Organic Process Research & Development

Editorial

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Crystallisation and Polymorphism

I was recently involved in a project as a consultant when we urgently needed to screen a new chemical entity for the most stable crystal form before scaling up the process to make the first kilogram batch. The previous forms, made by both the discoverer of the drug and an Indian outsource partner, were both hydrates, and they had never seen an anhydrous form. The initial screen produced some more hydrates and solvates, and some of these desolvated to anhydrates. However, it was not until late in the screen—the 19th crystal form to be found—that the most stable form appeared, and this was what was taken forward in development.

My guess is that this story is not unusual these days; I have the feeling, from extensive reading of the literature and from inside knowledge from consultancy projects, that modern drug candidates are predisposed to polymorphism much more than older candidates. Hydrogen bonding plays a key role in polymorphism, but drugs have always contained functional groups which are hydrogen-bond donors or acceptors (or both), particularly amines and amides, hydroxy derivatives, and carboxylic acids and their salts. Do modern drug candidates contain more of these groups than in the past, while still conforming to the requirements of Lipinski's rules, or is the difference caused by a change in conformational restriction or mobility brought about by the structure of modern drug candidates? The juxtapostion of two aromatic or heteroaromatic groups synthesised by the ever-popular cross-coupling reactions, particularly Suzuki–Miyaura reactions, could give rise to structures where packing of the molecule in the crystal lattice may lead to several crystalline forms with slightly different dihedral angles between the two rings. Overuse of these cross-coupling strategies in medicinal chemistry has been criticised in a recent article for different reasons,[1] but I wonder if the change in synthetic methods, over the last couple of decades, has had something to do with the perceived increase in the number of crystalline forms seen for each candidate. Flexible carbon chains with a polar or heterocyclic endgroup often occur in modern drugs and give conformational flexibility but also additional hydrogen bonding possibilities (with the headgroup). However, it is fair to say that several older drugs (e.g., chlorpromazine) were also of this type.

Of course, it could be that chemists are much more aware of polymorphism and solvation issues and thus are looking out for potential problems as well as getting involved with projects at an earlier stage. Thus, preliminary screening for polymorphs can, in some companies, occur before candidate selection. Also, the tools for screening for crystal forms have improved, with more automation meaning that the number of experiments carried out is increased, thus ensuring that, as far as is possible, all forms are detected in the screening process (though this will depend on a number of factors including the quality, particularly the number and level of key impurities, of the sample of API used in the testing).

It is clear that an understanding of crystallisation and polymorphism must be part of the skills of the organic development chemist (as well as the chemical engineer who is often taught these topics at undergraduate level) and that specialist training is required to bring organic chemists up-to-speed with current advances and knowledge. Development chemists love to tinker with the chemistry but must be made aware of the possibility of changing the crystal form of the product (API or intermediate) when they do. Whereas obtaining a new, more stable crystalline form of an intermediate is usually good news (since the lower solubility may allow a yield increase in the crystallisation stage), a more stable form of an API may be a mixed blessing, depending on how far the project is in development.

Since the subject of crystallisation and polymorphism is still a hot topic in process R&D, we will be publishing another special edition of OPRD on this area in early 2013. Contributions to this special issue are invited on any aspect of crystallisation and polymorphism but particularly on aspects which relate to process chemistry, scale up, consistent manufacture, process monitoring and process analytical technology (PAT), and even continuous operations. We have already received several promises of papers but wish to make this a bumper issue with 30–40 papers. Review articles are especially welcome. The closing date for receipt of papers is the end of August 2012. If you are interested in submitting a paper, please contact the editorial office, providing a preliminary title, as soon as possible (oprd@scientificupdate.co.uk).

I look forward to receiving your manuscripts.

Trevor Laird, Editor

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Published: March 20, 2012

   dx.doi.org/10.1021/op3000702 | *Org. Process Res. Dev.* 2012, 16, 525–525