# Micronization of Pharmaceutical Compounds Using the Supercritical Antisolvent Process

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## Extended Abstract

Supercritical anti-solvent (SAS) process has been demonstrated as a useful method for the recrystallization and micronization of organic compounds and the active pharmaceutical ingredients (API) [1-3]. The micronized pharmaceutical compounds allow the use of a more appropriate administration route with less required dosage or side effects. After the supercritical fluid technology treatment, the particle size of the pharmaceutical compound can be decreased to the range of 1 to 5 micron. The particle morphology and polymorphism can also be modified with enhanced pharmaceutical effects.

This study presents our experimental results for the micronization of some organic or pharmaceutical compounds including polymer and API. The experiments were conducted using the continuous SAS process. The equipments were similar to our previous work [4]. It consisted of three sections: (1) carbon dioxide supply, (2) solution supply, and (3) precipitator. One high flow rate HPLC pump was used for $CO_2$ delivery and another HPLC pump for delivery of drug solution. The precipitation section has a precipitator consisted of stainless steel tube with volume about 75mL, reducing union and stainless steel frits with different pore sizes. The $CO_2$ flow rate was adjusted by the micrometering valve at the exit and measured by the rotameter. The pressure in the precipitator was regulated by a back pressure valve. A typical continuous SAS experiment was started by delivering supercritical $CO_2$ to the precipitator until the pressure and flow rate reached steady state. The drug solution was then pumped into the precipitator through the nozzle at a specific flow rate. Upon contacting the drug solution with supercritical $CO_2$ in the precipitator, the drug particles formed due to volume expansion of the solution and the supersaturation of the solute. After sufficient solution was delivered, the flow of solution was stopped.

The flow of continuous flow of $CO_2$ was used to remove the residual solvent inside the precipitator. The precipitator was finally depressurized and the particles precipitated on the stainless steel frit were collected for further analyses.

Polymer like hydroxypropylcellulose (HPC) and drug like deoxycholic acid (DCA) were taken as examples for micronization tests. All compounds were operated for the conditions: 120 or 100 bar, and 308 K, using acetone or other commonly used solvents.

The SEM images of the original and SAS treated HPC particles are shown in Fig. 1 (a) and (b), respectively. The untreated HPC shown in Fig. 1(a) was block-like particles up to 160 μm. After the continuous SAS process, irregular particles were obtained. HPC particles were micronized to 3 μm as shown in Fig. 1 (b).

The particle sizes and morphologies of the original and SAS treated DCA were examined from the SEM images. Three solvents of acetone, ethanol and methanol were applied in this study. It was micronized from 30 μm to 13 μm (acetone or methanol as the solvent) and also with different morphologies. The DSC analyses indicated new endothermic peaks for SAS treated DCA. The XRD patterns were also different between the original and SAS treated DCA. These results implied that a new polymorphism could be obtained after the SAS process. For various solvents, the DSC curves and the particle size distributions are shown in Fig. 2 (a) and (b), respectively.

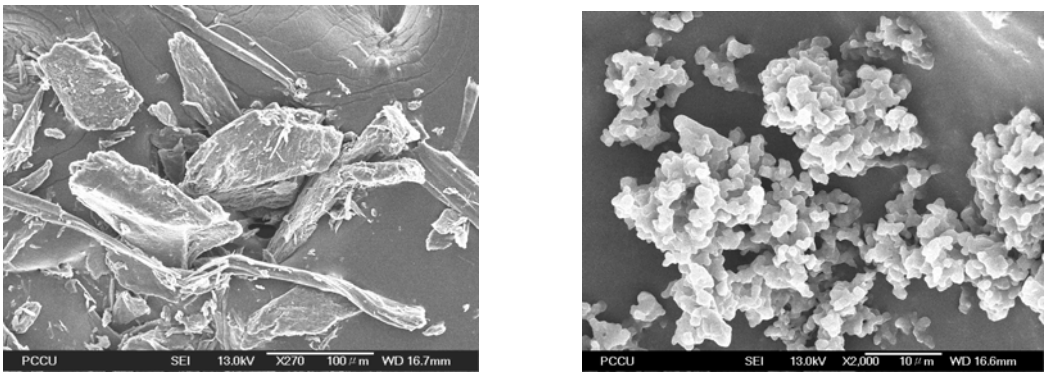


Figure 1 SEM image of HPC：(a) Original HPC (b)After the continuous SAS process.

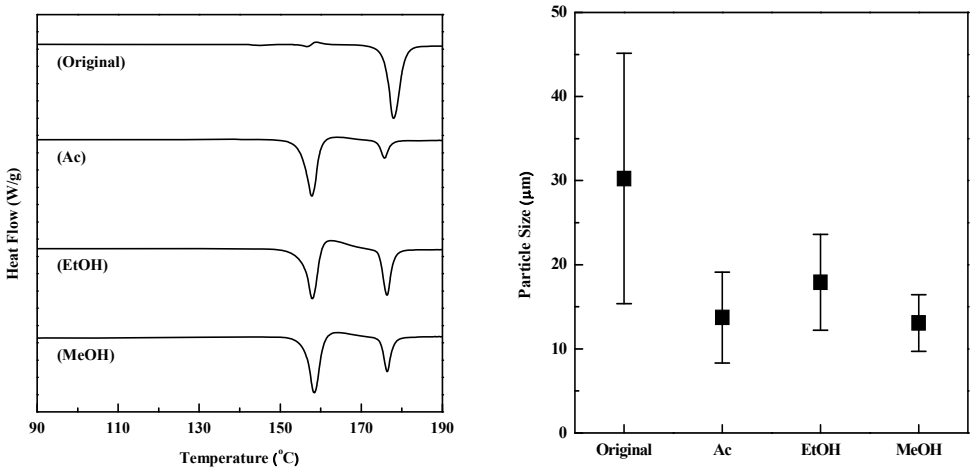


Fig. 2 The SAS treated results of DCA using various solvents (a) The DSC results of DCA, (b) The particle size distribution of DCA.

## References

[1] I. Pasquali, R. Bettini, F. Giordano, Eur. J. Pharm. Sci., 27 (2006) 299-310.

[2] M. Bahrami, S. Ranjbarian, J. Supercrit. Fluids, 40 (2007) 263-283.

[3] E. Reverchon, R. Adami, J. Supercrit. Fluids, 37 (2006) 1-22

[4] Y. P. Chang, M. Tang, Y. P. Chen, J. Mater. Sci. 43 (2008) 2328-2335