DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 10, pp. 1029–1035, 2004

Itraconazole Formation Using Supercritical Carbon Dioxide

Ali Hassan,[1,*] Yi-Min Tang,[2] and James W. Ayres[3]

[1]Department of Chemical and Petroleum Engineering, UAE University, Al-Ain, United Arab Emirates
[2]Wafertech LLC, Camas, Washington, USA
[3]College of Pharmacy, Oregon State University, Corvallis, Oregon, USA

ABSTRACT

A new method of preparing Itraconazole ($C_{35}H_{38}Cl_2N_8O_4$), a synthetic triazole antifungal agent, was developed using supercritical carbon dioxide (SC CO_2) while eliminating the use of toxic solvents. Dissolution amounts of the product were measured in gastric fluid and compared to those of conventional drug formulations. Different operating conditions (five levels of treatment temperature ranging between 110–140°C, four levels of treatment pressure ranging between 30–400 atm, and four different treatment times ranging from 10–60 minutes) were tested in order to produce a desired Itraconazole product, which does not degrade during the product formation and has the highest extent of dissolution in gastric fluid after one hour. Itraconazole dissolution of 100% at one-hour was achieved for the drug produced at the optimum treatment condition: 135°C, 300 atm, and 30 minutes. Extent of dissolution obtained from this solvent and detergent-free process is 10% higher than that of the conventional method involving toxic organic solvents. Itraconazole produced using SC CO_2 should provide minimal side effects in human body.

Key Words: Supercritical fluids; CO_2; Itraconazole; Dissolution rate.

INTRODUCTION

Antifungal and antiviral drugs are necessary in treating fungal and viral infections, especially in patients with aggressive diseases such as AIDS. The conventional methods for the formation of some antifungal and antiviral drugs require many preparation steps. Several drying steps at high temperatures for long periods of time are usually needed to remove toxic organic solvents that are used in the preparation of drugs before drugs can be used for human use. Removal of organic solvents to levels approved by Food and Drug Administration (FDA)

*Correspondence: Ali Hassan, Department of Chemical and Petroleum Engineering, UAE University, P.O. Box 17555, Al-Ain, United Arab Emirates; Fax: +9713-7624262; E-mail: hassana@uaeu.ac.ae.

DOI: 10.1081/DDC-200040241
0363-9045 (Print); 1520-5762 (Online)

is very difficult and this has limited the use of such drugs for human use.

The drug of interest is Itraconazole, which has therapeutic effects on patients with fungal diseases. Itraconazole is a white to slightly yellowish powder, which is poorly soluble in aqueous solutions and freely soluble in dichloromethane. The efficacy of Itraconazole can be severely limited by its poor solubility in aqueous solutions. Since Itraconazole is to be dissolved in gastric or intestine fluid, it is desirable to increase its solubility in aqueous solutions.

In conventional methods,[1] hydroxypropyl methylcellulose (HPMC) which is a hydrophilic agent, is added to Itraconazole to increase solubility of Itraconazole in aqueous media (i.e., gastric or stomach fluid). Dichloromethane and ethanol are used as solvents in order to form a uniform Itraconazole/HPMC solution with weight ratios of 1:1.5:17.25:11.5 (Itraconazole: HPMC:dichloromethane:ethanol). This solution is coated on sugar beads using a fluidized bed and dried at temperatures up to 80°C for 2–3 days to remove dichloromethane. A thin layer of polyethylene glycol (PEG) 20000 is used as a nonsticking agent in order to prevent sticking of the beads. PEG is first dissolved in dichloromethane and ethanol (1:5.4:3.6), and the solution is then sprayed on the previously coated sugar beads using a fluidized-bed granulator and dried to remove dichloromethane. These drug-coated beads are filled into hard-gelatin capsules and their dissolution rate is measured in simulated gastric fluid at 37.5°C, 100 rpm. This conventional itraconazole formulation (Sporanox) exhibits 90% drug dissolution at 60 minutes in gastric fluid.

Since dichloromethane is a hazardous solvent, its removal from the product is required before the drug can be used for human use. Removal of dichloromethane to levels approved by FDA is very difficult and thus conventional methods involve several drying steps for long periods of time, which affect the stability of Itraconazole.[1] The use of organic solvents is also expensive because of environmental regulations on contaminated solvents which are generated. Therefore, it is desirable to eliminate the use of dichloromethane used in the conventional method to prepare Itraconazole.

Supercritical fluid (SCF) science and technology have given new directions in research and applications in the last few years. Properties of SCFs can be changed from gas-like to liquid-like values by simply adjusting the pressure and temperature. Because of these special characteristics, supercritical fluids find use in applications of extraction, separation, chemical reactions, impregnation, polymer processing, food processing, environmental remediation and pharmaceutical processing.[2] Supercritical fluid technology has the potential to eliminate some of the problems associated with the conventional drug formulation. SC CO_2 is the most commonly used solvent in this technology because it is nontoxic, nonflammable, environmentally acceptable, inexpensive and leaves no solvent residue.

Preparation of pharmaceutical drugs with supercritical fluids has seen widespread interest using different techniques such as rapid expansion of supercritical solution (RESS) and gas antisolvent (GAS) crystallization processes.[3–8] In the RESS, the substance is first dissolved in the SCF and then the SC solution is rapidly expanded. Therefore, the substance must have sufficient solubility in the SCF. Like many other pharmaceutical compounds, Itraconazole is not soluble in SC CO_2, therefore, RESS cannot be considered for the formation of Itraconazole. On the other hand, GAS crystallization process is used for substances which have a low solubility in the SCF. In the GAS crystallization process, the substance is first dissolved in an organic solvent and then a SCF which is miscible with the organic solvent is added as an antisolvent to precipitate the substance. Since the objective is to eliminate the use of organic solvents such as dichloromethane, the GAS crystallization process cannot be considered for the preparation of Itraconazole.

Another technique used for particle generation with SCFs is known as particles from gas saturated solutions (PGSS) and has advantages over RESS and GAS processes.[9] In this process, the SCF is first dissolved in a melted substance (or mixture of substances) and the gas saturated solution is later expanded causing supersaturation and fine particle precipitation. The advantage of PGSS over RESS process is that the PGSS process can be used with substances that have low solubility in SCFs, and its advantage over the GAS crystallization process is that no organic solvents are required in the PGSS process.

In this study a new method similar to the PGSS process is used to produce an Itraconazole formulation, which has a higher extent of dissolution in gastric fluid than the conventional product. The main advantage of this method over the conventional method is the use of supercritical carbon dioxide instead of dichloromethane. Dissolution amounts of the products obtained at different operating conditions are measured in gastric fluid and compared to that of the conventional formulation.

EXPERIMENTAL METHOD AND PROCEDURE

The itraconazole formulation used in this study was developed by Kapsi in 1998 and includes five

ingredients: itraconazole, polyethylene glycol 20000 (PEG), hydroxypropyl methylcellulose (HPMC) which is a hydrophilic polymer, Sodium starch glycolate (Explotab), and glycerol which is a wetting agent (1:2.75:0.25:0.25:0.75).[10] PEG 20000 was selected between PEG 3350, 8000 and 20000 because itraconazole dissolution in gastric fluid improved considerably (10%) as the molecular weight of PEG increased. HPMC was found to prevent precipitation of the drug during dissolution. The sodium starch was added to speed up drug release in gastric fluid. The wetting agent was chosen to enhance the solubility of the drug.[10] In this study SC CO_2 was added to the above formulation in order to form a uniform itraconazole solution, which is highly porous when solidified.

A schematic of the SCF experimental apparatus used in this study is shown in Fig. 1. The experimental apparatus consisted of a 260-ml capacity syringe pump and controller system (ISCO 260D), and an ISCO series 2000 SCF Extraction system (SFX 2–10) consisting of a dual-chamber extraction module with two 10-ml stainless steel vessels. Temperature and pressure within the vessels were measured and could be independently adjusted.

First a desired amount of sample (1 to 10 g) including all ingredients (itraconazole, PEG 20000, HPMC, the sodium starch and the wetting agent) was loaded into the cell and well mixed before placing in the extraction chamber. The syringe pump was then filled with carbon dioxide from a supply cylinder. Parameters, such as cell temperature and pump pressure, were set to the desired values. The contents in the cell were mechanically mixed as the temperature approached the desired value. Supercritical carbon dioxide was added to the cell and the system was allowed to reach thermal equilibrium (about 15 minutes). SC CO_2 dissolved in the melted mixture of above ingredients and the solution was allowed to flow into the vial at a rate of 0.5 to 2.0 ml/min. After a desired period of time (10 to 60 minutes), the pressure in the cell was suddenly dropped to atmospheric pressure. This expansion caused supersaturation and possibly generated a more porous product than those obtained by the conventional method. The solution in the cell was cooled in dry ice. There was no secondary solvent removal step required using this method. Therefore, all waste disposal costs were eliminated. The product was ground in a blender (Waring commercial laboratory blender) and particle ranging in size between 0.2–1 mm were sieved through two different meshes. Dissolution profiles of itraconazole release were obtained using the United States Pharmacopoeia (USP) XXII apparatus II (VK 7000®, Vankel Industries, Inc., Edison, NJ). Dissolution media consisted of enzyme-free simulated gastric fluid (pH = 1.4 ± 0.1) at 37°C. In all dissolution measurements 100 mg of Itraconazole was dissolved in 900 ml gastric fluid. The solution was mixed at 100 rpm for 60 minutes. One ml dissolution samples were collected at 5, 10, 20, 30, 45 and 60 minutes through 5 μm filters. These samples were diluted to 10 ml with simulated gastric fluid. Samples of the diluted solutions were analyzed for Itraconazole concentrations using a UV analyzer (Beckman DU-600) at a fixed wavelength of 226 nm.

RESULTS AND DISCUSSION

Ninety percent itraconazole was dissolved in gastric fluid in the conventional itraconazole formulation (Sporanox) after 60 minutes. The dissolution profile of Sporanox is used as reference and dissolution profiles of all products obtained in this study are compared to that of

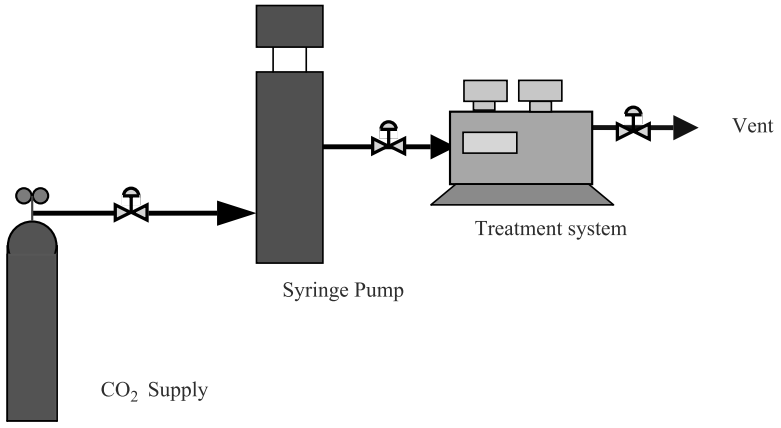

Figure 1. Schematic diagram of experimental equipment.

Sporanox. Better products with higher dissolution and faster drug release than Sporanox were produced in this study. Results obtained from scanning electron microscopy and dissolution measurements are presented here. Effects of SC CO_2, treatment temperature, and treatment time on dissolution profile and morphology of the products were examined.

Effect of Carbon Dioxide

Supercritical carbon dioxide had a significant effect on itraconazole and its dissolution profile. This effect is shown in two ways: the effect of SC CO_2 on particle morphology of the products, and the effect of SC CO_2 and its solvent power on itraconazole dissolution profile.

Effect of SC CO_2 on Particle Morphology of Itraconazole Formulations

Scanning electron microscopic (SEM) photomicrographs of two different samples are shown in Figs. 2 and 3. Both samples were kept at 135°C for 10 minutes. However, the sample in Fig. 2 was without supercritical carbon dioxide and that in Fig. 3 was treated with carbon dioxide at 300 atm. Visual observation confirms that the sample without SC CO_2 results in a solid network consisting of intertwining aggregated cubes (Fig. 2). The morphology in Fig. 3 consists of many thin layers with small pores. The different morphology in Fig. 3 was due to the effect of CO_2 during the treatment and depressurization. Carbon dioxide dissolved in the drug solution and came out of the solution when the pressure was dropped to the atmospheric pressure. The expansion of the drug solution by depressurizing SC CO_2 produced a more porous product than the sample without SC CO_2. BET measurements are needed to quantify the actual surface area of these samples.

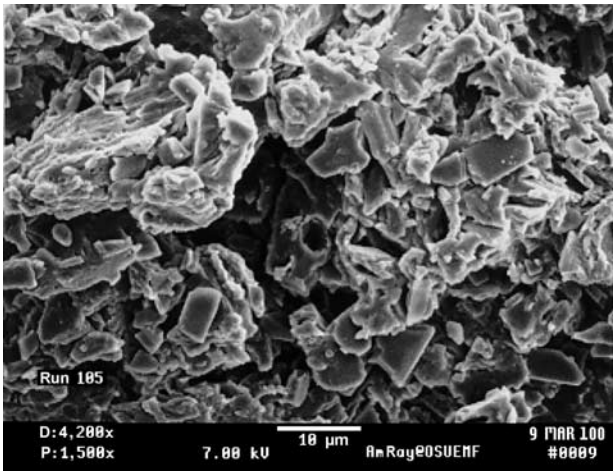

Figure 2. SEM photomicrograph of itraconazole formed at the treatment condition: without SC CO_2, T=135°C and t=10 minutes.

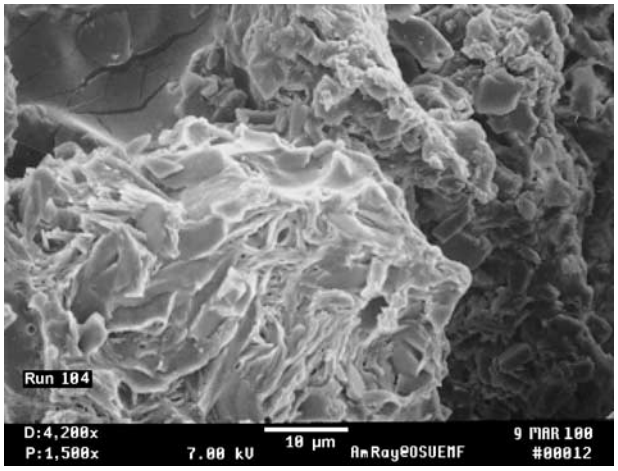

Figure 3. SEM photomicrograph of itraconazole formed at the treatment condition: with SC CO_2 (P=300 atm), T=135°C and t=10 minutes.

Effect of SC CO_2 and Its Solvent Power on Itraconazole Dissolution Profile

Supercritical fluid technology offers a convenient way to change solvating properties from gas-like to liquid-like without changing chemical structure. Supercritical carbon dioxide has some affinity with polar solutes due to its large molecular quadrupole.[11] To see the effect of CO_2 on itraconazole dissolution

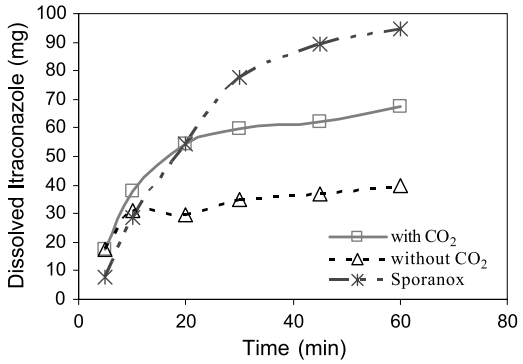

Figure 4. Effect of SC CO_2 on itraconazole dissolution profile. Treatment conditions: with CO_2 (P=300 atm) or without CO_2, T=130°C, t=10 minutes.

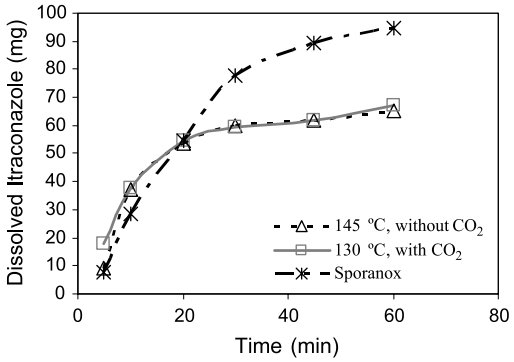

Figure 5. Effect of SC CO_2 on itraconazole dissolution profile. Treatment conditions: with CO_2 (P=300 atm, T=130°C) or without CO_2 (T=145°C), t =10 minutes.

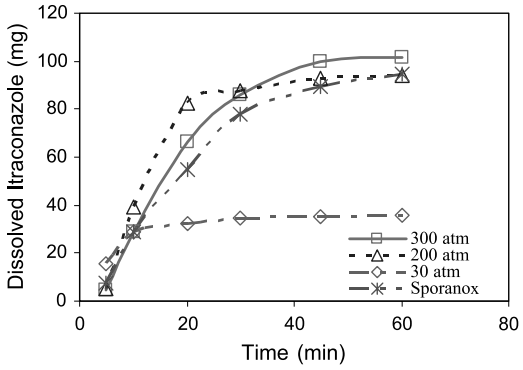

Figure 6. Effect of treatment pressure on itraconazole dissolution profile. Treatment conditions: P=30, 200 and 300 atm, T=135°C, t=30 minutes.

profile, experiments were performed with and without CO_2 at different conditions and the results are presented in Fig. 4. The amount of dissolved drug in gastric fluid increased significantly (40%) in one-hour dissolution experiment with CO_2 at 300 atm compared to runs without CO_2 but at the same temperature (130°C) and treatment time (10 minutes). Results from these dissolution measurements proved that CO_2 enhances the dissolution extent of the product in gastric fluid.

Another way of showing the importance of CO_2 is to look at the temperature needed to obtain the same extent of dissolution with and without CO_2 (Fig. 5). As shown in this figure, almost the same dissolution profiles are obtained for drugs produced with and without CO_2. However, the drug produced with CO_2 requires a 15°C lower temperature than that produced without CO_2. The product from SC CO_2 method was a white porous solid. Yellowish solids were formed when the treatment temperature was higher than 140°C or treatment time was longer than 30 minutes. DSC analysis of these products verified that the drug was decomposed. As higher temperatures (>140°C) result in drug decomposition, the product produced with CO_2 is more favorable since it requires lower temperature than that produced without CO_2.

Products at different treatment pressures were produced in order to see the effect of solvent power of SC CO_2 on itraconazole dissolution profile. Solvent power is the strength of solvent for dissolving solutes. Solvent power increases as pressure increases. Figure 6 presents the dissolved drug as a function of time at different treatment pressures while keeping the temperature and treatment time constant at 135°C and 30 minutes, respectively. Higher operating pressures give higher dissolution amounts. This is probably because the solvent strength increases and more SC CO_2 gets into the drug solution as pressure increases. More SC CO_2 in the drug solution may form a more porous product when expanded, causing higher dissolution of drug in gastric fluid. Results from these figures show that CO_2 and its solvent power are important in producing a product with a high dissolution rate in gastric fluid.

Effect of Treatment Temperature on Itraconazole Dissolution Profile

Dissolved itraconazole as a function of time at various treatment temperatures is shown in Fig. 7. Higher treatment temperatures resulted in products with higher extents of dissolution in gastric fluid. One explanation for the increase in dissolution of drug at higher treatment temperatures is that solubility of itraconazole in the solution may increase at higher

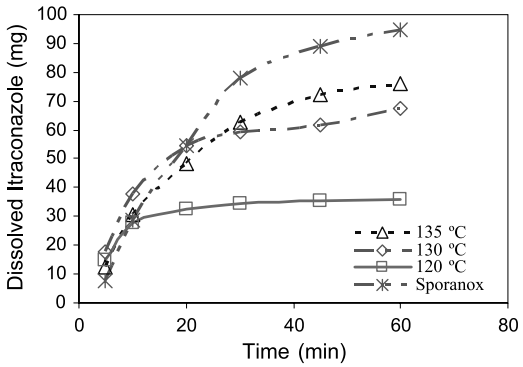

Figure 7. Effect of treatment temperature on itraconazole dissolution profile. Treatment conditions: T=120, 130 and 135°C, P=300 atm, t=10 minutes.

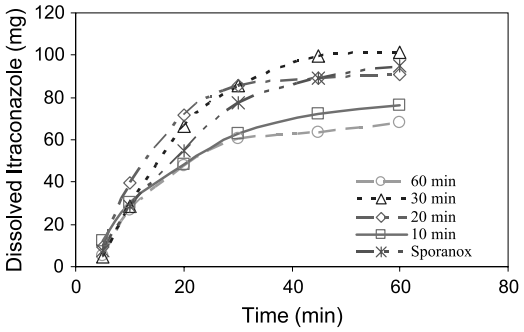

Figure 8. Effect of treatment time on itraconazole dissolution profile. Treatment conditions: t=10, 20, 30 and 60 minutes, T=135°C, P=300 atm.

temperatures. Since temperatures higher than 140°C resulted in decomposition or degradation of drug, the optimum temperature was found to be 135°C.

Effect of Treatment Time on Itraconazole Dissolution Profile

The effect of treatment time on dissolution profile of itraconazole in gastric fluid is shown in Fig. 8. The amount of dissolved itraconazole in gastric fluid increased with treatment time, except for the one-hour treatment time. The product that was treated for one hour was yellowish, representing a possibly decomposed sample due to a long exposure to a high temperature. Therefore, the optimum treatment time that gives a high extent of dissolution without altering the drug composition is 30 minutes.

Figures 4–8 show that the initial dissolution rate of the drug formulated under different conditions is almost the same (approximately 4 mg/min) for the first 10 minutes. The dissolution rate then either slows down or dissolution stops. One explanation for the same initial dissolution rate but different subsequent rates is that some of the formulations may produce different particle size and composition.

CONCLUSIONS

A new method was developed to form itraconazole, a poorly soluble anti-fungal agent, using pure supercritical carbon dioxide, instead of highly regulated organic solvents. The formulation process is easy since the treatment temperature and pressure can be controlled independently and the process can be operated continuously. This method requires no organic solvents and can be used for substances that have low or high solubility in SCFs.

Complete itraconazole dissolution was achieved in one-hour at the treatment condition: T=135°C, P=300 atm, t=30 minutes, with CO_2 flow through the treatment vessel. SC CO_2 improved the dissolution extent of itraconazole in gastric fluid by 23–40%. This increase in the extent of dissolution was due to the solvent power of CO_2 and possibly the higher porosity of the products. Higher pressures result in higher solvent powers, but treatment pressures in excess of 300 atm caused precipitation of drug in gastric fluid, which was observed by a decrease in the extent of dissolution. In order to get the same extent of dissolution, the product that was not treated with SC CO_2 had to be produced at a higher treatment temperature (15°C higher). The treatment temperature also has a significant effect on dissolution results. Treatment at temperatures higher than 140°C may degrade the drug or cause precipitation in gastric fluid. The use of low temperatures (<120°C) resulted in low extents of dissolution of itraconazole in gastric fluid. Therefore, the optimum treatment temperature was found to be 135°C. The treatment time was an important factor in dissolution experiments. At the same treatment temperature and pressure, the product treated for 30 minutes showed 25% higher dissolution than one that was treated for 10 minutes. Although dissolution of drug obtained from this method is only 10% higher than that of conventional methods, the main advantage of this method is that it does not involve the use of toxic organic solvents or detergents.

REFERENCES

1. Gilis, P.M.V.; De Conde, V.F.V.; Vandecruys, R.P.G. Beads Having a Core Coated with an Antifungal and a Polymer. US Patent 5,633,015, 1997.
2. Kiran, E.; Brennecke, J. *Supercritical Fluid Engineering Science, ACS Symposium Series 514*; American Chemical Society: Washington, DC, 1993.
3. Matson, D.W.; Fulton, J.L.; Peterson, R.C.; Smith, R.D. Rapid expansion of supercritical fluid solutions: solute formation of powder, thin films, and fibers. Ind. Eng. Chem. Res. **1987**, *26*, 2298–2306.
4. Gallagher, P.M.; Coffey, M.P.; Krukonis, V.J.; Klasutis, N. Gas antisolvent recrystallization: new

process to recrystallize compounds insoluble in supercritical fluids. In *Supercritical Fluid Science and Technology*; Johnston, K.P., Penninger, J.M.L., Eds.; ACS Symposium Series 406, American Chemical Society: Washington, DC, 1989; 334–354.

5. Mohamed, R.S.; Debenedetti, P.G.; Prud'homme, R.K. Effects of process conditions on crystals obtained from supercritical mixtures. AIChE J. **1989**, *35* (2), 325.
6. Mohamed, R.S.; Halverson, D.S.; Debenedetti, P.G.; Prud'homme, R.K. Solids formation after the expansion of supercritical mixtures. In *Supercritical Fluid Science and Technology*; Johnston, K.P., Penninger, J.M.L., Eds.; ACS Symposium Serier 406, American Chemical Society: Washington, DC, 1989; 355–378.
7. Tom, J.W.; Lim, G.B.; Debenedetti, P.G.; Prud'homme, R.K. Applications of supercritical fluids in the controlled release of drugs. In *Supercritical Fluid Engineering Science, ACS Symposium Series 514*; Kiran, E., Brennecke, J.F., Eds.; American Chemical Society: Washington, DC, 1993; 238–257.
8. Yeo, S.D.; Lim, G.B.; Debenedetti, P.G. Production of microparticulate protein powders using a supercritical fluid anti-solvent. Biotechnol. Bioeng. **1993**, *41*, 341–346.
9. Sencar-Bozic, P.; Srcic, S.; Knez, Z.; Kerc, J. Improvement of nifedipine dissolution characteristics using supercritical CO_2. Int. J. Pharm. **1997**, *148*, 123–130.
10. Kapsi, S. Development of an immediate release formulation of itraconazole. Ph.D. Thesis.; Oregon State University: Corvallis, OR, 1998.
11. Westwood, S. *Supercritical Fluid Extraction and its use in Chromatographic Sample Preparation*; CRC Press Inc., 1993.