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초임계 이산화탄소를 이용한 미립 항비듬제 제조

신 문 삼†

서울대학교 화학생물공학부
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Preparation of Micronized Anti-dandruff Agents Using Supercritical Carbon Dioxide

Moon Sam Shin†

School of Chemical & Biological Engineering, Seoul National University, San 56-1, Shillim-dong, Gwanak-gu, Seoul 151-742, Korea
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요 약: 화장품, 의약품에서 항비듬제로 널리 사용되는 요도프로피닐 부틸카바메이트와 클림바졸을 초임계 유체를 이용하여 미세입자를 제조하였다. 초임계 유체로는 임계온도와 임계압력이 상대적으로 낮은 이산화탄소가 사용되었다. 초임계 이산화탄소에 용해력이 있는 요도프로피닐 부틸카마메이트와 클림바졸을 항비듬제로 선택되었다. 초임계 용액 급속 팽창법을 이용하여 압력과 온도를 변화시켜 입자크기와 형상에 미치는 영향을 분석하였다.

Abstract: Iodopropynyl butylcarbamate and climbazole as anti-dandruff agents widely used in cosmetics and pharmaceutics were micronized using supercritical fluid. Supercritical carbon dioxide was selected due to relatively low critical temperature and critical pressure. Iodopropynyl butylcarbamate and climbazole were chosen because of their solubility in supercritical carbon dioxide. The rapid expansion of supercritical solution (RESS) experiments involved investigations of the effect of pressure, temperature on particle size and morphology.

Keywords: *supercritical fluid, micronization, anti-dandruff, IPBC, climbazole*

1. Introduction

Many cosmetic and pharmaceutical drugs are insoluble or only slightly soluble in water. The drugs, however, must be dissolved in water in order to be absorbed and to exert their effects. The bio-availability of the drug, the percentage of the drug absorbed compared to its initial dose, is limited by insolubility[1-3]. Micronization of the drug can be enhanced by drugs dissolution rate in the biologic environment. Dissolution rate is a function of solubility as well as particle surface area wherein the surface area can be increased through a reduction of particle size[4]. Several techniques are used to reduce particle size such as a crushing, grinding, milling, spray drying, freeze drying and recrystallization of solute particles from solutions by using liquid anti-solvent. These conventional techniques, however, have disadvantages such as thermal and chemical degradation of products, broad particle size distribution, large amounts of used solvent, and the related problems of solvent disposal and solvent residues[1-3,5-7]. Because of the aforementioned disadvantages, a reduction of particle size using supercritical fluids has been studied. Supercritical fluid processes have an advantage to produce solvent free production with narrow particle size distributions. Especially, supercritical carbon dioxide ($scCO_2$) offers a non-flammable nontoxic process that possesses low critical temperatures and pressures and

† 주 저자 (e-mail: moonsam7@snu.ac.kr)

an excellent solvent power applicable to many organic compounds. Therefore, $scCO_2$ is often used as a clean medium and has replaced traditional organic solvents for various industrial applications[8].

Processes for particle formation using supercritical fluids can be mainly divided into the following classes: supercritical anti-solvent (SAS) particles from gas-saturated solution (PGSS) rapid expansion of supercritical solutions (RESS). In the SAS process, a supercritical fluid issused as anti-solvent that must be miscible with a solvent, and a solute must be not soluble in $scCO_2$. A supercritical fluid is contacted with a solution to cause precipitation of the solutes dissolved initially in the solvent then loses its solubility for the solute and the solute is recrystallized from solution. The SAS process has been used to recrystallize many products e.g. explosives, polymers and biopolymers, pharmaceutical compounds, pigments and inorganic materials. In the PGSS, the supercritical fluid is dissolved in a liquid substrate or a solution of substrates and then the solution is forced to expand through a nozzle which causes the formation of solid particles. Recently, PGSS has found applications in the paint and powder coating manufacture industries. With the RESS process, the supercritical fluid is used as the solvent and the solutes are initially dissolved in the supercritical solvent. The solution expands when passed through a nozzle. The solute is recrystallized by gasification of the supercritical fluid. The RESS process has been used to micronize such as polymers and biopolymer, inorganic and organic materials and pharmaceutical compounds[9].

Iodopropynyl butylcarbamate (IPBC) is a halogenated unsaturated carbamate with significant widespread cosmetic and pharmaceutical applications such as anti-dandruff agent[10,11]. IPBC has been shown to be active against Malassezia strains, yeasts that cause some skin disorders (dermatitis, pruritus). IPBC is white crystalline powder and has poor solubility in water. Climbazole, 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl-2-butanone, is a conazole fungicide that has been shown to be active against Malassezia strains, yeasts that cause some skin disorders (dermatitis, pruritus). Climbazole has been used with significant widespread cosmetic and pharmaceutical applications such as anti-dandruff agent[12,13] and anti-itching agent[14].

Solubility information is crucial for choosing a supercritical fluid processes for particle design. If the solute is soluble in the supercritical fluid, the RESS process is considered, however, if the solute is not soluble in the supercritical fluid, an SAS process is preferred. Furthermore, precise solubility data is important for the designing of the RESS process experiment condition. In previous studies[15,16], Solubility of IPBC and climbazole was measured with static method in the pressure range from 10 to 40 MPa and at temperatures equal to 313.2, 323.2, and 333.2 K and successfully correlated the phase equilibria with a quasi-chemical nonrandom lattice fluid (QLF) model[17-19].

In this study, IPBC and climbazole were micronized using supercritical fluid. Supercritical carbon dioxide was chosen due to relatively low critical temperature and critical pressure. Since this drug was soluble in the supercritical carbon dioxide, the RESS process was used. The RESS experiments involved investigations of the effect of pressure, temperature on particle size and morphology.

2. Materials and Methods

2.1. Materials

Carbon dioxide (min. 99.5 %) was supplied from Korea Industrial Gases (Korea). IPBC (min. 97.0 %) and climbazole (min. 97.0 %) were supplied by SPC Co. Ltd. (Korea) and Bayer AG (Germany), respectively. These materials were used without further purification.

2.2. RESS Experiment

A schematic diagram of the experimental apparatus used for the RESS process is shown in Figure 1. The apparatus mainly consists of a CO_2 supplying system, a pressure system, a dissolution vessel, an expansion system and an expansion chamber in which the particle are collected. CO_2 is supplied from a gas cylinder and the gaseous CO_2 liquefied through a cooler (Jeio Tech. Co. Ltd., Korea) set to -10 ℃. CO_2 was pressured by a diaphragm metering pump (Pulsafeeder Inc., USA).

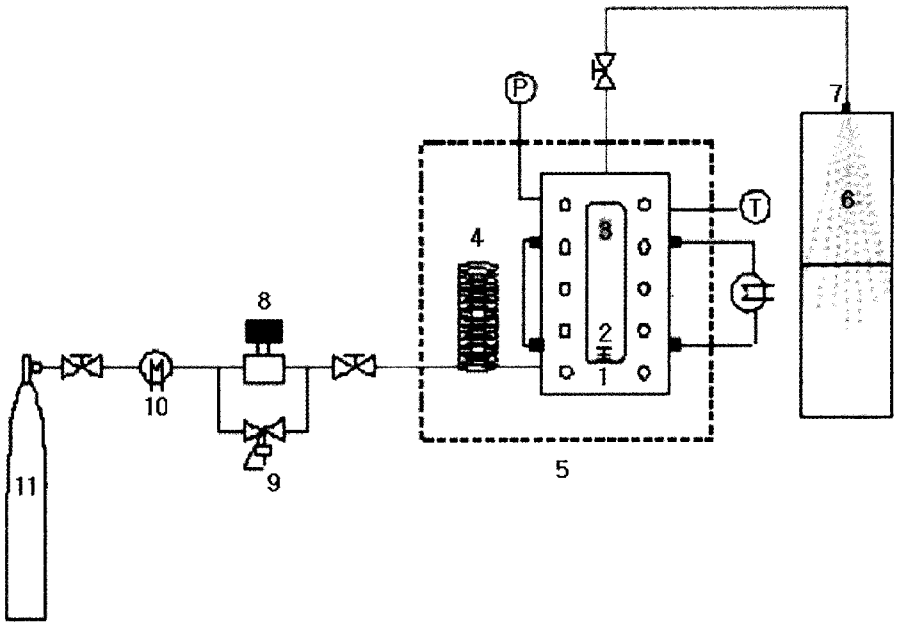


Figure 1. Schematic diagram of RESS apparatus. 1: dissolution vessel, 2: magnetic bar, 3: filter (0.5 μm), 4: pre-heater, 5: air bath, 6: expansion chamber, 7: nozzle, 8: pump, 9: back pressure regulator, 10: circulating bath, 11: CO_2 cylinder.

A back pressure regulator (Tescom Corp., USA) was installed after the pump exit. After the pressured CO_2 passed through the back pressure regulator, it was delivered to the dissolution vessel. Prior to entering the dissolution vessel, the CO_2 passed through a pre-heater to minimize temperature difference of the injected CO_2 and the interior of the dissolution vessel. The temperature of solution in dissolution vessel was controlled by thermostatic circulating water in the jacket using a refrigerated circulating bath. System temperature was measured by a K-type thermocouple. The magnetic bar was used to accelerate the dissolution rate of the drug. A metal fritted filter was installed between the dissolution vessel and the valve so that only drug dissolved was passed through the filter. Once $scCO_2$ was saturated with the drug, the valve was opened to spray the solution into the expansion chamber through a laser-drilled orifice nozzle with a hole. The nozzle used in this study was made of stainless steel 316 (150 μm thick and 9 mm outer diameter) and has inner diameters of 30 μm. The nozzle was heated using a heating tape. When the supercritical solutions were depressurized through the nozzle to ambient conditions, they rapidly expanded and the solute was recrystallized. Solutes were collected in the chamber. An expanded CO_2 was vented off through a filter paper which was located at the bottom of the chamber.

2.3. Particle Analysis

Particle size and particle size distribution were analyzed directly in the laser diffraction beam as an aerosolized dry powder using RODOS dry powder accessory (Sympatec Gmbh, Germany). The measuring range of particle size was from 0.1 to 35 μm. Particle morphology was analyzed by SEM (JEOL, Japan). The particles were initially spread on a carbon tape glued to an aluminum stub and coated with a silver to make the particle surface conductive to electrons by SEM. Particles were observed by SEM and the micrographs were taken and recorded.

3. Results and Discussion

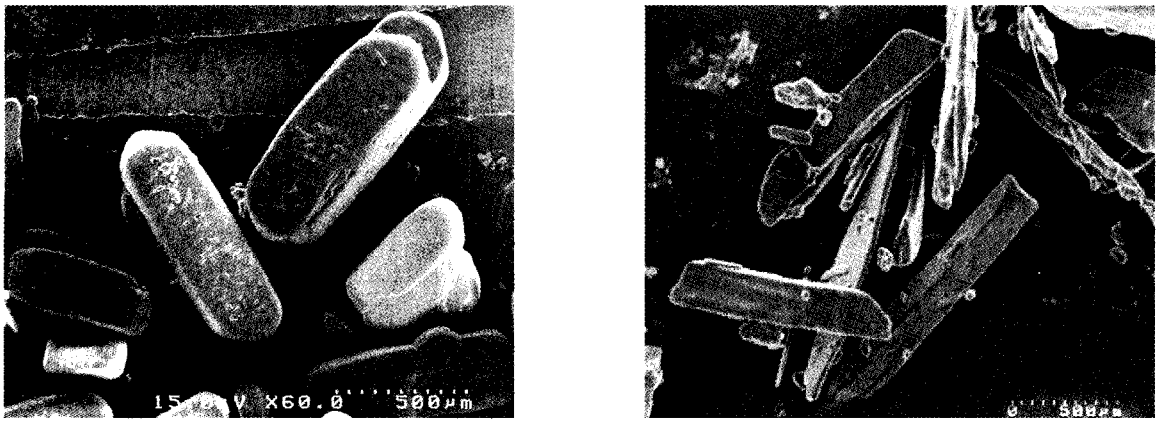
The RESS experiments were carried out to investigate the effect of extraction pressure and temperature on the size and morphology of IPBC and climbazole particles obtained by the RESS process. The experimental conditions and results are reported in Tables

Table 1. RESS Experiment Conditions and Results for IPBC

Run no.	T (K)	P (MPa)	Average particle size × 50 (μm)
Raw	-	-	287
1	313.15	15.0	2.15
2	323.15	15.0	2.38
3	333.15	15.0	3.28
4	313.15	10.0	2.69
5	313.15	20.0	2.01

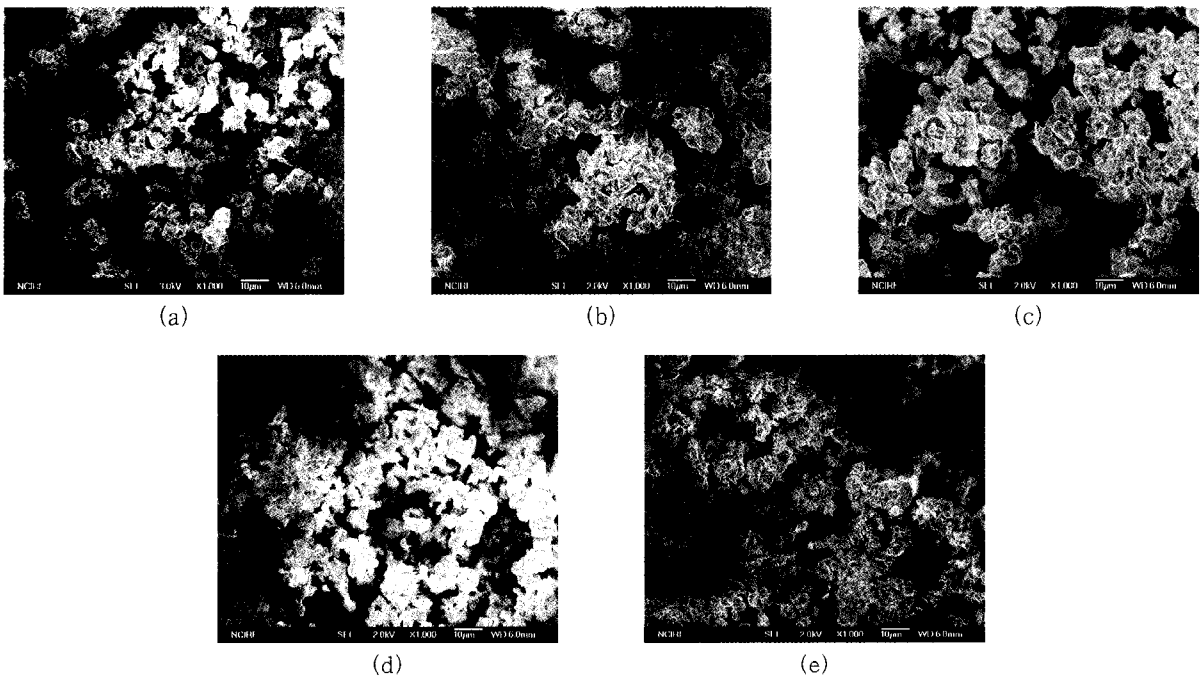
Table 2. RESS Experiment Conditions and Results for Climbazole

Run no.	T (K)	P (MPa)	Average particle size × 50 (μm)
Raw			295
1	313.15	15.0	2.07
2	323.15	15.0	2.12
3	333.15	15.0	3.06
4	313.15	10.0	2.65
5	313.15	20.0	1.97



(a) IPBC (b) Climbazole

Figure 2. SEM image of unprocessed IPBC and climbazole.



(a) (b) (c) (d) (e)

Figure 3. SEM image of IPBC particles obtained by RESS at various temperature and pressure. (a): T = 313.15 K, P = 15.0 MPa, (b): T = 323.15 K, P = 15.0 MPa, (c): T = 333.15 K, P = 15.0 MPa, (d): T = 313.15 K, P = 10.0 MPa, (e): T = 313.15 K, P = 20.0 MPa.

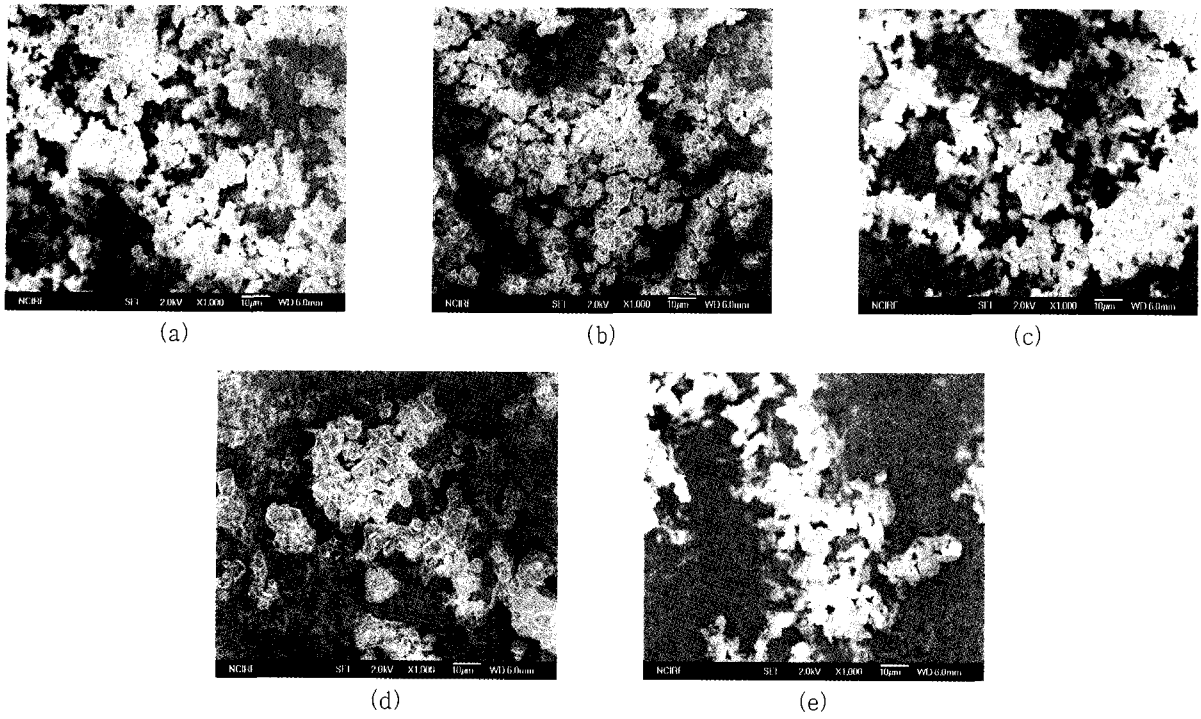


Figure 4. SEM image of climbazole particles obtained by RESS at various temperature and pressure. (a): T = 313.15 K, P = 15.0 MPa, (b): T = 323.15 K, P = 15.0 MPa, (c): T = 333.15 K, P = 15.0 MPa, (d): T = 313.15 K, P = 10.0 MPa, (e): T = 313.15 K, P = 20.0 MPa.

1 and 2. The extraction pressure and temperature were determined according to the solubility data[15,16] obtained for IPBC and climbazole in $scCO_2$.

Figure 2 is a SEM image of the raw IPBC and climbazole. The raw particles have a rectangular shape with a rounded edge and a smooth surface. Average particle size of the raw IPBC and climbazole were 235 and 95.7 μm, respectively. The RESS processed particles of these drugs are irregular and polyhedral in shape (Figure 3, 4). The average particles sizes of processed particles are between 1.97 and 3.28 μm.

3.1. Effect of Temperature

The effect of temperature for IPBC and climbazole was studied for the range of 313.15 to 333.15 K at 15.0 MPa. SEM images are shown in Figures 3 and 4. As the extraction temperature increases the average particle sizes increase from 2.15 to 3.28 μm for IPBC and from 2.07 to 3.06 for climbazole. An increase of temperature decreases the CO_2 density and leads to a decrease of a solvent power. As a result, a lower supersaturation and lower nucleation are achievableed. Consequently, particle size increases with temperature increases. Further, an increase of temperature cause to increase the solute's vapor pressure leading to higher solution concentration. The high concentration of the solution brings about the increase of the particle size as a consequence of the particle growth and coagulation among the particles.

3.2. Effect of Extraction Pressure

The effect of extraction pressure for IPBC and climbazole was investigated for the range of 10.0 to 20.0 MPa. SEM images of the particles obtained different pressure given in Figure 3 and 4. Increasing in extraction pressure resulted in decrease in the average particle size from 2.69 to 2.01 μm for IPBC and from 2.65 to 1.97 μm for climbazole.

The extraction pressure affects particle size in several aspects. First, the higher the pressure, the higher the solution concentration, this frequently leads to coagulation among particles. As a result, the particle size

increases. Second, higher pressure leads to a higher mass flow rate of the solution and causes reduced residence time in the nozzle. Consequently, time for particle growth will be decreased within a nozzle. Third, the higher the pressure, the greater the solubility of the drugs in $scCO_2$ since the CO_2 density increases as pressure increases. The increase of the drugs in $scCO_2$ solubility results in the greater the degree of supersaturation and higher nucleation rate. The second and third phenomena can lead to a decreased particle size. Therefore, it can be explained that the second and third phenomena can be dominant in this study.

4. Conclusion

Micronized IPBC and climbazole particles were successfully prepared using the RESS process. We investigated the effect of pressure and temperature on particles in RESS process. As the extraction temperature increases the average particle sizes increase from 2.15 to 3.28 μm for IPBC and from 2.07 to 3.06 for climbazole. Increasing in extraction pressure resulted in decrease in the average particle size from 2.69 to 2.01 μm for IPBC and from 2.65 to 1.97 μm for climbazole.

References

1. D. Kayrak, U. Akman, and O. Hortacsu, Micronization of ibuprofen by RESS, *J. Supercrit. Fluids*, **26**, 17 (2003).
2. M. Turk, P. Hils, B. Helfgen, K. Schaber, and H.-J. Martin, Micronization of pharmaceutical substances by the rapid expansion of supercritical solutions (RESS): a promising method to improve bioavailability of poorly soluble pharmaceutical agents, *J. Supercrit. Fluids*, **22**, 75 (2005).
3. M. Charoenchaitrakool, F. Dehghani, N. R. Foster, and H. K. Chan, Micronization by rapid expansion of supercritical solution to enhance the dissolution rates of poorly water-soluble pharmaceuticals, *Ind. Eng. Chem. Res.*, **39**, 4794 (2000).
4. M. Perrut, J. Jung, and F. Leboeuf, Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes Part 1: micronization of neat particles, *Int. J. Pharmaceu.*, **288**, 3 (2005).
5. N. Yildiz, Ş. Tuna, O. Doker, and A. Calimli, Micronization of salicylic acid and taxol (paclitaxel) by rapid expansion of supercritical fluids (RESS), *J. Supercrit. Fluids*, **41**, 440 (2007).
6. Z. Huang, G.-B. Sun, Y. C. Chiew, and S. Kawi, Formation of ultrafine aspirin particles through rapid expansion of supercritical solutions (RESS), *Powder Techno.*, **160**, 127 (2005).
7. P. Alessi, A. Cortesi, I. Kikic, N. R. Foster, S. J. Macnaughton, and I. Colombo, Particle production of steroid drugs using supercritical fluid processing, *Ind. Eng. Chem. Res.*, **35**, 4718 (1996).
8. E. J. Beckman, Supercritical and near-critical CO_2 in green chemical synthesis and processing, *J. Supercrit. Fluids*, **28**, 121 (2004).
9. J. Jung and M. Perrut, Particle design using supercritical fluids: literature and patent survey, *J. Supercrit. Fluids*, **20**, 179 (2001).
10. M. S. Shin, S. C. Choi, Y. D. Kwak, S. H. Seo, H. I. Jeong, and K. H. Seo, Hair-care cosmetic compositions having dandruff formation - suppressing effect, US Patent 5,886,031 (1999).
11. M. S. Shin, S. C. Choi, Y. D. Kwak, S. H. Seo, H. I. Jeong, and K. H. Seo, Hair-care cosmetic compositions having dandruff formation - suppressing effect, US Patent 6,054,450 (2000).
12. J. Asrar, E. F. Sanders, and Y. Ding, Method of improving yield and vigor of plants by treatment with triazole and strobilurin-type fungicides, US Patent 7,098,170 (2006).
13. H. J. Rother, M. Kugler, and J. Rehbein, Composition of a mixture of a phenolic compound and an azole or morpholine compound to protect animal hides and leather against microbes, US Patent 6,083,414 (2001).
14. P. N. Ramachandran, C. R. Robbins, and A. M. Patel, Scalp care products containing anti itching /anti irritant agents, US Patent 5,900,393 (1999).
15. M. S. Shin and H. Kim, Solubility of iodopropynyl butylcarbamate in supercritical carbon dioxide, *Fluid Phase Equilib.*, **270**, 45 (2008).

16. C. I. Park, M. S. Shin, and H. Kim, Solubility of climbazole and triclocarban in supercritical carbon dioxide: measurement and correlation, *J. Chem. Thermodyn.*, in press (2008).
17. M. S. Shin and H. Kim, A qausi-chemical non-random lattice fluid model: general derivation and application to pure fluids and mixtures, *Fluid Phase Equilib.*, **246**, 79 (2006).
18. M. S. Shin and H. Kim, A quasi-chemical non-random lattice fluid model for phase equilibria of associating systems, *Fluid Phase Equilib.*, **256**, 27 (2007).
19. M. S. Shin and H. Kim, Phase equilibria for mixtures containing nonionic surfactant systems: modeling and experiments, *J. Chem. Thermodyn.*, **40**, 1110 (2008).