Polymorph Control of Sulfathiazole in Supercritical CO_2

A. Kordikowski,[1,3] T. Shekunov,[1] and P. York[1,2]

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Purpose. Sulfathiazole was used to investigate polymorph control in liquid and supercritical CO_2. Conventional techniques require a variety of solvents and techniques to produce different polymorphs. The present approach involves precipitation from an organic solution with liquid or supercritical CO_2 using the SEDS™ process.

Methods. Sulfathiazole was precipitated from methanol or acetone solutions. Experiments were carried out within a temperature range of 0–120°C. Composition of the fluid phase was varied between $x(CO_2) = 0.27–0.99$. Pressure was constant at 200 bar. Samples obtained were analyzed using SEM, DSC, and XRPD.

Results. Pure polymorphs were obtained at different temperatures and flow rate ratios of CO_2/solvent. With methanol Form I, III, and IV and their mixtures could be crystallized. With acetone Form I or a mixture of Form I and amorphous sulfathiazole was obtained. The fluid composition was used as a control parameter to define the process areas (T-x diagram) where the pure forms or mixtures of different forms could be obtained.

Conclusions. The experiments enabled the relationship between flow and temperature for each polymorph to be determined. The crystallization method developed proved to be a simple and efficient technique for reproducible and consistent isolation of sulfathiazole polymorphs.

KEY WORDS: sulfathiazole; polymorph; supercritical fluid; enantiotropes.

INTRODUCTION

Polymorph control is paramount in pharmaceutical development. The appearance of a different form can have pronounced effects on shelf life, formulation and processing of a drug. Additionally, different polymorphs can have different bioavailability, activity, and even toxicity (1). Current methods for polymorph control use temperature, rate of crystallization, supersaturation or stirring as control parameters. To obtain a pure polymorph it is necessary to be able to control the supersaturation. Often a polymorph mixture instead of a pure form is obtained. Frequently conditioning, using several precipitation and dissolution steps is employed to achieve crystallization of the desired form (2). Also seeding is used in combination with the other techniques to precipitate the right form. Furthermore, it would be advantageous if the majority of the polymorphic forms could be produced from a single solvent. Nevertheless, polymorph control remains difficult and the crystallization of certain forms is often achieved by trial and error methods only.

The polymorphs of sulfathiazole have been intensively investigated for almost 60 years (3–9). Four polymorphs of sulfathiazole are well known and clearly described in the literature (10–12). Recently a fifth polymorph was discovered using solid-state NMR (13–14) and an amorphous form of sulfathiazole is known (6). Of these five polymorphs four exhibit an enantiotropic relationship, while the fifth is a monotrope. Although a variety of solvent systems have been studied over the past decades, it remains difficult to produce a pure polymorph from a given solvent. Often the desired polymorph contains impurities from at least one other form. Furthermore, each polymorph of sulfathiazole is crystallized from a different solvent or solvent mixture (15). Even then, pure forms are usually only obtained after recrystallization from the same solvent mixture (6,9,15).

In the past, supercritical carbon dioxide has been extensively used to precipitate a variety of materials (16–18) including pharmaceutical compounds. As shown over recent years, supercritical fluid crystallization offers many advantages over conventional crystallization techniques (19). It should therefore also be possible to control the crystallization of polymorphs. Recently, the GAS-process (*G*as *A*nti*S*olvent process) was used to crystallize polymorphs of sulfathiazole (Form I and III) (20). A solution of sulfathiazole was expanded with carbon dioxide applying different temperatures and pressurization modes. Although the crystallization speed and hence, supersaturation could be varied, a mixture of both forms was always obtained. Although the crystallization of enantiotropic polymorphs should almost solely depend on the chosen crystallization temperature, the GAS-process was not able to generate the pure forms. It seemed that nucleation did not occur from a completely controlled environment.

In contrast to other supercritical fluid techniques, the SEDS™ process offers improved control over the crystallization process (19,21). In simple polymorph systems different forms were successfully crystallized as pure and stable forms with the SEDS™ process (22). As far as we are aware, no other supercritical fluid crystallization technique has proved control over the polymorphic state. In this investigation the SEDS™ process (*S*olution *E*nhanced *D*ispersion using *S*upercritical fluids) was used to separate the enantiotropic forms of sulfathiazole to overcome these disadvantages.

EXPERIMENTAL

Chemicals

Sulfathiazole had a purity of 99% and was supplied by Avocado Chemicals (Heysham, UK). Methanol and acetone were more than 99% pure and were supplied by BDH Chemicals (Poole, UK). CO_2 was 99.99% and supplied by BOC (Manchester, UK). All chemicals were used without further purification.

Equipment

Experiments were carried out in a SEDS™ (Solution Enhanced Dispersion by Supercritical Fluids) apparatus for crystallization in supercritical fluids. A schematic representation of the equipment is given in Fig. 1. HPLC pumps P_{1-2} (JASCO, model 986) were used to feed CO_2, solute solution and solvent to the crystallization vessel. CO_2 was supplied

[1] Bradford Particle Design plc, 69 Listerhills Science Park, Campus Road, Bradford BD7 1HR, UK.
[2] Drug Delivery Group, School of Pharmacy, University of Bradford BD7 1DP, UK
[3] To whom correspondence should be addressed.

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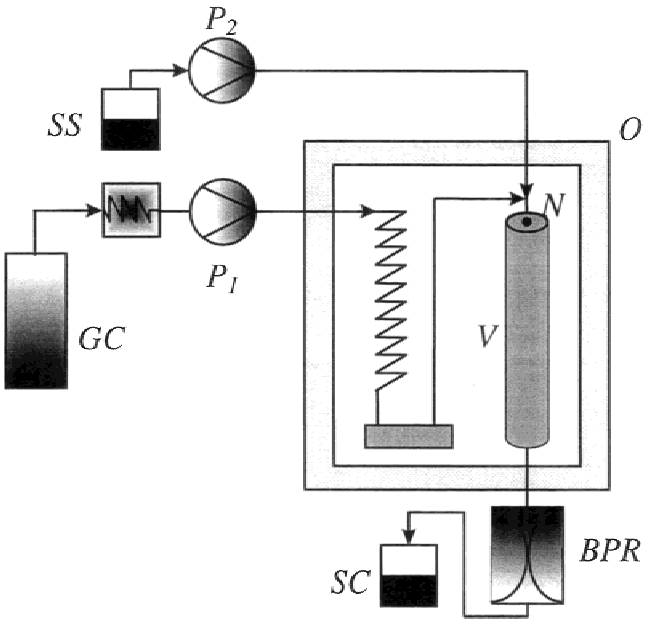

Fig. 1. Schematic representation of the SEDS™ apparatus with: pumps P_1, pulse dampener PD, CO_2 cylinder GC, cooler T, solute solution SS, nozzle N, crystallization vessel V, oven O, backpressure regulator BPR, solvent collection SC.

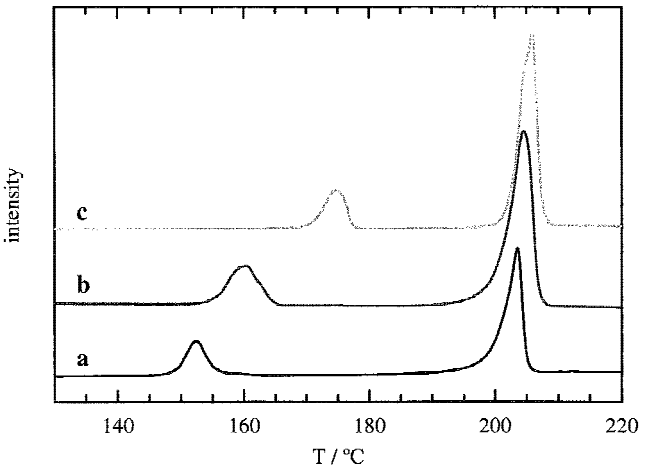

Fig. 2. DSC thermogram of conventionally crystallized sulfathiazole, from acetone (a), methanol (b), and as supplied material (c).

from a high-pressure cylinder *GC,* cooled to approximately –15°C and then pumped into the vessel. Simultaneously, solute solution *SS* was pumped into the crystallization vessel, through a specially designed nozzle *N,* consisting of two coaxial concentric tubes. The crystallization vessel *V* (Keystone, 50 ml) was placed inside an oven *O* (Vindon Scientific, model 210), which controlled the temperature. Pressure was controlled with a backpressure regulator *BPR* (JASCO, model

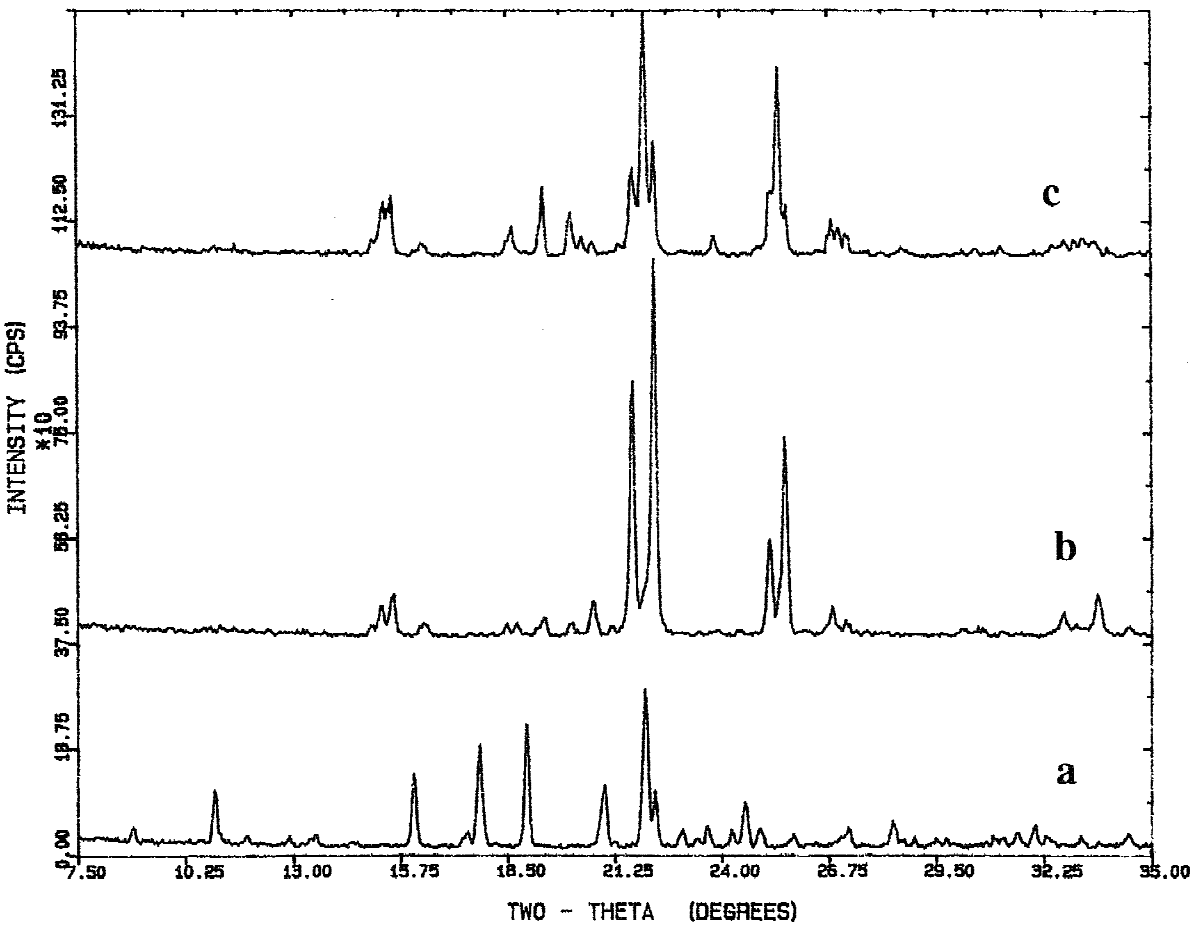

Fig. 3. XRPD Diagram of sulfathiazole polymorphs obtained using the SEDS™ process, Form I (a), Form III (b) and Form IV (c).

880-81). The used solvent was collected *SC* after the back-pressure regulator *BPR*. A more detailed description of the equipment and its operating procedure has been given elsewhere (23,24).

Procedure

The experimental procedure was as follows: A 1% w/v solution of sulfathiazole in methanol corresponding to a mole fraction of $x_{STZ} = 1.59 \cdot 10^{-3}$, or a 1.5% w/v solution of sulfathiazole in acetone corresponding to a mole fraction of $x_{STZ} = 4.30 \cdot 10^{-3}$ was pumped together with CO_2 into the vessel. The flow rate of the solvents varied from 0.2–25.6 ml · min^{-1} per 10 ml · min^{-1} of CO_2, effectively changing the flow rate ratio of solvent/CO_2 by two orders of magnitude. During the experiment, the solvent dissolved in the supercritical CO_2, leaving the solute behind. The precipitated sulfathiazole was collected on a filter plate at the bottom of the vessel. After all solute solution had been fed into the vessel, the apparatus was flushed with pure CO_2 for 15 min to remove solvent traces present in the vessel. Temperatures for the crystallization ranged from 0–120°C. Pressure was kept constant at 200 bar to provide a dense supercritical medium at all temperatures. Temperature during the crystallization was constant to ± 0.5°C, and pressure constant within 1 bar.

Additionally, sulfathiazole was crystallized from pure methanol and acetone to provide a reference for the crystallization from supercritical CO_2. To obtain saturated solutions (1% (w/v) in methanol and 1.5% (w/v) in acetone), 0.1 g of sulfathiazole were dissolved in 10 ml methanol, and 0.3 g of sulfathiazole were dissolved in 20 ml acetone. Both solutions were slowly evaporated to dryness at room temperature (23°C). The crystals were harvested and investigated in the same way as the SEDS™ samples.

Analysis

Samples were analyzed using X-ray powder diffraction (XRPD) using a D-5000 diffractometer (Siemens, Germany). For each sample data were collected between 2Θ angles of 7.5 and 35. Individual samples were carefully filled into a standard measuring cell avoiding grinding of the sample.

Samples were also investigated by differential scanning calorimetry (DSC) using a Mettler M3 system. DSC samples had a typical weight of 2–4 mg. A temperature program with a ramp of 20°C · min^{-1} from 50 to 225°C was used for all samples. Additionally, a nitrogen purge gas flow of 20 ml · min^{-1} was used. Melting or transition temperatures were determined as onset of the endotherm. The error in transition temperature was ± 0.5°C. Transition enthalpies (ΔH^{x-y}) were determined by integration of the endothermic peaks with an error of ± 1.5 kJ · mol^{-1}.

RESULTS AND DISCUSSION

Conventional Crystallization

Sulfathiazole was crystallized from pure acetone and methanol to obtain reference material. From pure acetone the melting diagram showed two endotherms at $T_{IV\text{-}I}$ = 149°C and $T_{I\text{-}L}$ = 200°C (Fig. 2a). The endotherm at low temperature is identical to the transformation of Form IV into Form I (8). At higher temperatures the melting of Form I is observed. The transition enthalpies were found to be $\Delta H^{IV\text{-}I}$ = 8.6 kJ · mol^{-1} and $\Delta H^{I\text{-}L}$ = 26.1 kJ · mol^{-1}. The occurrence of Form IV was confirmed by the X-ray pattern (Fig. 3c).

From methanol, the DSC diagram exhibited two endotherms at $T_{IV\text{-}I}$ = 155 and $T_{I\text{-}L}$ = 200°C (Fig. 2b). Enthalpies for the individual peaks were within the error of those for the material crystallized from acetone. A close investigation of the DSC trace from methanol shows a very small endotherm for the transition of Form III into Form I at 170°C, confirming literature data suggesting that sulfathiazole crystallizes as a mixture consisting predominantly of Form IV (6,8).

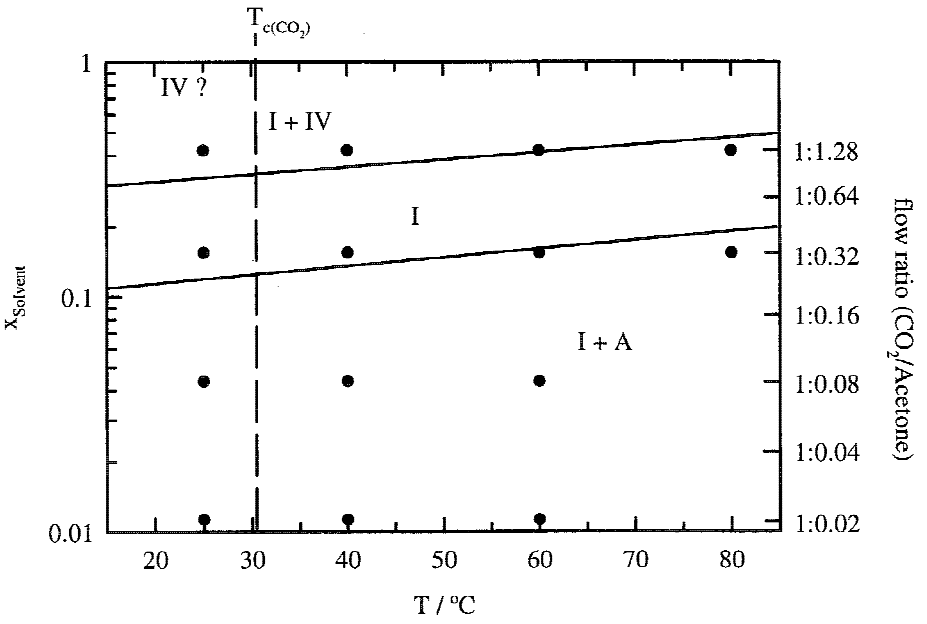

Fig. 4. Polymorphs of sulfathiazole crystallized from acetone using the SEDS™ process applying temperature and flow variation. Regions of stability for pure forms and mixtures are separated by lines.

Additionally the raw material was investigated. The DSC showed an endotherm at T_{III-I} = 171°C with a transition enthalpy ΔH^{III-I} = 7.3 kJ · mol^{-1}, proving that the starting material consisted solely of polymorph III (Fig. 2c). These values are identical to literature values given by Lagas *et al.* (6).

SEDS™ Crystallization from Acetone

In the SEDS™ experiments a saturated solution of sulfathiazole in acetone (1.5% (w/v)) was used. The temperature was raised from 20–80°C in an attempt to obtain as many of the four enantiotropic forms of sulfathiazole as possible. The flow rate of acetone was changed from 0.2–12.8 ml · min^{-1} per 10 ml · min^{-1} of CO_2, effectively varying the mole fraction of acetone in the mixture from $x_{acetone}$ = 0.01–0.42. Pressure was kept constant at 200 bar. Recovery rates of the crystalline material ranged from 85–95% depending on the CO_2/solvent ratio. Varying composition and temperature caused changes in the polymorphic form. Stability zones for different forms were determined using XRPD and DSC data obtained for the samples. Figure 4 shows that at low mole fractions ($x_{acetone}$ ~ 0.01–0.15) mixtures of Form I and amorphous sulfathiazole were obtained, almost regardless of the operating temperature. In the SEM photograph (Fig. 5a) spherical particles can be seen, which indicate a high amorphous content of the sample. The XRPD pattern for this sample exhibited a very low signal to noise ratio also indicative for a high amorphous content. Increasing the flow of acetone ($x_{acetone}$ ~ 0.15) enabled to obtain polymorph I (Fig. 5b). The XRPD and DSC spectra for Form I obtained under these conditions (Fig. 3a, 6a) equate to those found in the literature (6,8). Increasing the acetone flow further ($x_{acetone}$ > 0.4) led to a transition zone between Form I and Form IV. This transition zone has to border to a zone of pure polymorph IV, because sulfathiazole crystallizes as Form IV from pure acetone. The outline of this transition zone could not be determined experimentally because the flow rates of acetone needed were not achievable with the current experimental set-up.

From the four possible enantiomorphs only amorphous sulfathiazole and Forms I and IV could be crystallized from acetone using supercritical CO_2. This reflects earlier results by Anwar *et al.* (15) using pure acetone alone. Although Form I and Form IV are thermodynamically and crystallographically very different, the operating temperature of the supercritical fluid mixture did not have any significant effect. By contrast, the appearance of both polymorphs and the amorphous form could be controlled kinetically by varying the acetone flow relative to the CO_2 flow. Further, no difference between liquid and supercritical CO_2 could be seen. The operating pressure (200 bar) is significantly higher than the mixture critical pressure of the CO_2/solvent system. Therefore, the density difference between a near-critical and supercritical fluid close to the critical temperature of CO_2 is negligible and does not manifest itself in differences in the crystallization process.

SEDS™ Crystallization from Methanol

SEDS™ crystallizations from methanol also used a saturated solution (1% (w/v)). Temperature was changed from 0–120°C. The flow rate of methanol was changed from 0.2–25.6 ml · min^{-1} per 10 ml · min^{-1} of CO_2, changing the mole fraction of methanol in the mixture from $x_{methanol}$ = 0.02–0.72. Pressure was kept constant at 200 bar. Recovery rates of the crystalline material ranged from 75–95% depending on the CO_2/solvent ratio. Like with acetone, stability regions for the different forms were determined using XRPD and DSC data. Figure 7 shows that at low temperatures only polymorph IV was obtained. In the SEM photograph (Fig. 8c) regular hexagonal prisms with a diameter of up to 20 μm can be seen.

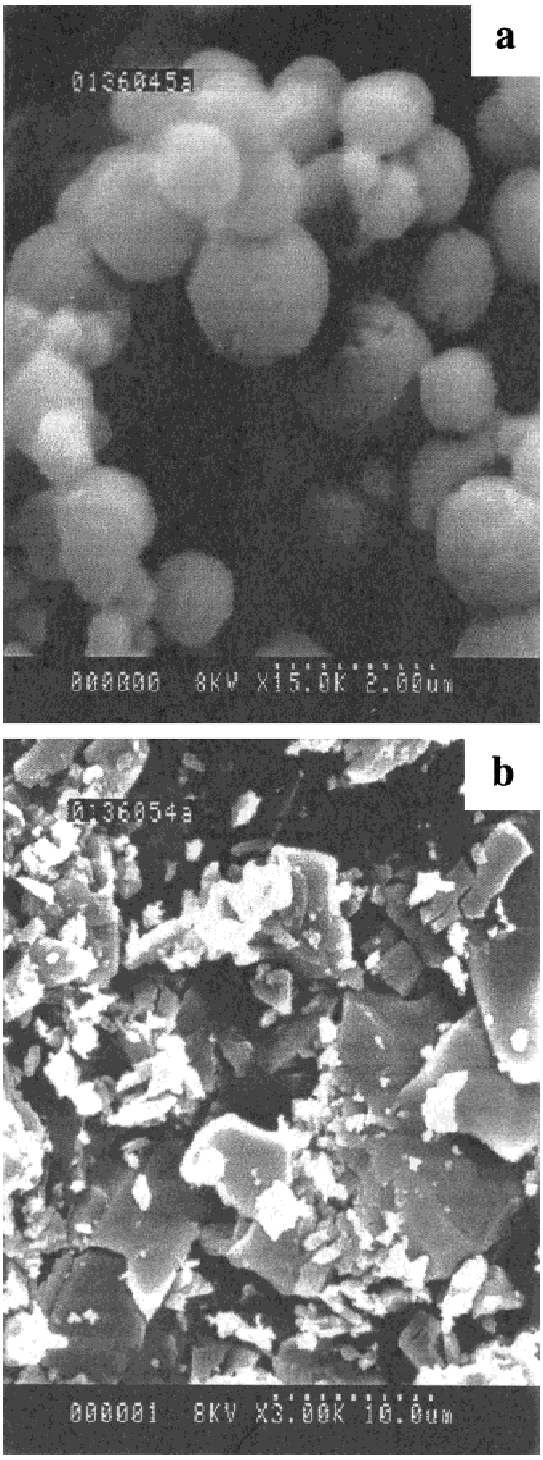

Fig. 5. SEM photographs of SEDS™ crystallized sulfathiazole from acetone, amorphous (a) and Form I (b).

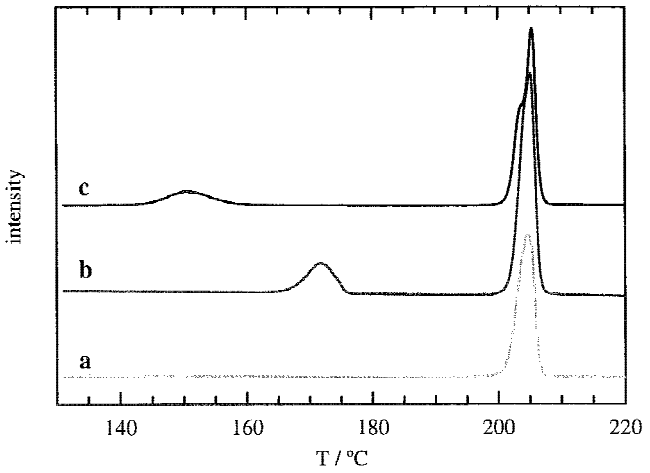

Fig. 6. DSC thermogram of SEDS™ crystallized sulfathiazole from methanol, Form I (a), Form III (b), and Form IV (c).

Thermal analysis of samples obtained at 0°C showed an endotherm at $T_{IV\text{-}I}$ = 144.5°C being the transition of Form IV into Form I with an enthalpy of $\Delta H^{IV\text{-}I}$ = 8.2 kJ · mol^{-1} (Fig. 6c) comparable to the literature value. Theses findings were confirmed by the XRPD pattern (Fig. 3c).

At temperatures above 80°C Form I of sulfathiazole was crystallized as small fused lumps shown in Figure 8a. The XRPD pattern (Fig. 3a) was identical to the literature spectrum (8). For SEDS™ produced Form I a melting point $T_{I\text{-}L}$ = 200.9°C with an enthalpy of $\Delta H^{I\text{-}L}$ = 27.5 kJ · mol^{-1} was found (Fig. 6a), which is identical to the literature values $T_{I\text{-}L}$ = 201°C and $\Delta H^{I\text{-}L}$ = 27.7 kJ · mol^{-1} (6). Bordering the zones of Form I and IV are regions consisting of mixture of polymorphs. Figure 7 shows that around 30°C a mixture of Form IV and Form III appears, and at temperatures around 60°C a mixture of Form I and Form III exists. Owing to the similarity of the polymorphs, these transition zones are broad compared with the stability zones for the pure forms. Nevertheless, at 40°C pure polymorph III could be produced. The habit of Form III was flat elongated hexagons (Fig. 8b). In the DSC analysis SEDS™ produced Form III showed a solid transition to Form I at $T_{III\text{-}I}$ = 167°C with $\Delta H^{III\text{-}I}$ = 7.5 kJ · mol^{-1} (Fig. 6b). These values are comparable to the literature values (6) of $T_{III\text{-}I}$ = 173.6°C with $\Delta H^{III\text{-}I}$ = 6.87 kJ · mol^{-1}. As with acetone, no difference for crystallizations from liquid or supercritical CO_2 could be seen for reasons explained earlier in this manuscript.

Occurrence of Polymorph V

In this investigation the presence of the new polymorph V was not detected. Form V is very similar to Form III and IV (14) and its habit is yet unknown. We speculate that its habit might be very similar to that of Form III and the phase region facilitating its formation is likely to partially overlap with that of Form III. To date the thermal behavior of Form V is unknown.

Polymorph Control

Figures 5 and 8 show that by choosing proper values of temperature and flow rate a specific polymorph or polymorphic mixture can be crystallized. Furthermore, by increasing the flow rate of solvent the size of the crystals can be manipulated. The SEDS™ process provides a reproducible environment from which crystallization can be performed in a uniform and consistent manner. Therefore, by choosing conditions where a polymorph mixture exists, mixtures with a certain ratio of two forms can also be crystallized consistently. With SEDS™, the least stable enantiotropic polymorph (Form I) is produced at the highest temperature fol-

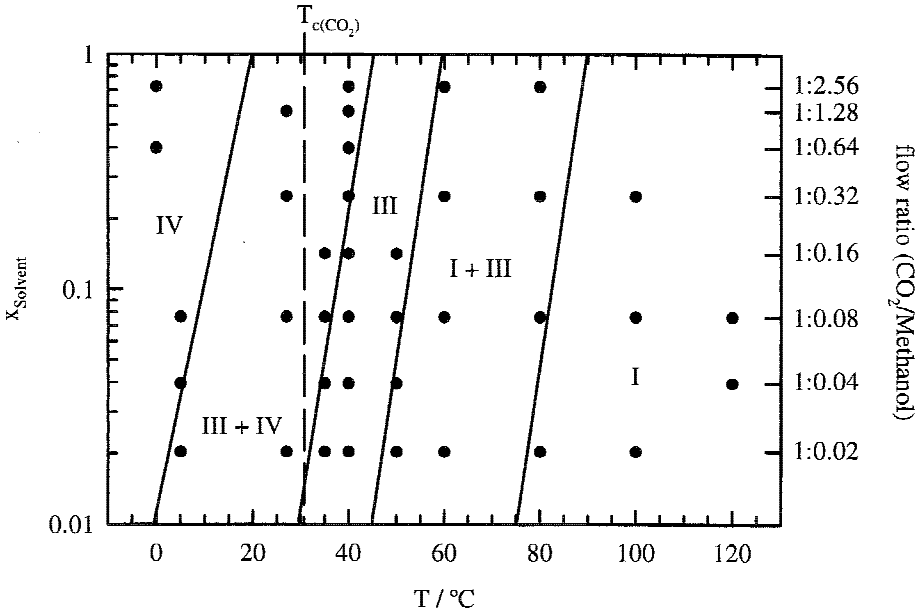

Fig. 7. Polymorphs of sulfathiazole crystallized from methanol using the SEDS™ process applying temperature and flow variation. Regions of stability for pure forms and mixtures are separated by lines.

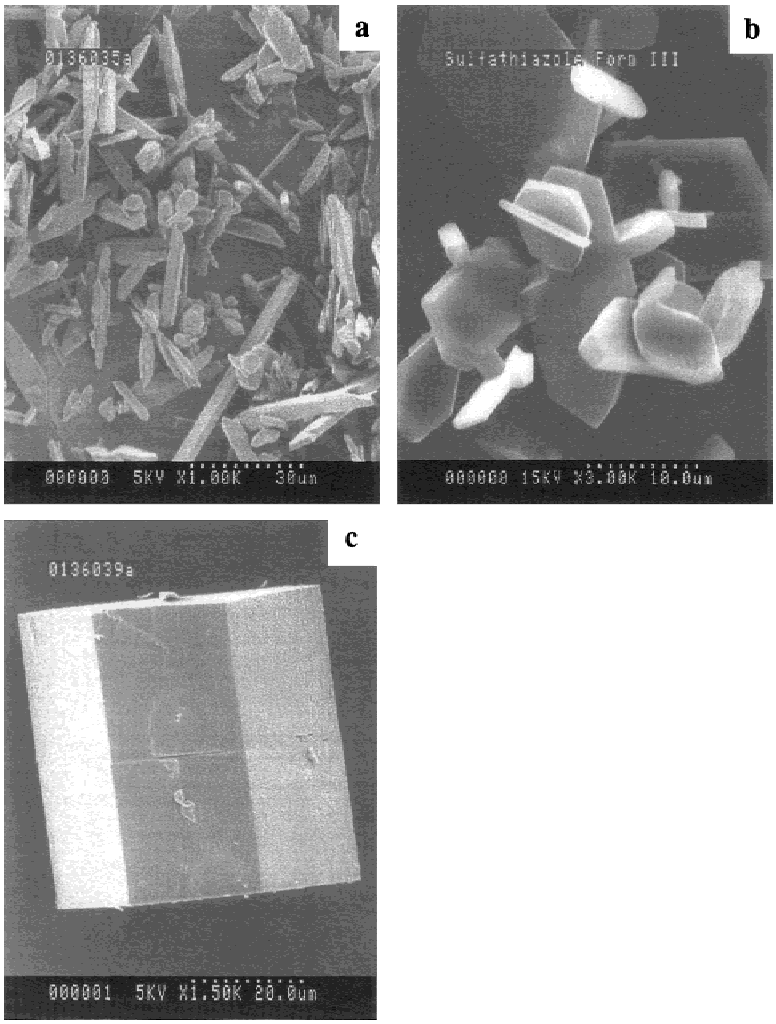

Fig. 8. SEM photographs of SEDS™ crystallized sulfathiazole from methanol, Form I (a), Form III (b) and Form IV (c).

lowed by the formation of Form III and IV at consecutively lower temperatures. This is consistent to conventional crystallizations where the same rank order of polymorphs is found (6,8,9).

It is surprising that the choice of solvent had such a different outcome to the polymorphs produced. With methanol it was possible to control polymorphism by changing the system temperature. Three pure forms could be obtained by choosing the appropriate temperature for all flow rates of methanol. Clearly, with methanol the crystallization is thermodynamically controlled. Comparing a conventional crystallization with the SEDS™ process, it becomes apparent that the transition temperatures between the individual forms are lowered (6,8,9). Figure 7 shows that the transition temperature of Form I to Form III can be lowered by 15°C. A possible explanation for this phenomenon is that precipitation becomes increasingly faster the more CO_2 is present in the mixture. Supersaturation is increased and leads to the formation of the less stable polymorph at lower temperatures. Additionally, the particle size for each form could be controlled by adjusting the flow rate of methanol for a given temperature. Changing the flow rate alone at constant temperature had only a minor effect. Figure 7 shows that a change in composition of almost two orders of magnitude could be counteracted by a change in temperature of less than 10°C.

With acetone, polymorph control by changing the operating temperature was minimal. Figure 4 shows that amorphous sulfathiazole could be obtained at any temperature if the flow rate of acetone was low enough. By contrast, changes in composition at constant temperature had a stronger influence. Increasing the mole fraction of acetone in the mixture led to the formation of polymorph I, and mixture of two forms. Clearly, the crystallization of sulfathiazole from acetone is kinetically controlled. Although composition of the mixture can be changed over two orders of magnitude, the effect in controlling the polymorphism of sulfathiazole stays relatively small. Additionally, the lack of thermodynamic control implies that acetone is interacting in a different way with a sulfathiazole molecule than methanol. Blagden *et al.* showed that depending if a solvent molecule was a hydrogen-bond donor or acceptor different sulfathiazole polymorphs were crystallized/inhibited (25). They speculated that molecular aggregation took place before nucleation, and hence, influenced the polymorphs generated. It is therefore likely that acetone as a hydrogen-bond acceptor interacts differently to methanol with sulfathiazole, and hence, favoring the crystallization of a

certain polymorph. These interactions also seem to play an important role in crystallizations from liquid or supercritical CO_2.

CONCLUSIONS

It has been shown that the generation of sulfathiazole polymorphs can be controlled by crystallization from liquid and supercritical CO_2. No difference in the crystallization behavior of sulfathiazole using liquid or supercritical CO_2 could be found. It was possible to generate three pure polymorphs of sulfathiazole using the SEDS™ process. Crystal habit, X-ray diffraction patterns, and melting points of SEDS™ crystallized polymorphs of sulfathiazole were identical to literature values. Variation of temperature and flow rate proved that thermodynamic or kinetic control could be applied to generate certain forms. The choice of solvent also influenced the crystallization of the polymorphic forms. It was apparent that methanol as a hydrogen bond donor possessed a far greater ability to stabilize different forms of sulfathiazole than acetone. Three polymorphs could be crystallized with methanol by choosing the appropriate temperature. Varying the flow of methanol could influence the particle size of the polymorphs. With acetone it was only possible to generate Form I of sulfathiazole. By fine tuning temperature and flow rates it was also possible to generate mixtures with a defined ratio between the polymorphic forms. Crystallization of polymorphs from near- and supercritical fluids using the SEDS™ process is a viable alternative to conventional methods.

REFERENCES

1. K. Knapman. Polymorphic predictions. *Modern Drug Discovery* **3**:53–57 (2000).
2. H. G. Brittain (ed.), *Polymorphism in Pharmaceutical Solids*, Marcel Dekker Inc., New York, 1999.
3. D. C. Grove and G. L. Keenan. The dimorphism of sulfathiazole. *J. Am. Chem. Soc.* **63**:97–99 (1941).
4. H. Miyazaki. Polymorphism and melting points of sulfathiazoles. *Jap. J. Pharm. Chem.* **19**:133–134 (1947).
5. G. Milosovich. Determination of solubility of a metastable polymorph. *J. Pharm. Sci.* **53**:484–487 (1964).
6. M. Lagas and C. F. Lerk. The polymorphism of sulfathiazole. *Int. J. Pharm.* **8**:11–24 (1981).
7. A. Burger and R. D. Dialer. New investigational results of sulfathiazole polymorphism. *Acta Helv.* **58**:72–78 (1983).
8. J. Anwar, S. E. Tarling, and P. Barnes. Polymorphism of sulfathiazole. *J. Pharm. Sci.* **78**:337–342 (1989).
9. N. Blagden, R. J. Davey, R. Rowe, and R. Roberts. Dissapearing polymorphs and the role of reaction byproducts: the case of sulfathiazole. *Int. J. Pharm.* **172**:169–177 (1998).
10. G. J. Kruger and G. Gafner. The crystal structure of polymorph II of sulfathiazole. *Acta Cryst.* **B27**:326–333 (1971).
11. G. J. Kruger and G. Gafner. The crystal structure of polymorphs I and III of sulfathiazole. *Acta Cryst.* **B28**:272–283 (1972).
12. F. V. Babilev, V. K. Bel'ski, A. Simonov, and A. P. Arzamastev. Polymorphism of norsulfazol. *Khim. Farm. Zh.* **21**:1275–1280 (1987).
13. D. Hughes, M. B. Hursthouse, R. W. Lancaster, S. Taverner, T. L. Threlfall, and P. Turner. How many polymorphs has sulfathiazole? *J. Pharm. Pharmacol.* **49**:S4 20 (1997).
14. D. C. Apperley, R. A. Fletton, R. K. Harris, R. W. Lancaster, S. Taverner, and T. L. Threlfall. Sulfathiazole polymorphism studied by Magic-Angle spinning NMR. *J. Pharm. Sci.* **88**:1275–1280 (1999).
15. J. Anwar and S. Khoshkhoo. Crystallization of polymorphs: The effect of solvent. *J. Phys. D: Appl. Phys.* **26**:B90–B93 (1993).
16. S. Palakodaty, P. York, and J. Pritchard. Supercritical fluid processing of materials from aqueous solutions: The application of SEDS™ to lactose as a model substance. *Pharm. Res.* **15**:1835–1843 (1998).
17. P. M. Gallagher, M. P. Coffey, V. J. Krukonis, and N. Klasutis. Gas-Antisolvent recrystallization—New process to recrystallize compounds insoluble in supercritical fluids. *ACS Symp. Ser.* **406**: 586–594 (1989).
18. R. Sloan, M. E. Hollowood, W. Ashraf, P. York, and G. O. Humphreys. Preparation of stable protein particles. *Proc. 5th Meet. On Supercrit. Fluids.* Tome**1**:301–306 (1998).
19. S. Palakodaty and P. York. Phase behavioral effects on particle formation processes using supercritical fluids. *Pharm. Res.* **16**: 976–985 (1999).
20. M. Kitamura, Y. Yoshinaga, and H. Masuoka. Crystallization of polymorphous sulfathiazole by gas-antisolvent method. *Proc. 14th Int. Symp. On Ind. Cryst.* 169 (1999).
21. P. York. Strategies for particle design using supercritical fluid technologies. *PSTT* **2**:430–440 (1999).
22. S. Beach, D. Latham, C. Sigdwick, M. Hanna,and P. York. Control of the physical form of salmeterol xinafoate. *Org. Proc. Res. Dev.* **3**:370–376 (1999).
23. M. Hanna and P. York. US patent 5851453 (1998); Eur. Patent 0706421B1 and 0767702B1 (1998).
24. B. Y. Shekunov, M. Hanna, and P. York. Crystallization process in turbulent supercritical flows. *J. Cryst. Growth* **198/199**:1345–1351 (1999).
25. N. Blagden, R. J. Davey, H. F. Lieberman, L. Williams, R. Payne, R. Robert, R. Rowe, and R. Docherty. Crystal chemistry and solvent effects in polymorphic systems—Sulfathiazole, *J. Chem. Soc. Farad. Trans.* **94**:1035–1045 (1998).