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Micronization of Poorly Water-Soluble Trichlorocarbanilide Using Supercritical Carbon Dioxide

Jeong-Lae Kim[1], Seonhwa Kim[2] and Moon Sam Shin[2,†]

[1] Department of Biomedical Engineering, Eulji University, Seongnam City, 13135, Gyunggi Do, Republic of Korea
[2] Department of Senior Healthcare and Beauty & Cosmetic Science, Eulji University, Seongnam City, 13135, Gyunggi Do, Republic of Korea
{Jeong-Lae Kim, Seonhwa Kim, Moon Sam Shin, msshin@eulji.ac.kr}

Abstract. Trichlorocarbanilide has widely been used in cosmetics and household products, but the extremely low solubility of trichlorocarbanilide in water constrains the development of water-based products. In order to enhance the bioavailability, trichlorocarbanilide were micronized using supercritical fluid. Supercritical carbon dioxide was selected due to relatively low critical temperature and the rapid expansion of supercritical solution (RESS) process was chosen because trichlorocarbanilide was soluble in supercritical carbon dioxide. The effects of temperature and pressure on particle size were investigated using phase behavior data and correlated results from the quasi-chemical nonrandom lattice fluid model.

Keywords: Trichlorocarbanilide, Micronization, Poorly Water-Soluble, Supercritical, Carbon Dioxide.

1 Introduction

Trichlorocarbanilide is an anti-bacterial and anti-fungal agent widely used in cosmetics, pharmaceuticals and household products such as in soaps, lotions, deodorants, toothpaste [1]. However, the exceedingly poor solubility of trichlorocarbanilide in water (approx. 50 ng cm^{-3}) constrains the development of water-based antibacterial trichlorocarbanilide-containing products. In cosmetic and household products, many bioactive ingredients are poorly soluble in biological environment, but they must be dissolved in water in order to be absorbed and to exert their effects. The bioavailability is defined as ratio of drug absorbed in target area by body compared to initial dosage and the bioavailability of poorly soluble compounds is limited by poor solubility [2], [3], [4]. Micronized processes of the biomaterials can enhance the dissolution rates of bioactive ingredients into the biological media. Dissolution rate is a function of the surface area of particles and solubility. The surface area can increase through the reduction of particle size.

Supercritical fluids have been considered as an appropriate alternative for extraction and purification process of cosmetics and pharmaceuticals and has replaced traditional organics solvent for various industrial applications [5], [6]. Various processes for fine particles using supercritical fluids (SCF) have been studied including rapid expansion of supercritical solutions (RESS) [7], [8] and supercritical

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anti-solvent (SAS) [4]. Due to non-toxic, inexpensive and low critical temperature of 304.2 K, supercritical carbon dioxide is a promising solvent for extraction and purification of cosmetics, pharmaceuticals, food supplements and natural products. Although supercritical fluid solvents possess many desirable features for separations of biomaterials, the development of new processes has been hindered by lack of engineering data and thermodynamic models. Solubility information is essential for choosing a supercritical fluid processes for particle design [9, 10]. If the solute is soluble in the supercritical fluid, the RESS process [2], [7], [8] is considered; however, if the solute is not soluble, an SAS process [4] is preferred. Furthermore, precise solubility data is important for the designing experiment condition in the RESS process. The solid solubility in supercritical fluid can be calculated by the equation of state (EOS) method such as Peng and Robinson EOS [11]. Most recently, a quasi-chemical nonrandom lattice fluid (QLF) model [12], [13] was presented and it could successfully calculate the solubility of biological compounds in supercritical fluid [14].

In this study, trichlorocarbanilide was micronized using supercritical carbon dioxide and experiments were carried out to investigate the effect of temperature (313.2 - 333.2 K) and pressure (10.0 - 20.0 MPa). The effects of temperature and pressure on particle size were analyzed using phase behavior data and correlated results from the quasi-chemical nonrandom lattice fluid model.

2. Experiment

2.1 Materials

Carbon dioxide (min. 99.5%) and trichlorocarbanilide (min. 98.0%) was supplied from Korea Industrial Gases and Hunan Dajie Technology Co. Ltd., respectively. These materials were used without further purification.

2.2 RESS Experiment

Fig. 1 shows schematic diagram of RESS apparatus. RESS process consists of a carbon dioxide supplying system, a pressure system, a dissolution vessel, an expansion system and an expansion chamber. Carbon dioxide is supplied from a gas cylinder and the gaseous carbon dioxide liquefied through a cooler (Jeio Tech. Co. Ltd, RW-0525G) set to 263.15 K. Carbon dioxide was compressed by a diaphragm metering pump (Pulsafeeder Inc., PULSA 680). A back pressure regulator (Tescom Corp., 26-1761-24-161) was set up after the pump exit. When the compressed carbon dioxide got through the back pressure regulator, it was made a delivery to the dissolution vessel. Prior to going into the dissolution vessel, the carbon dioxide passed through a pre-heater to minimize temperature difference of the injected carbon dioxide and the interior of the dissolution vessel. The temperature of solution in dissolution vessel was modulated by thermostatic circulating water in the jacket using a refrigerated circulating bath. System temperature was observed by a K-type thermocouple. The magnetic bar was used to accelerate the dissolution rate of trichlorocarbanilide. A metal fritted filter was installed between the dissolution vessel

and the valve so that only trichlorocarbanilide dissolved was passed through the filter. Once supercritical carbon dioxide was saturated with trichlorocarbanilide, the valve was opened to spray the solution into the expansion chamber through a laser-drilled orifice nozzle with a hole. The nozzle used in this study was made of stainless steel 316 (150 µm thick and 9 mm outer diameter) and has inner diameters of 30 µm. The nozzle was heated using a heating tape. As the supercritical solutions were de-pressurized through the nozzle to ambient conditions, they rapidly expanded and the solute was re-crystallized. Trichlorocarbanilide was collected in the chamber. An expanded carbon dioxide was vented off through a filter paper which was located at the bottom of the chamber. We measured particle size and particle size distribution by the laser diffraction beam as an aerosolized dry powder using RODOS dry powder accessory (Sympatec Gmbh, HELOS/BF). The particle size was measured in the range from 0.1 to 35 µm. Particle morphology was observed by Scanning Electron Microscope (SEM, JEOL, JSM-6700F). The particles were first spread on a carbon tape glued to an aluminum stub and coated with a silver to make the particle surface conductive to electrons by SEM. Particles were measured by SEM and the micrographs were taken and recorded.

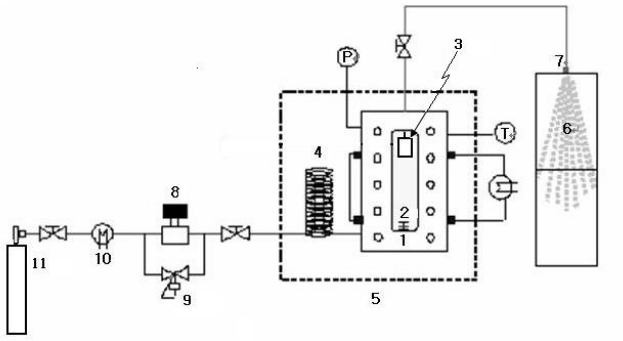


Fig. 1. Schematic diagram of RESS apparatus; (1) dissolution vessel, (2) magnetic bar, (3) filter (0.5 µm), (4) pre-heater, (5) air bath, (6) expansion chamber, (7) nozzle, (8) pump, (9) back pressure regulartor, (10) circulating bath, (11) CO_2 cylinder.

3 Results and Discussion

3.1 Solubility of Trichlorocarbanilide in Supercritical Carbon Dioxide

Solubility of trichlorocarbanilide in supercritical carbon dioxide [15] was corrected with the the QLF model and shown in Fig. 2. An isothermal increase in pressure causes increase in trichlorocarbanilide solubility. A common feature of trichlorocarbanilide solubility in supercritical fluid is the existence of what has been termed crossover pressure. Below the crossover pressure, an isobaric increase in temperature causes decrease in solubility, so that is retrograde. Above the crossover pressure, the opposite effect occurs.

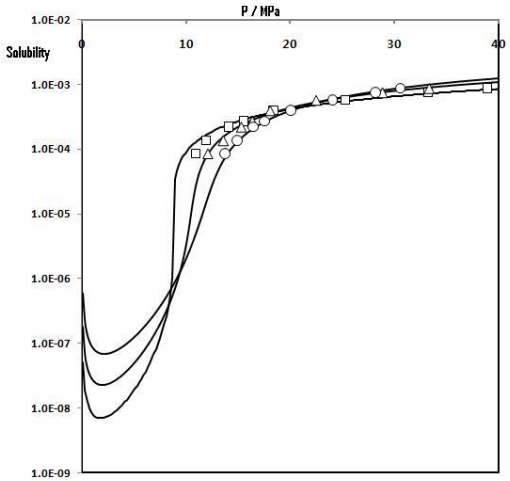


Fig. 2. Solubility of trichlorocarbanilide in supercritical carbon dioxide with the QLF model. □, 313.2K; △, 323.2K; ○, 333.2K

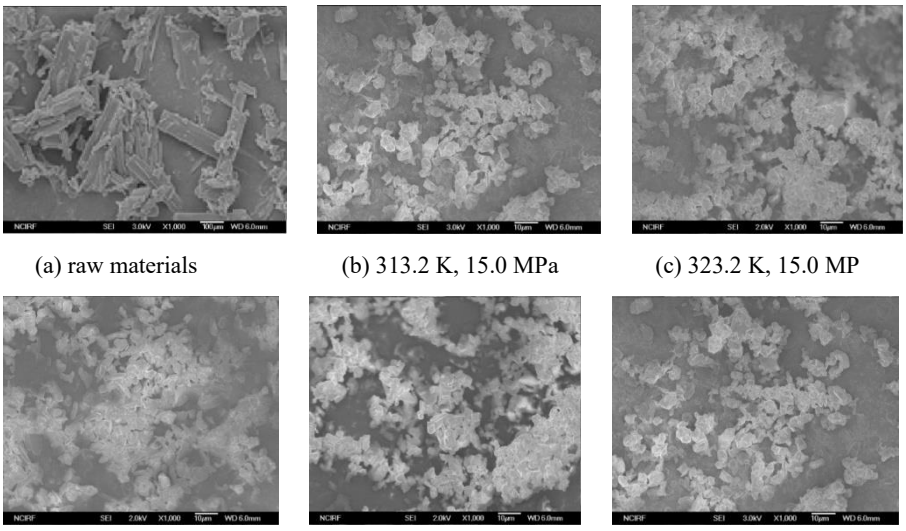
3.2 Micronization of Trichlorocarbanilide

The experiments were carried out to look into the effect of temperature from 313.2 to 333.2 K and pressure from 10.0 to 20.0 MPa on the size and morphology of triclorocarbanilide particles by the RESS process. The experimental conditions and results are reported in Table 1.

Table 1. RESS experimental conditions and results

T(K)	P(MPa)	Average particle size (μm) Mean ± Standard Deviation
raw material		185.2 ± 2.3
313.2	15.0	2.28 ± 0.13
323.2	15.0	2.41 ± 0.15
333.2	15.0	3.32 ± 0.18
313.2	10.0	2.57 ± 0.16
313.2	20.0	2.06 ± 0.11

SEM images of the raw material and the RESS processed crystals were shown in Fig. 3. The raw particle has shaped like a sharp rectangle and the RESS processed particles were irregular and polyhedral in shape. Average particle size of the raw particle was 185.2 μm. The average particles sizes of processed particles were between 2.06 and 3.32 μm.



(a) raw materials (b) 313.2 K, 15.0 MPa (c) 323.2 K, 15.0 MP

(d) 333.2 K, 15.0 MPa (e) 313.2 K, 10.0 MPa (d) 313.2 K, 20.0 MPa

Fig. 3. SEM images of the raw materials and the RESS processed particles.

The effect of temperature was carried out from 313.2 to 333.2 K at 15.0 MPa and the isobaric increase in temperature resulted in increase in the average particle sizes from 2.28 to 3.32 μm. The effect of pressure was carried out in the range of 10.0 to 20.0 MPa at 313.2 K and the isothermal increase in pressure resulted in decrease in the average particle sizes from 2.57 to 2.06 μm. This behavior can be explained by considering as followed; an isothermal increase in pressure caused increase in the carbon dioxide density and decrease in the intermolecular distance of its molecules. The specific interaction between the solute and solvent molecules, therefore, is increased and solute solubility is increased. Fig. 2 also showed below the crossover pressure, an isobaric increase in temperature caused decrease in solubility but above the crossover pressure, the opposite effect happened. This phenomenon could be understood by considering two opposing effects of temperature on solubility. The vapor pressure of the solid always increased with temperature, while the density (or solvent power) of supercritical carbon dioxide decreased. Below the crossover pressure where the compressibility was larger, the density effect dominated, and the solubility decreased with increasing temperature. At pressure above the crossover, the vapor-pressure effect dominated; hence solubility increased with temperature.

The effect of extraction temperature was carried out for the range of 313.2 to 333.2 K at 15.0 MPa. Increasing in extraction temperature resulted in increase in the average particle size from 2.28 to 3.32 μm. An increase of temperature decreases the CO_2 density and leads to a decrease of a solvent power. As a result, a lower supersaturation and lower nucleation are achieved. Consequently, particle size increases with temperature increases. Further, an increase of temperature cause to increase the solute's vapor pressure leading to higher solution concentration. The high concentration of the solution brings about the increase of the particle size as a consequence of the particle growth and coagulation among the particles.

The effect of extraction pressure was performed in the range of 10.0 to 20.0 MPa. As the extraction pressure increases the average particle sizes decrease from 2.57 to 2.06 μm. The extraction pressure affects particle size in several aspects. First, the higher the pressure, the greater the solubility of trichlorocarbanilide in supercritical CO_2 since the CO_2 density increases as pressure increases. The increase of the trichlorocarbanilide in supercritical CO_2 solubility results in the greater the degree of supersaturation and higher nucleation rate. Second, higher pressure leads to a higher mass flow rate of the solution and causes reduced residence time in the nozzle. Consequently, time for particle growth will be decreased within a nozzle. Both phenomena can lead to a decreased particle size. Third, the higher the pressure, the higher the solution concentration, this frequently leads to coagulation among particles. As a result, the particle size increases. Therefore, it can be explained that the first and second phenomenon is dominant in this study.

4 Conclusion

Micronization of poorly water-soluble trichlorocarbanilide was satisfactorily carried out using the RESS process with the average particles in the range between 2.06 and 3.32 μm. The effect of temperature was performed from 313.2 to 333.2 K at 15.0 MPa and the isobaric increase in temperature resulted in increase in the average particle sizes from 2.28 to 3.32 μm. The effect of pressure was carried out in the range of 10.0 to 20.0 MPa at 313.2 K and the isothermal increase in pressure resulted in decrease in the average particle sizes from 2.57 to 2.06 μm. The effects of temperature and pressure on particle size were investigated using solubility data and the thermodynamic behavior.

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References

1. Charlton, L.R., McGillycuddy, J.T.: Skin wash compositions comprising triclocarban and surfactants. US Patent 6,224,886 (2001).
2. Turk M., Hils P., Helfgen B., Schaber K., Martin H.J.: Micronization of pharmaceutical substances by the rapid expansion of supercritical solutions (RESS); a promising method to improve bioavailability of poorly soluble pharmaceutical agent. J. Supercrit. Fluids 22, 75--84 (2002).
3. Kayrak D., Akman U., Hortacsu O.: Micronization of ibuprofen by RESS. J. Supercrit. Fluids 26, 17--31 (2003).
4. Perrut M., Jung J.,Leboeuf F.: Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes: Part I: Micronization of neat particles. Int. J. Pharmaceu. 288, 3--10 (2005).
5. Teja A.S., Eckert C.A.: Commentary on supercritical fluids; research and application. Ind. Eng. Chem. Res. 39, 4442--4444 (2000).

6. Beckman EJ: Supercritical and near-critical CO_2 in green chemical synthesis and processing. J Supercrit Fluids 28, 121--191 (2004).
7. Huang Z., Sun G., Chiew Y.C., Kawi S.: Formation of ultrafine aspirin particles through rapid expansion of supercritical solutions (RESS), Powder Techno. 160, 127--134 (2005).
8. Yildiz N., Tuna S., Döker O., Çalimli A: Micronization of salicylic acid and taxol (paclitaxel) by rapid expansion of supercritical fluids (RESS). J. Supercrit. Fluids 41, 440--451 (2007).
9. Jung J., Perrut M.: Particle design using supercritical fluids: literature and patent survey, J Supercrit Fluids 20, 179--219 (2001).
10. Knez Z., Weinder E.: Particles formation and particle design using supercritical fluids. Curr Opin Solid State Mater Sci 7, 353--361 (2003).
11. Peng D.Y., Robinson D.B.: A new two-constant equation of state. Ind Eng Chem Fundam 15, 59--64 (1976).
12. Shin M.S., Kim H.: A qausi-chemical nonrandom lattice fluid model; general derivation and application to pure fluids and mixtures. Fluid Phase Equilib 246, 79--88 (2006).
13. Shin M.S., Kim H.: A qausi-chemical nonrandom lattice fluid model for phase equilibria of associating systems. Fluid Phase Equilib 256, 27--33 (2007).
14. Shin M.S., Kim H.: Solubility of iodopropynyl butylcarbamate in supercritical carbon dioxide. Fluid Phase Equilib 270, 45--49 (2008).
15. Park C.I., Shin M.S., Kim H.: Solubility of climbazole and triclocarban in supercritical carbon dioxide: measurement and correlation. J. Chem. Thermodyn. 41, 30--34 (2009).