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Editorial

Polymorphism and Impurities

There have been a number of conferences on Polymorphism this year, including the American Chemical Society's Perspectives meeting in Florida and Scientific Update's Symposium in New Orleans, LA. In addition, *Organic Process Research & Development* produced a special issue on the subject in 2003 (*Org. Process Res. Dev.* **2003**, *7*, 957−1027). Thus, this continues to be a hot topic in the pharmaceutical industry. One of the reasons for the high level of interest has to do with intellectual property—the large pharmaceutical companies who have blockbuster drugs are sometimes using patents on salt forms, polymorphs, and pseudopolymorphs to extend the patent life of the drug, whereas the generic competition are interested in new salts or crystal forms to get around existing patents and to enable earlier marketing of a generic drug. In many cases the question of infringement of patents arises, resulting in lengthy court cases which seek to establish whether such infringements have occurred.

A key issue which arises in such cases is the reproducibility of the experimentation, a topic on which I have written before in these editorials. For reproducible production of polymorphs, a critical issue may be the presence or absence of key impurities in the material used to make the polymorphs, but often this information is not recorded in early experiments. Similarly, the rate of cooling in a cooling crystallisation or the rate of addition of antisolvent may be critical factors in determining whether one polymorph or another is obtained in an experiment. Of course these factors may be examined in detail once scale-up to production and validation of the process is required prior to regulatory submission and approval to market a product. But leaving such investigations to a late state of drug development may be counterproductive, since reproducibility issues may occur in process R&D, scale-up, and pharmaceutical development.

The subject of "disappearing polymorphs" continues to fascinate chemists and engineers, and I suspect it is the serendipitous nature and the lack of predictability that excites the interest—and the worry! At this year's conferences, there were many tales—both in the conference presentations and in casual discussions—of new polymorphs appearing in phase II and phase III studies, and even one case where a new polymorph appeared when the company was making launch supplies—i.e., after the validation had been completed. In this case, the company had done intensive polymorph screening, but I always question whether the screening was done on only a single batch of drug substance. If this batch has key impurities present, then a new polymorph may be missed.

Drug substances these days are becoming more complex, with a larger number of functional groups, which may form a number of hydrogen bonds and which also may tend to be conformationally flexible. Both of these effects would tend to predispose a drug to polymorphism. Some salt forms give several polymorphs, whereas others give only one polymorph for the same drug substance; thus, it is worthwhile to screen for salts at an early stage to potentially minimise a polymorphism problem later. However, early studies are nearly always done with impure drug substance, and this can be dangerous if it leads to inhibition of nucleation of the most stable polymorph or to failure of crystallisation of a particular salt.

Process chemists love to tinker with a developing process and aim to produce higher yields and better-quality products. A possible consequence of the removal of certain impurities in the late stages of a drug synthesis is the appearance of new crystal forms, and process chemists must therefore be vigilant to ensure that this is caught.

The only way I can see to minimise the chance of a new polymorph appearing is to carry out polymorph screening on highly purified drug substance—but how many companies do this? The ideal material should have related substance impurities—which are the most likely nucleation inhibitors—at very low levels (below 0.1, 0.01%, or even lower?), and this may mean the ideal drug substance batch for these tests should be the analytical reference standard. An alternative approach is to carry out polymorph screening on a range of

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different-quality batches throughout development. With the development of high-throughput screening for salts and polymorphs, which requires a small number of grams of drug substance, maybe the preparation of a few grams of highly purified batch would be a useful enterprise. However, I know of few companies who actually do this routinely.

In this field, forewarned is forearmed, but you may also have to cross your fingers, touch wood, or check the phases of the moon.

As always, these editorials are designed to stimulate discussion, so letters and e-mails on the subject are always welcome. These are occasionally published if the author is willing to give permission.

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