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SPECIAL FEATURE SECTION: POLYMORPHISM AND CRYSTALLIZATION

Editorial

Polymorphism and crystallization issues affect many industries where solid products are produced and marketed; those industries include explosives, colour chemicals, food additives, and agrochemicals, particularly pharmaceuticals. The ability to obtain in a reproducible manner, the correct crystal habit and physical form requires a deep understanding of the crystallization process and the phase diagrams which allow some control over the kinetics and thermodynamics of the process. Key issues are solvent, nature, and quantities of impurities as well as the exact crystallization conditions (concentration, temperature, seeding, etc.). A failure to understand the issues can lead to the production of product unsuitable for sale, which can be expensive. Even though the crystallization process appears to be understood, new polymorphs or solvates can appear, particularly in late-stage development projects or even after the product has been launched; the appearance of these forms may delay the launch of the product or result in a product being withdrawn from the market until further studies have been carried out.

The chemists and engineers involved in developing crystallization processes are often placed in a difficult situation—the formulator of the product often wants the crystal form which is the most soluble, and yet the more thermodynamically stable form will be the least soluble, although this may vary with solvent competition. The most stable form will be the easiest to isolate on large scale and, being the least soluble, should give the best isolated yield from a crystallization process. Many of these issues were discussed at a recent conference held in the UK in 1999, and it was the tremendous interest in the topic at that meeting which encouraged the editors of *Org. Process Res. Dev.* to suggest that issue No. 5 in 2000 should contain papers on the theme of crystallization and polymorphism. The speakers at the 1999 symposium—and many other scientists—were invited to submit papers, and several responded to allow production of this special section. One or two papers did not make the deadline and will appear in future issues of OPRD.

A crucial controlling parameter in crystallization is seeding, an area where there has not been too much discussion from an industrial viewpoint in the previous literature. Wolfgang Beckmann from Schering AG in Germany has produced an excellent and thought-provoking review of the subject of seeding techniques, with particular emphasis on the scale-up from well-controlled conditions in the lab to full-batch plant scale, where time scales to carry out key operations may be crucial. A number of published and unpublished case studies are discussed in detail.

He also mentions the importance of the solvent quality in affecting solubility and hence crystallization parameters—even a small quantity of water in a solvent can affect solubility by up to 5%. Terry Threlfall from the University of York, UK, examines the role of solvent from a thermodynamic viewpoint in polymorph crystallizations, and his conclusions have importance in determining the way in which screening for polymorphism is carried out, that is, it is not sufficient to crystallize a compound from many different solvents—the concentration in the solvent and the solvent quality (particularly water content) are also critical parameters, as is the quality of the compound being studied.

A group from Pharmacia Corporation in collaboration with Michigan State University, U.S.A., has presented a case study of an investigation into a solvent-mediated polymorphic transformation of progesterone. Many analytical techniques, including differential scanning calorimetry, X-ray diffraction, and infrared and solid-state NMR spectroscopy have been used to differentiate between polymorphic forms. In their paper, however, in situ Raman spectrosocopy was used, allowing monitoring of solid-phase behaviour while in a mixed suspension of solid and liquid.

One question which chemists often ask is "are the new molecules being produced in discovery departments more susceptible to multiple polymorphic states than in the past?" Or is it that we detect more forms because we are more rigorous in looking for polymorphism? The structural factors which affect polymorphism are usually intermolecular hydrogen bonding and conformational flexibility. The food industry knows a lot about the latter since polymorphism of fats is a crucial issue, for example, in the manufacture of chocolate. A paper from Lian Yu and colleagues at Eli Lilly, U.S.A., discusses the crystallization and polymorphism of conformationally flexible molecules and introduces special techniques which have been devised to introduce molecular level control of the crystallization process.

Robert Spruijtenburg from Roche AG in Switzerland presents two case studies to show how the influence of operating parameters can be used to control the desired crystallization modification. The first example is that of a food colorant with four forms, where conventional conditions produced form D that was difficult to filter. By changing the manufacturing process, form C, which was easier to filter and dry, could be produced. His second example is of a pharmaceutical, where the transition from form A to form B took place in a vacuum dryer.

In a summary of a presentation made at the 1999 conference on Polymorphism and Crystallisation: Chemical Development Issues, Norman Lewis of SmithKline Beecham

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discusses two case studies of products in early development. In one example, the light stability of one of two polymorphic forms was significantly reduced, and this was attributed to a facile $2\pi + 2\pi$ cycloaddition in the solid state.

One of the drugs, which developed problems with a new polymorph, was Abbott's Ritonavir marketed for AIDS treatment as Norvir. Although comprehensive screening for alternative polymorphic forms was carried out prior to the launch of the drug, only one crystalline form was found at that time. Two years after the launch, however, a new, less soluble (and therefore more stable) form appeared which had different physical properties. The problems associated with this phenomenon and the methods of circumventing the difficulty are discussed openly and in detail in a paper from Sanjay Chemburkar at Abbott, U.S.A. The moral of his story is also innovative "Dealing with Polymorphs Is Potentially Precarious Practice and the Proper way to Play the game is with Patience and Perseverance!"

One aspect of crystallization, which is often forgotten, is the importance of time-dependent phenomena on scale up of the process. This is particularly important in the separation of diastereoisomeric salts by crystallization where the required diastereoisomer can be contaminated by crystallization of the unwanted isomer if the crystallization or filtration takes a long time (i.e., if the particle size of the required product is poor). In the paper from Martin Woods and colleagues at Celltech Chiroscience in collaboration with High Force Research (UK), an efficient crystallization resolution process for a new salt form of the drug *S*-etodolac is described, where the effect of crystallization time on diastereomeric excess was examined for several solvents. This helped with the development of a new salt form for the single enantiomer form of the drug.

A key area related to crystallization and polymorphism of pharmaceuticals is the selection and optimization procedures for new chemical entities, particularly the most appropriate salt form, which modifies the characteristics of the potential drug substance and allows the required dosage form to be developed. A paper from Michael Bowker and colleagues of Aventis Pharma in UK (former Rhone-Poulenc Rorer) introduces their philosophy and three case studies are presented.

The papers presented in this special edition should enhance the knowledge of those involved in the scale up of crystallizations and in the understanding and control of production of the desired polymorphic form.

I wish to express my thanks to the authors for their submissions and to the reviewers, whose comments often improved the quality of the manuscripts, for their efficient reviewing of the papers.

Dr. Trevor Laird
Editor

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