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Investigation of Physical Effects on Nanoparticle Size in Aerosol Solvent Extraction System

Li Tian*, Kim Row

1-Institute of Frontier Material, Yonghyun-Dong, Shanghai, China

Abstract

Aerosol solvent extraction system (ASES) was used to prepare micro-particle of acetaminophen by supercritical carbon dioxide as an anti-solvent. Experiment was carried out at various temperatures, pressures, solvents and investigated the effects of these parameters on particle size, size distribution and morphology by SEM and laser diffraction particle size analyzer. It seems that the choice of solvent is very important for getting specific shape and size of the particle. The temperature and pressure increased with the increase in particle size. After the process, the particle size decreased as 1/20 of the raw material and the morphology was more spherical and regular.

Keyword: Supercritical fluid, Anti-solvent, Nano-particle, Acetaminophen.

1. Introduction

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 [1-6]. Several processes of applying supercritical fluids in manufacturing micro-particles are investigated and developed. Rapid expansion of supercritical solution (RESS) is a process which uses supercritical fluids as a solvent [7-10]. A solid dissolved in supercritical carbon dioxide (sc-CO2) and expanded to the surrounding at an ambient pressure. Particles from gas saturated solution (PGSS) is a technique that dissolves the supercritical fluid in molten solution and sprays through the capillary nozzle8. Supercritical anti-solvent (SAS) is solid dissolved in the certain solvent and sprayed into the flowing supercritical fluid [9-11]. The process used in this experiment is one kind of the SAS processes named aerosol solvent extraction system (ASES). 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 to design improved controlled delivery systems. Acetaminophen, N-acetyl-*p*-aminophenol, is a widely used pharmaceutical analgesic and antipyretic agent [12]. However, the low solubility in water made it hard to be bioavailable in the human body which is a limitation in pharmaceutical applications. A new form of drug delivery system of poorly water-soluble drug needs to be considered. Various methods to improve bioavailability of the drug have been developed [13-15]. Micronization of the drugs is one of the most common methods to control the release of drugs. Small particles with controlled particle size and particle size distribution can improve the drugs'

* Corresponding author. email address: li.tian@IFMC.com

therapeutic efficacy, *in vitro* and *in vivo* stability, bioavailability, targetability and biodistribution to reduce toxicity [16-18]. The present research aims to investigate the effect of the solvent, operating temperature and pressure on the particle size, particle size distribution and morphology of the final product. And estimate the relationship of particle size to the temperature and pressure.

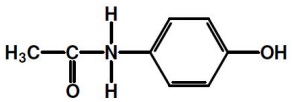

Figure 1. Chemical structure of acetaminophen

2. Materials and Methods

Carbon dioxide (99.0 %) was supplied by Shin Yang Co., Korea. Acetaminophen (N-acetyl-*p*-aminophenol, purity = 98 % (HPLC)) was purchased from Fluka (figure 1). The solvents, methanol, acetone (Junsei Chemical Co., Ltd.), ethanol (Samchun Pure Chemical Co., Ltd.), 2-propanol, tetra hydrofuran (THF) (J.T. Baker, USA), acetonitrile (Duksan Pure Chemical Co, Ltd) and ethyl acetate (Kanto Chemical Co., Inc.) were used. An aerosol solvent extraction system was self-designed and the diagram of experimental apparatus is shown in figure 2. 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 de-pressuring and solvent separation part. The precipitator was packed with water jacket and the volume was 34 mL. In order to observe the process of the particle formation clearly, both sides of the precipitator were installed with glass windows. A capillary tube (stainless steel, 254 μm) used as a nozzle was allocated on the top of the precipitator to spray acetaminophen solution. A stainless steel filter (Tee-type filter, 0.5 μm, millipore) was installed below the precipitator to collect the particle and the backpressure regulator (Tescom; 26-1721-24) arranged after the filter to adjust the pressure. Solution was pumped into the precipitator by a reciprocation pump (Milton Roy, USA) and sc-CO_2 was introduced into the precipitator by a diaphragmmetering pump (PULSA 680, Pulsafeeder, Inc, USA) at a speed of 12.8 g/min. A wet gas flow meter was arranged to check the flow rate of CO_2.

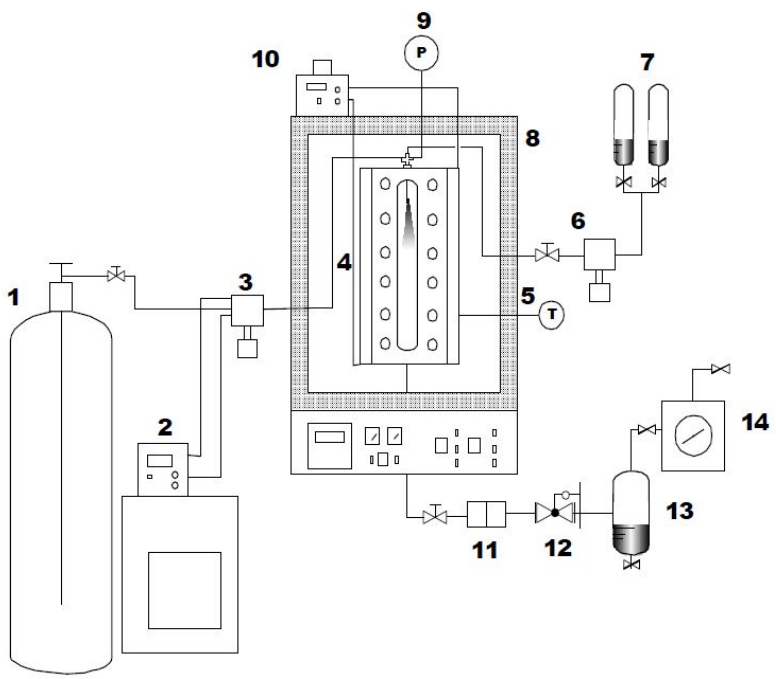

Figure 2. Schematic diagram of the ASES apparatus

2.1 Method

Acetaminophen was dissolved in 10 mL ethanol, methanol, acetone, acetonitrile, THF, 2-propanol and ethyl acetate, respectively. Before injecting, the precipitator was preheated to a desired temperature by a heat exchanger. Sc-CO_2, as an anti-solvent, was introduced into the precipitator from the top of the vessel by a diaphragm-metering pump. The backpressure 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 finished, the sc-CO_2 was fed for 15 min continuously to eliminate the residual solvent in the particles. After the whole process, the particles were collected and analyzed.

2.2 Analysis

Particle morphology was analyzed with a scanning electron microscope (SEM) (Hitachi 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 was 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. Solubility test also was done. Excess amounts of acetaminophen particles were dissolved in 10 mL of seven different solvents separately. The samples were stirred in a water bath at 25ºC for 24 h. The suspensions were subsequently filtered through the membrane filter and diluted with the solvents. The filtered sample solutions were analyzed using a UV-Vis spectroscopy (Heliosa, England) at wavelength of 243 nm.

3. Results and Discussion

3.1 Analysis of particle size on the solubility of solvent

To investigate the effects of various solvents on morphology and size of the particle, acetaminophen was dissolved in 10 mL of seven different solvents, *viz.*, ethanol, methanol, acetone, acetonitrile, 2-propanol, THF and ethyl acetate, separately. While the temperature, pressure and flow rate of sc-CO2 was fixed at 40 ºC, 100 bar and 12.8 g/min, respectively the solution was fed into sc-CO2 at 0.78 mL/min. Figure 3 shows the SEM image of raw material 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 broad particle size distribution range that is from 3.3 μm (x10) to 85 μm (x90). After the ASES process, remarkable changes could be seen in particle size and morphology. Compared with the original acetaminophen, the particle size after processing reduced to 1/3-1/20 and the shape changed to regular in case of THF and ethyl acetate. As the SEM images show in figure 4, different sizes and morphologies by different solvents were observed.

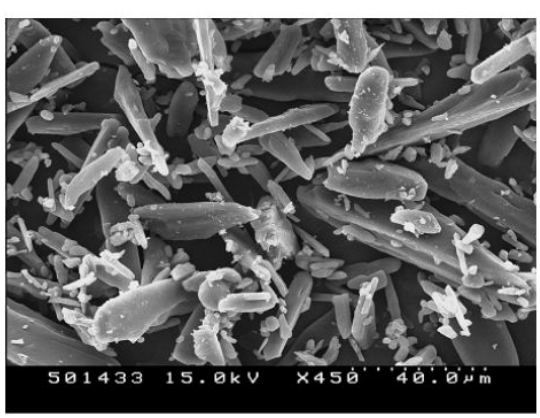

Figure 3. SEM image of acetaminophen before ASES process

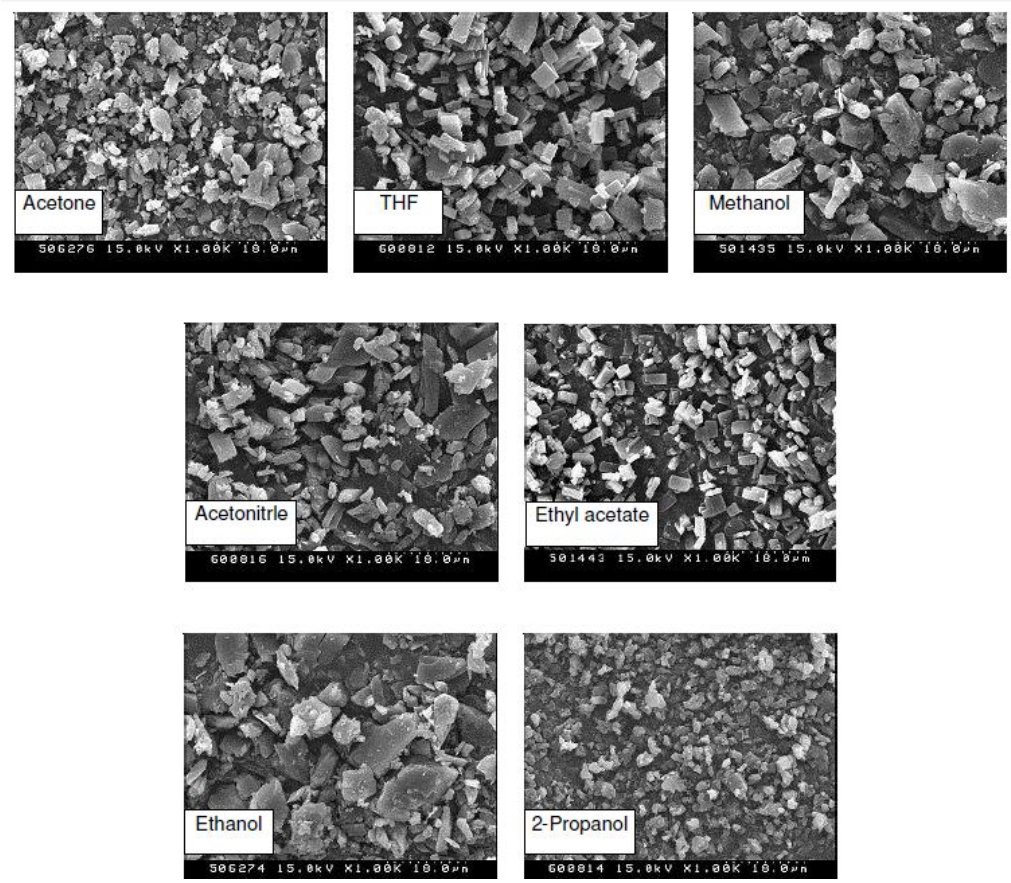

Figure 4. SEM images of acetaminophen by different solvents

The particles, which were made by methanol and ethanol as the solvents had rather irregular shape and bigger sizes than the particles made by other solvents. Compared with ethanol, the cases of other solvents showed smaller size and narrower particle size distribution. Table-1 shows the measurement of particle sizes (x50) made by different solvents. According to the Table-1, methanol shows the highest solubility of acetaminophen. 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 it was hard to control the system pressure. 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. Generally, during experiments, the rapid supersaturation results into small particle size. There are many factors, which affect the supersaturation and solvent is one important factor of them. Different solvents have different solubility in sc-CO2.

Acetonitrile is small soluble in carbon dioxide due to its large dipole moment and ethanol is close to liquid-liquid immiscibility either due to hydrogen bonding or to an extreme value of the dipole moment. The results of particle size in this study approved that if a solvent is well soluble in supercritical carbon dioxide, it will have longer super saturation time and make the bigger particle and if a solvent is less soluble in supercritical carbon dioxide, it will shorten the super saturation time and make smaller particle. The solvent power on the material also affects the supersaturation. Table-1 shows different solubility of acetaminophen in seven kinds of solvents. The result of particle size shows a close linear relationship to the solubility (figure 5). High solubility shows larger particles size and low solubility shows smaller particle size. It is quite probable that the low solvent power shortens the nucleation time. Conversely, the sc-CO2 can't react sensitively as antisolvent, when high solubility solvents, like methanol and ethanol were used as a solvent.

Table 1. Particle Size on Different Solvents.

	Methanol	Ethanol	2-Propanol	THF	Acetonitrile	Acetone	Ethyl acetate
Density (g/mL)	0.79	0.79	0.83	0.89	0.78	0.71	0.90
Solubility (g/L)	311.56	227.12	54.64	50.11	49.61	40.80	34.54
Particle size (μm)	–	7.57	4.32	3.59	4.10	3.84	3.73

Table 2. Particle Size on Different Temperature and Pressure

Temperature (°C)	Pressure (bar)	Particle size$_e$ (μm)	Particle size$_c$ (μm)
10	100	3.15	2.83
15	100	2.91	3.02
20	100	3.34	3.21
30	100	3.28	3.58
35	100	3.43	3.77
37	100	3.72	3.84
40	100	3.73	3.95
40	125	3.74	4.39
40	150	5.22	4.83
40	175	5.43	5.26
40	200	5.54	5.70
45	100	5.03	4.14

3.2 Analysis of particle size on the 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 10 to 45 ºC. When the temperature was fixed at 40 ºC, pressure was varied from 70 bar to 200 bar. Experiments were carried out at three different phases, Liquid CO2, sub-critical CO2 and sc-CO2. As in Table-2, the particle size increased nearly an order of the temperature and pressure. Below the critical temperature, particle size decreased with the temperature decreasing. The smallest particle was obtained at 10 ºC that the size was 3.15 μm. With increasing the pressure, the mean particle size increased slightly from 3.73 to 5.54 μm.

Generally, the relationship between droplet and particle size can be discussed using Weber number (We) as

$$We = \frac{\rho u^2 d}{\sigma} \quad (1)$$

where r is the density of the solution, d is the nozzle diameter, s is the interfacial tension, u is the solution feed rate. In this experiment u, d and s were fixed. With the temperature increasing, the density of sc-CO2 (r) decreased. It may cause small Weber number and big droplet size. As a result, the supersaturation becomes slow and the particle size increases. The solubility of acetaminophen is larger at high temperature, so the super saturation time slowed and the particle size increased. Moreover, the diffusivity of CO2 decreased with the increasing pressure which also resulted in larger particle size. It may cause big Weber number and small droplet size. As a result, the supersaturation becomes fast and the particle size decreases. In this case, the particle size increased meaning that the first phenomenon seemed to be dominant. The following equation of particle size was suggested and fitted in terms of linear form of temperature and pressure from the experimental data in table 2.

$$d = 0.017 \times P + 0.037 \times T + 0.713 \quad r_2 = 0.8241 \quad (2)$$

where d is the particle size and T, P are temperature and pressure, respectively. The correlation coefficient (r2) is 0.8241. Normally the particle size increased almost linearly with temperature and pressure of the operating conditions.

4. Conclusion

Acetaminophen micro particles were successfully prepared by ASES process with supercritical carbon dioxide. The solvent, temperature and pressure were changed to investigate the effect on the particle size and morphology. The monoclinic crystal form of morphology and the smallest size particles were formed when using ethyl acetate as a solvent. It proved that bigger solubility of acetaminophen made bigger particle and solubility was a big factor of forming particle. With the temperature and pressure increasing, bigger particles were observed. An empirical equation was suggested according to the linear relationship of particle size to temperature and pressure.

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