

## **Microparticle Formation of Ethyl Cellulose Using Compressed CO<sub>2</sub> Antisolvent Precipitations**

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**Abstract:** In the present research, two methods of Supercritical Fluid (SCF) anti-solvent precipitation, i.e., gas anti-solvent process (GAS) and solution enhanced dispersion by supercritical fluid (SEDS), were investigated to form micro-particles of ethyl cellulose (EC). The experiments of GAS and SEDS were carried out at different operational conditions. The mean particle diameters ranging from 1 to 10 $\mu$ m were obtained. The effects of temperature and pressure on particle sizes and their distribution were evaluated. The results showed that the two processes had the same trend affected by the changing of experiment parameters, however, the particles made by SEDS were much smaller than by GAS. The nucleation processes of the two methods, which were in the expanded 'liquid' or inside the emulsion droplets, were also discussed theoretically in the current study.

**Key words:** Ethyl cellulose, compressed CO<sub>2</sub>, microparticle, GAS, SEDS

### **INTRODUCTION and LITERATURE REVIEW**

Nearly two decades ago, supercritical fluid (SCF) was first used to produce fine particles with a narrow size distribution (Irene et al., 2008). This technique is called rapid expansion of a supercritical solution (RESS). Several years later, Gallagher et al. first proposed a SCF process alternative to RESS to overcome the limitation of poor solubility of most organic compounds in supercritical CO<sub>2</sub>. In this technique, the compressed CO<sub>2</sub> works as anti-solvent. For example, the Gas anti-solvent process (GAS) and the solution enhanced dispersion by supercritical fluids process (SEDS) belong to this technique (Masoud and Ranjbarian, 2007). Nowadays, the SCF technology is a very popular method currently used for producing microparticles in a variety of applications, especially in the pharmaceutical, food and fine chemical industries. Supercritical fluid techniques for materials precipitation have been proposed as an alternative to conventional precipitation processes as they allow improving the performance of these processes in terms of reduction of particle size and control of morphology and particle size distribution, without degradation or contamination of the product (Martin and Cocero, 2008).

Microencapsulation is a useful tool to improve the delivery of bioactive compounds into foods,

particularly probiotics, minerals, vitamins, phytosterols, lutein, fatty acids, lycopene and antioxidants (Claude and Fustier, 2007). Among the many variants of cellulose, ethyl cellulose (EC) has attracted considerable attention since it can be used as a binder, taste mask, dispersing agent, stabilizer, water conserving agent, and a sustained-releasing agent in medicinal and functional-food applications (Dan and Mchugh, 2004). Ashok et al. (2003) investigated the technical feasibility of adding folic acid onto rice and coating with edible polymers, such as EC. Ana et al. (2006) employed the supercritical anti solvent (SAS) technique to prepare the microspheres of EC/methyl cellulose blends.

In this research, due to the poor solubility of EC in the supercritical CO<sub>2</sub> (Bodmeier et al., 1995, Dan and Mchugh, 2004), microparticle of EC was produced by two methods, GAS and SEDS. The effects of temperature and pressure were investigated. The experimental results of the two methods were compared and analysed as well.

### **MATERIALS and METHODS**

#### **Materials and characterizations**

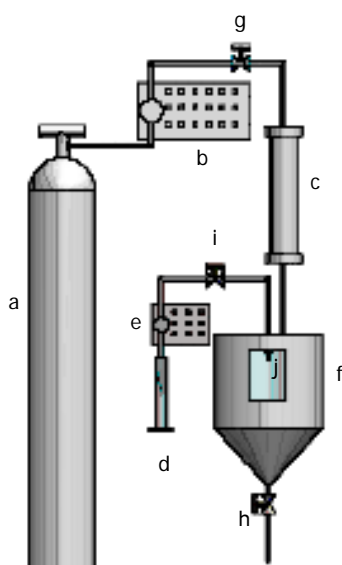
Ethyl cellulose (20cP) was obtained from the Medical centre of Fudan University (China). Acetone with a purity of 99.9% was also supplied by Fudan

University. Carbon dioxide was purchased from the Fifth Steel Bottle Factory of Shanghai (China).

The mean particle sizes and their volume distributions were measured by a laser diffractometer (Winner2005, China). The particle morphology analysis was carried out using scanning electron microscope (SEM, JSM-6360, JEOL Co., Tokyo, Japan).

### Apparatus and procedure for the GAS and SEDS micronization

The experimental equipment used for the preparation of micro-sized EC is depicted in Figure 1.



**Figure 1. Schematic diagram of the experimental apparatus: (a) CO<sub>2</sub> tank, (b) CO<sub>2</sub> pump, (c) heater, (d) EC solution, (e) HPLC pump, (f) microparticle precipitator, (g), (h) and (i) valves, (j) coaxial nozzle**

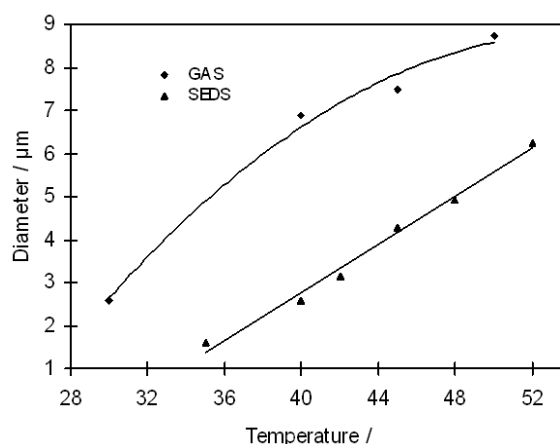
GAS is a batch technique that involves the gradual introduction of CO<sub>2</sub> inside a vessel filled with the solution of the solute of interest (Irene et al., 2008). In the GAS process, a known volume of acetone solution of EC was loaded in the 0.5L high-pressure vessel (f). Water was circulated in the water jacket to keep the temperature inside the autoclave constant during the process. The autoclave was then pressurized up to the working pressure by CO<sub>2</sub> injected from the nozzle (j) within several minutes. Then the valve (h) was opened, while still keeping the same working pressure. After maintaining the magnetic agitation in the system under the same conditions for 20 min, the washing step was ended,

the CO<sub>2</sub> injection was stopped, and the autoclave was depressurized to atmospheric pressure.

In the SEDS method, the compressed CO<sub>2</sub> and solution were co-introduced into a precipitation vessel through a coaxial nozzle (Masoud and Ranjbarian, 2007). First, a constant flow of CO<sub>2</sub> was continuously supplied into the autoclave (f) by a coaxial nozzle (outer orifice). The CO<sub>2</sub> was heated to the desired temperature in the heater (c). When the pressure of the autoclave reached the working value, the back pressure regulator valve (h) was opened and the whole system was maintained in equilibrium. Then the EC-acetone solution was fed into the high-pressure vessel through the coaxial nozzle (inner orifice). After a certain volume solution was injected, its flow was stopped, and washing step was followed which also lasted for 20 min.

### RESEARCH RESULTS

It is known that temperature and pressure are the two most important parameters in SCF technologies. In order to investigate how the two methods (GAS and SEDS processes) influence the particle size and the particle size distribution, the experiments were carried out at various temperatures and pressures in GAS and SEDS processes, respectively. The concentration of EC-acetone solution was 3.5g/100mL (every 100mL acetone solved 3.5g EC) for all experiments. The carbon dioxide flow rate was 3.5kg/h. In SEDS, the solution flow rate was 9.2mL/s, and a fixed coaxial nozzle was used.



**Figure 2. Processed microparticle diameters of EC in different temperatures**

The precipitation temperature was set up according to previous experiments which were from 30° to 52°. The pressure was fixed at 9.0MPa. The mean particle sizes are reported in Figure 2. Obviously, in both processes, the particle sizes all increased with the increase of temperature, but the microparticles made by SEDS were smaller than by GAS.

At 40°, the influences of pressure were studied. Figure 3 shows the results. The GAS and SEDS processes still had the same trends: the particle sizes were reduced with the increase of the pressure.

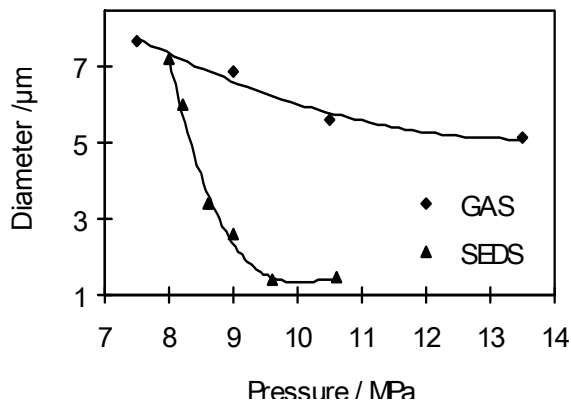


Figure 3. Processed microparticle diameters of EC under different pressures

Finally, the particle size distributions in the two processes are compared in Figure 4. It can be illustrated that the span of the particle size distribution in SEDS process was much narrower than in GAS.

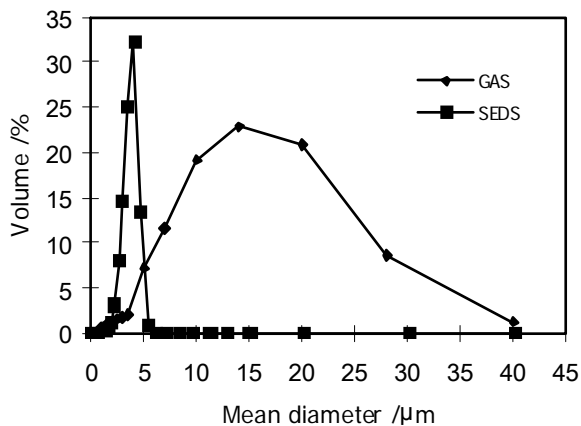


Figure 4. Frequency distribution of EC microparticle diameters in two processes on the same condition (T=40°, p = 9.0MPa)

## DISCUSSION

### GAS process

In the GAS process, the driving force for the precipitation is the anti-solvent effect caused by the solubilization of CO<sub>2</sub> in the liquid solution. When CO<sub>2</sub> is dissolved in the liquid, the liquid will be expanded, and its density decreased. Thus, its solubility becomes lower and lower. So, it is possible to select the optimum thermodynamic conditions for this process by studying the volumetric expansion in the solvent caused by CO<sub>2</sub> (Martin and Cocero, 2008).

The usual definition of the volumetric expansion is the ratio between the increase in volume caused by the CO<sub>2</sub> and the initial volume of the solution. Badilla et al. (2000) found that this definition could not distinguish the differences in the behavior of different organic solvents with the same antisolvent (CO<sub>2</sub>). They presented an alternative definition of the volumetric expansion based on the variation of the partial molar volume of the solvent, as shown below:

$$\frac{\Delta V}{V} = \frac{\tilde{V}_L(T, p, x_1) - \tilde{V}_2(T, p_0)}{\tilde{V}_2(T, p_0)} \quad (1)$$

$\tilde{V}_L$  is the expanded molar volume of the solution,  $\tilde{V}_2$  is the initial volume of the solution,  $x_1$  is the molar fraction of CO<sub>2</sub> in the liquid phase,  $p_0$  is the atmospheric pressure.

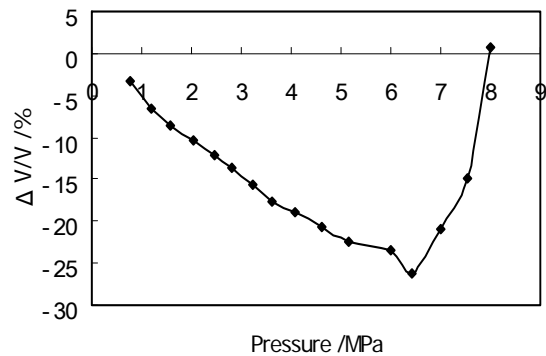
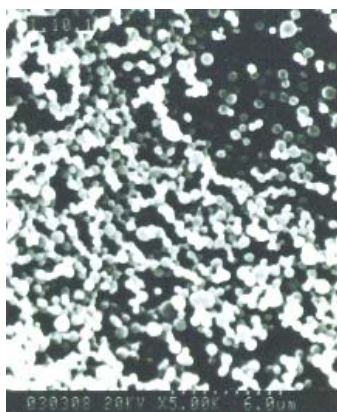


Figure 5. Relative expansion of the liquid phase as a function of pressure, calculated according to Eq. (1) for the systems carbon dioxide – acetone at 40°



**Figure 6. Processed EC at 6.5MPa, 25°, 1% (magnified 5000 times with SEM)**

According to Equation (1), the relative volume expansion of acetone-CO<sub>2</sub> system was calculated based on data from Adrian and Maurer (1997), Chang et al. (1997) and Bamberger (2000). The results were shown in Figure 5. The figure shows that at about 6.5MPa, the solution density reaches the maximum in this condition. Badilla et al. (2000) pointed out that at this experimental condition, 95% solute would separate out, and this was verified in this research (see Figure 6). However the problem is that although this definition can distinguish the difference of solvents, it cannot tell the difference of the solutes.

### SEDS process

SEDS process is a delicate technique, which is similar to the supercritical fluid anti-solvent (SAS) precipitation process. In SEDS, the nozzle structure design is very important. In order to obtain a complete theoretical description of the process, it is necessary to model all the physical phenomena which includes the phase equilibrium, mass transfer, the fluid mechanics of the mixing between the organic solution and the supercritical anti-solvent, as well as kinetics of particle nucleation and growth (Martin and Cocero, 2004). Sara et al. (2006) compared the capability of three equations of state, based on different physical models, for describing phase equilibrium of systems containing compressed gases and supercritical fluids. The perturbed – hard – sphere equation of state was considered as a valid tool to study and predict optimal operating conditions for micronization processes involving supercritical fluids, as the particle size is controlled by the droplet

size and by the interrelationship between three time scales. Dukhin et al. (2005, 2007) studied droplet mass transfer time, the nucleation time, and the droplet residence in the supersaturated stream. Diego et al. (2006) modelled the initial droplet diameter on the drying time of the particles. Philip et al. (2005) studied the relationship between the droplet and the particle sizes by experiments. Based on many simplifying assumptions, Marek et al. (2005) used computational fluid dynamics (CFD) successfully predicted all basic trends of the microparticle sizes observed in their experiments.

### Comparison of the two processes

From Figures 2, 3 and 4, it can be seen that GAS and SEDS processes had the same trends as affected temperature and pressure, but SEDS could make much smaller and more uniform microparticles. Because of the differences of micronization mechanisms, the particle size and its distribution were different.

In GAS process, microparticle formation is governed by the diffusion of the anti-solvent into the organic phase and the evaporation of the anti-solvent into the organic phase. As for SEDS process, it should be discussed at two conditions, subcritical condition and supercritical condition. In the former condition, the classic theory of jet break-up could be applied to the droplet formation; however the latter is in a miscible condition (above the critical point of the mixture organic solvent + CO<sub>2</sub>), and the surface tension decreases to zero in a short distance. Therefore, distinct droplets are never formed at this conditions, and the jet spreads forming a gaseous plume (Werling and Debenedetti, 2000). So, as discussed above, it is obviously that the mass transfer rates are quite different, which is due to the differences in mass transfer area and in the diffusion coefficients.

### CONCLUSIONS

The micronization of EC with a narrow particle size distribution had been successfully achieved with high yields through GAS and SEDS processes. The mean particle size was mostly ranging from 1µm to 10µm, but in some conditions, it could be even about 200nm. In the two methods, the microparticle sizes of

EC had the same changing trends as affected temperature or pressure. The SEDS micronization of EC is fundamentally more suitable than the GAS process, since the particle sizes were smaller, the particle size distributions were narrower and the precipitation process could be continuous.

So far, very few literatures are available about microparticle formation of EC using SCF technologies.

Therefore, the results presented in the current could contribute to furthering SCF technology research on the microencapsulation of EC, the coating material, in the food or pharmaceutical industries.

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