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Shedding Some Light on Crystallization Issues: Lecture Transcript from the First International Symposium on Aspects of Polymorphism and Crystallization − Chemical Development Issues[1]

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Over the past 15 years the major effort in process research and development has been focused on control of organic purity of the products made. Much of this focus has been driven by advances in HPLC methodology and progress achieved by a deeper understanding of the chemistry leading to greater control of the chemistry. More recently, one of the major challenges faced by process research groups is gaining a greater understanding and control of physical form through crystallization. A more rational approach to this challenge can be made by learning from earlier experiences, and the subject of this lecture is work that was carried out in SmithKline Beecham (SB) in the early 1990s.

The two case studies presented in this lecture involve compounds that emerged from SB's Inflammation and Tissue Repair programme and are LTB_4 antagonists (see Figure 1). Since leukotrienes have been implicated in the formation of psoriatic plaque, SB-201993 and SB-209247 were being developed for the treatment of psoriasis.[2−4] SB-201993 did not show oral bioavailability and thus was being developed solely as a topical agent where a solution/suspension of the active component in a paraffin wax would be applied directly to the affected skin. As some relief from psoriasis occurs on exposure to sunlight, it was important that the topical formulations showed good light stability. In contrast, SB-209247 was shown to possess oral activity, and thus it was being developed for both oral and topical application.

SB-201993 and SB-209247 are both trisubstituted pyridines which contain an acrylic acid moiety at the 2-position, an ether side chain at the 3-position, and a substituted thioether moiety at the 6-position (see Figure 1). The common structural motif is the pyridyl acrylic acid and, being a reactive group, was anticipated to lead to further chemistry.

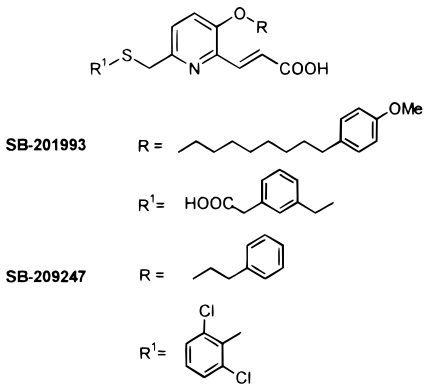

Figure 1. **Structures of LTB_4 antagonists.**

Case Study 1: SB-201993. The medicinal chemistry route to SB-201993[2,3] (see Scheme 1) started from 3-hydroxy-2-hydroxymethyl-6-methylpyridine and involved selective oxidation of the 2-position with manganese dioxide and protection of the 3-hydroxyl function with the desired side chain, followed by elaboration of the acrylic acid side chain. The synthesis concluded by oxidation of the 6-methyl group via a Katada rearrangement of the *N*-oxide[5] followed by conversion to a leaving group and functionalization with the desired thioether moiety.

The final stages of the medicinal chemistry route involved base hydrolysis of the ester groups with aqueous sodium hydroxide, followed by acidification and extraction with ethyl acetate. The ethyl acetate solution of SB-201993 was washed with water, concentrated to 10 vol, and cooled. Crystallization occurred at 52 °C to give a white solid with onset of melting at 111 °C, recrystallization and melting at 133 °C. The medicinal chemistry route was scaled up and run in the pilot plant. Five batches up to 10 kg scale were successfully prepared to support early development and all IRs and DSCs were identical. The DSC trace (see Figure 2) was the first warning of potential problems to be faced, but at the time our major concern was discovery of a viable route and control of organic purity of the product.

As mentioned earlier, the medicinal chemistry route to SB-201993 is long; therefore, a programme of work was undertaken to discover a commercially attractive synthetic route. The chosen commercial route to SB-201993 involved

(1) Conference held at Hinkley, Leicestershire, UK, June 23−25, 1999. Contact Scientific Update for details of other papers at the meeting at: Scientific Update, Wyvern Cottage, High Street, Mayfield, East Sussex, TN20 6AE, UK. Telephone: +44 1435 873062. FAX: +44 1435 872734. E-mail: sciup@scientificupdate.co.uk.

(2) Daines, R. A.; Chambers, P. A.; Pendrak, I.; Jakas, D. R.; Sarau, H. M.; Foley, J. J.; Schmidt, D. B.; Griswold, D. E.; Martin, L. D.; Kingsbury, W. D. *J. Med. Chem.* **1993**, *36*, 2703.

(3) Daines, R. A.; Chambers, P. A.; Eggleston, D. S.; Foley, J. J.; Griswold, D. E.; Haltiwanger, R. C.; Jakas, D. R.; Kingsbury, W. D.; Martin, L. D.; Pendrak, I.; Schmidt, D. B.; Tzimas, M. N.; Sarau, H. M. *J. Med. Chem.* **1994**, *37*, 3327.

(4) Daines, R. A.; Chambers, P. A.; Foley, J. J.; Griswold, D. E.; Kingsbury, W. D.; Martin, L. D.; Schmidt, D. B.; Sham, K. C.; Sarau, H. M. *J. Med. Chem.* **1996**, *39*, 3837.

(5) McKillop, A.; Bhagrath, M. K. *Heterocycles* **1985**, *23*, 1697.

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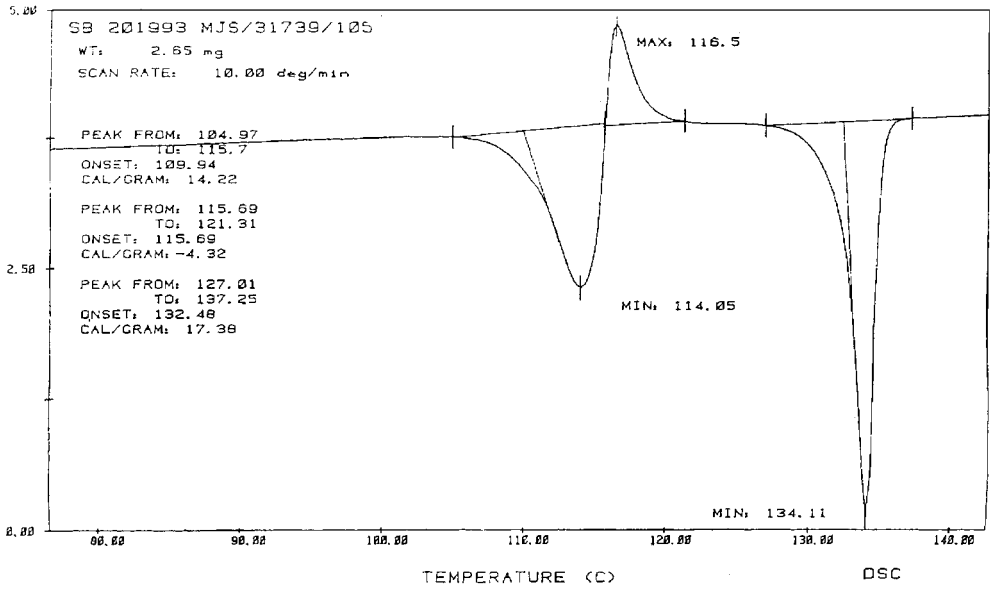
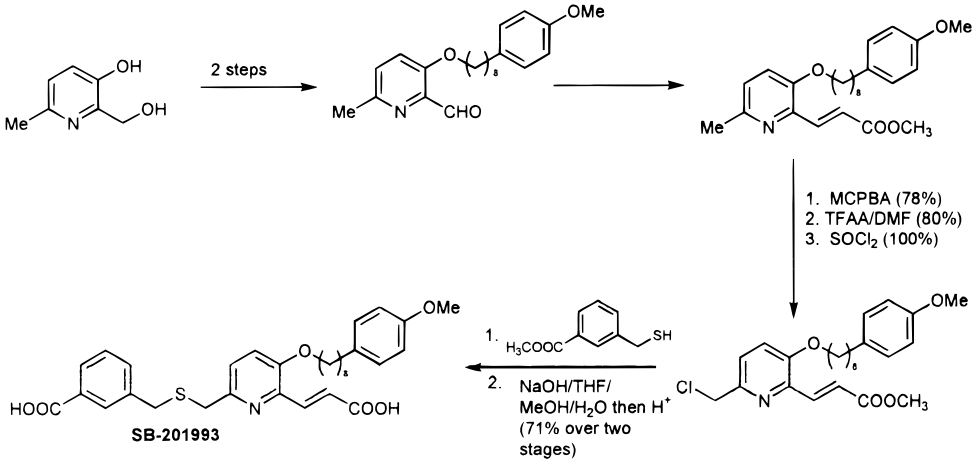
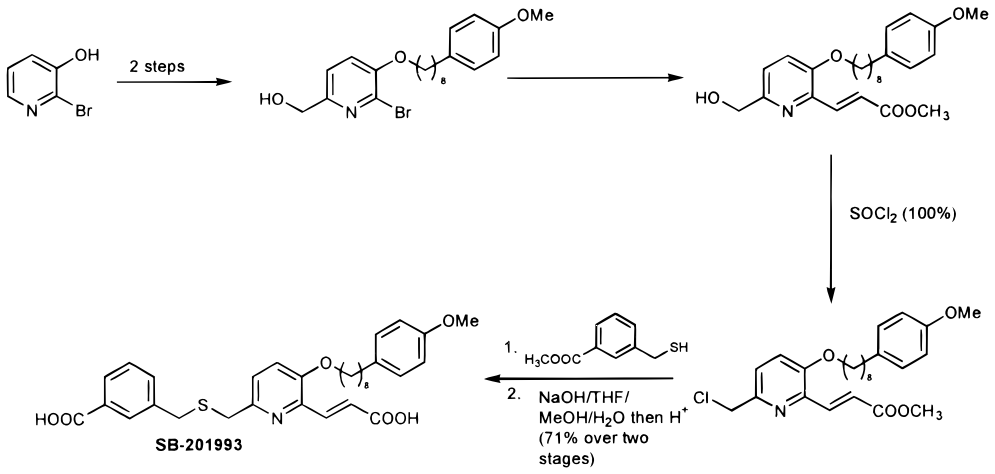


Figure 2. **DSC trace of SB-201993 formed.**

Scheme 1: **Medicinal chemistry route to SB-201993**



Scheme 2: **Heck coupling route to SB-201993**



a palladium-catalysed Heck coupling as the key step,[6] and this led to the readily available and cheap starting material 2-bromo-3-hydroxypyridine (see Scheme 2). The Heck coupling route involved hydroxymethylation in aqueous potassium hydroxide and selective protection of the phenolic hydroxyl group with the desired side chain, followed by Heck coupling with an acrylic ester to give a late stage intermediate common to the medicinal chemistry route. Conversion of

(6) Sheldrake, P. W.; Powling, L. C.; Bickle, P. W. PCT Int. Appl. WO 9,-500,487, 1995; *Chem. Abstr.* **1995**, *123*, 198630.

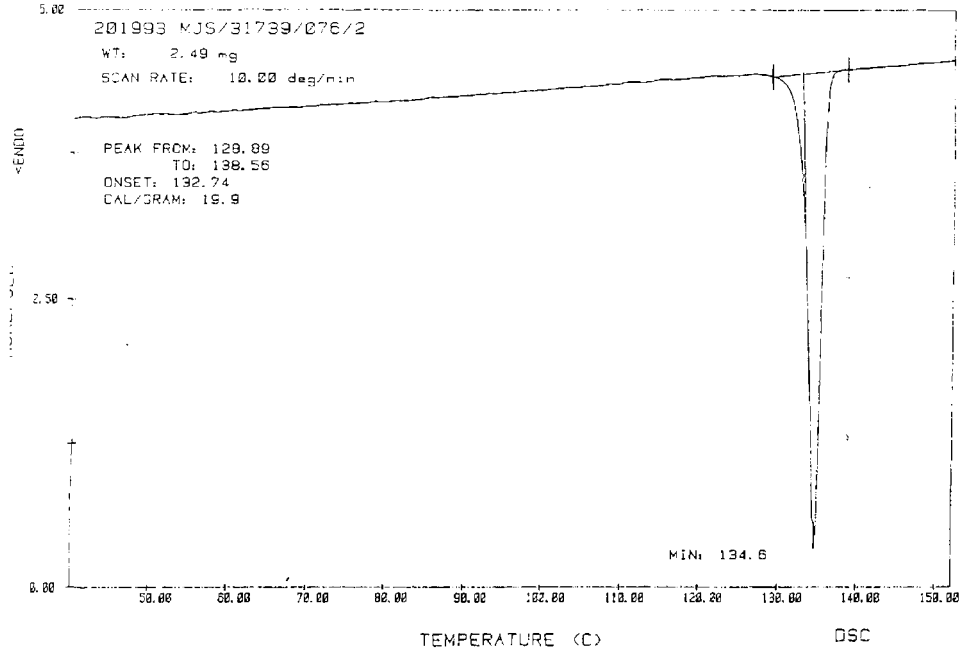


Figure 3. **DSC trace of new form of SB-201993.**

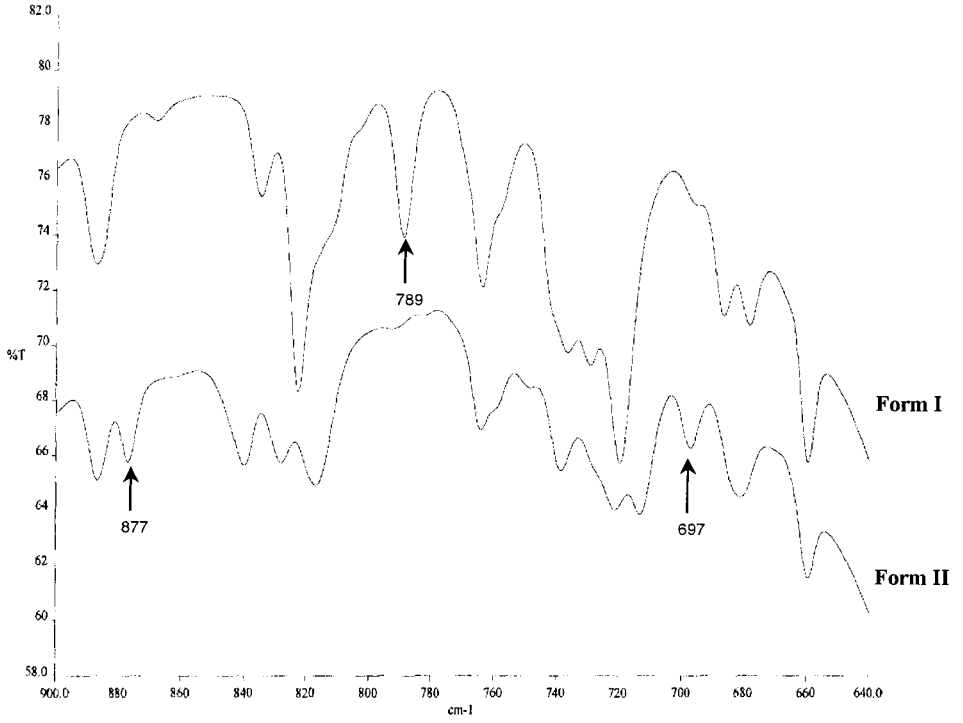


Figure 4. **Comparison of IR spectra for SB-201993 forms I and II.**

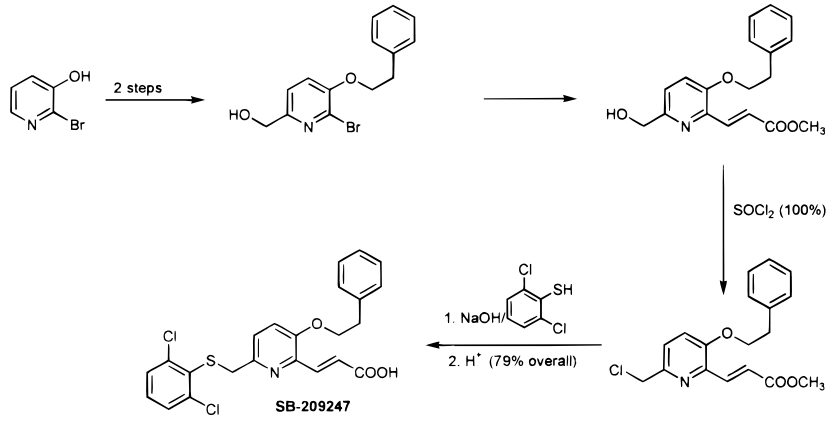
this intermediate to SB-201993 was carried out in an identical way to the medicinal chemistry route.

Optimization work on the final isolation and crystallization indicated high recoveries were possible from 3 to 10 vol of ethyl acetate, and 5 vol was a good balance between purity and yield. The revised crystallization procedure was used with the Heck coupling route to SB-201993 to increase throughput, and the product obtained crystallized at 67 °C to give a white solid with a melting point of 133 °C. The IR and DSC of the product were different from those of the material made by the medicinal chemistry route (see Figures 3 and 4).

It was clear from these data and XRPD patterns that we had produced a new polymorph of SB-201993 (form **II**), and in hindsight a more rigorous evaluation of polymorphs should have been carried out when a DSC of the type shown in Figure 2, which displays thermal events at 114 and 118 °C consistent with a thermally induced polymorphic change,[7] was first obtained. Since all early toxicology and clinical data were obtained with the original polymorph (form **I**), it was important to demonstrate that SB-201993 produced by the commercially viable Heck coupling route could be

(7) Giron, D. *Thermochim. Acta* **1995**, *248*, 1.

Scheme 3: **Heck coupling route to SB-209247**



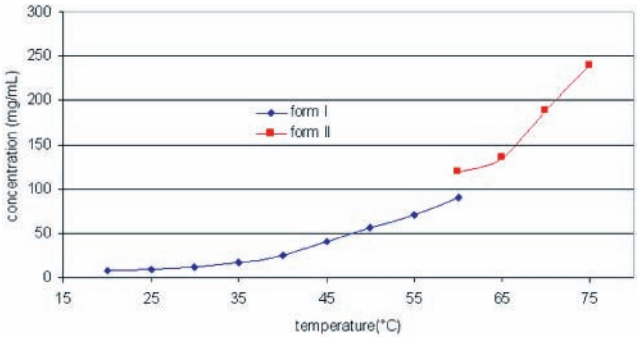


Figure 5. **Equilibrium solubility curve for SB-201993.**

crystallized in that form in a controlled manner. At this stage it was not clear whether impurities from the Heck coupling route or the crystallization conditions were driving the change in polymorph. Measurement of an equilibrium solubility curve in ethyl acetate gave important data to answer this question (see Figure 5).

It can be seen in Figure 5 that there is a dislocation at 60 °C in the solubility curve. It was found that crystallization at 67 °C reproducibly gave form **II** and crystallization at 52 °C reproducibly gave form **I** *irrespective* of the route of synthesis. From the solubility curve the concentration required to give a crystallization temperature below 60 °C was chosen, and this led to control of the polymorph produced. The commercially viable Heck coupling route was subsequently successfully scaled up to 11 kg batches, and SB-201993 form **I** was routinely obtained from 8 to 10 vol of ethyl acetate without seeding.

The crude, wet product was dissolved in 8−10 vol of ethyl acetate and dried under Dean−Stark conditions. The dried ethyl acetate solution was filtered and cooled slowly to ∼37 °C, whereupon crystallization occurs. The slurry is cooled to ambient temperature and stirred for 1−2 h prior to isolation and drying.

Case Study 2: SB-209247. When SB-201993 failed to show efficacy in Phase II clinical studies, the backup compound SB-209247 was rapidly brought into development.[4] The structural similarities between the two compounds were discussed earlier, and we therefore applied our experience with the Heck coupling route to this backup.[6] As we had experienced problems with polymorphs of SB-201993 a crystallization study was carried out. At this time we only had a small quantity of one medicinal chemistry batch of SB-209247 available. Recrystallization from isopropyl alcohol, *tert*-butyl methyl ether, toluene, *n*-butyl acetate. ethanol, and isopropyl ketone gave only one polymorph (form **I**) as shown by IR, DSC, mp, and XRPD data. With these encouraging data in hand the Heck coupling route to SB-209247 was scaled up to make the first development batches (see Scheme 3). In this case identical conditions to the medicinal chemistry route were used for final hydrolysis and crystallization stages.

The SB-209247 produced by the Heck coupling route was found on analysis to show a different DSC and melting point (see Figure 6). It was clear from these as well as from IR and XRPD data that we had found a new polymorph (form **II**) and this new form was thermodynamically more stable! We found that at this stage form **II** could be prepared routinely from SB-209247 made by the Heck coupling route when ethyl acetate, ethyl acetate/hexane, and isopropyl alcohol were used as solvent for final crystallization. Furthermore, we had difficulty preparing further supplies of form **I**. Crystallization from 2-propanol with seeding under conditions of slow stirring was found to be successful, but not very reproducible, in making form **I**. It was clear that form **II** would be easier to prepare on scale, but additional data were required to confirm that form **II** was the most appropriate for future development.

Routine studies on active pharmaceutical ingredients involve light stressing. A significant difference in behaviour was seen between forms **I** and **II** of SB-209247.[8] Exposure to Xenon light at 85 klux for 4 h gave 100% loss in HPLC assay of form **I** compared with only 4% loss in HPLC assay of form **II**. It was clear from these data that not only was form **II** the thermodynamically more stable polymorph and easier to prepare, it was also the more light-stable. Form **II** was therefore chosen for development. The Heck coupling route to SB-209247 was successfully scaled up to 20 kg batch size, and eight batches routinely gave form **II** from ethyl acetate/hexane.

(8) Orford, C.; Webb, M. L.; Cattanach, K. H.; Cottee, F. H.; Escott, R. E.; Pitfield, I. D.; Richards, J. J. In *Drugs, Photochemistry and Photostability*; Albini, A., Fasani, E., Eds.; Royal Society of Chemistry: Cambridge, 1998.

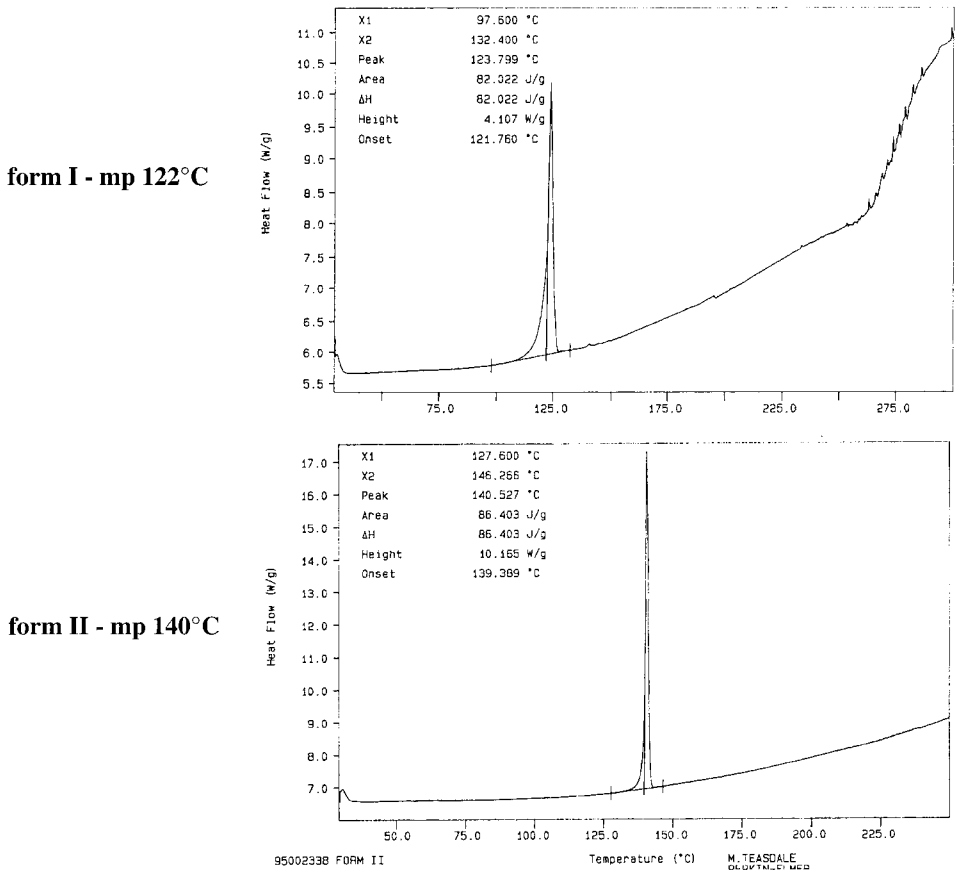


Figure 6. **DSC traces of SB-209247 forms I and II.**

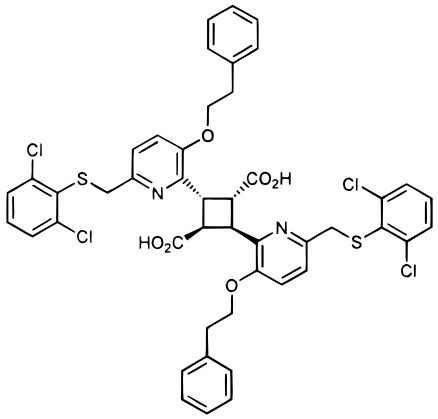


Figure 7. **Structure of light degradant from form I.**

The crude product dissolved in ethyl acetate is filtered and then concentrated under vacuum before adding *n*-hexane and seed crystals of form **II**. The resulting mixture is cooled to 3 °C and strirred for 2 h prior to isolation and drying.

To ensure that further problems were not missed, the origin of the light stability of form **II** of SB-209247 needed to be understood. A sample of the light degradant derived from form **I** was isolated and purified by preparative HPLC. Analysis by mass spectroscopy and NMR suggested a dimeric species containing a cyclobutane ring had been formed and the structure shown in Figure 7 was confirmed by single-crystal X-ray data.[8,9]

It was clear from the structural assignment that a light-induced $2\pi + 2\pi$ cycloaddition reaction had occurred, and there is elegant precedent for this behaviour from the work of Schmidt on cinnamic acids.[10] Single crystal X-ray structure of form **I** (see Figure 8) was virtually identical in nature to that published by Schmidt[10] for cinnamic acids, where the acrylate double bonds are stacked one above another with the carbon atoms about 3.5 Å apart. In these circumstances, from earlier work, a light induced $2\pi + 2\pi$ cycloaddition in the solid state can be predicted.[10] To complete the study a single crystal X-ray structure of form **II** was also obtained (see Figure 9), and this clearly shows that the acrylic acid double bond of one molecule is centered above the pyridine ring of adjacent molecules and the closest intermolecular distances are between the double bond and dichlorophenyl rings. These data explain the light stability of form **II** relative to form **I**.

Conclusions

Polymorphism studies carried out early in development enable a rational choice to be made; however, early results can be misleading. Thus, continued vigilance throughout development of the commercial route of synthesis is required. Further polymorphism studies should also be carried out when the final route of synthesis has been chosen and there

(9) Haltiwanger, R. C.; Daines, R. A.; Eggleston, D. S. *18th IUCR Congress and General Assembly*; Glasgow, August, 1999; Abstract P09.06.015.

(10) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.

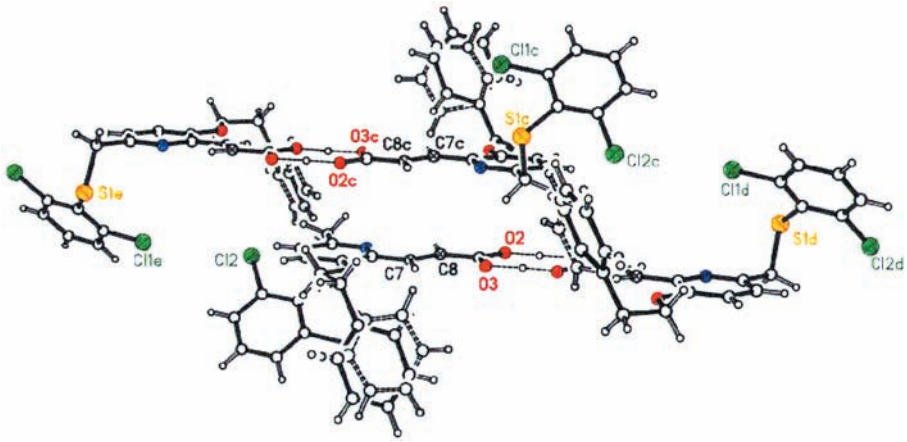


Figure 8. **Single-crystal X-ray structure of SB-209247 form I.**

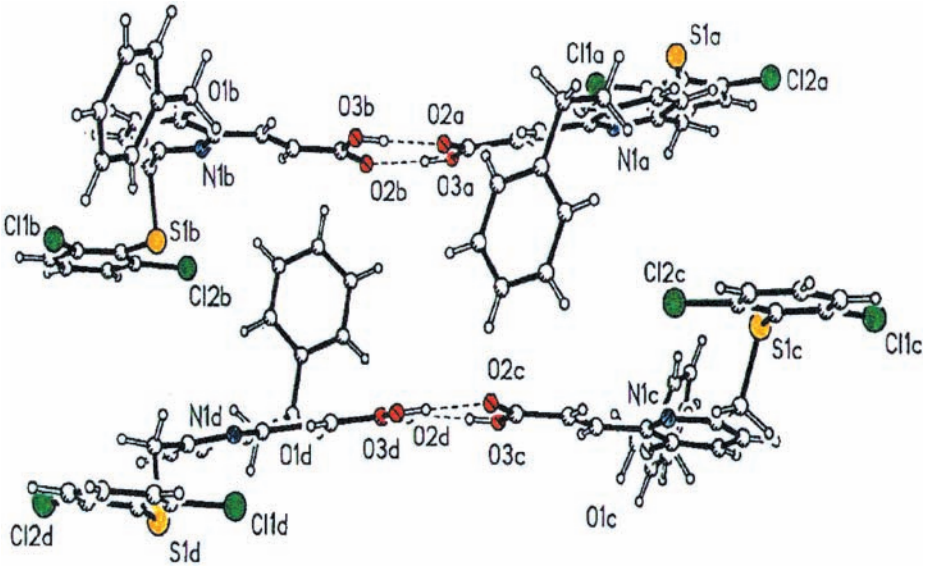


Figure 9. **single-crystal X-ray structure of SB-209247 form II.**

are books giving a description of the type of experiments to consider, for example, the recent publication by Brittain.[11] It is also important to use a variety of techniques in the evaluation of polymorphism, such as IR, DSC, mp, hot stage microscopy, solid-state ^{13}C NMR, Raman, measurement of equilibrium solubility curve, modulated DSC, and aging studies at elevated temperatures. It is worth remembering also that chemistry can occur in the solid state and this can lead to significant differences in stability between forms.

(11) Brittain, A. G. In *Drugs in the Pharmaceutical Sciences*; Polymorphism in Pharmaceutical Solids, Vol. 95; Marcel Dekker: New York, Basel, 1999.

Acknowledgment

The work described in this lecture was carried out by a number of people, but primarily by Richard Anderson, Peter Bickle, Mike Harris, Martin Gilges, Laurence Powling, Mike Sasse, Peter Sheldrake, and Mike Webb. Single crystal X-ray data was obtained by Curt Haltiwanger and Drake Eggleston. I thank all these collaborators for their efforts, and I thank SB for allowing me to present this work.

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