Korean J. Chem. Eng., **23**(3), 482-487 (2006)

Crystallization of acetaminophen micro-particle using supercritical carbon dioxide

Guanghua Li, Junho Chu*, Eun-Seok Song*, Kyung Ho Row, Kyong-Hwan Lee and Youn-Woo Lee*,†**

Center for Advanced Bioseparation Technology, Department of Chemical Engineering, Inha University, 253 Yonghyun-dong, Nam-gu, Incheon 402-751, Korea
*School of Chemical & Biological Engineering and Institute of Chemical Process, Seoul National University, San 56-1, Sillim-dong, Gwanak-gu, Seoul 151-744, Korea
**Energy Conversion Research Department, Korea Institute of Energy Research, Daejeon 305-343, Korea
(*Received 25 February 2006 • accepted 7 April 2006*)

Abstract–Fine particles of acetaminophen were produced by Aerosol Solvent Extraction System (ASES). The experiments were conducted to investigate the effects of various temperatures, pressures, solvents, solution concentrations and solution feed volume rates on particle size and morphology. The choice of solvent appears to be very important for getting specific particle shape and size. The result shows that when ethyl acetate is used as a solvent, the irregular and acicular morphology of raw material is recrystallized to be regular and monoclinic. The average particle size of recrystallized acetaminophen from ethyl acetate solution has been measured to be 3-4 μm, which was about 1/20th of raw acetaminophen in size. The particle size distribution range also became narrow from 82 μm to 4.9 μm.

Key words: Acetaminophen, Supercritical Fluid, Anti-solvent, Particle

INTRODUCTION

Acetaminophen, *N*-acetyl-p-aminophenol, is a widely used pharmaceutical analgesic and antipyretic agent over the world. It is used as a treatment in many conditions such as headaches, muscle aches, arthritis, backaches, toothaches, colds, and fevers [Perez-Ruiz and Martinez-Lozano, 2005]. However, the low solubility in water make it difficult to be bioavailable in the human body. This is a limitation in pharmaceutical applications. A new form of drug delivery system for a drug with poor water-solubility needs to be considered. Various methods to improve bioavailability of the drug have been done. Micronization of the drug is one of the most common methods to control the release of drugs. This method can improve the drug's therapeutic efficacy, in vitro and in vivo stability, bioavailability, targetability, and biodistribution to reduce toxicity.

In recent years, micronization techniques with supercritical fluids have been developed for manufacturing fine particles in various fields, such as chemical, pharmaceutical, munitions, cosmetic, coating and toiletry industries [Lee, 2003, 2004]. Moreover, pharmaceutical products are designed as a nano-scale by using supercritical technology that has enhanced pharmaceutical activity or that uses different delivery routes and/or overcomes human body internal barriers. Several processes of applying supercritical fluids in manufacturing micro-particles were investigated and developed. RESS (rapid expansion of supercritical solution) is a process that uses supercritical fluids as a solvent [Jung and Perrut, 2001; Matson et al., 1987]. A solid is dissolved in sc-CO_2 and expands to the surrounding at an ambient pressure. PGSS (particles from gas saturated solution) is a technique that dissolves the supercritical fluid in molten solution and sprays through a capillary nozzle [Matson et al., 1987]. SAS (supercritical anti-solvent) is a technique that supercritical fluid process as an anti-solvent. A solid is dissolved in a certain solvent and sprayed into the flowing supercritical fluid [Reverchon, 1999].

The process used in this experiment is named ASES (aerosol solvent extraction system), which is one kind of SAS process [Lee, 2003; Jung and Perrut, 2001; Reverchon and Adami, 2005]. The low solubility of acetaminophen in supercritical carbon dioxide and its relatively high solubility in organic solvents provide suitable conditions to preferably employ this process for particle formation and design of improved controlled delivery systems. Many researches about processing nano particles of acetaminophen have been done [Chattopadhyay and Guta, 2001]. Gilbert et al. [2000] produced fine acetaminophen particles using the SEDS process. They absorbed needle-shaped particles of 6-8 μm using sc-CO_2 (35 °C, 100 bar) while ethyl alcohol was used as a solvent. Wubbolts et al. [1999] manufactured 500 μm acetaminophen micro particles at sub-critical CO_2 (25 °C) conditions using the SAS process.

In our research, we investigated the effect of the operating temperature, pressure, solution concentration and the feed volume rate of solution on the particle size, particle size distribution, and morphology of the final product.

EXPERIMENTAL

1. Materials

Carbon dioxide (99.0%) used as an antisolvent was supplied by Shin Yang Co., Korea. Acetaminophen (*N*-acetyl-*p*-aminophenol, purity ≥98% (HPLC)) was purchased from Fluka. The solvents, such as methanol (Junsei Chemical Co., Ltd.), ethanol (Samchun Pure Chemical Co., Ltd.), acetone (Junsei Chemical Co., Ltd.) and ethyl acetate (Kanto Chemical Co., Inc.), were used without further purification.

2. Apparatus

An aerosol solvent extraction system was designed and a dia-

†To whom correspondence should be addressed.
E-mail: ywlee@snu.ac.kr

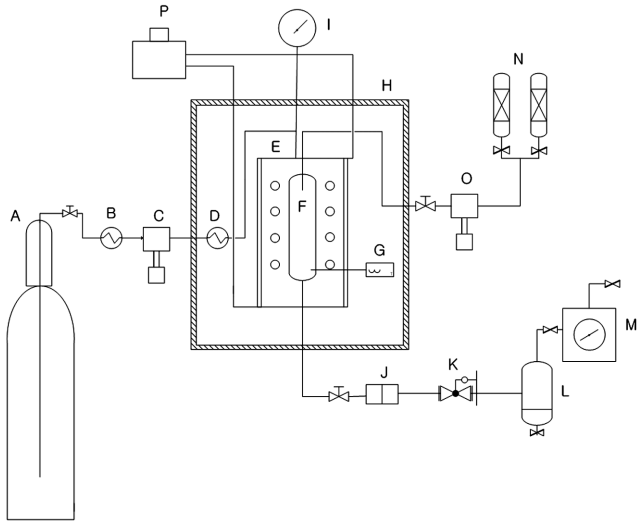

Fig. 1. Schematic diagram of the ASES apparatus.

A: CO_2 cylinder	I: Pressure gauge
B: Cooler	J: Filter
C: CO_2 pump	K: Back pressure regulator
D: Preheater	L: Vapor-Liquid separator
E: Precipitator	M: Wet gas meter
F: Nozzle	N: Solution reservoir
G: Thermocouple	O: Solution pump
H: Oven	P: Circulator

gram of experimental apparatus is shown in Fig. 1. As the diagram shows, the apparatus consists of mainly three parts, a solvent and anti-solvent supplying part, a precipitation and particle collection part, and a depressurizing and solvent separation part. The volume of the precipitator is 34 cm^3 and it is packed with a water jacket to maintain the temperature. A glass window is installed outside of the precipitator so that particle formation can clearly be observed. A back pressure regulator (Tescom; 26-1721-24) was arranged after the stainless steel filter (Tee-type filter, 0.5 mm, Millipore) to adjust the pressure. The solution was pumped into the precipitator by reciprocation pump (Milton Roy, U.S.A.). A capillary tube (stainless steels, 254 μm) used as a nozzle is located on the top of the precipitator to spray acetaminophen solution.

3. Experimental Procedure

Acetaminophen was dissolved in 10 ml ethanol, methanol, acetone and ethyl acetate, respectively. Before the solution was injected, the precipitator was preheated to a desired temperature. The temperature was controlled by a heat exchanger. Supercritical CO_2, as an anti-solvent, was introduced into the precipitator from the top of the vessel by a diaphragm metering pump (PULSA 680, Pulsafeeder, Inc, USA), which continuously delivers supercritical CO_2 at 12.8 g/min. The back pressure regulator was used to control the pressure. When the desired pressure and temperature were achieved, acetaminophen solution was sprayed into the precipitator through the 254 μm nozzle by a reciprocating pump. Fine acetaminophen particles were formed as soon as sprayed into sc-CO_2 and then collected on the filter. After the injection was finished, the sc-CO_2 was fed for 15 minutes continuously to eliminate the residual solvent in the particles.

4. Analysis and Characterization

Particle size analysis was carried out by using a Particle Size Analyzer (Sympatec HELOS, LD, Germany). The detection range of particle size is from 0.1 μm to 3,500 μm. The powder was put into the PSA system and it flowed into the particle size analyzer by RODOS dispersing system. Particle morphology was analyzed with a scanning electron microscope (SEM) (Hitach S-4200, Japan). The particles were initially spread on a carbon tape glued to an aluminum stub and coated with platinum by means of a sputter coater (GATAN 682, Japan). The platinum layer is coated to make the particle surface conductive to electrons in the SEM. The particles were coated for 3 min in the sputter, then observed under SEM, and micrographs were recorded. The FT-IR spectrum was recorded with a spectrometer (Nicolet Magna 550 series II) in the range of 800-4,000 cm^{-1} and the IR spectra were determined by using KBr wafers or disks. The acetaminophen was mixed with KBr and pressed to obtain the self-supporting disks. These disks were then placed inside the infrared spectrophotometer to record the spectrum.

RESULTS AND DISCUSSION

1. Effect of Solvents

To investigate the effects of various solvents on morphology and size of the particle, acetaminophen was dissolved in 10 ml ethanol, methanol, acetone and ethyl acetate, respectively. While the temperature, pressure, and flow rate of sc-CO_2 were fixed at 40 °C, 100 bar, and 12.8 g/min, respectively, the solution was fed into the sc-CO_2 at 0.78 ml/min. Fig. 2 shows the SEM image of raw materials of acetaminophen. The original acetaminophen shows mainly two types of morphologies: 20-100 μm of aciculate particles and 0.7-3 μm of oval plate like particles. It has a broad particle size distribution range that is from 3.3 μm (x_{10}) to 85 μm (x_{90}). After the ASES process, we can see the remarkable changes in particle size and morphology. Compared to the original acetaminophen, the particle size after processing has reduced to 1/3-1/20 and the shape has been changed to be regular in case of acetone and ethyl acetate. In the case of Fig. 3(d), the particle size distribution range is from 1.3 μm (x_{10}) to 6.2 μm (x_{90}). As the SEM images show in Fig. 3(a)-(d), we observed different sizes and morphologies by different solvents. The particles, which were made by methanol and ethanol as the solvents,

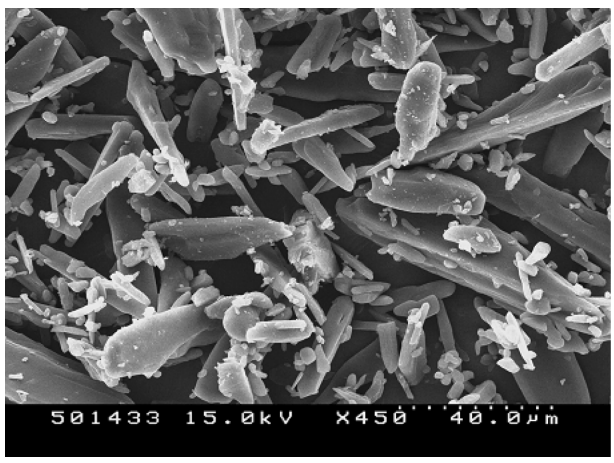

Fig. 2. SEM image of acetaminophen before ASES process.

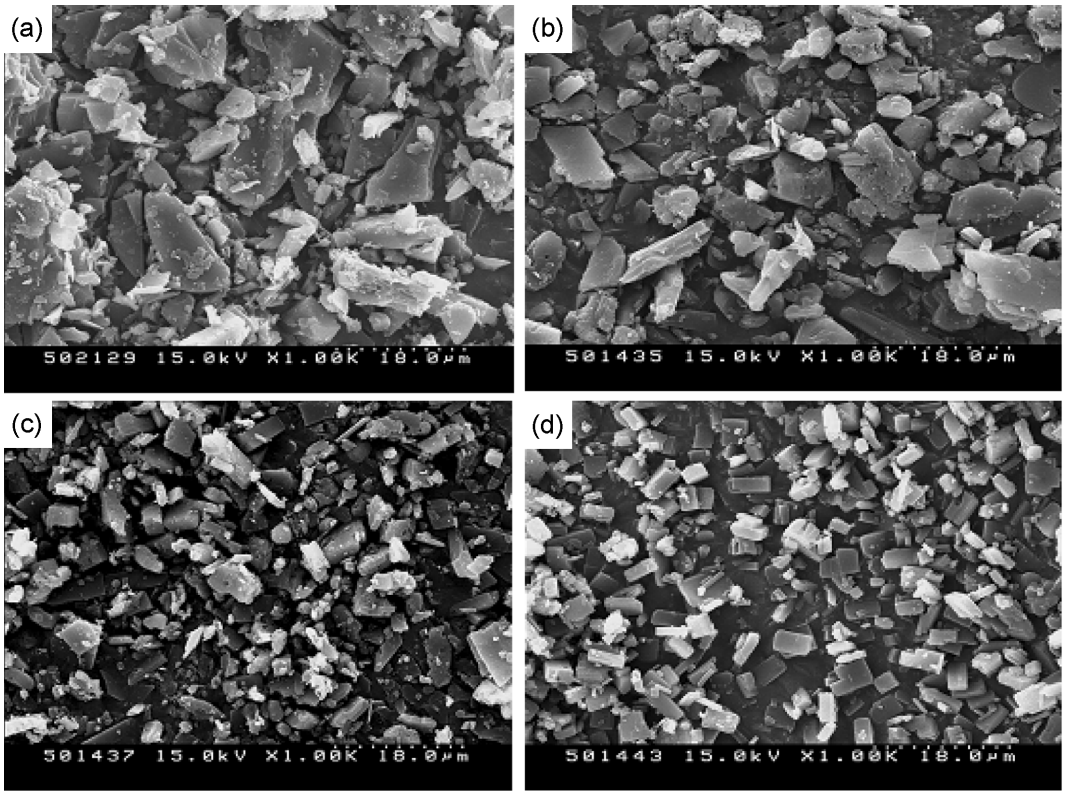

Fig. 3. SEM images of acetaminophen after ASES process (sc-CO_2 condition: 40 °C, 100 bar, solution feed rate: 0.78 ml/min).
(a) ethanol (b) methanol (c) acetone (d) ethyl acetate

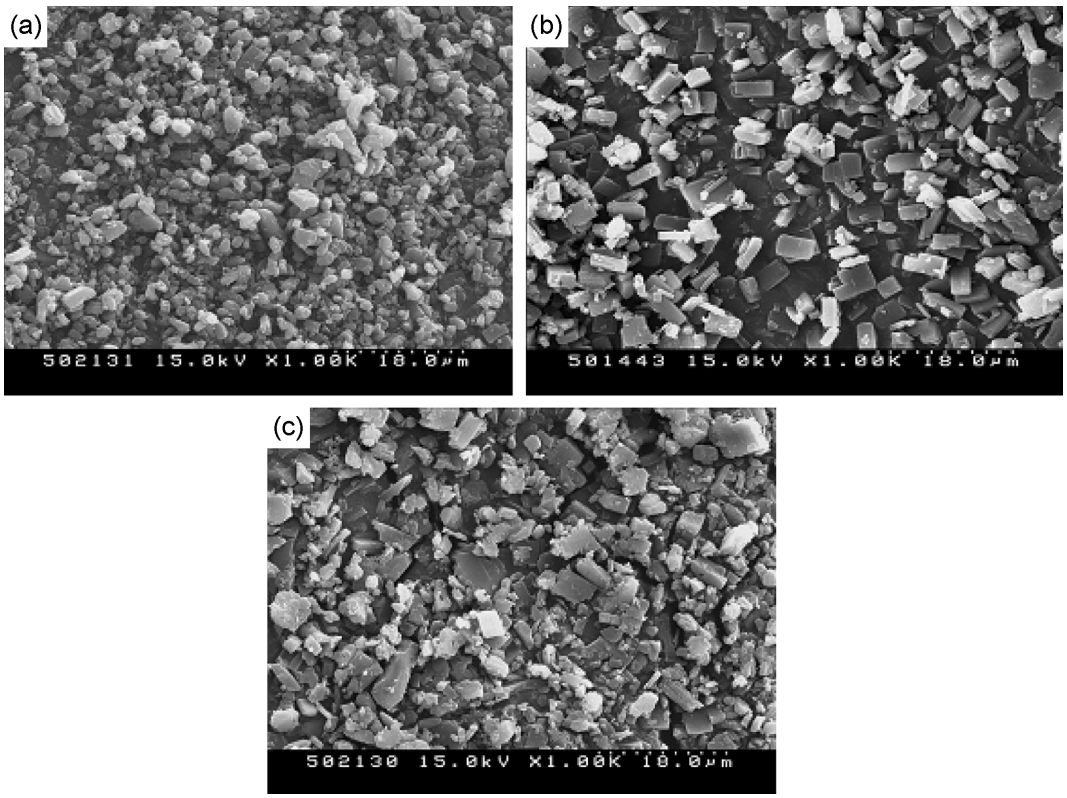

Fig. 4. SEM images of acetaminophen after ASES process (solvent: ethyl acetate, sc-CO_2 condition: 100 bar, solution feed rate: 0.78 ml/min).
(a) 35 °C (b) 40 °C (c) 45 °C

have rather irregular shapes and bigger sizes than that made by acetone and ethyl acetate. When methanol was used as a solvent, the particles were coated as a thin film on the surface of the filter, so the pressure was rising and hard to control. Compared to the methanol and ethanol, the cases of acetone and ethyl acetate are showing smaller size and more regular shape. Especially, the smallest size and the most regular shape was observed when ethyl acetate was used as a solvent. ASES is a complex process involving the interaction of jet hydrodynamics, droplet formation, and mass transfer into and out of the droplets, phase equilibrium, nucleation, and growth. The rapid nucleation results in the small particle size. It is quite probable that the low solvent power of ethyl acetate shortened the nucleation time, which is the main factor of particle size. Conversely, methanol and ethanol have big solubility that cannot react sensitively when the sc-CO_2 acts as an antisolvent, which is the important fact of the big particle size.

2. Effect of Temperature and Pressure

Experiments were carried out at various temperatures and pressures. When the pressure was fixed at 100 bar and the solution concentration was fixed at 0.8 wt%, the solvent was introduced into the precipitator at 0.78 ml/min and the temperature was varied from 35 °C to 40 °C. When the temperature was fixed at 40 °C, pressure was varied from 100 bar to 200 bar. As the SEM images (Fig. 4, 5) and the PSA results (Fig. 6, 7) show, the particle size increased nearly an order of the temperature and pressure. The average particle size at 35 °C was measured to 3.43 μm and every particle has a rather spherical shape. Compared to the 35 °C, the particle size increased at 40, 45 °C and the morphology was turned to crystalline form.

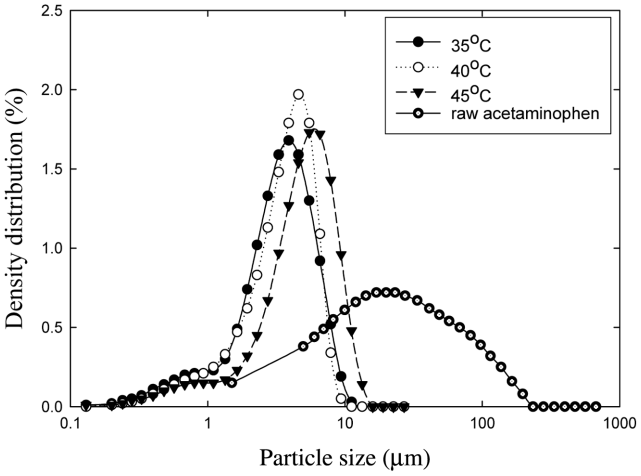

Fig. 6. The effect of temperature on acetaminophen particle size distribution.

With the increase of the pressure, the mean particle size increased slightly from 3.73 μm to 5.54 μm.

It is assumed that two competing phenomena exist in the particle formation as the temperature changes.

(1) The change of temperature affects the density of sc-CO_2. As the temperature increases, the density of the sc-CO_2 will decrease. Therefore, the diffusivity of the sc-CO_2 will increase and the solubility of the solute in sc-CO_2 will decrease so that the supersaturation will be reached faster. As a result, the particle size will decrease.

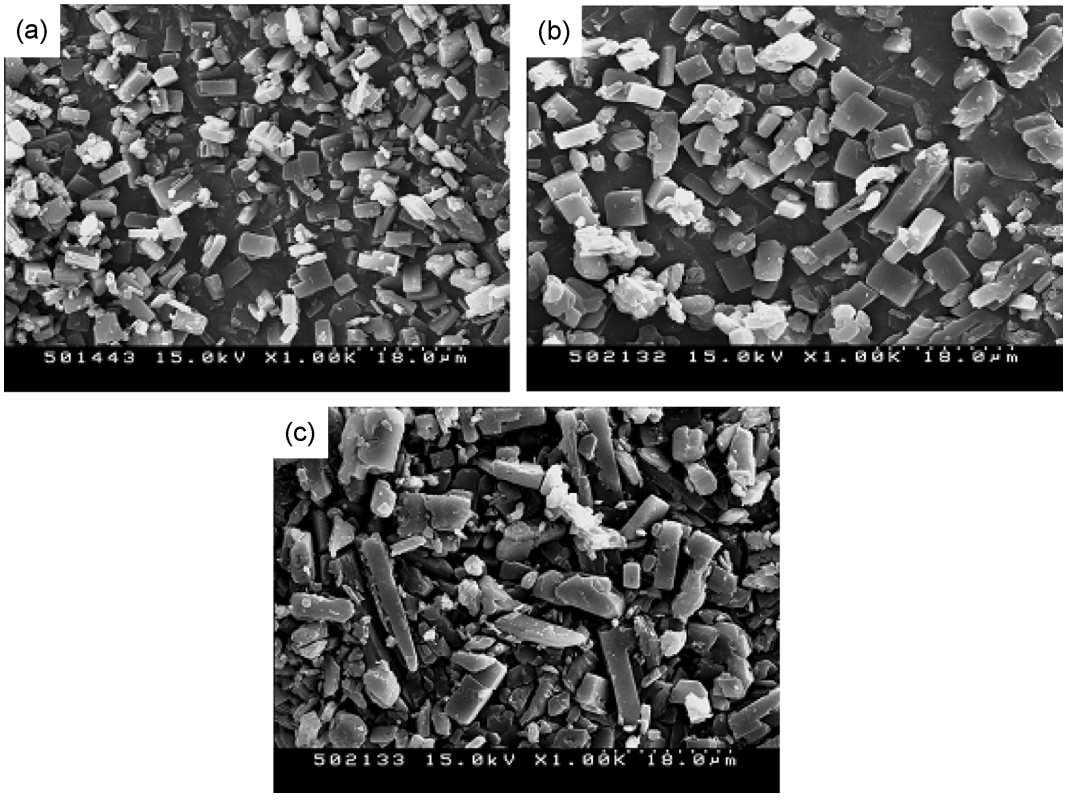

Fig. 5. SEM images of acetaminophen after ASES process (solvent: ethyl acetate, sc-CO_2 condition: 40 °C, solution feed rate: 0.78 ml/min). (a) 100 bar (b) 150 bar (c) 200 bar

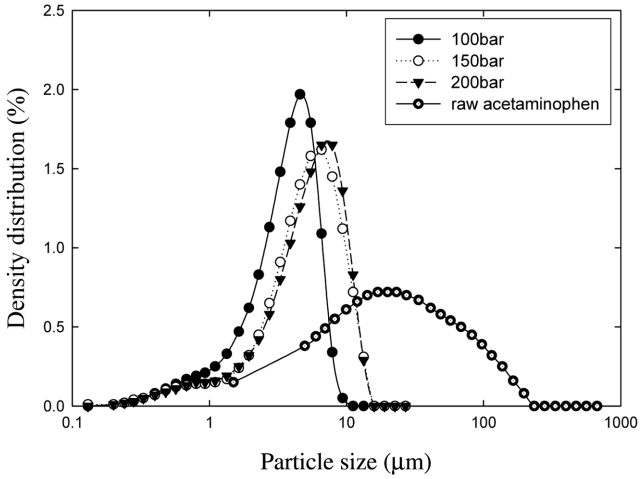

Fig. 7. Effect of the pressure on acetaminophen particle size distribution.

(2) When the temperature increases, the solubility of acetaminophen in the solvent will increase. Therefore, the supersaturation will be attained slower. As a result, the particle size will increase.

In this case, the particle size increased so that the second phenomenon seems to be dominant.

When the pressure increases, the diffusivity of sc-CO_2 will decrease so that it will increase the supersaturation time, which will result in the larger particle size. Other researchers also obtained the following results. Hanna and York [1995] have done the formation of salmeterol xinafoate using the SEDS process. The effect of pressure on mean particle size was small and the mean diameter of particles increased slightly with increasing temperature from 308 to 333 K at constant pressure. The result agrees with our work.

3. Effect of Solution Concentration and Solution Feed Volume Rate

In addition, a series of experiments were carried out to find the effects of different solution concentration and solution feed volume rate on the particle size. As Fig. 8 shows, the particle size decreased with the increase of the solution concentration. At high solution concentration, the saturation takes place more easily than the case of low solution concentration, so the supersaturation time will be shortened. The shorter supersaturation time results in smaller particles.

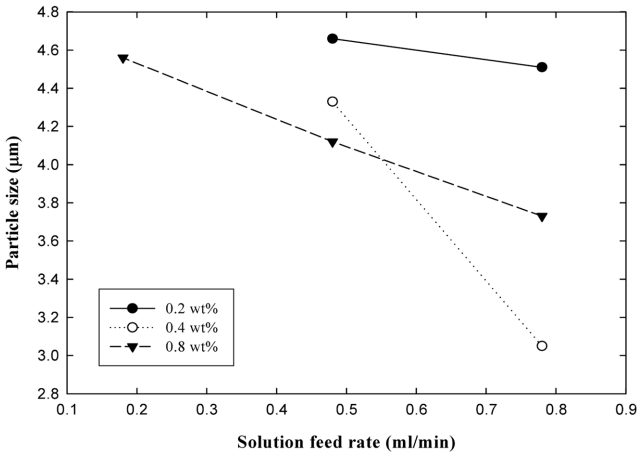

Fig. 8. Effect of solution feed rate on particle size.

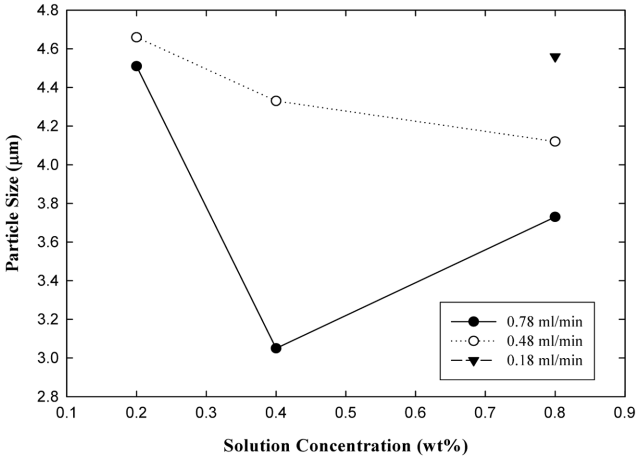

Fig. 9. Effect of solution concentration on particle size.

As Fig. 9 shows, the particle size decreased with the increase of the volumetric solution feed rate. When volumetric solution feed rate increased at a fixed CO_2 feed rate, the ratio of the volumetric feed rate of sc-CO_2 to the volumetric feed rate of solution decreased. It means that it reaches supersaturation slowly, so the particle size must increase. However, in this case, smaller particles were observed. This can be explained by the Weber number.

$$We = \frac{\rho u^2 d}{\sigma}$$

where ρ is the density of the solution, d is the nozzle diameter, σ is the interfacial tension, u is the solution feed rate. In these experiments ρ, d and σ were fixed. As the solution feed rate increased, the Weber number increased. The bigger Weber number will result in the smaller liquid droplet of the solution followed by formation of small particle size. This indicates that the two competing phenomena are coexisting during the particle formation, but the effect of Weber number seems to dominant in our experiment.

4. FT-IR Analysis of Acetaminophen Particles

An FT-IR analysis was performed to determine whether there is

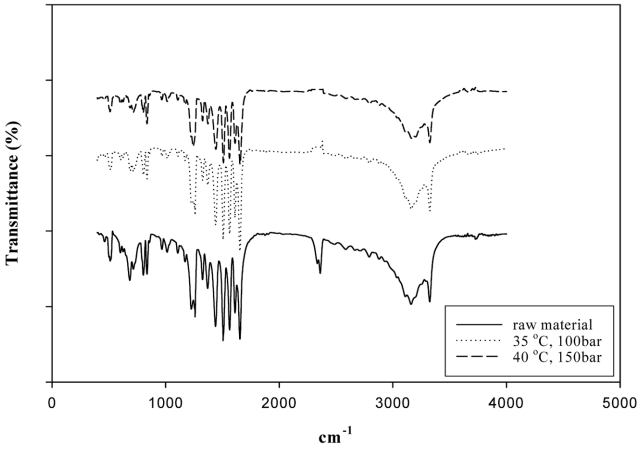

Fig. 10. Comparison of the FR-IR patterns between raw and processed acetaminophen.

any difference in the structures of the original acetaminophen (as supplied by the manufacturer) and that obtained from the precipitation experiments using the ASES process. Fig. 10 shows the FT-IR spectra of acetaminophen particles obtained in the three cases. A comparison of the three spectra indicates that there is no variation in the molecular structure of the acetaminophen before and after processing.

CONCLUSION

Acetaminophen particles were successfully prepared by ASES process with supercritical carbon dioxide. The solvent has the biggest effect on the particle size and morphology of acetaminophen. The monoclinic crystal form of morphology and the smallest size particles are formed when ethyl acetate is used as a solvent. As the temperature and pressure increase, bigger particles are observed. The average particle size is measured to be 3-4 μm, and it has the possibility to be used in the drug delivery system to increase bioavailability.

REFERENCES

Chattopadhyay, P. and Guta, R. B., "Production of antibiotic nanoparticles using supercritical CO_2 as antisolvent with enhanced mass transfer," *Ind. Eng. Chem. Res.*, **40**, 3530 (2001).

Gilbert, D. J., Palakodaty, S., Slaan, R. and York, P., "Particle engineering for pharmaceutical application - a process scale up," The 5th International Symposium on Supercritical Fluids, April, Atlanta (2000).

Hanna, M. and York, P., "Method and apparatus for the formation of particles," WO 95/01221, International Publication Date 12, 01 (1995).

Jung, J. and Perrut, M., "Particle design using supercritical fluids: literature and patent survey," *J. Supercrit. Fluids*, **20**, 179 (2001).

Lee, J.-H., "Preparation of polymeric fine particles with various morphologies using supercritical fluid," *Korean Chem. Eng. Res.*, **42**, 202 (2004).

Lee, Y.-W., "Design of particles using supercritical fluids," *HWAHAK KONGHAK*, **41**, 679 (2003).

Matson, D. W., Peterson, R. C. and Smith, R. D., "Production of powders and films from supercritical solutions," *J. Mater. Sci.*, **22**, 1919 (1987).

Perez-Ruiz, T. and Martinez-Lozano, C., "Migration behavior and separation of acetaminophen and p-aminophenol in capillary zone electrophoresis: analysis of drugs based on acetaminophen," *J. Pharm. Biomed. Anal.*, **38**, 87 (2005).

Reverchon, E. and Adami, R., "Nanomaterials and supercritical fluids," *J. Supercrit. Fluids*, **37**, 1 (2006).

Reverchon, E., "Supercritical antisolvent precipitation of micro- and nano-particles," *J. Supercrit. Fluids*, **15**, 1 (1999).

Wubbolts, F. E., Bruinsma, O. S. L. and Rosmalen, G. M., "Dry-spraying of ascorbic acid or acetaminophen solutions with supercritical carbon dioxide," *J. Crystal Growth*, **198/199**, 767 (1999).