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Editorial

A couple of weeks ago, we received, in the UK editorial office, a paper from an industrial author—a chemical engineer as it happened—about a polymorphism problem, which had appeared during very late stage development work of a new chemical entity, and how this problem had been solved by meticulous attention to detail. In the same week, two of the companies that I consult for also had problems with different physical forms of the same chemical substance, one attributed to polymorphism, the other to solvate formation. In one example, two different contractors making the same drug substance produced material differing in melting point by approximately 50 °C—fortunately the drug was to be used in solution and not in a solid dosage form.

To understand some of these issues, I had to go back to the literature, which in this field could be in an organic chemical book or journal,[1] in analytical chemistry publications,[2] or in the chemical engineering literature.[3] (OPRD is therefore an ideal forum for this area of research!) When I looked at the structure of molecules which displayed polymorphism (or different solid state forms), I was struck by the number of recent examples which contained a central aromatic or heteroaromatic portion—essentially a planar structure—on which were attached at more or less opposite ends two conformationally flexible chains, sometimes with polar groups at the end, sometimes with aromatic groups. Is this type of arrangements predisposing the molecules to exist in more than one solid state form? It reminded me that polymorphism is also a problem in "oils and fats" where a central glycerol unit (far from conformationally rigid, I would imagine, unless strongly hydrogen bonded) is attached to conformationally mobile chains. This is an extremely complex problem for the food industry, since the different polymorphs can affect the taste/texture of the product. For example, the "blooming" of milk chocolate—the white surface covering which affects products stored incorrectly—is said to be caused by a polymorphic change in the fat, leading to separation from the chocolate.[4]

Later in the same week, I had to give a talk about industrial synthesis of optically active compounds, discussing crystallisation of single enantiomers and racemates. Of course a single enantiomer crystallises in a different space group from the racemic mixture (unless the racemate forms a conglomerate) and has different solid state properties and so can be regarded as a pseudo-polymorphic form of the same compound. Since many companies have developed techniques to manufacture the less stable polymorph of a substance under reproducible, production-scale conditions (usually because less stable polymorphs may have more favourable properties, particularly solubility), it set me thinking on whether we could devise conditions where the less stable or even metastable form of a racemate (i.e., the single enantiomer crystal form) could be produced from a racemic mixture by seeding with one enantiomer under very controlled conditions. This is regularly done when the single enantiomer crystalline form is the stable form (i.e., a conglomerate), but I do not know of many examples where it has been done with a true racemic crystal (i.e., where the crystal lattice contains both enantiomers in the unit cell).

The earliest example,[2] I suppose, dates back to Pasteur in the 1850s, who, whilst studying the crystallisation of sodium potassium tartrate, produced three crystalline forms of the substance: a conglomerate (containing separate crystals of each enantiomer), a true racemate, containing each enantiomer in the unit cell, and a hydrate. The conglomerate could only be formed by seeding the crystallisation below 28 °C.

The other example which springs to mind is one which I heard in a lecture on alternative syntheses of the drug diltiazem, where I think some esters of the intermediate epoxycinnamic acid exhibited polymorphism; one polymorphic form was a true racemate whereas the other was a conglomerate, so in theory, a single enantiomer would have been produced by low-temperature seeding (I seem to remember that this form had a low melting point, too).

Perhaps readers of OPRD know of further examples which are used in industry; in which case, I would be pleased to hear from you. Anyway, I hope this discussion may have helped to crystallise your thoughts. It has only succeeded in starting me thinking about chocolate!

T. Laird
Editor

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(2) Threlfall, T. *Analyst* **1995**.
(3) Beckmann, Ottow, W. *Trans. Inst. Chem. Eng.* **1996**, *74A*, 750.
(4) Garti, N.; Satu, K. *Crystallisation and Polymorphism of fats and fatty acids*; Marcel Dekker: New York, 1988.

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