Particle Design Algorithm by Supercritical Fluid Processes

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INTRODUCTION

Supercritical Fluids (SCFs) are known as green solvents that have been used in various areas of extraction, polymerization, wastewater treatment, and material processing [1]. Among them, supercritical carbon dioxide is an attractive process medium for thermal liable materials such as food and pharmaceutical compounds, and bio-molecules with no residual solvents [2, 5, 6]. Micronization processes with SCFs were performed using various interesting compounds such as formation of stereocomplex, dispersion polymerization in fields of polymer engineering and recrystallization for high energetic materials like 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (HMX) and 1,3,5-Trinitroperhydro-1,3,5-triazine (RDX). RDX and HMX, extremely sensitive high explosives, are difficult to recrystallize in a form free of intragranular cavities by conventional techniques. For example, solvent evaporation or liquid anti-solvent recrystallization methods may result in the inclusion of a liquid that causes voids during drying process. Since voids are detrimental to the performance of RDX-containing propellant and explosive formulations, and since the only present means of reducing both the void volume and the particle size involves grinding, itself a difficult and dangerous operation, it is desirable to produce cavity-free RDX by direct recrystallization. In addition, CO_2 in polymer processes has recently been a particular focus of research and development since it has relatively mild critical conditions and is one of the least expensive solvents [3]. It is reported that dispersion polymerization in supercritical fluid readily allows the production of monodispersed micron-sized polymer particles in a single step. In dispersion polymerization, monomer, initiator, and surfactant must be miscible in the supercritical fluid, whereas the resulting polymer must be immiscible at the end of the polymerization step [4].

For particles of thermal liable compounds, precipitation processes with SCFs provide excellent environments. Thus, numerous researches focused on the fields of pharmaceutical, natural substances, and explosives have been carried out [7-9]. There are two major SCF precipitation processes which can be classified according to the role of the supercritical fluid in the process (Figure 1). In the Rapid Expansion of Supercritical Solution (RESS) process, SCF can serve as a solvent while in the Supercritical Anti Solvent processes (SAS), SCF can act as an anti-solvent. In the SAS process, SCF is served as an anti-solvent to reduce the solubility of solute in solvent and to cause rapid nucleation of solute due to fast mass transfer between solvent and solute. Particle size and crystal properties of pharmaceutical are easily manipulated by process parameters with no solvent residual in the final product. The main

purpose of the design of particle is to control polymorphism, morphology, and size of crystals based on the specification of the final product. It is well known that supercritical fluid process of precipitation has great advantage for controlling the particle quality since SCFs provide adjustable solvent power, diffusivity, interfacial tension, and viscosity. Most important parameter to control particle quality is the selection of solvent in which solvent-solute interaction play a crucial role to formation of polymorphism and morphology. Particle size may controlled by simple manipulation of pressure, temperature, or concentration. In this work, it is examined about SCF processes with various goals and its applications for formation of fine particles based on research data accomplished.

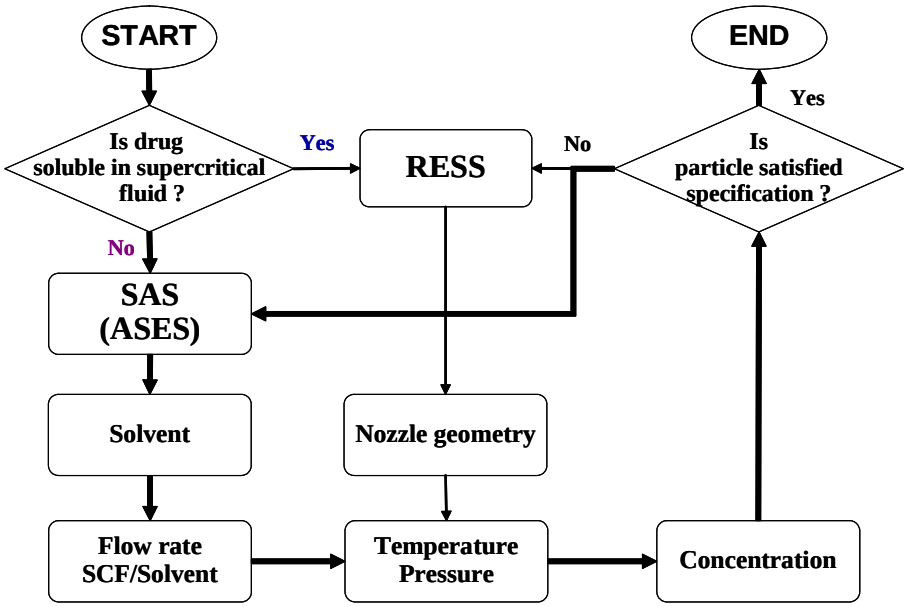


Figure 1. Design algorithm of drug particles

MATERIALS AND METHODS

Ibuprofen, cefpodoxime proxetil (CPD), itraconazole, acetaminophen, valsartan and clartithromycin were supplied from Hanmi Fine Chemical Co., Ltd in Korea. RDX and HMX are supplied from Agency for Defence Development in Korea. Another drug such as lysozyme, insulin, and trypsin were purchased from Sigma-Aldrich with purity greater than 90 wt%.

The precipitation unit of RESS, applied when target materials have solubility in SCF, consists of gas supply, a dissolved vessel and an expansion chamber. Most of the precipitated particles are collected in the expansion chamber through a laser-drilled orifice nozzle with a hole. On the other hand, the system for semi-batch for SAS process consists of three sections for carbon dioxide supply, recrystallization, and depressurization. High-pressure carbon dioxide was fed into the system through pre-heater from the gas cylinder by a diaphragm metering pump. A precipitator in the recrystallization section consisted of a capillary tube (stainless steel, 0.01”I.D., 0.0625”O.D.) and a high pressure glasses. Volume of the precipitator was

60mL. In the depressurization section, a regulator (Pressure regulator, 26-1721-24, TESCOM) was used to control the gas pressure, a filter to collect products and a separator to solvent recovery.

RESULTS

In this study, we are going to demonstrate that both processes of RESS and ASES could be selected according to the solubility of target materials in SCF. For example, fine particles of aspirin can be obtained by either SAS or RESS process depending on solubility in $scCO_2$. Figure 2 is solubility of aspirin in CO_2, in which the solubility of aspirin increases with CO_2 density [8].

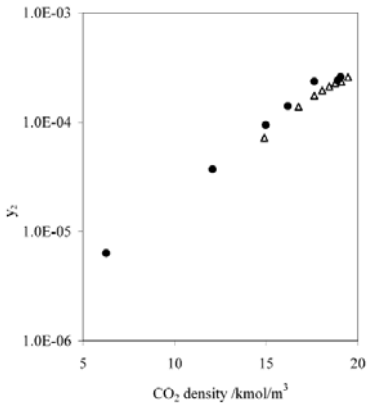
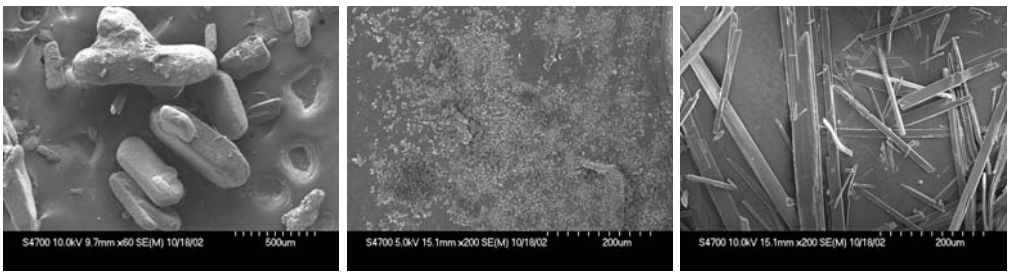


Figure 2. Solubility of aspirin in CO_2

Aspirin is one of the pharmaceutics succeeded in micronization using RESS process by supercritical CO_2 to enhance bioavailability because they are hardly soluble in water. Figure 3 is SEM images of the unprocessed and processed aspirin by both RESS and SAS systems. Raw aspirin has a rectangular parallelepiped shape with 250 μm in length and 200 μm in width approximately of typical particle size. However treated aspirin by RESS shows irregular type of morphology with about 2 μm of particle size. On the other hand, rod type of aspirin particles is obtained by SAS process.

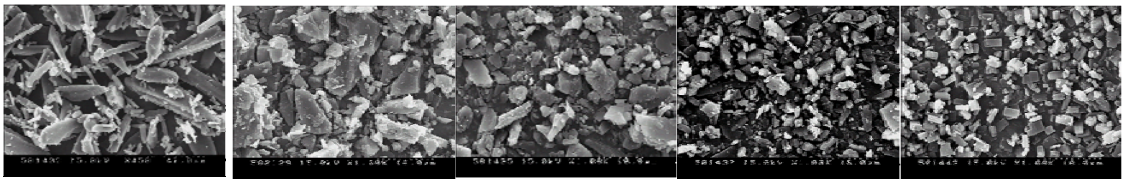


(A) (B) (C)

Figure 3. Aspirin particles (a) unprocessed, (b) process by RESS and (C) by SAS

We will also show micronized Ibuprofen particles by RESS, which has low crystallinity, show fast dissolution rate in water.

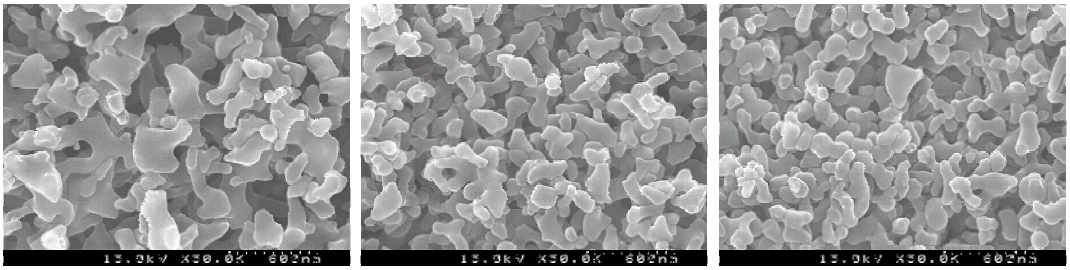
Such as Cefpodoxime proxetil (CPD) and acetaminophen fine particles were prepared using an Aerosol Solvent Extraction System (ASES), one of SAS processed, with supercritical CO_2. In SAS process, a sharp increase in the level of supersaturation within the liquid mixture causes the formation of small and uniformly sized particles without solvent. it is investigated the effect of various solvents on acetaminophen fine particles. The raw materials show two types of morphologies that include aciculate particles and oval plate like particles. The particle size distribution range is from 3.3 ㎛ to 196.72 ㎛ in Figure 4. After the process, we can see the remarkable changes in particle size and morphology. As the SEM images show in Figure 4 (B) ~ (E), we observed different morphologies by different solvents. The particles, which were made by methanol and ethanol as the solvents have rather irregular shapes and bigger sizes than that were made by acetone and ethyl acetate. It shows that selection of solvent is very important to decide to shape of processed particles in the initial step of experiment.



(A) (B) (C) (D) (E)

Figure 4. SEM images of unprocssed and processed acetaminophen particles obtained from various solvents ; (A) unprocessed acetaminophen (B) processed by EtOH solution(C) MeOH solution(D) acetone solution (E) ethyl acetate solution

To reduce the agglomeration by remove solvent, the ratio of carbon dioxide weight to CPD solution weight was increased to obtain solvent-free particle. The shape of particles was closed to spherical type as well as size of the particle with high weight ratio of CO_2 was smaller than that of low weight ratio. The size and shape can be controlled by changing the process parameters in Figure 5.



(A) (B) (C)

Figure. 5 The effect of weight ratio (CO_2 / CPD solution) on CPD particles at 35℃, 100bar. Concentration: 0.3 wt% in MC; (A) weight ratio: 22 (B) 44 (C) 88

Besides, itraconazole, acetaminophen, lysozyme, insulin, trypsin and so on are micronized by RESS by CO_2 solvent or SAS by CO_2 anti- solvent (Figure 6). As very typical result in SAS process, it is generally attribute to a better atomization of the liquid phase that results in formation of smaller droplets and thus to accelerated mass transfer phenomena. The increase of the carbon dioxide transfer rate, induces higher supersaturation in the liquid phase which are more favorable to the formation of nuclei than the crystal growth.

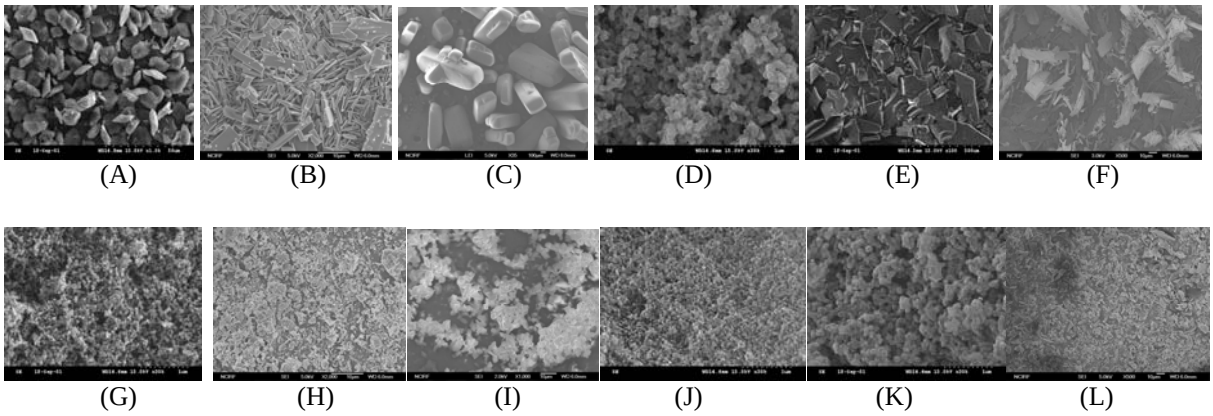


Figure 6. SEM images of (A) insulin and (B) ketorolac acid and (C) ibuprofen by RESS, (D) insulin, (E) trypsin, and (F) itraconazole by SAS; (A) ~ (F) unprocessed materials & (G) ~ (L) processed materials

Precipitation of particle by SCF technology is applied to obtain polymer particles because the advantages of using SCF in polymer engineering as polymerization solvents and forming agents include their ability to plasticizer many polymers and dissipate energy during the process. Fluoroacrylate and fluoroether polymers are highly soluble in CO_2, but they are very expensive. Therefore, the design and development of a CO_2-philic, cost-effective surfactant is very important. For this work, even two supercritical fluids, a mixture of CO_2 + DME, were used as the polymerization medium in polymerization studies in Figure 7 [4]. Dimethyl ether (DME) is often used as an aerosol propellant, assistant solvent, fuel additive, liquefied petroleum gas substitute, and alternative refrigerant. At the same time, as a chemical raw material, it plays an important role in the synthesis of many chemicals. Recently, DME has been used successfully as a solvent for dispersion polymerization [7].

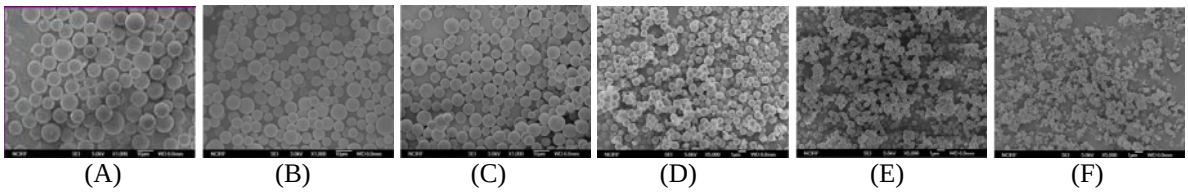


Figure 7. SEM images of PMMA particles polymerized with (A) 5.0, (B) 10.0, and (C) 15.0 wt % of MMA (12.3 wt%) with AIBN (1.0 wt%) and PVK particles polymerized with (D) 1.28, (E) 5.97, and (F) 16.80 g of DME as the co-solvent in $scCO_2$ at 300 (10 bar and 70 °C)

Polymerization of NVCA in a mixed solvent of CO_2 and DME was conducted at various ratios of CO_2 and DME with AIBN (1 wt %), poly (HDFDMA) (10 wt %, based on the monomer), and 2 g of monomer in all cases. Under these conditions, not only could the particle size be decreased but also, as the DME ratio was increased, the percentage of small particles (0.5 nm) was reduced.

CONCLUSION

The experimental results obtained in this study will provide direction for future experimental and theoretical investigations into the potential use of SAS and RESS recrystallization technology for particle formation. We have demonstrated that the fully developed atomization of the solution is important to get the ultra fine particles such as drugs and polyemrs.Subsequent studies will focus on the mechanism of particle formation, agglomeration and quantitative analysis. Moreover, this work will provide the basis for the development of novel particle formation mechanisms.

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