed pump (7) (Nihon Seimitsu Kagaku Co., Ltd., NP-KX-500). When the carbon dioxide passed through the preheater in the thermostated water bath (12) at an experimental temperature which was controlled within ±0.1 K, it became a supercritical fluid. We used the preequilibrium cell (9) and the equilibrium cell (10) (Taiatsu Techno Co., TVS-N2), which were made of SUS316, and inner diameter, height, and volume of which were 30 mm, 150 mm, and 120 cm^3, respectively. The preequilibrium cell was equipped to obtain sufficient equilibrium conditions. Solid solute was packed into the cells with glass beads to prevent channeling. The cells were immersed into the thermostated water bath. Valve V3 was closed, and valves V2 and V4 were opened to admit supercritical carbon dioxide into the pre- equilibrium and equilibrium cells. When supercritical carbon dioxide passed through the preequilibrium and equilibrium cells, the supercritical carbon dioxide was in contact with solid solutes under an equilibrium pressure. The equilibrium pressure was measured by the pressure transducer (5) (Tem-Tech Lab., SE700T) with accuracy ±0.035 MPa. The supercritical carbon dioxide saturated with the solutes was expanded rapidly through a drilled

capillary nozzle (13) (D = L = 50 μm) into the collection chamber (14) with a jacket to control temperature after passing through the heated tube (pre-expansion section) at a selected pre-expansion temperature. The particles produced were collected on a membrane filter (15) (pore size: 100 nm) set at the outlet of the collection chamber and the membrane filter was sucked by the suction pump (17).

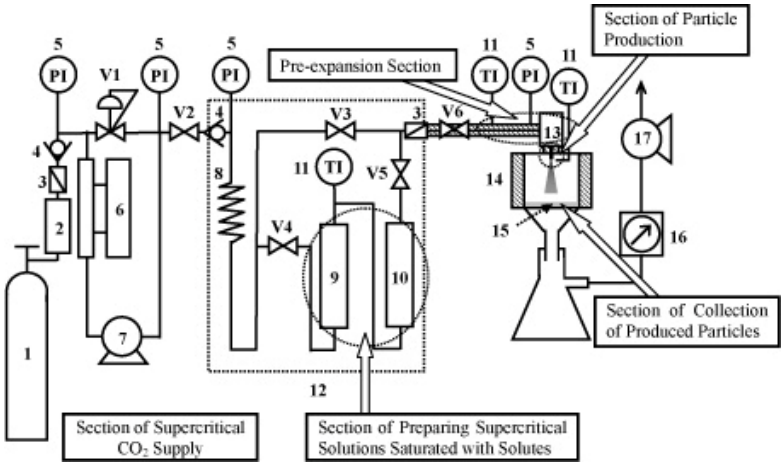

Figure 1. Schematic diagram of experimental apparatus: (1) gas cylinder, (2) dryer, (3) filter, (4) stopper, (5) pressure indicator, (6) cooling unit, (7) feed pump; (8) preheater, (9) preequilibrium cell; (10) equilibrium cell; (11) temperature indicator, (12) thermostated water bath, (13) expansion nozzle, (14) collection chamber, (15) membrane filter, (16) wet gas meter, (17) suction pump, (V1) back-pressure regulator, (V2–V6) stop valves.

The morphology of original and particles produced was observed with scanning electron microscope (SEM) (Keyence Co., VE-9800). The SEM samples were prepared by the covering with a thin layer of gold using a sputter coater. Particle sizes and the size distribution were determined by an image analysis of photomicrographs that is the counting at least 800 particles from the photomicrographs. The particle size was determined by the diameter based on the Ferret diameter. The crystallinity and melting temperature of the particles were analyzed with powder X-ray diffractometer (XRD) (Shimadzu Co., XRD-6000) and differential scanning calorimetry (DSC) (Seiko Instruments Inc., EXSTAR6000 DSC-6200), respectively. Specific surface areas of original sample and particles produced were measured by nitrogen gas absorption (BET method) using the Chem-BET-3000 (Quantachrome Instruments). The effect of particle size and degree of crystallinity of the original and particles produced on the dissolution kinetics were examined by means of the Pharmacopoeia of Japan (JP) paddle method. Powder samples were compressed directly by the hydraulic pump (Riken Seiki Co., P-18B) (5 MPa, 10 s) to form 35 pills of a 3mm diameter. The pills were introduced into a phosphate buffer solution. The phosphate buffer solution (1 L), pH 6.8, was equilibrated at 310.2 K and used as the dissolution medium. The solution was stirred at 50 rpm using a paddle. Samples of 6 mL were taken at fixed time intervals for 540 min and were analyzed by UV spectrophotometer to determine the solute concentration after filtering the solution.

Figure 2. Photograph of experimental apparatus.

The temperature and pressure of the section of preparing the supercritical solution saturated with the solute; the equilibrium temperature and pressure, were 308.2 and 313.2 K, and within the range of 13.5–20.0 MPa, respectively to examine the effect of the parameters on the production of particles by RESS. The temperatures of the nozzle and collection chamber were constant by 323.2 K, and 273.2 K, respectively. The temperature of the pre-expansion section was adjusted by 315.2 K which corresponds to of supercritical phase [2].

Table 1. Experimental Results of the Mean Particle Size and Melting Temperature of the Particles Produced by RESS

Equilibrium temperature (K)	Original	308.2				313.2			
Equilibrium pressure (MPa)		13.5	15.0	18.0	20.0	13.5	15.0	18.0	20.0
Mean particle size (nm)	57000	215	214	209	200	217	211	201	196
Melting temperature (K)	348.6	347.6	347.6	347.4	347.3	347.6	347.5	347.3	347.4
Supersaturation (-)		15.9	17.1	17.4	18.3	16.3	17.1	18.4	18.3

Pre-expansion temperature = 315.2 K, Nozzle temperature = 323.2 K, Collection chamber temperature = 273.2 K

RESULTS AND DISCUSSION

The experimental results are shown in Table 1 and Figures 3–8. The particle size of the original sample as received was as high as 57 μm, as shown in Figure 3 and the particle size distribution (CV: 59%) was also shown in Figure 4. Table 1 shows the effect of the equilibrium temperature and pressure on the particle production by RESS. Although the particles produced were of agglomeration of spheric particles, the particle size of the primary particles was very small (the minimum size: about 50 nm, and the mean size: about 200 nm), with the narrow particle size distribution (CV: about 30%) as shown in Figure 5, which was 290 times smaller than that of the original sample and was significantly smaller than that reported in the previous studies [3, 4]. The BET surface area of the micronized particles was 0.8624 m^2 g^{-1} at equilibrium temperature 308.2 K and equilibrium pressure 13.5 MPa and 1.0641 m^2 g^{-1} at 308.2 K and 20.0 MPa, which was three times higher than that of the original sample; 0.3261 m^2 g^{-1}. The results of BET surface area also confirmed that *RS*-(±)-ibuprofen was micronized successfully by the present RESS technique.

As can be seen from Figure 6, XRD analysis showed that the crystal structure of the particles was not been changed after the micronization by RESS. However, the melting temperature from DSC analysis was slightly lower and the halfwidth of the XRD peaks of the micronized particles was slightly broader compared with those of the original sample. These results indicated a slight reduction in the degree of crystallinity after the RESS processing.

JP Paddle method showed the initial dissolution rate of the micronized particles was 1.2–2 times higher than that of the original

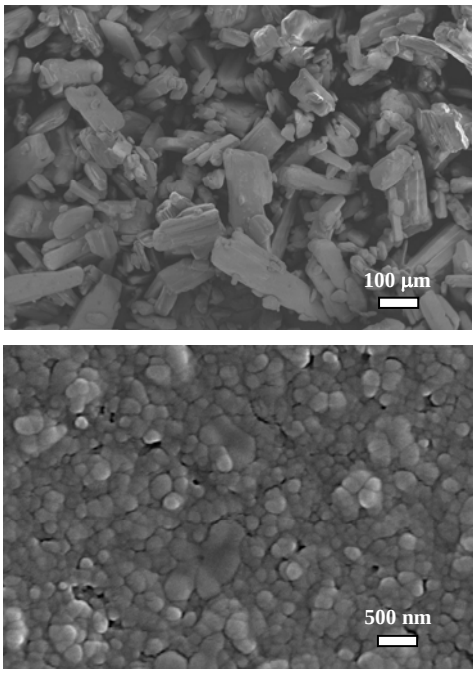

Figure 3. SEM photographs of particles of *RS*-(±)-ibuprofen; upper: original, lower: produced by RESS at equilibrium temperature 308.2 K, equilibrium pressure 20.0 MPa, and pre-expansion temperature 315.2 K.

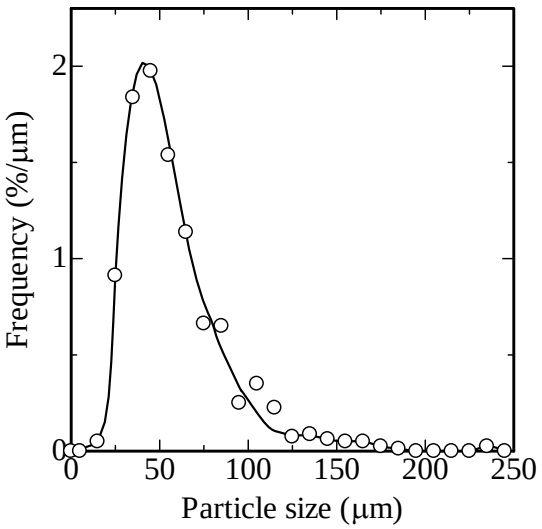

Figure 4. Particle size distribution of original sample of *RS*-(±)-ibuprofen.

sample. This enhanced dissolution rates indicated the high dissolution of drugs into the living body due to the reduction in particle size and the degree of crystallinity after the RESS process.

As can be seen from Table 1 and the BET surface area results, the mean size of the micronized particle decreased with increasing of equilibrium pressure, though that was little affected by the equilibrium temperature. Here we will discuss on the mean size of the micronized particle on the basis of supersaturation. The supersaturation as driving forces for nucleation and crystal growth, σ was thermodynamically defined as the chemical potential difference, $\Delta\mu$, between the chemical potential of the solute at the section of preparing the supercritical solution saturated with the solute and that at the section of the collection of the particles produced as follows:

$$\sigma = \Delta\mu / RT = \ln\left(y_2 / y_2^*\right) \qquad (1)$$

where the activity coefficient of the solute at the section of preparing the supercritical solution saturated with the solute and that at the section of the collection of the particles produced were approximated by unity. R is the gas constant, T is the absolute temperature, y_2 is the solubility of the solute in supercritical carbon dioxide at the section of preparing the supercritical solution saturated with the solute in mole fraction, and y_2^* is the solubility in gaseous carbon dioxide at the section of the particle collection in mole fraction. The solubility of *RS*-(±)-ibuprofen in supercritical or gaseous carbon dioxide was estimated by the Peng-Robinson (PR) equation of state and the van der Waals-type mixing rules with two binary interaction parameters introduced into both the attraction and the size terms. The binary interaction parameters were evaluated by linear functions of absolute temperature which were determined to give good representation of the solubility of *RS*-(±)-ibuprofen in supercritical carbon dioxide at 308.2, 313.2, and 318.2 K [3]. The calculated results of the solubility are shown in Figure 7. The estimated values of the supersaturation at all of the conditions were shown in Table 1 and the relationship between the supersaturation and the mean size of the micronized particles are shown in Figure 8. This figure shows that the mean size of the micronized particles decreased with increasing of supersaturation and was a linear function of the supersaturation.

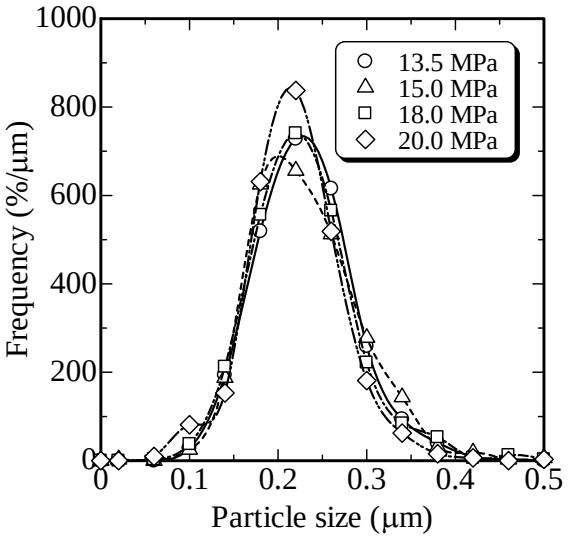

Figure 5. Particle size distribution of *RS*-(±)-ibuprofen produced by RESS at equilibrium temperature 308.2 K.

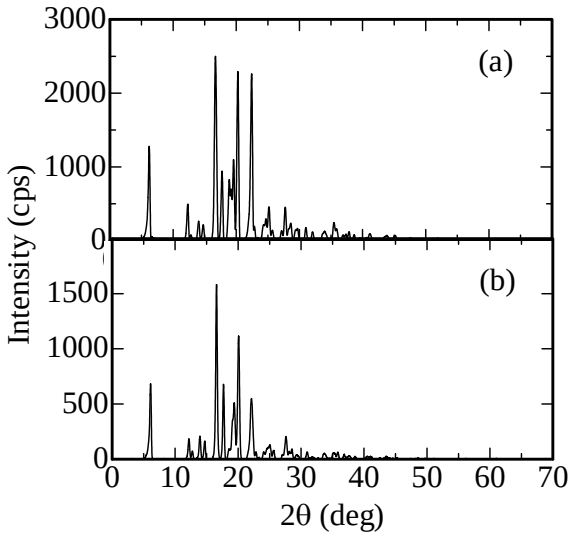

Figure 6. XRD patterns of (a) original sample, and (b) particles produced by RESS at equilibrium temperature 308.2 K and equilibrium pressure 20.0 MPa.

CONCLUSION

The production of nano-sized; the mean particle size of about 200 nm, particles of *RS*-(±)-ibuprofen with narrow particle size distribution was successfully performed by the RESS technique using carbon dioxide as a supercritical solvent. A slight reduction in the degree of crystallinity of the particles produced by RESS was showed. The initial dissolution rate of the micronized particles was 1.2–2 times higher than that of the original sample. This enhanced dissolution rates indicated the high dissolution of drugs into the living body due to the reduction in particle size and the degree of crystallinity after the RESS processing. RESS technique will allow the formation of nano-sized particle with slight reduction of the crystallinity of the material, thus confirming the possibility of processing pharmaceutical materials with this technique. Moreover, the mean size of the particles micronized by RESS can be estimated by the supersaturation defined as the difference between the chemical potential of the solute at the section of preparing the supercritical solution saturated with the solute and that at the section of the collection of the produced particles. This idea would be very useful and a strategy for the particle design by RESS technique.

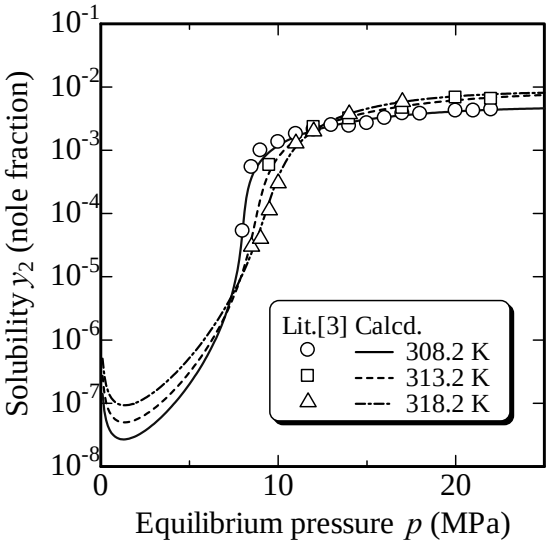

Figure 7. Literature and calculated solubility of *RS*-(±)-ibuprofen in supercritical carbon dioxide.

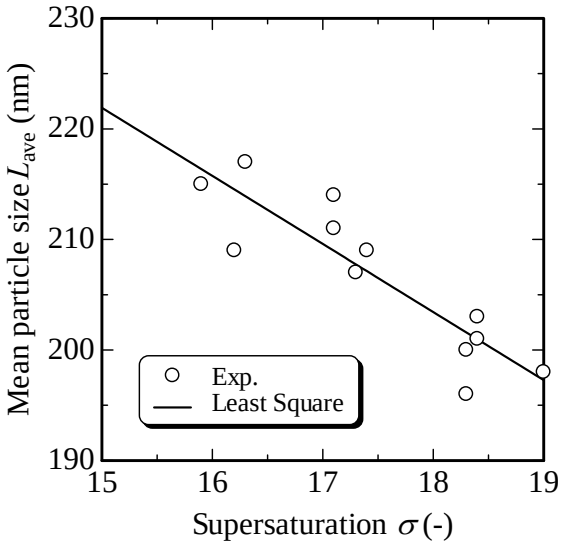

Figure 8. Relationship between supersaturation and mean particle size of *RS*-(±)-ibuprofen produced by RESS.

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