THE FORMATION OF ASPIRIN MICRO PARTICULATE USING SUPERCRITICAL CO_2 AS SOLVENT AND ANTI-SOLVENT

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ABSTRACT

The scope of nano-technology with supercritical fluids has been enlarged by Rapid Expansion of Supercritical Solution and Supercritical Anti Solvent processes, which are complementary to each other. The principle of these processes is based on the rapid super saturation of solution that is followed by the nucleation of solute. However, in addition to the capability of supercritical CO_2 to dissolve solutes, they have the great difference in terms of the growth of nuclei. A lot of works have investigated the effects of operating conditions, shapes of nozzle, and geometry of these processes devices. Also, various methods were tested, according to the way of contacting a solution with antisolvent, supercritical CO_2. Results of these works have showed the possibility of supercritical fluids technologies as an alternative way to replace many traditional size-reduction methods in various areas. But, there ever exists discrepancy even between the same processes, up to which system is used and how to set up devices. This study is intended to examine the mechanism of ASES process and inspect what has not been approached so far. In this work, we used PLA and acetylsalicylic acid as a solute with continuous RESS and ASES process.

INTRODUCTION

In supercritical state, CO_2 has the high density like liquid. This dense CO_2 is able to dissolve the solute or lower the solvation power of organic solvent. This variable value of density is one of the reasons why supercritical fluid technologies are worthy of notice. Compared to other technology like the emulsification in pharmaceutical area, remarkable advantages of these processes are that successive stages can be facilitated in just one step and that adjustable density of CO_2 can cause the perfect separation of solute from solvent. Due to these attractive aspects of supercritical fluids, its technologies have been expanding applications in major fields of chemical engineering and a lot of publications [1] have reported the effect of various parameters and modified devices of RESS and SAS processes with various kinds of material.

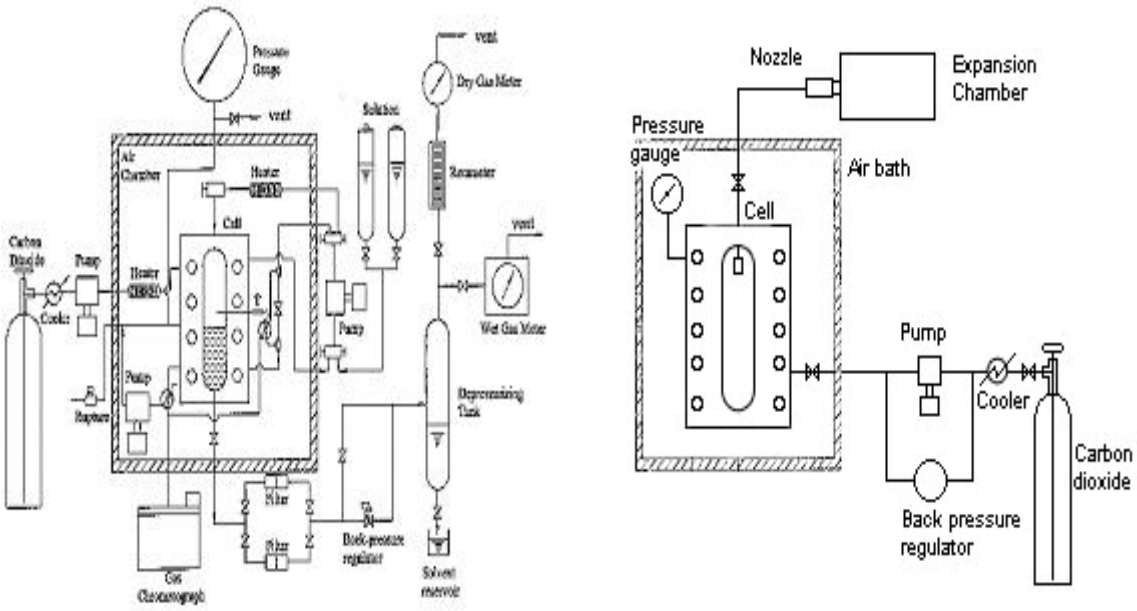
In the former process, RESS, after solute is dissolved in supercritical fluid, this solution is expanded through a nozzle. Consequently, supercritical fluid used as a solvent loses solvation power in a very short time and solute is precipitated in the form of very fine solid. Aspirin micro-particulates [2] are formed with the RESS process and drug encapsulation as one of RESS application [3, 4] was reported. In case of ASES, supercritical fluid is used as a non-solvent, because it causes organic solvent to lose the ability to dissolve solute during the injection of solution. After the precipitator is full of supercritical fluid, solution is injected

into the cell. That solution jet is disintegrated into numerous droplets. In the aftermath of this atomization, there happens mutual diffusion between solvent and supercritical fluid. Finally, solvent loses solvation power and solute is nucleated. According to how to have antisolvent contact organic solution and the type of nozzle, this SAS process is called another names: GAS, SEDS, ASES and PGSS. Many kinds of material; explosives, polymers, pharmaceutics and inorganic materials [5-9] were micronized with this antisolvent process.

As Perrut [1] pointed, RESS process is limited, because of the poor solubility of substrate in supercritical fluid. In SAS, this is available to only high-value materials requiring the fine particle form. Also, some publication [10-13] tried to make quantitative analysis for the scale-up. However, as referred above, all of systems using the micronization with supercritical fluids don't follow these analyses. In other words, the problem of these methods is difficulty in reproduction with the same quality. We will approach these from the other point of view and this study is to show how different RESS and ASES processes are, in terms of the role of solvent for the nucleation and the growth of nuclei, observing the mixed state of supercritical solution.

MATERIALS AND METHODS

As shown in figure 1, precipitation with ASES was carried out in a 34cm^3 observable cell with a water jacket for controlling temperature. Pressure is adjusted by using a back pressure regulator (Tescom; 26-1721-24) arranged after the filter (Tee-Type filter, 0.5?) Carbon dioxide, the antisolvent, is supplied into the cell by a reciprocating pump and reaches the supercritical temperature by being preheated through a heat exchanger. Solution enters into the cell by a reciprocating pump (Milton Roy, USA) as well. Acetylsalicylic acid and dichloromethane were used as solute and organic solvents, respectively.



(a) (b)

Figure 1. Experimental apparatus: (a) ASES process, (b) RESS process

First, after the supercritical state was made with the carbon dioxide, solution is injected with a nozzle (254? I.D.) in the cell. The injected solution goes broken to many solution droplets. And then, the mutual diffusion between organic solvent and antisolvent follows. Experiments were usually conducted under the operating conditions, 100 bar and 35 °C.

RESS apparatus was designed in the way that the supercritical solution can be depressurized through the nozzle continuously. The type of nozzle is a disk with 0.15 mm thickness and 50 um ID hole. The pressure of 250 ml sapphire window cell is controlled by adjusting the amount of CO_2 from the pump (Pulsafeeder, USA) and one through the nozzle. In other words, the operating pressure of RESS system is maintained by the amount of resident CO_2 between the continuously flowing CO_2 at the nozzle and pump. The back pressure regulator (Tescom; 26-1721-24) is connected at the back and forth points of pump in order to set up the pressure of system. Also, heat band was installed around the disk nozzle to remove frost caused by the expansion of supercritical solution. Excessive acetylsalicylic was put into the cell. Then, CO_2 was pumped into the vessel until the system reaches the operating conditions. Also, inner space of the cell was agitated to get the homogeneous mixed state. The expansion chamber is made of transparent acryl with the cylindrical form and the paper filter separates free flowing particulate from the expanded solution. The influence of CO_2 density on the yield of particulate was recognized as one of the most important parameters.

A macro scope (Leica, wild M420) and camcorder (Sony, PC-110) were used for the observation of inner space in the ASES and RESS precipitation cell. The morphology of the precipitated solute was analyzed by a Hitachi 4300 Electron Scanning Microscope (SEM).

RESULTS AND DISCUSSION

Figure 2 shows SEM images of aspirin processed by RESS and ASES. As shown in Figure 2, the morphology of aspirin formed by ASES is the needle, while the aspirin with RESS process has the form of fine powder. Furthermore, the length of particulate with ASES process is longer rather than the one of raw aspirin.

From the comparison of (b) with (d) in Figure 2, it is easy to know that ASES process gives nuclei the chance to grow, after the organic solution is injected into the vessel that is full of supercritical CO_2. Generally, it has been thought that the perfect homogeneous supercritical state seems to exist in the ASES process or other processes that use supercritical CO_2 as antisolvent. However, we realize that we need to consider this ASES system like a traditional liquid extraction in which the interface between two liquids with different densities can be seen. Figure 3 collaborates this observation with PLA particle micronized by the same ASES apparatus.

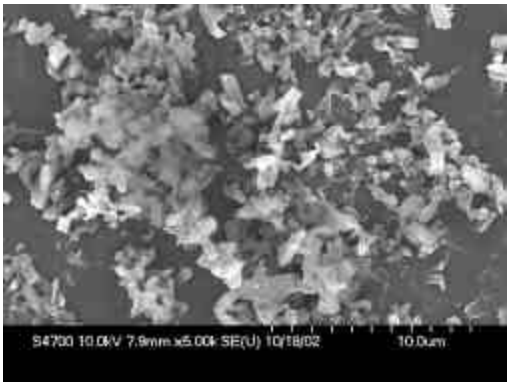
It is observed that the higher flow rate of solution is, the bigger size of the processed particle. At the solution flow rate of 0.4 ml/min, the average particle size was 0.2 μm or less and particle size distribution was found to be narrow, whereas the average particle size was 1 μm or bigger with a wide particle size distribution at the higher solution flow rate of 5.4 ml/min. Also, it is interesting to note that L-PLA was produced with the form of fiber at higher concentration, contrary to particle processed at lower concentration.

Therefore, the size reduction process by using supercritical CO_2 as an antisolvent seems to be related to the amount of resident solute in the cell. This results from the operating condition in which solvent was not removed effectively or crystal growth is more dominant

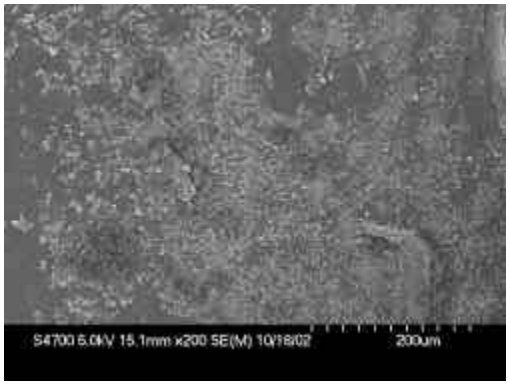
than nucleation. Thus, it is expected that the amount of antisolvent will be key points for the better performance in ASES process as a size-reduction process.

(a) Raw aspirin (x200)

(b) ASES process (x200)

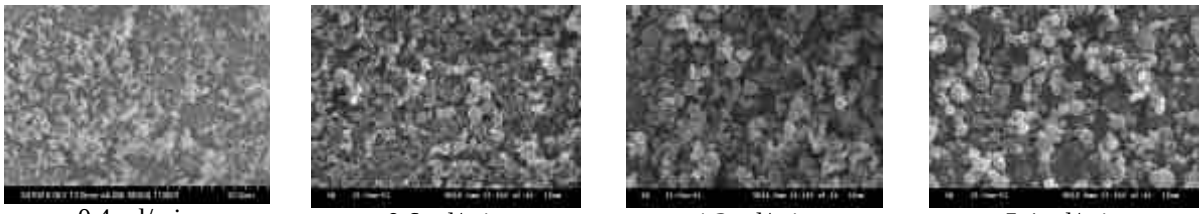


(c) RESS process (x5000)



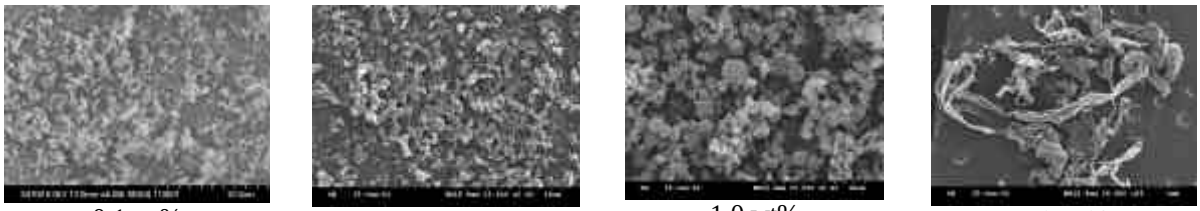
(d) RESS process (x200)

Figure 2. Raw aspirin (a) and aspirin processed with ASES (b) and RESS (c), (d)



0.4 ml/min 0.6 ml/min 1.2 ml/min 5.4 ml/min

(a) Particles processed under the conditions of 35 ^{o}C, 100 bar, 0.3 wt% and different solution rate



0.1 wt% 0.3 wt% 1.0 wt% 4.0 wt%

(b) Particles processed with different concentration of solution at 35 ^{o}C, 100 bar

Figure 3. L-PLA particles produced by ASES process

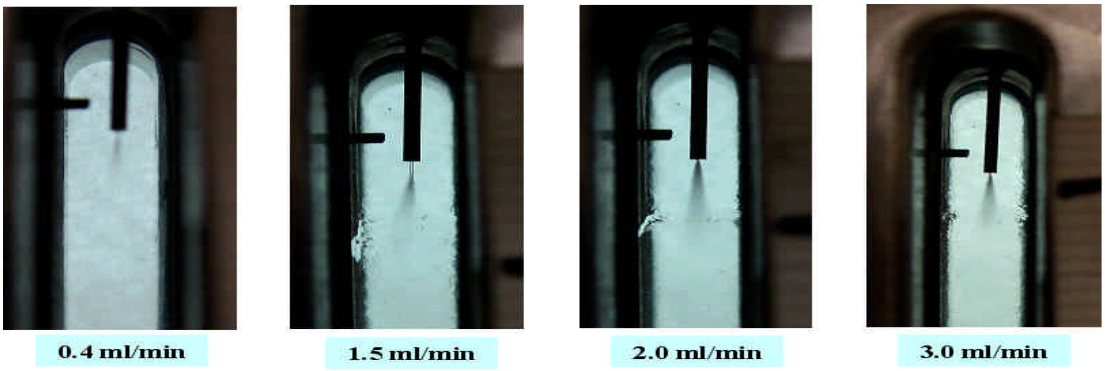


Figure 4. The inner space of precipitator of ASES process with different solvent rate

Fig. 4 is the picture of inner space of precipitator. As the flow rate of solution is increasing, we observe that the interface between pure CO_2 and mixture of solvent and CO_2 is becoming clearer and approaching to the end of nozzle. At the condition of lower flow rates, there exists relatively little solvent in precipitation cell. Therefore, higher supersaturation due to much CO_2 will bring the rapid nucleation in which finer particles are formed favorably. Followed by fast nucleation, the further particle growth occurs through addition of solute dissolved in CO_2 and methylene chloride mixture. However, when solution is injected at lower flow rate, the amount of PLA dissolving in CO_2 and methylene chloride mixture is expected to be low. As the result, the rate of further particle growth and/or aggregation between particles was relatively slow.

So far, it is admitted that diffusion of antisolvent inside the organic phase and the diffusion of the organic solvent into the antisolvent phase are the main mechanism of antisolvent process. However, from the our results, we conclude that when the supercritical CO_2 of ASES process gets mixed with the solvent, it is hard to consider the mixture as the homogenous phase. That is, there can be two layers with different density in the precipitator of ASES process when the rate of solution is too high. Also, P.subra [14] points out that crystals of larger average size and sizes distribution will be formed in conditions where only few nuclei are formed and grown. With this point of view, even though supercritical CO_2 is known to have the feature like gas and liquid, it would be needed to consider that it is much closer to the liquid state. In other words, we feel that supercritical CO_2 is the second liquid state, which is just somewhat lighter than the original liquid state.

Contrary to ASES process, RESS process doesn't require the organic solvent. While the particulate in RESS is formed with the rapid change of phase of supercritical solution, particle in ASES is generated in the space without the change of phase of solution. Therefore, as long as solute exists with solvent that dissolves it, it would be hard to overlook the effect of solvent. It would be key to the formation of much finer particulate to separate solute from solvent effectively in ASES process. High solution flow rate will cause the stagnation of organic solvent and enhance the growth of nuclei.

Also, there was remarkable influences of atomization and density of supercritical CO_2 on the quality of PLA particle. Jet break-up of solution injected into the precipitator is relevant to the enlargement of surface area for the diffusion between solvent and antisolvent. Too high density of supercritical CO_2 for the better atomization is rather drawback for the diffusion. However, as a conclusion, we suggest that how to lower the solvation power of solvent and how to isolate solute from solvent should be the first considerations.

CONCLUSION

Supercritical fluids technology is powerful for manufacturing fine particles in various areas as well as in the pharmaceutical field. Many advantages of supercritical fluid based processes have been emphasized, compared to drawbacks of traditional processes. Also, it is true that a lot of technologies with supercritical fluids have been developed, due to these noteworthy properties of supercritical fluids. However, it seems that these properties known for advantages of supercritical technologies have problems of these processes overlooked. This work focuses on the influence of solution in the ASES process and suggests a new angle for the analysis of this process.

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