Private prescription:

A thought-provoking tonic on the lighter side

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Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

Crystal gazing – seeking that elusive polymorph

For centuries, crystals in their various forms, for example, gemstones, minerals, salts and even snowflakes, have held a fascination for both scientists and non-scientists alike. Their specific properties, both physical and chemical including their regularity of shape, their colour and their hardness, have stimulated much research, and have created a class of multi-disciplinary scientists called crystallographers. One of these, Dame Kathleen Lonsdale, the first female Fellow of The Royal Society, once described a crystal[1]:

> …a crystal is like a class of children arranged for drill, but standing at ease, so that while the class as a whole has regularity both in time and space, each individual child is a little fidgety.

This analogy allows for all that is known about the structure of crystals, including the fact that some have at least two different arrangements of the 'children', a property that is known as polymorphism.

Polymorphism was first discovered in 1798, when the German chemist and one-time apothecary, Martin Heinrich Klaproth discovered that the minerals calcite and aragonite both had the same chemical composition ($CaCO_3$). This was contrary to all the accepted ideas at that time, and it was not until almost 25 years later, after the seminal work of another German chemist, Eilhardt Mitscherlich, that it was accepted that a chemical compound could exist in more than one crystalline form. Since then, numerous substances have been discovered to be polymorphic, so much so that it has been suggested, somewhat provocatively, by the American microscopist Walter McCrone[2], that:

> …every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on the compound.

The elusive polymorph

It is the variation in the physical and chemical properties of organic compounds, such as the melting point, chemical reactivity and solubility that, at the practical level, makes polymorphism such a potentially important issue for the pharmaceutical industry. Polymorphs can seemingly appear and disappear for no apparent reason and new ones can appear when least expected. The occurrence of new polymorphs, in particular, can have disastrous consequences, not least the disruption of production. A celebrated example of this is the protease inhibitor, ritonavir (Abbott Laboratories, Abbott Park, IL, USA); the unexpected appearance of a new crystal form of this drug that had different dissolution characteristics resulted in a shortage of the capsule formulation during the summer of 1998[3].

Predicting when a new polymorph will occur would appear to be a serendipitous activity. It is well known that crystallization can be affected by numerous factors, including the solvent, solution concentration, degree of supersaturation, heating and cooling profiles, seeding and agitation, and all can result in the production of different polymorphs. However, these factors do not always explain why a process that has remained stable and under control for many years can suddenly go out of control.

…know your reaction chemistry, for it may come back to haunt you.

Recent research by Roger Davey at the University of Manchester Institute of Science and Technology (UMIST, Manchester, UK) and colleagues at AstraZeneca (Macclesfield, UK), has indicated that the reaction chemistry could be partly to blame. If, during a chemical reaction, by-products of sufficient stereochemical similarity to the crystallizing solute are formed, then it has been argued that these could act as selective crystallization additives and inadvertently direct the polymorphic outcome of the crystallization process. Indeed, it has been shown with sulfathiazole, a model drug that is known to exist in five polymorphic forms, that a low level

1359-6446/01/$ – see front matter PII: S1359-6446(01)01766-4

(0.01 mol per cent) of the reaction by-product, ethamidosulfathiazole, can have a significant impact on the polymorphic purity of the sulfathiazole. At higher concentrations (5 mol per cent), the polymorphic outcome switched dramatically, from 100% of one form to 100% of a second form, with intermediate concentrations resulting in mixtures of polymorphs[4].

In the context of process chemistry, particularly process development and route selection, this finding has profound implications. The general philosophy of continual improvement could give rise to increasingly selective chemistry, whereby the decreasing level of an important reaction by-product could affect the polymorphic purity of the product. Further, changes in the supplier of an intermediate could cause a change in the impurity profile, thus allowing another polymorph to appear. Finally, the by-product that directs the crystallization of a specific polymorph during pilot scale or early manufacturing trials could be eliminated at the full scale, again allowing a different polymorph to appear. All of these scenarios are possible, and all could have disastrous commercial consequences.

The way forward?

There is light at the end of the tunnel and all is not lost. The same authors[4] have shown that it is possible to use molecular modelling to test whether a specific by-product can enter the surface site in the crystal lattice of a polymorph, and prevent crystallization by discouraging other host molecules from joining the crystal. For sulfathiazole they have shown that the by-product ethamidosulfathiazole can enter the surface sites of two of the known polymorphs. In one polymorph it can mimic a sulfathiazole molecule and does not affect the crystallization of this form. In the other polymorph, it disrupts the formation of the crystal structure and inhibits the crystallization of this form[4].

Of course, modelling can only help if the crystal structures of either some or all of the known polymorphs of the host are available. However, this is generally not the case with a new drug, and here pragmatism must be applied. This should involve a screening process whereby the drug is crystallized in the presence of the known by-products and the polymorphic purity assessed by X-ray diffraction. In all cases, it is essential that the reaction chemistry be known, and that both synthetic organic chemists and physical chemists should work together from the outset. In the words of Roger Davey and his colleagues[5]:

> …know your reaction chemistry, for it may come back to haunt you in the form of unwanted polymorphs.

This is valuable advice for all synthetic chemists!

References

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5 Blagden, N. and Davey, R.J. (1999) Polymorphs take shape. *Chem. Br.* 35, 44–46

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Consider the following two opposite views of Process R&D: 'this is a core activity of significant value making important contributions to the business' and 'they only have to produce kilogram quantities of known compounds'. Do they strike you as being familiar? Are you in favour of one over the other or do you assume a position midway? Well, the main purpose of this contribution is to seriously try to influence those of you primarily belonging to the latter group to change your mindset towards the other end of the spectrum!

There are actually several timely reasons as to why this question is brought to your attention right now and I will focus on three of the most important ones. First is the ever-increasing pressure to achieve shorter times-to-market, from candidate drug (CD) nomination to launch. Second is the demand for considerable quantities of the chosen CD right from the start, and third is the structural complexities of the target compounds.

The idea of addressing these issues in a more concise way has grown ever since attending (as invited lecturer) a series of conferences and symposia during the autumn of 2000 (*ChiraSource 2000* in Lisbon, Portugal; *Chiral Europe 2000* in Malta, and the *18th SCI Chemical Process Development Symposium* in Cambridge, UK) largely devoted to endeavours in the field of Process R&D. Here, the current standing of the whole area was displayed before an international audience and the array of achievements reported was, in several cases, stunning or even spectacular. In many of the talks, the strength and ability to master many (if not all) of the intricacies they were confronted with (for example, multiple stereogenic centres, unconventional substitution patterns, regioisomeric features and arrays of functionalities) were amply demonstrated. It should therefore be evident to anyone in the business that the success potential for developing a new chemical entity (NCE) showing a high level of architectural complexity into a future drug rests on the ability to design, optimize and scale-up a chemical process to commercial manufacturing.

Just the fact that the three aforementioned major international events were organized in a time window as short as 2.5 months is testimony to the maturity that this 'science' has reached. Some people might raise their eyebrows when referring to Process R&D as a scientific discipline in its own right. The truth is, however, that during the past quarter-of-a-century, it has grown from being considered as a somewhat obscure and 'low-tech' shovelling of larger quantities of compounds of various types (performed mainly by unqualified workers!) to the present state-of-the-art, where unique production methods are devised that often brilliantly circumvent shortcomings or technical limitations of laboratory-based medicinal chemistry procedures. Needless to say, many of the processes thus developed have such creative and innovative qualities that they can be both patented and/or otherwise openly publicized for everyone to share (and eventually admire).

Taking the constantly ongoing trend to reduce the time-span from appointing a new CD to launch of a registered pharmaceutical product on the market (preferably on the entire global arena within the first year after approval by the authorities) into account, it is only too obvious that securing the availability of large volumes (meaning in reality non-laboratory accessible quantities) is a key driver in assuring that the narrow time-limits are met. This often poses an enormous logistical challenge on a Process R&D function in the sense that some kind of scalable procedure has to be quickly established while concomitantly trying to identify suitable external suppliers of starting materials and building blocks of frequently relatively high structural complexity (which are increasingly chiral in nature and requested in stereochemically defined form).

The fact that we, by far, focus our efforts on target molecules of unique structures previously never manufactured (except for the minute quantities required in initial screening) adds to the 'burden' in the sense that the compounds to be used for their construction are most likely not 'sitting' on the shelf waiting to be ordered. This is especially true as the synthetic strategy tends to be forward-integrated to reduce the number of required in-house transformations. Actually, the likelihood is that many of the

1359-6446/01/$ – see front matter PII: S1359-6446(01)01741-X