Recrystallization of Salicylamide Using a Batch Supercritical Antisolvent Process

By *Chie-Shaan Su* and *Yan-Ping Chen**

Recrystallization of the nonsteroidal anti-inflammatory drug salicylamide was investigated using a batch supercritical antisolvent (SAS) precipitation process. Carbon dioxide was used as the antisolvent, and acetone, ethanol and ethyl acetate were used as solvents. Particle morphology determined by SEM showed that particles with a regular shape were obtained from the SAS process. The crystal structure analyzed by XRD showed that the intensities of specific peaks were modified. No decomposition or deterioration was confirmed by DSC measurements where the melting temperature remained the same after SAS recrystallization. The effects of process parameters were investigated with acetone as the solvent. At a higher pressure of 110 bar, a higher saturation concentration of 90 %, and a lower temperature of 293 K, the length of the rectangular particles decreased to 50 μm. This showed a significant change from the irregular and broken particle shapes with particle sizes up to 200 μm before processing by SAS.

1 Introduction

Supercritical fluids (SCFs), especially carbon dioxide, are widely used in various fields including reaction, extraction and chromatography [1]. In recent years, particle formation using SCFs has been extensively discussed because of their operational flexibility and environmental compatibility in such processes. Although various particle formation techniques using SCFs can be chosen [2], the supercritical antisolvent (SAS) process is the one most widely used in the literature [3, 4].

In this study, batch-type SAS processes were employed to investigate the recrystallization of salicylamide. The samples were first dissolved in an organic solvent which was then injected into a precipitator at atmospheric condition and pressurized by adding supercritical CO_2 as the antisolvent. The antisolvent dissolved in the solution caused volume expansion and decreased the saturated solubility of solute. Crystalline and much smaller particles were obtained from the SAS process as solute concentration reached supersaturation within a very short time. SAS processes have been used in micronization or recrystallization for a wide variety of pharmaceuticals. For example, Yeo et al. [5] recrystallized two pharmaceuticals, sulfathiazole and chlorpropamide, using a batch SAS process. Thiering et al. [6] used this process to produce protein microparticles with a spherical shape. In addition to pure pharmaceutical processing, drug/polymer microcapsules were also successfully investigated using the SAS process [7].

Pharmaceuticals with smaller particle sizes or specific crystal properties may offer many advantages such as higher efficiency, lower dosage requirement and lesser side effects [3]. Conventional techniques for pharmaceutical processing including mechanical methods or spray drying have drawbacks like thermal degradation or residual solvents. In the SAS process, particle size and distribution are controllable by changing the operating temperature and pressure without decomposition of the drug or solvent residues in the final product. Although scale-up and cost study of the supercritical fluid process are still going on [8], this green chemical technology has received increased attention in recent years.

Salicylamide is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties, used to treat fever, headache and pain associated with colds, influenza and arthritis. The potential therapeutic action and the appropriate dosage in biological fluids have been the research topics of recent papers. Pulgarin et al. [9] and Fielding et al. [10] determined the concentration of salicylamide and its metabolites in complex matrices like serum or urine by modified liquid chromatography or fluorescence spectrometry. Aukunuru et al. [11] and Nivaud-Guernet et al. [12] used high-performance liquid chromatography to separate a mixture containing salicylamide and other analgesic agents like acetaminophen, phenacetin or aspirin for multicomponent analgesic tablet analysis. Ribeiro et al. [13] showed the thermal properties of different analgesic agents including salicylamide by TGA (thermogravimetric analysis) and DSC (differential scanning calorimetry). In this study, the recrystallization of salicylamide was investigated using a batch SAS process. The effects of various process parameters such as pressure, pressurization rate, temperature, and concentration on particle size and particle morphology of the final products were also discussed.

2 Experimental

2.1 Materials

The nonsteroidal anti-inflammatory drug (NSAID) salicylamide ($C_7H_7NO_2$) was purchased from Sigma in a purity greater than 99 mass %. Acetone (99.8 mass %), ethanol (99.8 mass %) and ethyl acetate (99.8 mass %) were used as

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solvents in the experiments. Carbon dioxide (San Fu Co., Taiwan) was used as the antisolvent with a purity greater than 99.8 mass %. All chemicals were used without further purifications.

2.2 Apparatus and Procedures

A batch SAS precipitation process was employed. The schematic diagram of the experimental apparatus is shown in Fig. 1. The apparatus consisted of three sections for carbon dioxide supply, recrystallization and depressurization. High-pressure carbon dioxide was fed into the system directly from the gas cylinder or through a HPLC pump (SSI, series II). The recrystallization section had a precipitator comprised of a stainless steel tube, a reducing unit and stainless steel frits with different pore sizes (0.1 and 0.5 μm). The volume of the precipitator was about 75 mL. In the depressurization section, a metering valve was used to control the gas flow rate, a cold trap was used for solvent recovery, and a wet test meter (Ritter, TG1) to record the CO_2 flow rate.

First, a solution of salicylamide with a specific concentration was prepared. Impurities in the precipitator were removed by degassing and CO_2 purging and 3 to 10 mL of the salicylamide solution was fed into it. Temperature in the precipitator was controlled within an accuracy of ± 0.1 K using a water bath. Pressure and temperature were measured by a pressure transducer and a thermocouple with a resolution of 0.1 bar and 0.01 K, respectively. Carbon dioxide was injected from the bottom of the precipitator after the system reached thermal equilibrium. The gas injection rate was regulated by a micrometering valve (Autoclave). The pressure in the system increased from atmospheric condition to 100 bar within 20 seconds. This pressurization effect caused volume expansion and supersaturation of the solution in the precipitator. Nucleation and crystal growth of solute occurred, resulting in the formation of microparticles.

Supercritical drying was then employed to remove any residual solvent after the precipitation step. Carbon dioxide flowed continuously through the top and bottom of the precipitator, the stream leaving it was depressurized to atmospheric condition. The solvent was condensed and separated from the CO_2 stream. The total amount of CO_2 used in supercritical drying was measured by a wet test meter. After no solvent condensation was observed, the precipitator was depressurized to ambient pressure. The drug particles precipitated on the stainless steel frits were collected for further analyses.

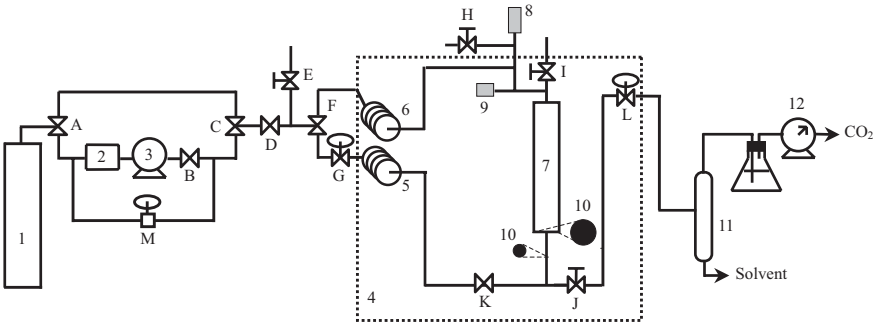

Figure 1. Experimental apparatus in this study. Valve description: A, C, F – Three way needle valve, B, D, K – Check valve, E, H, I, J – Two way needle valve, G, L – Micrometering valve, M – Back pressure regulator; Element description: 1 – CO_2 cylinder, 2 – Cooler, 3 – HPLC pump, 4 – Water bath, 5, 6 – Pre-heater, 7 – Precipitator, 8 – Pressure transducer, 9 – Thermometer, 10 – Stainless frit, 11 – Solvent trap, 12 – Wet test meter.

2.3 Analytical Methods

Particle morphology was examined before and after the experiments by a scanning electron microscope (SEM, JOEL JSM-6300). The crystal structure of the drug particles was determined by an X-ray diffractometer (XRD, Philips X'pert diffractometer). Heat variation of phase transition was measured by differential scanning calorimetry (DSC, DuPont TA 2010) with a heating rate of 10 K/min. Particle size and distribution were determined by an optical microscope. More than 200 drug particles were counted and particle size and distribution were calculated using statistics.

3 Results and Discussion

In this study, salicylamide was recrystallized using a batch SAS process. The crystal morphology and structure of the drug particles before and after processing were compared and the effects of various process parameters on the recrystallization of the drug were further investigated.

3.1 Recrystallization of Salicylamide

In the batch SAS experiments, acetone, ethanol and ethyl acetate were used as solvents. The operating conditions were a final pressure of 100 bar, with an average pressurization rate of 5 bar/sec, and an experimental temperature of 308 K, the solution injection amount was 3 mL, and solute saturation was 100 %. The saturated solubility of the drug in various solvents was determined by gravimetry. No particle formation was obtained when ethanol was used as the solvent, whereas for the other two solvents, particle recovery was greater than 99 %.

The SEM images for salicylamide before and after the SAS process are shown in Fig. 2. Originally, the salicylamide particles were irregularly shaped and broken (see Fig. 2a)). After the SAS process, they were rectangular in shape when either ethyl acetate or acetone was used as the solvent (see Figs. 2b) and 2c)).

With acetone as the solvent, particles observed were relatively small compared to those obtained with ethyl acetate as the solvent. It is demonstrated that after the SAS process salicylamide exhibits a better and regular appearance, a smooth surface and a specific crystal habit. This result offers the possibility for reducing imperfections and improving the efficiency of pharmaceuticals, as has been discussed in previous literature [5].

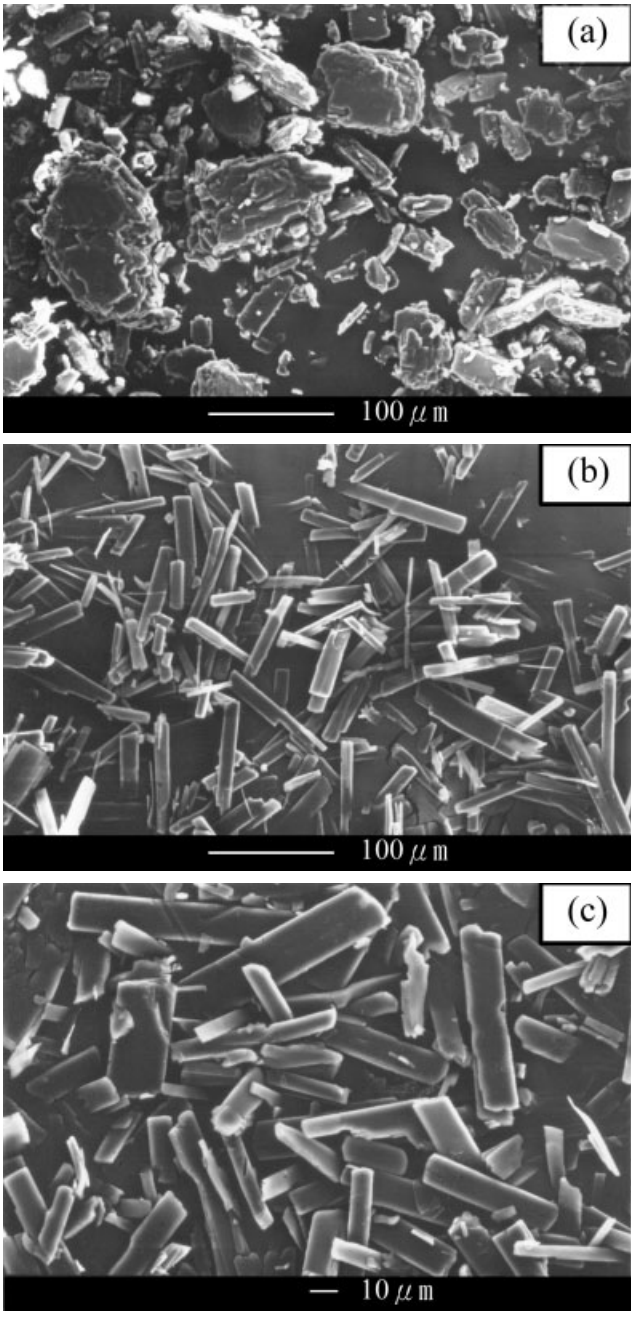

Figure 2. SEM images of salicylamide before and after the SAS process (a) original salicylamide (b) salicylamide after the SAS process using ethyl acetate as the solvent (c) salicylamide after the SAS process using acetone as the solvent.

The variation of the crystal structure of salicylamide before and after the SAS precipitation process was examined by XRD, as shown in Fig. 3 with different solvents. It is indicated that the positions of constructive interference peaks contributed by specific crystal planes in the XRD pattern are the same. The intensities of some specific peaks, however, are modified after SAS precipitation. As shown in Fig. 3c), the intensities of peaks at $2\theta = 7.5°$ and $16°$ increased significantly after the SAS process when ethyl acetate was used as the solvent. This result indicates a change in crystallinity after the SAS process, and is similar to that described in the literature for chlorpropamide as a model drug [5].

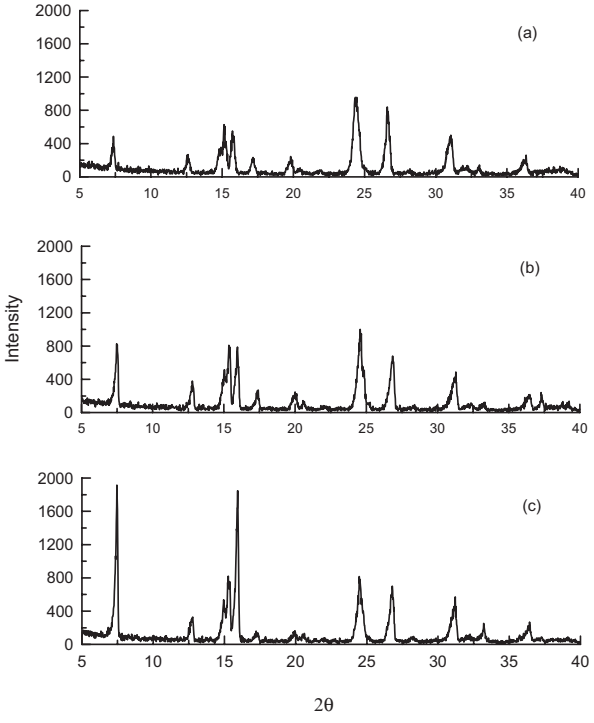

Figure 3. XRD spectrum of salicylamide before and after the SAS process (a) Original (b) Acetone as the solvent (c) Ethyl acetate as the solvent.

The measurement of the melting point by DSC before and after SAS precipitation provides information about the decomposition of pharmaceuticals during the SAS process. Decomposition causes a loss of activity of the drugs and should be avoided in pharmaceutical processing. Fig. 4 shows the DSC measurement results for salicylamide. The melting temperatures are almost invariant after the SAS process with either solvent. No decomposition, deterioration or solid-solid phase transition is observed.

3.2 Effects of Process Parameters in SAS Precipitation

With higher saturated solubility and recovery of salicylamide, acetone was used as the solvent to investigate the ef-

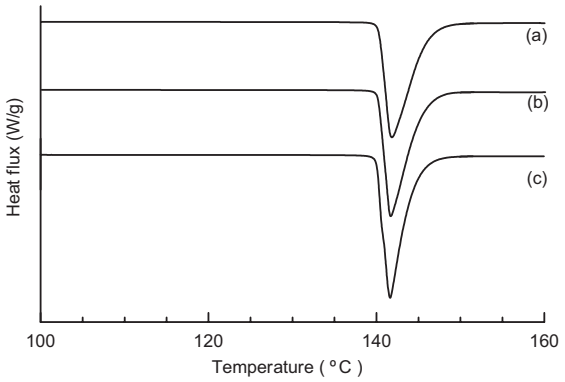

Figure 4. DSC results of salicylamide before and after the SAS process (a) Original (b) acetone as the solvent (c) ethyl acetate as the solvent.

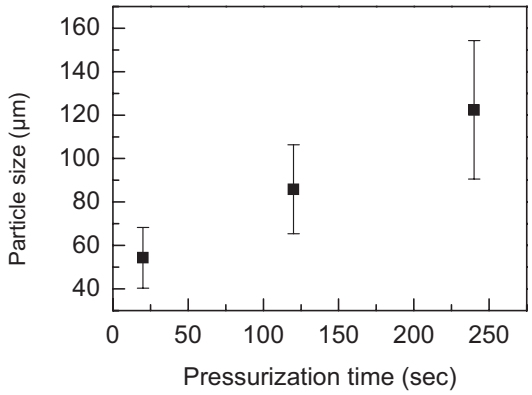

Figure 5. Effect of pressurization time (20, 120, 240 sec) on particle size and distribution after the batch SAS process.

fects of process parameters in SAS precipitation. The variables considered were temperature, final pressure, solution concentration, injection amount of solute and pressurization rate. The shape of the particles remained rectangular in all experiments. Particle size was defined as the length of each rectangular shape. The experimental results for various operating conditions are summarized in Tab. 1.

The pressurization rate is proportional to the expansion rate of the solution. In general, a faster pressurization rate implies that solute concentration reaches supersaturation within a shorter time where smaller particles with narrower size distributions are obtained. In this study, three pressurization rates were tested where the time required to reach 95 % of the final pressure of 110 bar was 20, 120, and 240 seconds, respectively. As shown in Fig. 5 and for cases A, B, and C in Tab. 1, particle size and distribution decreased with increasing pressurization rate. Particle sizes and distributions decreased from 122.4 ± 31.9 to 54.3 ± 14.0 μm when the pressurization time decreased from 240 to 20 seconds. This result is similar to that for the recrystallization of chlorpropamide and β-carotene [5, 14].

The effect of temperature in the SAS process is more complicated. In general, volume expansion increases with decreasing temperature, favoring the formation of smaller particles in the SAS process. On the other hand, the kinetic rate constant and mass transfer coefficient for nucleation and crystal growth decrease with decreasing temperature. This competitive effect is unfavorable to particle formation. In this study, three temperatures (293, 308, and 323 K) were selected for comparison. Cases D, A, and E in Tab. 1 show that particle size decreases from 70.4 ± 14.6 to 46.8 ± 12.8 μm as temperature decreases from 323 to 293 K. Volume expansion is thus a dominating factor for the recrystallization of salicylamide. This result is consistent with the processing of pharmaceuticals like β-carotene [14, 15] although in some studies the temperature effect was negligible for sulfathiazole and copper indomethacin as model drugs [5, 16].

Table 1. Comparison of experimental results from various operating conditions.

Exp. case	Time to reach 95 % of final pressure (sec)	Temp. (K)	Conc. (% sat.)	Pressure (bar)	Injection amount of solution (mL)	Particle size (μm)	Recovery (%)	Melting temp. T_m [d] (K)
A	20	308 [b]	90	110	3	54.3 ± 14.0	98.9	414.96
B	120	308	90	110	3	85.8 ± 20.5	98.0	415.03
C	240	308	90	110	3	122.4 ± 31.9	98.8	414.93
D	20	323 [c]	90	110	3	70.4 ± 14.6	98.2	415.24
E	20	293 [a]	90	110	3	46.8 ± 12.8	97.4	414.95
F	20	308	60	110	3	76.8 ± 16.3	98.1	414.87
G	20	308	30	110	3	94.7 ± 18.8	97.2	414.72
H	20	308	90	90	3	66.4 ± 15.1	92.4	414.86
I	20	308	90	80	3	68.8 ± 15.9	89.8	414.87
J	20	308	90	110	5	66.0 ± 17.4	95.6	414.83
K	20	308	90	110	10	94.5 ± 24.2	92.1	414.98

a) Saturated solubility at 293 K is 208.47 mg/mL. b) Saturated solubility at 308 K is 257.64 mg/mL. c) Saturated solubility at 323 K is 281.76 mg/mL. d) T_m for original salicylamide is 415.03 K.

The solution concentration also shows a competing effect. A higher solute concentration favors a higher degree of supersaturation and a higher driving force for the formation of smaller nuclei. In contrast, a higher solution concentration increases the probability that larger aggregated particles will form due to collision. As shown in Fig. 6 and for cases G, F, and A in Tab. 1, the particle size of salicylamide decreased from 94.7 ± 18.8 to 54.3 ± 14.0 μm as solute concentration increased from 30 to 90 % saturation. A similar solution concentration effect has been shown for copper indomethacin in previous studies [16].

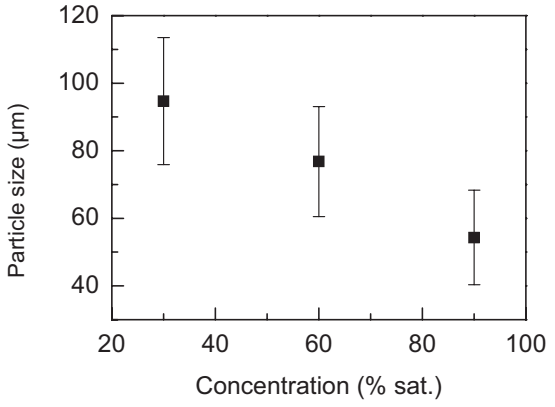

Figure 6. Effect of solution concentration (30, 60, 90 % sat.) on particle size and distribution after the batch SAS process.

The effect of final pressure is closely related to the end point of volume expansion. With a higher final pressure and volume expansion ratio, the saturated solute solubility decreased to a lower value that favored the formation of smaller particles and solute recovery. As shown for cases I, H, and A in Tab. 1, the particle size of salicylamide decreased from 68.8 ± 15.9 to 54.3 ± 14.0 μm as the final pressure increased from 80 to 110 bar. The recovery also increased from 89.8 to 98.9 %. At pressures above a certain value where no further decrease in saturated solute solubility was observed, the effect of pressure was negligible as described in previous papers [14, 17].

The solution injection amount affected the contact ratio of solution and antisolvent. For a larger amount of solution injected, volume expansion becomes incomplete, which is unfavorable to the formation of smaller particles. The results for cases K, J, and A in Tab. 1 show that the particle size of salicylamide decreased from 94.5 ± 24.2 to 54.3 ± 14.0 μm when the solution injection amount decreased from 10 to 3 mL. This result is also consistent with the literature evidence for the recrystallization of acetaminophen using the batch SAS process [17].

In the experiments conducted, the pressurization rate is the most important factor for the micronization of salicylamide. It is also demonstrated that the effects of solute concentration and the amount of solution injected are more sensitive compared to those of temperature and final pressure.

4 Conclusion

Recrystallization of salicylamide was investigated using a batch SAS process. The particles obtained from this process were changed from irregular and broken to rectangular and particle size was micronized from 200 μm to 50 μm. The effects of various process parameters were investigated. At lower temperature, higher final pressure, higher solution concentration, higher pressurization rate, and smaller amount of injected solution, smaller crystals were obtained. Melting temperatures of salicylamide measured by DSC showed no decomposition or deterioration during the batch SAS process.

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References

[1] E. J. Beckman, *J. Supercrit. Fluids* **2004**, *28*, 121.
[2] J. Jung, M. Perrut, *J. Supercrit. Fluids* **2001**, *20*, 179.
[3] B. Subramaniam, R. A. Rajewski, K. Snavely, *J. Pharm. Sci.* **1997**, *86*, 885.
[4] P. York, *Pharm. Sci. Technol. Today* **1999**, *2*, 430.
[5] S. D. Yeo, M. S. Kim, J. C. Lee, *J. Supercrit. Fluids* **2003**, *25*, 143.
[6] R. Thiering, F. Dehghani, A. Dillow, N. R. Foster, *J. Chem. Technol. Biotechnol.* **2000**, *75*, 29.
[7] N. Elvassore, A. Bertucco, P. Caliceti, *Ind. Eng. Chem. Res.* **2001**, *40*, 795.
[8] J. Jung, J. Y. Clavier, M. Perrut, *Proc. of the 6th Int. Symp. on Supercritical Fluids*, Versailles, France, **2003.**
[9] J. A. M. Pulgarin, A. A. Molina, *Talanta* **2002**, *56*, 557.
[10] R. M. Fielding et al., *J. Liq. Chromatogr.* **1984**, *7*, 1221.
[11] J. V. Aukunuru, U. B. Kompella, G. V. Betageri, *J. Liq. Chromatogr. Relat. Technol.* **2000**, *23*, 565.
[12] E. Nivaud-Guernet, M. Guernet, D. Ivanovic, M. Medenica, *J. Liq. Chromatogr.* **1994**, *17*, 2343.
[13] Y. A. Ribeiro et al., *J. Therm. Anal.* **1996**, *46*, 1645.
[14] M. J. Cocero, S. Ferrero, *J. Supercrit. Fluids* **2002**, *22*, 237.
[15] M. Muller, U. Meier, A. Kessler, M. Mazzotti, *Ind. Eng. Chem. Res.* **2000**, *39*, 2260.
[16] B. Warwick et al., *Ind. Eng. Chem. Res.* **2002**, *41*, 1993.
[17] F. Cristini et al., *Proc. of the 8th Meeting on Supercritical Fluids*, Bordeaux, France, **2002.**

