초임계 이산화탄소를 이용한 이트라코나졸 미세입자의 제조 및 물성 평가

윤용석, 주준호, 김대성, 정진성, 김화용, 이윤우*
서울대학교 화학생물 공학부, 화학공정신기술연구소
(ywlee@snu.ac.kr*)

Fine Particle Formation of Itraconazole using Supercritical Carbon Dioxide via Aerosol Solvent Extraction System (ASES) and Evaluation of its Material Property

Yong-Suk Youn, Junho Chu, Dae Sung Kim, Jin Seong Jeong,
Hwayong Kim, Youn-Woo Lee*
School of Chemiclal & Biological Engineering and Institute of Chemical Processes,
Seoul National University
(ywlee@snu.ac.kr*)

Introduction

In the pharmaceutical industry, the conventional micronization methods have a lot of problems due to the use of organic solvents. Residual organic solvents in pharmaceutical industry are restricted and controlled with regulation. In addition, organic solvents are very toxic to human and pollute the environment. Supercritical fluid processes have been recently proposed as alternatives to conventional methods. There are several methods to design the particle, where Aerosol Solvent Extraction System (ASES) are widely used to prepare a particle with supercritical carbon dioxide (sc-CO_2) [1-3]. Many researchers have employed the ASES process for micronization and recrystallization of various pharmaceutical substances [4]. The objective of micronization using ASES process was to enhance the availability of drug usages such as in controlled release applications by reducing the size of drug particles. The use of carbon dioxide as solvent for ASES process is attractive to non-toxicity, non-flammability, recyclability and low cost. Sc- CO_2 makes it an ideal substitute to organic solvents, because sc-CO_2 condition is mild. A lot of works have been focused on the size control of pharmaceutical compounds using the ASES process. Itraconazole (ICZ) has therapeutic effects on patients with fungal diseases as orally active triazole antifungal drug.

This work reports the production of different crystalline form of pharmaceutical compounds using ASES process at various temperatures and flow ratios. The precipitated particles were measured particle size distribution and morphology using Scanning Election Microscopy (SEM), Particle Size Analyzer (PSA) and drug release study get accomplished according to dissolution rate. Physical properties are investigated as verifying Powder X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) data. After process shape is changed to plate type and the size of processed particles is about 5 ㎛~10 ㎛. As DSC result, melting point drops about 2℃ and the crystallinity of processed particles is changed to more amorphous than that of raw material. Therefore dissolution rate of processed itraconazole is very improved compared to raw material.

Experimental method

The precipitation of Itraconazole was performed with a self-designed and manufactured ASES apparatus. As shown in Figure 1, the apparatus consists of a solvent and anti-solvent supplying part, a precipitation and particle collection part, and a de-pressuring and solvent separation part. The precipitator has a 80cm^3 observable cell with a water jacket. Pressure is adjusted by using a back pressure regulator (Tescom; 26-1721-24) arranged after the filter (Tee-type filter, 0.5 μm). Carbon dioxide, as an anti-solvent, is supplied into the cell by a reciprocating pump (Thar p-50 high pressure pump) and reaches the desired temperature by a heat exchanger. Itraconazole solution enters into the cell by a reciprocation pump (Milton Roy, U.S.A.). A capillary tube (stainless steels, 0.04" I.D., 1/16" O.D.) used as a nozzle is allocated on the top of the precipitator to spray Itraconazole solution. After injection of solution, the particles are precipitated and collected on the filter that is arranged after the precipitator.

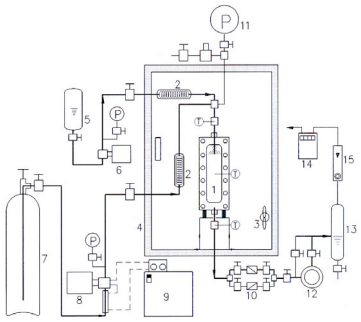
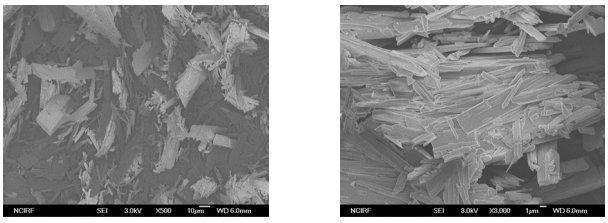


Figure 1. Schematic diagram of ASES apparatus: 1, precipitator; 2, pre-heater; 3, fan; 4, bath; 5, itraconazole solution; 6, solvent feed pump; 7, CO_2 cylinder; 8, CO_2 feed pump; 9, circulator; 10, filter; 11, pressure gauge; 12, back pressure regulator; 13, separator; 14, gas meter; 15, flow meter.

Itraconazole in methylene chloride was injected into the precipitator through the 0.04" I.D. nozzle at the flow rate of 0.65mL/min and 1mL/min. Carbon dioxide was introduced using a high pressure pump and the flow rate of carbon dioxide was changed from 10 g/min to 50 g/min. The temperature was changed from 30℃ to 50℃. When supercritical CO_2 was set on desired pressure and temperature, itraconazole solution was introduced into the precipitator. The concentration of itraconazole solution was maintained 1 wt%. The itraconazole particles were formed as soon as the solution was injected into the precipitator and collected in the filter. After injection of the solution was stopped, sc-CO_2 was maintained for 15 minutes to eliminate any residual solvent in the particles.



(a) Magnification (x 500) (b) Magnification (x 3,000)

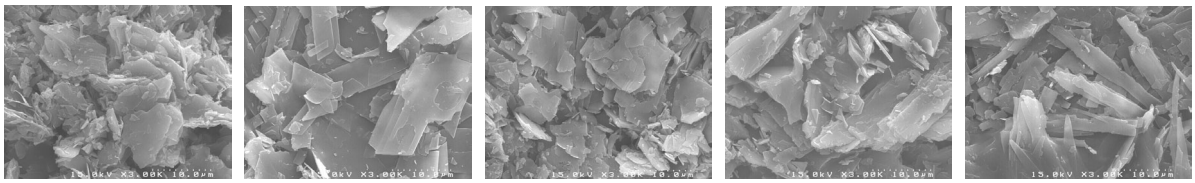
Figure 2. SEM images of raw itraconazole

Results and discussion

Itraconazole particulates prepared by ASES process were performed by changing experimental conditions: temperature, CO_2 flow rate. Figure 2 shows the SEM images of raw itraconazole particulates.

The raw materials have rod shape, which were stacked in many folds. After the process, the observed morphologies have various shapes.

Figure 3 shows the SEM images of the particles obtained by various temperatures. The morphology which was processed at near critical condition [Figure 3 (a)] shows long plate shape. But the processed particle morphologies were different with raw materials. The other morphologies were observed as a long and square plate shape [Figure 3 (b)]. As it can be seen from Figure 3 (c) ~ (e), particle morphologies were changed as thin plate shapes. The obtained particle morphologies of operation condition at 40℃ appeared as thin plate shape. Also the particle morphologies of operation condition at 45℃, 50℃ appeared as thin plate shape at 40℃ similarly but were smaller particles than the obtained particles of operation condition at 40℃.



(a) T= 31℃ (b) T= 35℃ (c) T= 40℃ (d) T= 45℃ (e) T= 50℃

Figure 3. SEM images of processed itraconazole with various temperatures (100bar, 1wt% solution concentration, 0.04” nozzle diameter, 1g/min solution flow rate, 10g/min CO_2 flow rate).

The particle size and size distribution with various experimental temperature conditions was shown Figure 4. The processed particle size was measured to be 3~12μm. The micronized particle sizes were decreased with increasing the temperature. The micronized particle sizes at 35℃, 45℃, 50℃ were measured to be 11.5μm, 4.0μm, 3.4μm respectively. As a result, the important variance for obtaining micronized itraconazole particles is temperature. As temperature was changed, the particle size can be manipulated.

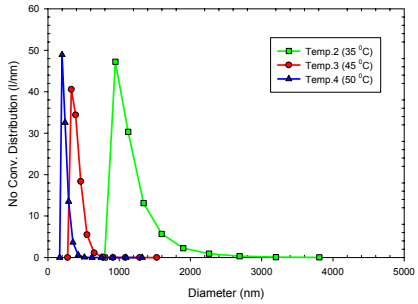
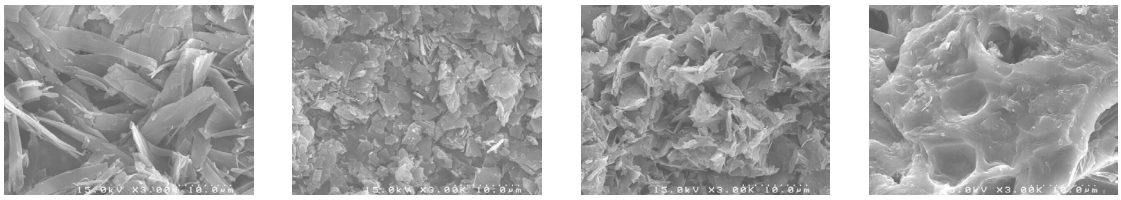


Figure 4. The particle size and distribution of processed itraconazole with various temperatures (100bar, 1wt% solution concentration, 0.04” nozzle diameter, 1g/min solution flow rate, 10g/min CO_2 flow rate).

Figure 5 shows the SEM images of the particles obtained by various CO_2 flow rates. As CO_2 flow rate was changed by increasing pump pulse, the obtained particle morphologies were observed like the agglomerated particles. The figure 5 (a) shows rod shape like near critical temperature condition. Figure 5 (b) ~ (d) shows that particle was agglomerated with increasing CO_2 flow rate.



(a) 20 g/min (b) 30 g/min (c) 40 g/min (d) 50 g/min

Figure 5. SEM images of processed itraconazole with various CO_2 flow rate (100 bar, 40℃, 1wt% solution concentration, 0.04" nozzle diameter, 1g/min solution flow rate).

The particle size and size distribution with various experimental CO_2 flow rate was shown Figure 6. The processed particle size was measured to be 3~15μm. The micronized particle size is difficult to distinguish particle size distribution between low CO_2 flow rate and high CO_2 flow rate with increasing CO_2 flow rate. Because the particle size in CO_2 flow rate 20g/min was measured to be 3.8μm. Also the particle sizes in CO_2 flow rate 30g/min, 40 g/min, 50g/min were respectively measured to be 4.8μm, 6.3μm, 15.6μm . But the results of average particle size and the results of diagram were different. The reason of the difference is that the large agglomerated particles at high CO_2 flow rate were little.

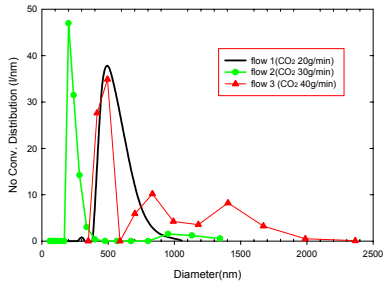


Figure 6. The particle size distribution of processed ICZ with various CO_2 flow rate , 100 bar, 40℃, 1wt% solution conc., 0.04"nozzle diameter, 1g/min solution flow rate, 10g/min CO_2 flow rate

Conclusion

The modified itraconazole particles were successfully obtained by ASES process with supercritical CO_2. The micronized particles of itraconazole were precipitated into filter by changing various temperatures and various CO_2 flow rate. The obtained particle size is 3~15μm and the particle morphologies were similar to thin plate and rod. Especially, the operating temperature condition influenced remarkably the characterization of drug particles.
Finally, future work should be conducted in detail regarding the temperature and should be found the optimal condition of CO_2 flow rate.

References

1. P. M. Gallagher, M. P. Coffey, V. J. Krukonis, W. W. Hillstrom, 'Gas antisolvent recystallization of RDX: Formation of ultrafine particles of difficult-to-comminute explosive', *Journal of Supercritical Fluids*, **1992**, 5, 130
2. B. Yu. Shekunov, P. York, 'Crystallization processes in pharmaceutical technology and drug delivery design', *Journal of Crystal Growth*, **2000**, 211, 122
3. J. Jung, M. Perrut, 'Particle design using supercritical fluids: Literature and patent survey', *Journal of Supercritical Fluids*, **2001**, 20, 179
4. Sang-do Yeo, Min-su Kim, Jong-Chan Lee, 'Recrystallization of sulfathiazole and chlorpropamide using the supercritical fluid antisolvent process', *Journal of Supercritical Fluids*, **2003**, 25, 143