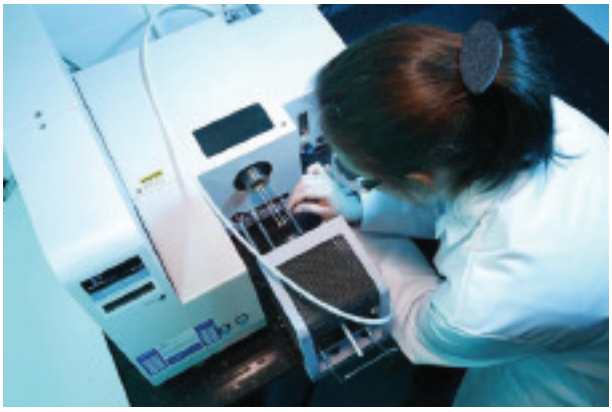
Why are Solid Forms Still Causing Headaches?

By Noel Hamill
at Almac

An insight into how, despite advances in technology, the formulation of solid dosage forms still presents ongoing challenges.

The need to investigate the solid-state properties of an active pharmaceutical ingredient (API) has become common practice in the pharmaceutical development arena. Many will recall the sobering tales, now widely reported in the literature, of solid forms with little or no bioavailability appearing late in development or after launch (1,2). Since the requirement to investigate polymorphism for all new drug substances was enshrined in regulatory guideline ICH Q6A in 1999, the pharmaceutical industry has turned this former problem of solid form diversity into an opportunity (3). Novel solid forms, such as cocrystals and amorphous solid dispersions, have emerged as valuable resources in rescuing drugs with poor bioavailability and getting them into the clinic, in addition to generating intellectual property (see Figure 1).



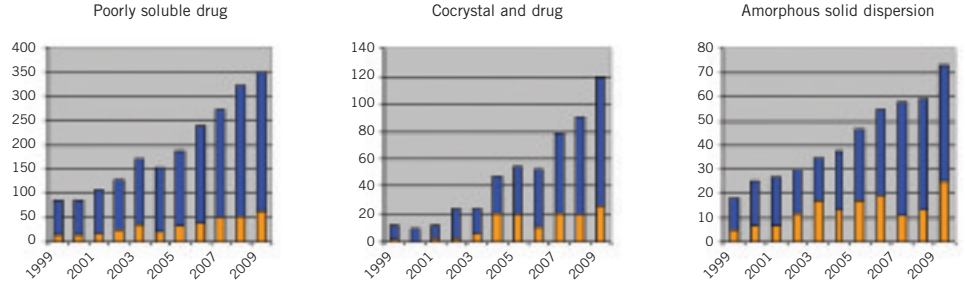
RECURRING ISSUES

Considering the increasing volume of research published in the last decade, one could be forgiven for thinking that solid-state chemistry is well established in the pharmaceutical sector and that major dilemmas are a thing of the past. As a solid-state service provider, we at Almac can say that this is not yet the case. From our collaborations with pharmaceutical and biotech companies of all sizes, a number of recurring issues have been identified. Some of the most common of these are outlined below.

Batch to Batch Variability

Physical properties can vary widely between manufacturing batches of API. Sometimes this can be attributed to a difference in crystalline form, or mixtures of amorphous and crystalline forms. Usually, this issue is first noticed as a failed dissolution test or a

Figure 1: Number of hits for topic searches in Scifinder® (patents in orange)



poor filtration. In later phase processes, variances in particle size distribution and crystal habit are the most common issues encountered, and this suggests that crystallisations at scale are still under inadequate process control. In one client example, batches of API used in preclinical and Phase I studies were retrospectively analysed and found to be mixtures of three polymorphs, amorphous material and a hydrate. In this case, multiple contract manufacturers had been used. Difficulties associated with technology transfer and a lack of scientific continuity will have almost certainly contributed to the batch variation in this instance.

Developing the 'Wrong' Form

Delaying the polymorph screen for as long as possible is a common cost-saving strategy employed by smaller companies, particularly where poor solubility was not a complication in early phase work. However, this delay carries significant risks in later phase development. One company, relying solely on in-house expertise, identified the most stable form of an API late in Phase II, by which point the decision had been taken to progress to a metastable form. At Phase III, it was discovered that a mixture of two metastable forms was being produced in the plant. Although we were able to assist in solving this problem, the late stage discovery of a more stable form added significantly to the cost of controlling and analysing the future batches, which far exceeded the cost of outsourcing a comprehensive screen or seeking guidance at an earlier stage. To complicate matters, automatic selection of the most stable form for development may not always offer a straightforward solution to such problems. The presence of kinetically favoured forms with similar free energy, a tendency to form hydrates, or changes in the order of stability with temperature (enantiotropism), warrant careful examination prior to a decision being made.

Late Discoveries

Although guideline ICH Q6A requires that a polymorph screen be performed on new drug candidates, it does not state how much effort should be employed in such activities. The most stable form, polymorphs or solvates, are still appearing late in development, sometimes after a client or contractor has already completed a polymorph screen. Despite heroic efforts to produce reliable polymorph prediction methods that would

prove invaluable for process chemists, researchers still have some way to go (4). Due to the understandable focus on the API, screening is not generally performed on key intermediates or registered starting materials, and this poses an expensive risk to fixed routes in late phase projects. One supplier produced the stable form of a key raw material for a launched compound on their 86th plant batch, which proved insoluble in their client's manufacturing process. Generic manufacturers are encountering

Table 1: Common issues faced in the filing and defence of solid form patents

Lack of robust data	Poorly written claims	Patent office opposition
Variables not specified for the invention (for example temperature, heating rate, particle size)	**Too broad: difficult to defend** (for example "all pharmaceutical cocrystals")	**Lack of novelty** (for example disclosed in prior art)
API data not applicable to the drug product (for example XRPD, melting point of API)	**Too narrow: difficult to prove infringement** (for example claiming a form with 50 XRPD peaks)	**Obvious** (for example a new salt)
Only one technique used to define the invention (in particular melting point or elemental analysis)	**No analytical method descibed to prove infringement** (in particular, formulation and process patents)	**Lack of utility** (in particular, claims without analytical data)

new forms of established compounds for which no screening data may exist – leaving them scrambling for answers.

Poor Quality Intellectual Property (IP)

The development of a new drug is estimated to take up to 15 years at present (5). The first generation of patents protecting an innovator's right to exploit the molecule only lasts 20 years. To extend the market lifetime of a drug, it is common practice to file a second generation of patents around six to eight years into the development programme. Patents relating to novel solid forms (for example, salts, cocrystals, polymorphs, hydrates and so on) are a very popular means of obtaining this profitable patent protection. However, obtaining these patents and preventing others from marketing generics through litigation is much more challenging. Ironically, in the majority of cases it is the innovator's first generation patents that prove to be the major obstacle. The most common issues faced when attempting to obtain and defend solid form patents are outlined in Table 1 and reflect that, in the rush to file early, the first patents may be poorly constructed. This haste often proves to be the most expensive mistake of the entire development programme.

CONTRIBUTING FACTORS

Our experience suggests that a number of factors are contributing to these recurring issues that beset the industry. It is interesting to note that these factors, discussed below, relate to drug development strategy, rather than a lack of solid-state awareness or technical ability.

Automated High-Throughput Screening

One factor is a continued reliance on automated high-throughput (HT) screening. The use of robotic platforms for solid-state screening was obvious, given the enthusiastic adaptation of HT technology for drug discovery in the 1990s. However, it has since become clear that the well plates employed in such platforms are prone to cross-contamination. Also, the number of nucleation techniques that can be automated is limited. The many late discoveries of new solid forms suggest that the API is experiencing conditions during processing that are not being mimicked in the screening methodology. Fundamentally, a diversity of nucleation techniques maximises the chance of finding new forms, and accessing all of these is not possible with HT screening alone (6). A tailored, manual/semi-automated investigation conducted by experienced specialists is widely regarded as the preferred approach and has been found to perform as well as, or better, than HT screens and with fewer experiments (7).

Increased In-Licensing

Another factor relates to increased in-licensing of drug candidates. In their haste to get a product for sale, biotech and virtual companies can be tempted to minimise cash-burn by delaying the screening or doing it on a limited basis, thereby loading the project with more risk. Fortunately, this approach is gradually changing to the view that a good solid-state technical package is not only a valuable asset, but also comes with the benefit of new intellectual property.

The Importance of Working Together

With the trend to drug development in virtual companies and increased outsourcing to low-cost economies, the lack of an integrated approach will most likely lead to knowledge being lost during technology transfer. The synergy created by having synthetic chemists, solid-state specialists and formulators working together cannot be underestimated. The impact of the solid state does not end with the screening at Phase I. Based on our experience, changes in impurity profiles, processing conditions and excipients can influence the solid form of the API, requiring careful monitoring at all stages of drug development.

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Patent Strategy

Even if all of the technical work has been thorough and timely, the success of the drug can still be undermined by a lack of a good patent strategy. This guides not only when to file but also what to claim. Patents relating to solid forms, especially crystalline forms, are successfully protecting the market share of the innovators of current top-selling pharmaceuticals, such as Lipitor®. In order to protect an invention in the pharmaceutical field, scientifically strong data are absolutely essential in making robust patents. The acquisition of good quality data from complementary analytical techniques and careful construction of claims are paramount. Consulting a patent agent or IP specialist can assist in this regard, as well as provide advice on what further work should be performed to strengthen an existing IP portfolio.

CONCLUSION

Although solid forms are still causing headaches, they also offer lucrative opportunities to be exploited. The collective knowledge and experience built from a large volume of diverse projects allows experienced service providers to not only overcome obstacles for their clients but to add value to their products.

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Noel Hamill is the Team Leader of the Physical Sciences Group at Almac (Craigavon, Northern Ireland) where his main activities are crystallisation development, solid form screening and characterisation, method development and validation, consultancy and hazard assessment. Noel acts as an adviser to clients on solid-state issues, both technical and legal, in the manufacture of drug substance and drug product. With over eight years in the pharmaceutical industry, his roles have encompassed technology transfer, process development, crystallisation science, physical organic chemistry and reaction engineering.
Email: noel.hamill@almacgroup.com