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Recrystallization of fluconazole using the supercritical antisolvent (SAS) process

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Abstract

The supercritical antisolvent (SAS) process was used to modify solid state characteristics of fluconazole. Fluconazole was recrystallized at various temperatures (60–80 °C) and pressures (8–16 MPa) using dichloromethane (DCM) as a solvent. Acetone and ethanol were also employed as solvents. The fluconazole polymorphs prepared by the SAS process were characterized by differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM). Furthermore, the equilibrium solubility of the samples in aqueous solution was determined. Fluconazole anhydrate form I was obtained at low temperature (40 °C) and anhydrate form II was obtained at high temperature (80 °C). The variation of pressure during the SAS process may influence the preferred orientation. Anhydrate forms I and II were also obtained using various solvents. Therefore, it was shown that solid state characteristics of fluconazole, including the polymorphic form and preferred orientation, can be controlled by changing operating conditions of the SAS process such as temperature, pressure, and solvent.

Keywords: Fluconazole; Supercritical antisolvent (SAS) process; Polymorphism; Preferred orientation

1. Introduction

Supercritical fluids (SCF) processes have been widely used to crystallize various organic and inorganic compounds (Jung and Perrut, 2001). Particle formation of pharmaceutical compounds is a particularly promising area in which the SCF process could be partially commercialized.

SCF processes in pharmaceutical applications have been developed using supercritical carbon dioxide (SC-CO_2) as a solvent (rapid expansion of supercritical solutions, RESS) or antisolvent (supercritical antisolvent, SAS) in particle formation (Jung and Perrut, 2001; Fages et al., 2004). The use of carbon dioxide (CO_2) is a major advantage of the SCF process, as CO_2 is nontoxic and has mild critical conditions, making it an ideal substitute for organic solvents. Moreover, CO_2 is gaseous at ambient conditions, which simplifies the problem of solvent residues (Fages et al., 2004). SCF processes using SC-CO_2 have been widely used in the pharmaceutical arena with two objectives: micronization and modification of solid state characteristics.

The SAS process is a one-step process that facilitates control of particle formation characteristics and direct formation of dry and fine particles through an increased rate of mass transfer. In addition, the SAS process offers the special advantage that solid state characteristics of a drug can be regulated simply by varying operating parameters, allowing solvent-free particles with desired characteristics to be prepared in a single step. In recent years, the modification of solid state characteristics such as crystal habit, crystallinity, and polymorphism has gained increasing attention in pharmaceutical research and has been successfully achieved through the recrystallization of drug particles using various SAS processes (Beach et al., 1999; Tong et al., 2001; Kordikowski et al., 2001; Velaga et al., 2002; Yeo et al., 2003; Yeo and Lee, 2004; Moneghini et al.,

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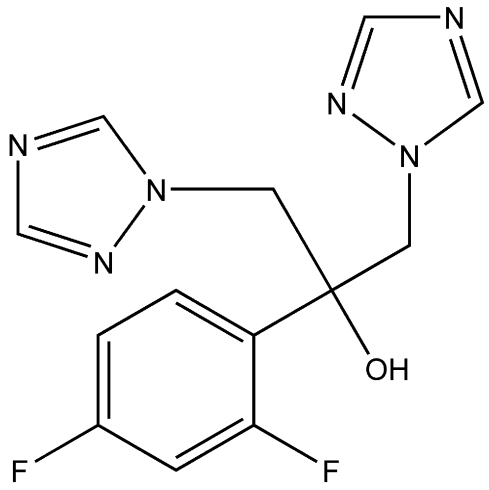

Fig. 1. Chemical structure of fluconazole.

2003). In particular, SCF process operating parameters can be adjusted to vary supersaturation and conditions for nucleation and crystal growth across a wide range. Accordingly, the different crystalline forms of a compound in which the molecules have different arrangements and/or conformations can be controlled to exploit compound polymorphism using the SAS process. Polymorphism is important in pharmaceuticals because different polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility (Grant, 1999).

Fluconazole is designated chemically as 2,4-difluoro-(alpha),(alpha)[1]-bis(1H-1,2,4-triazol-l-ylmethyl) benzyl alcohol (Fig. 1) and is the first of a new subclass of synthetic triazole antifungal agents. Fluconazole is a white crystalline solid which is slightly soluble in water but has high oral efficacy caused by high solubility in gastric juice (Physicians' Desk Reference, 2004). Different polymorphic forms of fluconazole have been prepared by varied experimental conditions and crystallization techniques and then evaluated by solid state characterization methods such as differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FT-IR) (Lo et al., 1994; Gu and Jiang, 1995; MacSweeney, 1999; Dash and Elmquist, 2001; Janos et al., 2001; Alkhamis et al., 2002; Desai et al., 2003; Caira et al., 2004). Anhydrate forms I and II have been prepared and characterized by Alkhamis et al. (2002).

There has been no published research involving the control of solid state characteristics of fluconazole using the SAS process. Consequently, we investigated the solid state characteristics of fluconazole by varying SAS operating conditions such as temperature, pressure, and type of solvent. We particularly focused on the resulting polymorphisms. Fluconazole particles obtained by the SAS process at various conditions were identified using DSC, thermogravimetry analysis (TGA), PXRD, FT-IR, and scanning electron microscopy (SEM), and were compared with polymorphs described in the literature (Alkhamis et al., 2002). Furthermore, the solubility of fluconazole polymorphs was determined in deionized water at 25 °C.

2. Materials and methods

2.1. Materials

Raw fluconazole (99.0% purity) was kindly provided by Hwail Pharm. Co., Ltd. (Korea). CO_2 was 99.9% pure (Hanmi Gas, Korea). All other chemicals were of reagent grade and used without further purification.

2.2. Recrystallization of fluconazole using the SAS process

We used the experimental apparatus of the SAS process as reported by Won et al. (2005). First, 0.5 mol% drug solution was prepared in dichloromethane (DCM). SC-CO_2 was pumped to the top of the precipitation vessel (internal volume, 1908 cm^3; i.d., 9 cm; length, 30 cm) through the outer capillary of the two-flow coaxial spray nozzle (Sonimist® HSS-600-1, Misonix Inc., NY, USA) by an ISCO syringe pump (Model 260D, USA). Once the precipitation vessel reached steady state (above critical temperature and pressure), the drug solution was introduced into the vessel by an HPLC liquid pump (NP-AX-15, Nihon Seimitsu Kagaku Co. Ltd, Japan) through the two-flow coaxial spray nozzle. Meanwhile, the SC-CO_2 continued to flow through the vessel to maintain the steady state as precipitates were collected on the wall and bottom of the vessel. The flow rates of CO_2 and drug solution were 40 and 3.5 ml/min, respectively. Residual solvent (mixture of SC-CO_2 and organic solvent) was drained out of the precipitation vessel by the backpressure regulator (Tescom, model 26-1723-24-194, USA). After complete delivery of the drug solution into the precipitation vessel, SC-CO_2 continued to flow into the vessel for an additional 60 min to remove residual solvent from precipitated particles before slowly dropping to atmospheric pressure. Temperature and pressure for recrystallization ranged from 40 to 80 °C and 8 to 12 MPa, respectively. Further, the SAS experiments at 40 °C and 8 MPa were carried out with 0.2 mol% drug solution in either ethanol or acetone as a solvent. Finally, the precipitation vessel was depressurized to atmospheric pressure and precipitated particles were collected and kept in an airtight container at a temperature not exceeding 25 °C.

2.3. Solid state characterization

2.3.1. Thermal analysis

DSC samples were analyzed on a DSC S-650 (Scinco, Ltd., Korea). Temperature and enthalpy were calibrated with indium (melting point = 156.6 °C) and zinc (melting point = 419.5 °C) standards at a heating rate of 5 °C/min. Samples (1–2 mg) were accurately weighed and sealed in aluminum pans and an empty sealed pan was used for reference. Measurements were performed at a heating rate of 1 °C/min under a nitrogen purge with a flow rate of 20 ml/min. TGA was carried out using a 2940TMA (TA instrument, USA). Samples weighing 2–3 mg were heated at a rate of 10 °C/min under a nitrogen purge.

2.3.2. Powder X-ray diffraction analysis

PXRD patterns were performed with a Rigaku powder X-ray diffraction system (Model D/MAX-2200 Ultima/PC, Japan)

using Ni-filtered Cu Kα radiation. The samples were run over the most informative range, which was from 5 to 35° 2θ. The step scan mode was performed with a step size of 0.02° at a rate of 1.2 step/s.

2.3.3. Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectroscopy was conducted on an FT-IR spectrometer (Bruker, FT-IR Tensor 27, Germany) using the attenuated total reflectance method. The scanning range was 600–3200 cm^{-1} and the resolution was 4 cm^{-1}. Thirty-two reference scans were done.

2.3.4. Scanning electron microscopy

Individual particle shape was examined by SEM microscope (XL30SFEG, Philips, Netherlands). Particles were coated with gold and palladium using a vacuum evaporator and examined using SEM at a 10-kV accelerating voltage.

2.4. Equilibrium solubility test

The equilibrium solubilities of raw fluconazole and fluconazole polymorphs prepared by the SAS process under various experimental conditions were measured in deionized water at 25 °C. An excess amount of sample was added to 10 ml of deionized water in screw-top bottles. The screw-top bottles were sonicated for 10 min. They were kept in a constant-temperature shaking bath maintained at 25 ± 0.5 °C until reaching equilibrium (3 days). A portion of solution was withdrawn and then filtered through a 0.45-μm membrane (6784 1304 PTFE, Whatman, USA). The concentration of fluconazole was determined at a wavelength of 262 nm using a UV spectrophotometer (Beckman, DU-650, USA). The particles harvested at the end of each solubility run were checked for polymorphism by DSC and FT-IR as described above.

3. Results and discussion

3.1. Recrystallization of fluconazole using the SAS process

Table 1 shows the approximate product yield by the SAS process using DCM as a solvent at various conditions (40–80 °C and 8–16 MPa). Particles were obtained at 8 MPa and all temperatures investigated. As soon as drug solution was injected into the precipitation vessel at 8 MPa, the supercritical solution became cloudy and nucleation occurred. In contrast, neither nucleation nor particle precipitation was observed during injection of drug solution and removal of residual solvent at 16 MPa. However, nucleation was observed at around 12.6 MPa during the depressurization process. This may be due to the increased solubility of fluconazole in SC-CO_2 at high pressures, resulting in complete extraction of both solvent and drug and a reduction in product yield. This hypothesis was confirmed by the presence of fluconazole collected at the back pressure regulator (Velaga et al., 2002).

Table 1
Recrystallization of fluconazole under various SAS experimental conditions (CO_2 flow rate of 40 ml/min and drug solution injection rate of 3.5 ml/min)

Pressure (MPa)	Temperature (°C)		
	40	60	80
8	P (25%[a])	P (55%)	P (95%)
12	NP[b]	P (25%)	P (60%)
16	NP	NP	NP

[a] Approximate product yield shown in parentheses.
[b] NP: no product.

The product yield increased with increasing temperature from 40 to 80 °C at constant pressure. Increased solubility of organic solvent in SC-CO_2 at high temperatures may have caused faster extraction of the solvent and the associated increased precipitation of drug (Lora et al., 2000; Shekunov et al., 2001; Fages et al., 2004).

No mass loss was observed for the two polymorphs of fluconazole in TGA curves (Fig. 2). As a result, we conclude that differences of solid state characteristics between fluconazole polymorphs are not due to the solvates.

3.1.1. Influence of temperature

The DSC thermogram (Fig. 3(a)) of irregularly shaped raw fluconazole (Fig. 4(a)) showed two endothermic peaks. The first broad peak near 100 °C is attributed to dehydration of the crystal, and the temperature agrees with the boiling point of water. The second endothermic peak at 139.2 °C corresponds to the

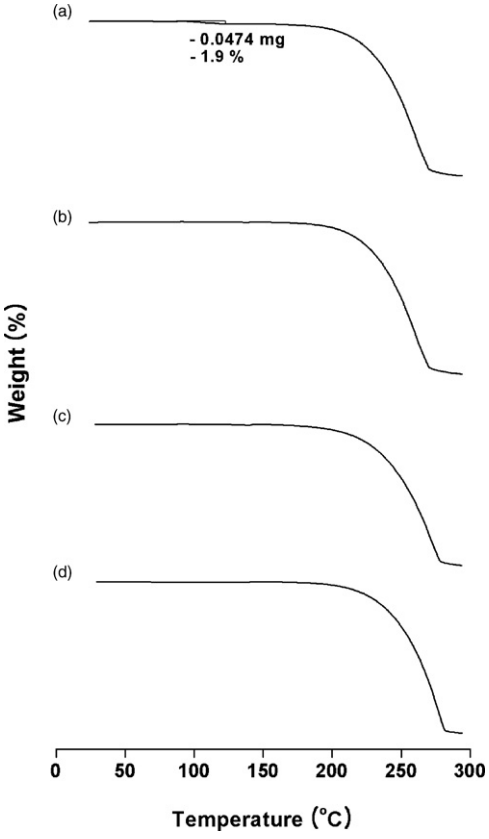

Fig. 2. TG curves of fluconazole before and after the SAS process: (a) raw fluconazole, (b) anhydrate form I prepared at 40 °C and 8 MPa, (c) anhydrate form II prepared at 80 °C and 8 MPa, and (d) anhydrate form II prepared at 80 °C and 12 MPa.

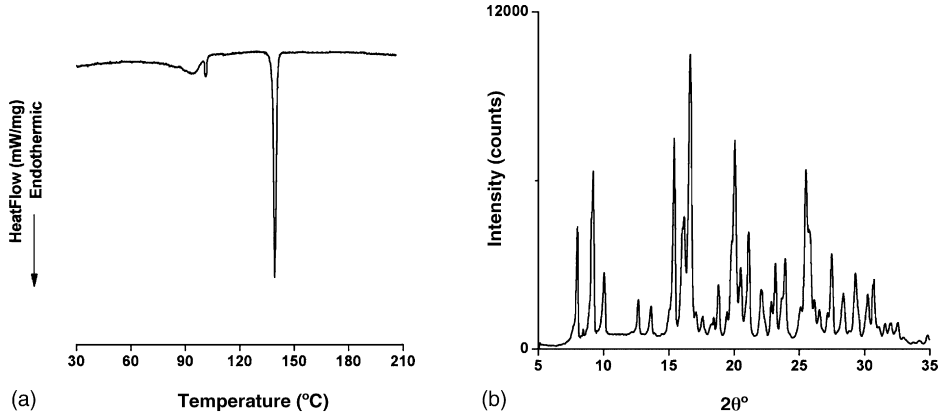

Fig. 3. DSC thermogram (a) and PXRD pattern (b) of raw fluconazole.

melting point of the crystal. Additionally, the FT-IR spectrum (Fig. 5 and Table 2) of raw fluconazole, which has a solvent peak at 3155.3 cm^{-1}, was very similar to that of the monohydrate reported in the literature (Alkhamis et al., 2002; Caira et al., 2004). At first it was thought that the raw fluconazole may be the monohydrate. To confirm this, the TGA curve (Fig. 2) and PXRD pattern (Fig. 3(b)) of raw fluconazole were compared with the results of the monohydrate in the literature (Alkhamis et al., 2002; Caira et al., 2004). The TGA curve (Fig. 2) of raw fluconazole yielded a 1.81% weight loss in the temperature range of 100–130 °C, which corresponds to the boiling point of water. From the information given about the molecular weights of both water and fluconazole, and the percent weight loss, it was determined that the raw fluconazole did not solely consist of a monohydrate (Alkhamis et al., 2002; Caira et al., 2004). Furthermore, the PXRD pattern (Fig. 3(b)) of raw fluconazole presented characteristic peaks of both monohydrate and anhydrate form I. Consequently, the raw fluconazole was identified as a mixture of monohydrate and anhydrate form I.

On the other hand, particles prepared by the SAS process at 80 °C (8 MPa) were needle-like with rounded edges (Fig. 4(c)). The DSC thermogram showed an endothermic peak (T_{m2} = 136.9 °C) corresponding to the melting temperature of the unstable form, an exothermic peak (T_c = 138.1 °C) attributed to recrystallization (Clas et al., 1999) of the unstable form, and an endothermic peak (T_{m1} = 139.5 °C) (Fig. 6) corresponding to the melting temperature of the stable form. In addition, the PXRD pattern (Fig. 7) of this sample was consistent with anhydrate form II (Alkhamis et al., 2002). Therefore, we concluded that the polymorph prepared by the SAS process at 80 °C (8 MPa) was unstable anhydrate form II, as described in the literature (Alkhamis et al., 2002). Interestingly, particles with needle-like acicular crystals (Haleblian, 1975) (Fig. 4(b)) were obtained at 40 °C (8 MPa) and the DSC thermogram of

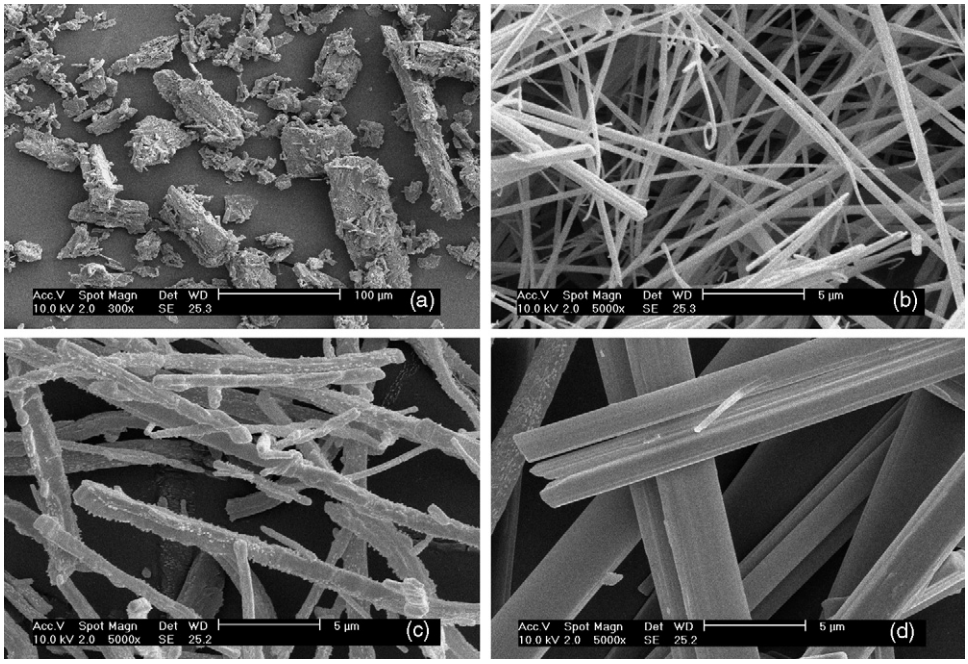

Fig. 4. SEM images of fluconazole before and after the SAS process: (a) raw fluconazole, (b) anhydrate form I prepared at 40 °C and 8 MPa, (c) anhydrate form II prepared at 80 °C and 8 MPa, and (d) anhydrate form II prepared at 80 °C and 12 MPa.

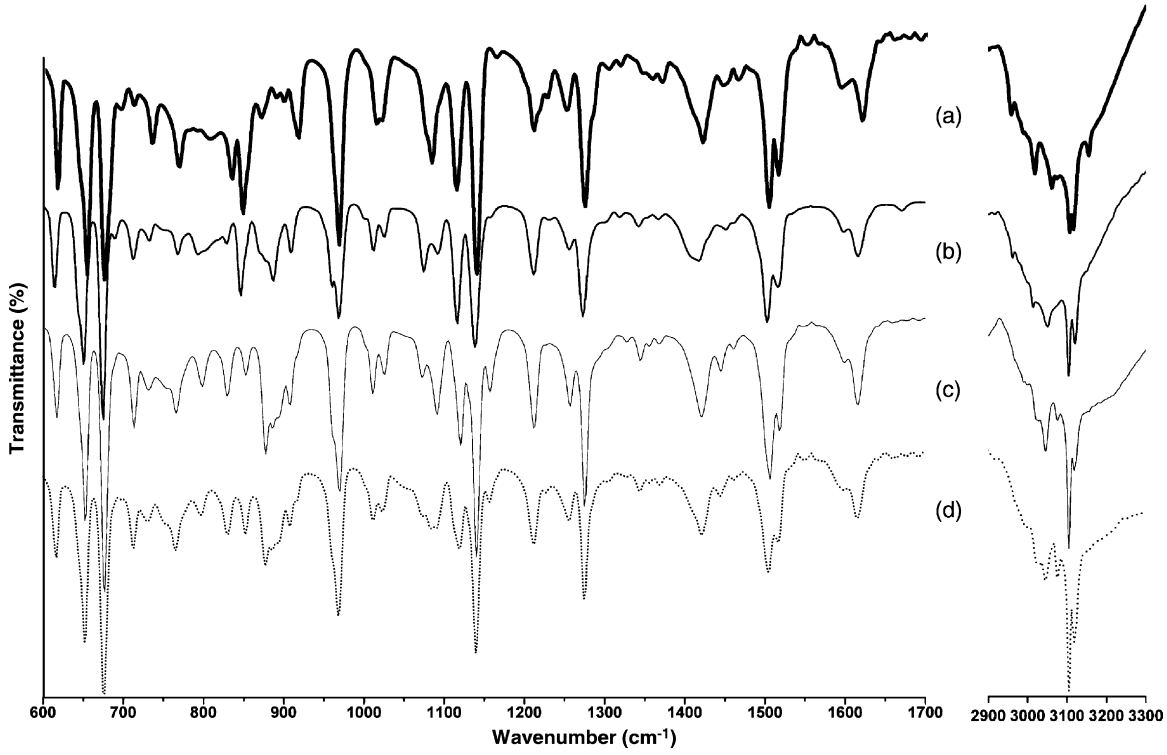

Fig. 5. FT-IR spectra of fluconazole before and after the SAS process: (a) raw fluconazole, (b) anhydrate form I prepared at 40 °C and 8 MPa, (c) anhydrate form II prepared at 80 °C and 8 MPa, and (d) anhydrate form II prepared at 80 °C and 12 MPa.

Table 2
FT-IR peaks of raw fluconazole and anhydrate forms I and II prepared by the SAS process

Assignment	Wavenumber (cm^{-1})			
	Raw	Anhydrate form I	Anhydrate form II[a]	Anhydrate form II[b]
Triazole group				
CH stretch	3116.7	3120.6	3118.6	3118.6
Ring stretch	1502.4	1502.4	1506.3	1504.4
Ring stretch	1419.5	1417.6	1421.4	1421.4
Ring stretch	1249.8	1255.6	1257.5	1255.6
Ring breathing	1137.9	1137.9	1139.8	1139.8
Ring bend	966.3	968.2	970.1	968.2
2,4-Difluorobenzyl group				
CH stretch	3107.1	3105.1	3105.1	3105.1
CH stretch	3060.8	3051.1	3076.2	3076.4
CH stretch	3018.4	3014.5	3045.4	3045.5
C═C stretch	1618.1	1616.2	1616.2	1616.2
CF stretch	1272.9	1272.9	1274.8	1274.8
CH deform	1082.0	1074.3	1072.3	1074.2
Ring breathing	732.9	732.9	731.0	731.0
Propane backbone				
CH_2 stretch	2958.6	2962.4		
CH_2 scissor	1444.6	1450.4	1444.6	1444.6
CH bend		1342.3	1344.3	1344.3
C—C stretch	1112.8	1116.7	1120.6	1118.6
C—(OH) stretch	1020.3	1026.0	1026.0	1024.1
Solvent peak	3155.3			

[a] Anhydrate form II prepared at 8 MPa.
[b] Anhydrate form II prepared at 12 MPa.

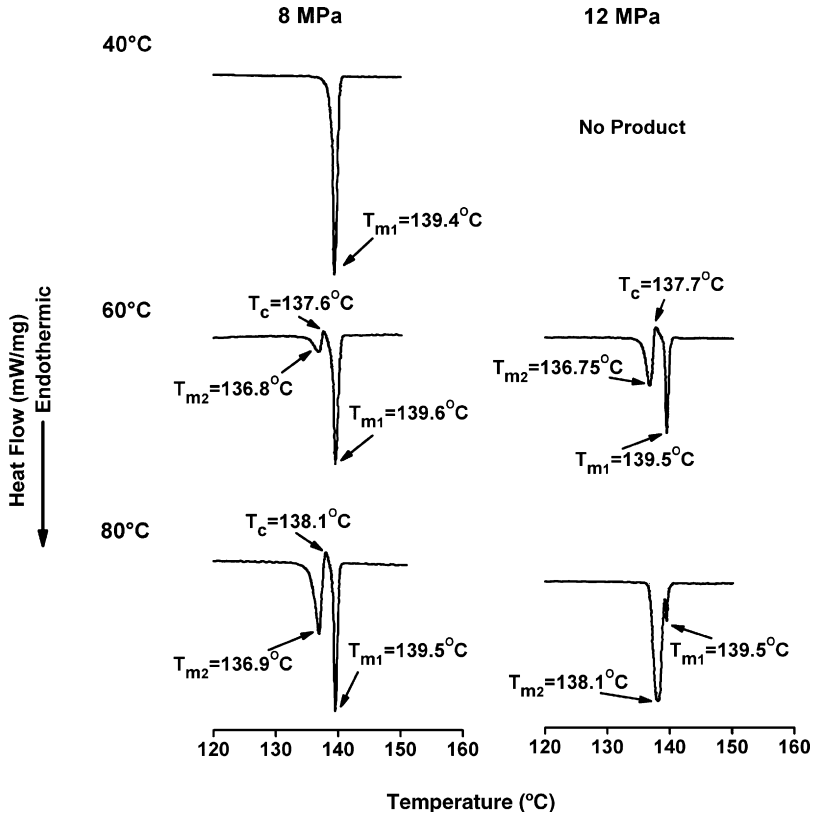

Fig. 6. DSC thermograms of fluconazole prepared by the SAS process at various temperatures (40–80 °C) and pressures (8–12 MPa). T_{m1} and T_{m2} correspond to the melting temperature of anhydrate forms I and II, respectively, and T_c corresponds to the recrystallization exothermic temperature of metastable anhydrate form II.

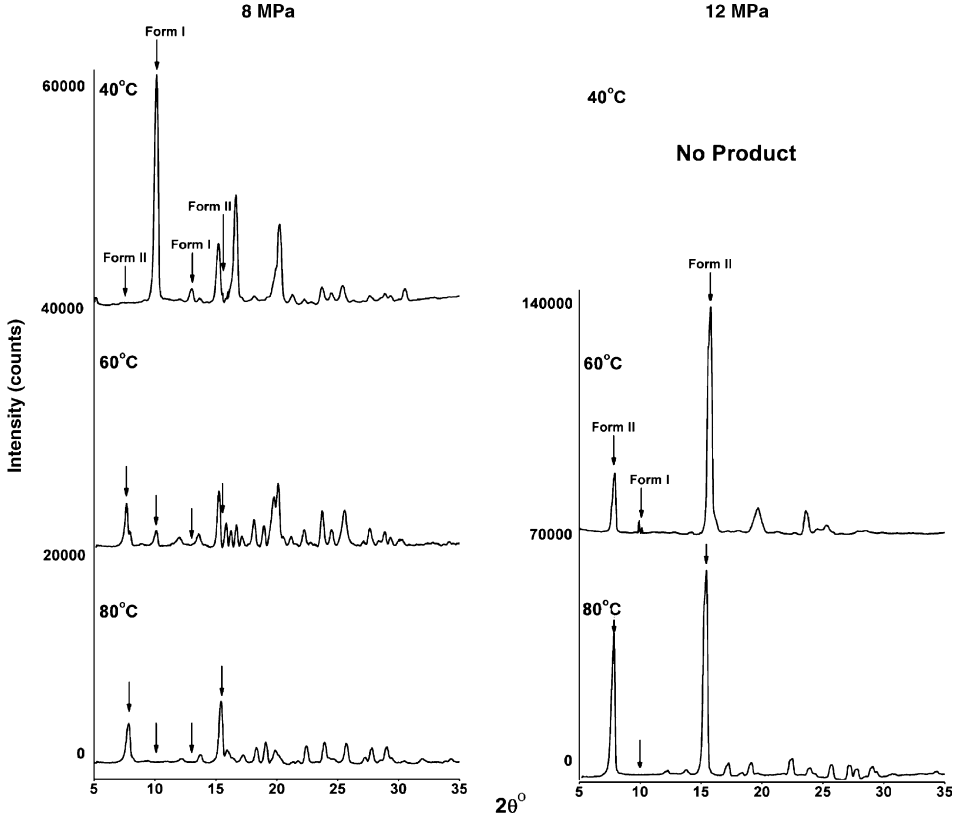

Fig. 7. PXRD patterns of fluconazole prepared by the SAS process at various temperatures (40–80 °C) and pressures (8–12 MPa).

this sample (Fig. 6) exhibited only a single endothermic peak (T_{m1} = 139.4 °C), which corresponds to the melting of the crystal. Furthermore, the PXRD pattern of this sample (Fig. 7) was very similar to that of stable anhydrate form I as reported in the literature (Gu and Jiang, 1995; Alkhamis et al., 2002). Based on these findings, we determined that the sample prepared by the SAS process at 40 °C (8 MPa) was anhydrate form I.

Furthermore, FT-IR analysis over the frequency range of 600–1700 cm^{-1} and 2900–3300 cm^{-1} was carried out to precisely identify anhydrate forms I and II (Fig. 5 and Table 2). The differences in FT-IR spectra between anhydrate forms I and II prepared by the SAS process confirmed the results of DSC and PXRD.

The samples prepared at 60 °C (8 MPa) displayed thermal behavior (Fig. 6) (T_{m2} = 136.8 and T_c = 137.6 °C) similar to anhydrate form II during DSC analysis. However, characteristic peaks corresponding to both anhydrate forms I (at 10.1° 2θ) and II (at 7.8 and 15.4° 2θ) were observed in PXRD analysis (Fig. 7). These results identified the sample as a mixture of anhydrate forms I and II. Collectively, the variation of temperature between 40 and 80 °C resulted in the formation of different polymorphs. This finding was probably due to the increased extraction rate between SC-CO_2 and DCM, resulting in supersaturation at high temperature. An increased extraction rate between SC-CO_2 and organic solvents at high temperature has previously been reported (Lora et al., 2000; Shekunov et al., 2001; Fages et al., 2004).

3.1.2. Influence of pressure

DSC thermogram (Fig. 6), PXRD pattern (Fig. 7) and FT-IR spectra (Fig. 5) of the sample prepared at 12 MPa and 80 °C corresponded to anhydrate form II as classified in the literature (Alkhamis et al., 2002). Although two samples prepared at 8 and 12 MPa (80 °C), respectively, also appeared to be the same anhydrate form II, some differences between the two polymorphs were observed.

First of all, although the PXRD peak locations were identical (2θ degree) between the two anhydrate form II polymorphs, the relative integrated intensity (I/I_0 (%)) of each of the peaks (Table 3) was significantly different. This difference can be explained by preferred orientation, in which the distribution of crystal orientation is nonrandom and crystal may tend to grow greater or lesser degree to some specific orientation (Azaroff, 1968; Yeo et al., 2003). These PXRD patterns show that the orientation of a particular molecular arrangement (corresponding to the peak at 7.8 and 15.4°) was preferred in the crystals prepared at high pressure when compared with the crystals prepared at low pressure. This preferred orientation is frequently observed for crystallites with a needle-like habit (Campbell Roberts et al., 2002). Differences in the crystal habit (Haleblian, 1975) were also observed in SEM analysis (Fig. 4). With increasing pressure at 80 °C, the particles changed from acicular crystals with rounded edges to bladed crystals (flattened acicular crystals). Crystal habit can be influenced by the degree of supersaturation (Haleblian, 1975). The differences in the crystal habit with

Table 3
Powder X-ray diffraction of raw fluconazole and anhydrate forms I and II prepared by the SAS process

Raw		Anhydrate form I		Anhydrate form II[a]		Anhydrate form II[b]	
2θ	I/I_0 (%)[c]	2θ	I/I_0 (%)	2θ	I/I_0 (%)	2θ	I/I_0 (%)
8.0	26.45			7.8	59.20	7.8	57.54
9.2	50.01						
10.0	17.19	10.1	100				
13.6	7.13	13.0	4.36				
15.4	54.27	15.2	37.36	15.4	100	15.4	100
16.1	31.72						
16.6	100	16.6	73.98				
17.6	3.71			17.2	9.08	17.2	4.70
18.4	3.37			18.3	15.74		
18.8	10.71			19.1	20.81	19.1	4.73
20.0	65.64			19.9	21.07		
20.5	10.29	20.2	55.16				
21.1	27.58						
22.1	18.63			22.4	17.74	22.5	7.44
22.9	10.82						
23.1	21.65	23.7	5.07	23.9	31.11	23.9	3.67
23.9	26.12	24.5	3.72				
25.5	98.62	25.4	7.00	25.7	23.05	25.7	5.28
26.5	3.74						
27.5	26.54			27.8	11.45	27.1	11.59
28.4	13.11						
29.3	23.42			29.0	12.23	29.1	8.00
30.2	11.39	30.5	4.95				
30.7	13.05						

[a] Anhydrate form II prepared at 8 MPa.
[b] Anhydrate form II prepared at 12 MPa.
[c] Percentage of relative integrated intensity of each peak.

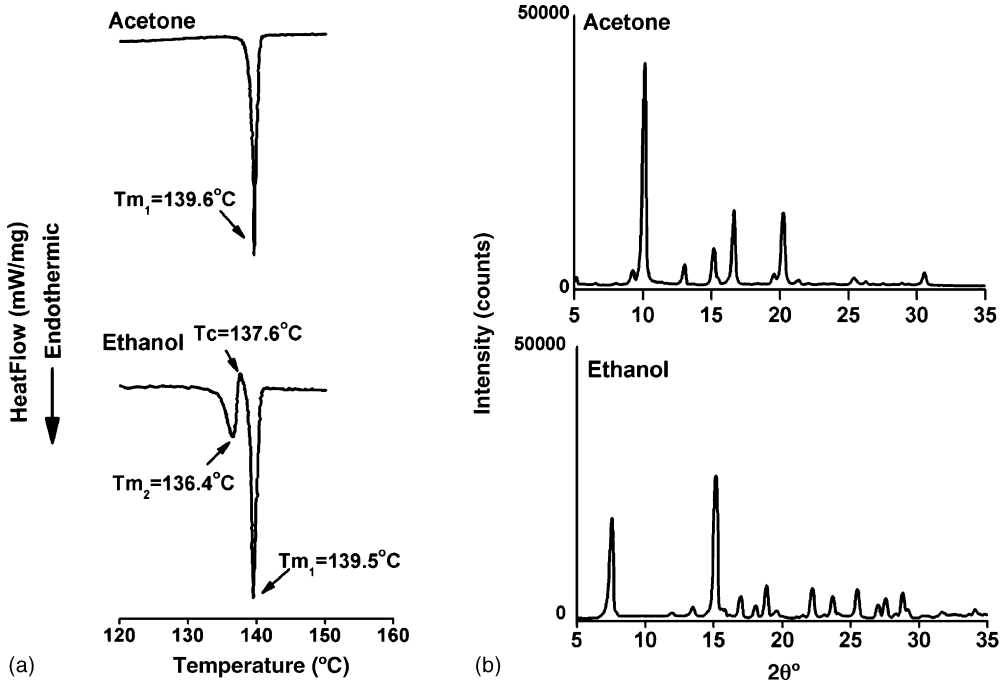

Fig. 8. DSC thermograms (a) and PXRD patterns (b) of anhydrate forms I and II prepared by the SAS process using acetone and ethanol as a solvent at 40 °C and 8 MPa, respectively.

increase in pressure may be caused by the increased extraction of the fluconazole which results in lower degree of supersaturation. These results show that pressure selection in the SAS process can control the preferred orientation of the forming crystals.

3.1.3. *Influence of solvent*

It was surprising that the different polymorphs could be obtained simply by choice of solvent. The samples prepared by the SAS process at 40 °C and 8 MPa using acetone or ethanol as a solvent were identified as anhydrate forms I and II, respectively, by DSC and PXRD analysis (Fig. 8). The choice of organic solvent is, therefore, very important for the control of crystallization of fluconazole polymorphs because the type of organic solvent may affect supersaturation during the SAS process.

Table 4
Solubility and polymorphic forms of fluconazole prepared by varying SAS processing conditions (CO_2 flow rate of 40 ml/min and drug solution injection rate of 3.5 ml/min; solubility data in deionized water at 25 °C, $n = 3$)

Solvent	Pressure (MPa)	Temperature (°C)	Polymorphic forms	Solubility (mg/ml) ± S.D.
DCM	8	40	I	5.25 ± 0.08
DCM	8	60	I + II	5.38 ± 0.04
DCM	8	80	II	5.51 ± 0.10
DCM	12	40	NP[a]	
DCM	12	60	I + II	5.34 ± 0.06
DCM	12	80	II	5.39 ± 0.12
DCM	16		NP	
Acetone	8	40	I	5.22 ± 0.14
Ethanol	8	40	II	5.54 ± 0.08
Raw fluconazole			I + monohydrate	5.25 ± 0.11

[a] NP: no product.

3.2. *Solubility test*

The different polymorphic forms of fluconazole obtained by the SAS process under various experimental conditions and their solubility in deionized water at 25 °C ($n = 3$) are presented in Table 4. All polymorphs showed little difference in solubility and all forms harvested at the end of each solubility test were anhydrate form I. This finding may be due to the easy transformation of unstable anhydrate form II to stable anhydrate form I in contact with water, as has been suggested by Alkhamis et al. (2002).

4. Conclusion

The solid state characteristics of fluconazole have been modified by recrystallization using the SAS process. The polymorphic forms of fluconazole were significantly affected by the experimental conditions of the SAS process, including temperature and type of organic solvent. The variation of pressure resulted in a change of preferred orientation. Furthermore, all polymorphs could be prepared in solvent-free form using a single step operation and a single organic solvent. Therefore, solid state characteristics can be effectively controlled through the recrystallization of fluconazole using the SAS process.

Acknowledgments

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