De-risking the solid form landscape of an API

A Cambrex webinar overview

Dr David Pearson, Chief Scientific Officer of Cambrex Edinburgh, discusses how a full understanding of the crystalline landscape of an active pharmaceutical ingredient (API) molecule can predict stability and solubility, minimizing development timelines and cost, and how hydrates can be both a challenge and an opportunity.

The market for solid state services is largely driven by the dynamics of the small molecule pipeline, which has been growing strongly over the last five years. The compound annual growth rate (CAGR) for preclinical and Phase I to Phase III clinical trials for the period from 2014–2018 ranged from just under 6% to almost 10%; and market research carried out by Cambrex indicates that the number of small molecules in the pipeline has risen from 5,500 five years ago to more than 7,000 in 2018.

The progression of a small molecule drug through the clinical pipeline to commercialization typically requires extensive solid state analytical data, ranging from salt screening, polymorph screening, crystallization studies and process development, as well as intellectual property screens. The larger pharmaceutical companies will usually have access to in-house screening capabilities, but it is becoming increasingly common within the industry to outsource these analyses to expert laboratories. Some large drug companies have started to divest this capability completely, while several have expanded and even set up as service providers in their own right.

The total market for solid state services is estimated at in excess of $150 million[1], of which the outsourced contract development and manufacturing organization (CDMO) market represents more than half the total at $80 million. The CDMO solid state services market is forecast to grow by 7.3% CAGR over the next five years, reaching an estimated value of $114 million by 2024[1].

Contributors

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Dr Pearson joined Cambrex following the acquisition of Avista Pharma Solutions in January 2019. Previously, Dr Pearson led the solid state activities of Charles River Laboratories in Harlow (UK), supporting in-house drug discovery and development projects, with a focus on inhalation and external standalone projects. In 2017, Dr Pearson joined the team in Edinburgh to nurture its growth to a leading solid state group, supporting the pre-formulation development of APIs from discovery to commercial manufacturing and beyond.

Dr. Matthew Moorcroft,
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Dr Moorcroft joined Cambrex in 2014 as Vice President of Global Market Intelligence & Communications. He is also involved in the M&A and corporate development team that worked on a number of recent acquisitions, helping Cambrex to become the leading end-to-end small molecule CDMO. Prior to Cambrex, Dr Moorcroft worked for Lonza in a number of roles including Vice President of Strategy, Director of Marketing Intelligence and Head of Global Marketing. Matt holds a Ph.D. in chemistry from the University of Oxford.

In the global market there are approximately 30 CDMOs that offer salt selection, polymorph screening, co-crystal screening or related services; of which two-thirds are based in the UK and Europe.

Cambrex is the largest global CDMO focusing on small molecules and has 12 facilities across the US and Europe, in which it has invested significantly. Much of the company's growth has been organic but recent acquisitions have allowed the company to expand into new markets and broaden Cambrex's small molecule reach from API all the way through to drug product, early clinical trial supply and analytical services. The site in Edinburgh, Scotland, is the hub for its solid state services and was part of the 2019 acquisition of Avista Pharma Solutions.

Solid form chemistry

Before looking at the advantages that can arise from understanding the crystalline landscape of an API molecule, it is first necessary to ask what is solid form chemistry and why does it matter? The answer is that solid form chemistry has a massive impact on a wide range of disciplines, including chemistry, manufacturing and control (CMC), medicinal chemistry, process chemistry and drug metabolism and pharmacokinetics (DMPK). To understand, modify and control the solid state properties of a molecule can help to drive forward its development, de-risk its progress from the laboratory to the clinic, and shorten timelines; ensuring that high quality medicines reach the market – and the patients who need them – as rapidly as possible.

It is not uncommon to bring about a change in the solid form of an API between batches, even without trying. Medicinal chemists making compounds as quickly as possible will frequently use

preparative high performance liquid chromatography (HPLC) to purify the material, and often lyophilized fractions, to isolate their molecule as quickly as possible. This may well yield amorphous material, and when process chemists optimize the chemistry to scale up the synthesis, this can often involve the crystallization of the product material, sometimes unintentionally. This crystallization can have a significant effect, not only on the solubility of the molecule but on other attributes such as stability, hygroscopicity, handling properties and purity. By nominating a robust solid form at the early stages of a development program, high quality material to feed further studies will be consistently delivered.

Even with modern modeling software and the computing power of the cloud, the crystalline nature of an API still cannot be reliably predicted. Comprehensive experimental screening of the material using a variety of solvents, experimental conditions and processes, along with all the associated analytical techniques, can be critical in understanding the crystalline landscape. At Cambrex Edinburgh, for example, an initial run may involve in excess of 120 experiments across the crystallization landscape, followed up by more focused experiments to go into greater depth for the most interesting forms from that preliminary screen.

There are a number of ways to classify the different solid forms that a material can produce, and there is a clear scientific distinction between true polymorphs – which have a thermodynamic relationship between each other – and solvates. Solvates, which have a consistent amount of a solvent molecule within the asymmetric unit cell of a crystalline material, are relatively easy to recognize for a solid form scientist during screening activities.

Solvated forms of an API, where the solvent in question is an organic molecule (such as ethanol) are rarely used for development. Hydrates, however, where the solvent molecule is itself water, present a special case. Hydrate formation can influence many properties and is believed to affect up to 75% of all pharmaceutical compounds[2].

There are two main reasons why development programs need to be very mindful of hydrates and actively look for them. Firstly, the vapor pressure of ethanol for example, above a drug substance is effectively zero once isolated, making desolvation of the ethanol solvate a one-way process. But the vapor pressure of water is rarely zero, therefore hydrates need to be considered because the hydration and dehydration can be a reversible process and occur under ambient conditions, such as storage.

Secondly, water is often used during the drug substance manufacture and in drug product formulations, such as solutions of reagents in salt formation, wet granulation in drug product manufacture, and as a solvent for lyophilization, as well as being the solvent of life itself. For example, dosing in an anhydrous form that converts upon storage or in the body to a lower-solubility hydrated form may have an impact on the observed solubility and dissolution of the API, making the in vitro/in vivo correlation work more difficult to understand. Knowledge of the material's potential to form hydrates, however, would alert the team to this possibility.

As hydrates can pose a risk to the development of an API, there are many ways these can be de-risked at an early stage, including: dynamic vapor sorption (DVS) analysis; early stability at International Council for Harmonisation (ICH)-like conditions, such as 40°C, 75% relative humidity (RH) or 25°C/60% RH; as well as various water-activity solvent systems using the screening work.

The following two case studies illustrate how a good understanding of the crystalline forms of a compound can have implications for selecting the most appropriate solid form chemistry going forward and any potential risks down the development pathway.

Case study 1: Racemic model compound

Starting from an amorphous input material, the screening of the molecule uses a wide range of process-relevant solvents across the ICH classification system coupled to a variety of experimental conditions.

Table 1: Results from primary polymorphism screen

Solvent	Thermal Cycle	Cooling (2°C)	Cooling (-18°C)	Anti-Solving Addition	Evaporation
1,4-Dioxane	1	1		1	1
1-Propanol	1	1			1
2-Ethoxyethanol	1	1		1	1
2-Propanol	1	1			1
Acetone	1				1
Acetonitrile	1				1
Anisole	1	1			
Diisopropyl ether	1		1		1
Dimethylformamide	1	A		1	
Dimethylsulfoxide	1				
Ethanol	1		1	1	1
Ethyl acetate	1				1
Heptane	1				1
Isopropyl acetate	1	1	1		1
Methanol	1	1			1
Methanol:water (50:50 v/v)	1		2		
N-Methyl-2-pyrrolidone			1		
Methyl ethyl ketone	1				
Methyl isobutyl ketone	1		1		
tert-Butanol	1	1	1		
tert-Butyl methyl ether	1	1			
Tetrahydrofuran	1		1		
Form 1	1				1
Form 2	2				
Amorphous	A				
Solution					

Table 1 above shows that form 1 material predominates from the thermal cycling of the amorphous input material as well as the other process-relevant conditions that the material might encounter during manufacture. However, it also shows that the form 2 material may be a hydrate, isolated from water and also the methanol-water mixture (shown in orange in the table). While the X-ray powder diffraction (XRPD) data alone does not confirm this, it raised a question which needed further investigation. This is where a deep understanding of the solid state area is critical to understanding form 2 as a polymorph or a hydrate of form 1.

The freebase form 1 is highly crystalline with good thermal properties, and showed only slight hygroscopicity when analyzed by dynamic vapor sorption. There was no evidence of any form change in the DVS data and this was, of course, confirmed by XRPD post DVS analysis. The single crystal structure confirmed it was a racemate, as opposed to a conglomerate, and the density and packing indicated that this was probably the most stable polymorphic form of the anhydrous material in a racemate form. There were no holes in the crystal structure, there were no channels and it was very dense, which indicated it was probably the most stable polymorphic form.

DVS analysis of the free base form 2 material yielded some interesting data: form 2 was stable until taken below 10% RH, when a 3.2% mass loss was observed. The material it converted to, though, was stable when exposed to excess of 40% RH and then it regained the mass (shown in Figure 1). This data suggests that the material converts back to form 2. Performing a variable-humidity XRPD experiment by altering the humidity over the sample and acquiring the resulting data in situ offered absolute proof that form 2 converts to a new form 3 that was not observed in the primary screen, but that it also converted back to form 2 when rehydrated (as shown in Figure 2).

Figure 1: DVS isotherm plot of form 2

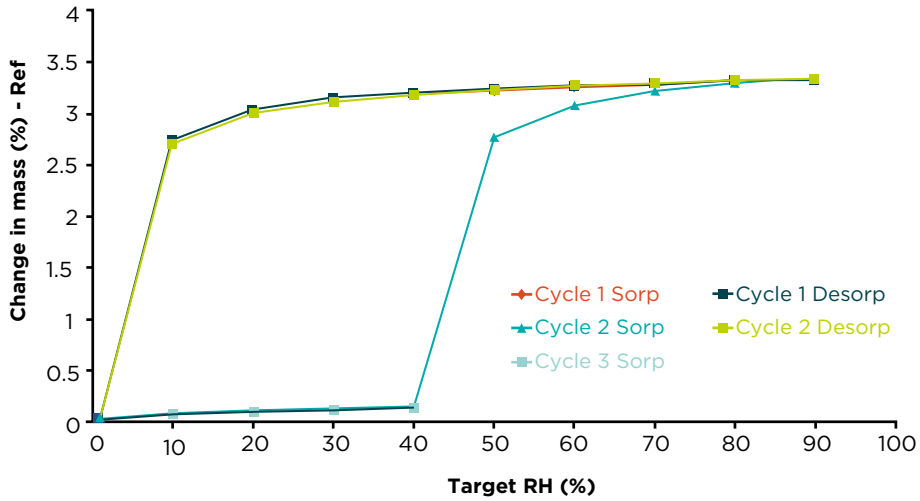
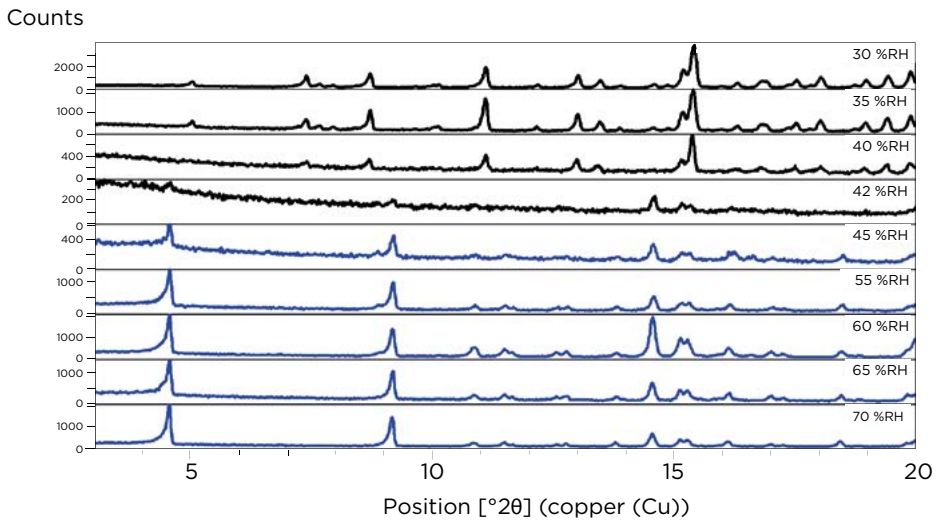


Figure 2: VH-XRPD data for form 2 converting to form 3

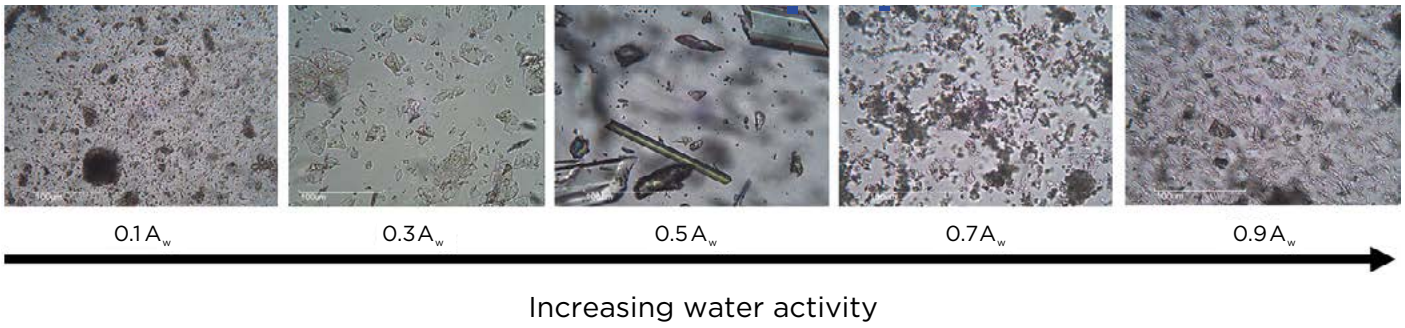


This is a good example of a solvate – and in this case, this hydrate is a special case of solvates – that dehydrates to a novel form that was not isolated during the screening experiments. It is not too difficult to imagine a situation where this might be the most suitable form for further development. This would not normally be a recommended route to manufacture a crystalline form, as desolvation takes time, it often struggles to go to completion and the crystals often shatter during the process. However, if these conditions and this form provides seed material, there is the potential to use these seeds as a true crystallization process.

Although the inter-conversion poses a risk for form 2, this could, in theory, be controlled with even deeper understanding of the experimentation. There is a considerably wide humidity range where form 2 is stable, but it must be noted that this experiment took place at 25°C and different temperatures will affect these results. Experiments with variable temperature DVS can therefore de-risk the hydrates even further, if that is the chosen form to move forward with.

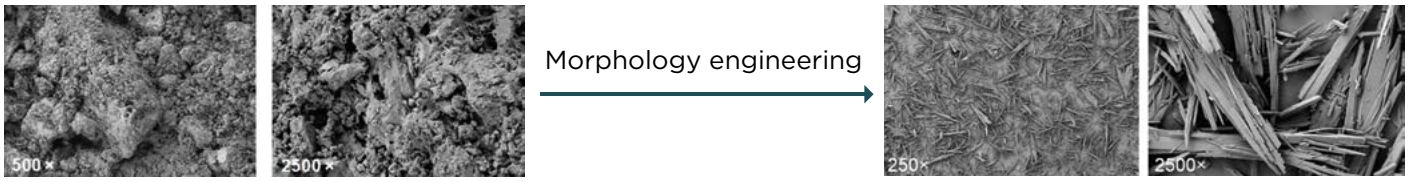
Hydrated forms, as opposed to anhydrous forms, can offer a different route to a crystallization space where solubility, metastable zone width, particle morphology and growth rates can all be different and sometimes used to the advantage of developers. Rapid polarized light microscopy (PLM) analysis of samples from a variety of different water activity systems, for example, can clearly show that mixtures of tipping point or critical water activity between two forms can be obtained (Figure 3). This information can be used to help develop a crystallization process that controls the desired crystal form produced, while controlling and optimizing other factors, such as particle size, yield, morphology and purity.

Figure 3: PLM images of material at different water activities (A_w)



It should be noted that different crystal morphology is not proof of a new crystal form or polymorph. Different solvent systems can affect the growth rates of different faces of the crystal, which can lead to fine, acicular, high-aspect crystals or more block-like, lower-aspect crystals; this has implications for filtration, drawing and handling, for example. As shown in Figure 4, by judicious choice of solvent systems, initial experiments which yield irregular, ill-defined particles can be engineered to yield much bigger, more discrete crystals that are easier to filter, dry and handle.

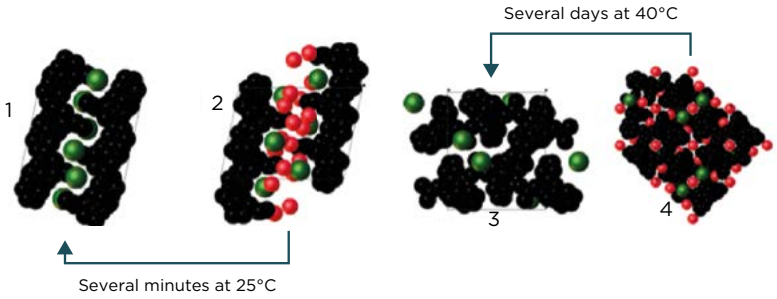
Figure 4: Morphology engineering – better filtration



Case study 2: Racemic API as a hydrochloride salt

During detailed polymorph screening studies of an API, four different crystal forms were obtained from organic solvent and solvent/water mixtures. Form 1 was an anhydrous racemate, which was the desired form, form 2 was a hydrated racemate form, form 3 was an anhydrous conglomerate form and form 4 was a hydrated conglomerate. The rate at which these hydrated forms dehydrated varied massively from several minutes under ambient conditions, to several days at 40°C in a stability oven (Figure 5).

Figure 5: Different structures of API – different dehydration rates



Initial data indicated that there were two anhydrous and two hydrated forms with the same amount of water observed in the two hydrated forms. Only detailed analysis by XRPD, single-crystal X-ray diffraction, DVS and thermal analysis showed that they were not true polymorphs of each other. This understanding then allowed the targeting of the desired form, selected on the basis of a variety of data.

Hydrate mapping, in which the water activity and organic solvent system is systematically altered with more or less water, is a powerful technique to enable understanding of the hydrate formulation in solvent-based systems. While DVS and variable humidity XRPD can provide a wealth of information on critical water activities and kinetics, a more practical method is solvent-based and more closely related to real world scaling-up. This results in production of a table to help guide the process to the desired solid form, Table 2 below shows the results from the hydrate mapping for this particular API and its four forms.

Table 2: Hydrate mapping of the 4 API forms

		Water activity in ethanol										
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Input form	Form 1											
	Form 2											
	Form 3											
	Form 4											

Form 1	Anhydrous racemate
Form 2	Hydrated racemate
Form 3	Anhydrous conglomerate
Form 4	Hydrated conglomerate

If results show that an undesired hydrate is isolated, there are a number of ways to attempt to convert it back to a preferred form. Hydrates may be stable because the ambient relative humidity is really zero, so reducing the relative humidity – for example, by storing the material over a desiccant or heating it in a vacuum in a tray dryer – can often force a hydrate to dehydrate. Slurrying or crystallization in solvent systems that have a low water activity can also be used to help recover an unwanted hydrate formation; however, this process can only be guided with deep understanding of the relationship between the anhydrous and the hydrated forms.

In this case study, form 1 was nominated as the best to move forward with, and the crystalline landscape data to hand could be used to develop a crystallization protocol to produce it in a reliable manner. Accurate solubility measurements, with quantification by ultra performance liquid chromatography (UPLC), in a variety of solvents can help guide the choice for further crystallization optimization.

While water is a great antisolvent for many APIs, in this case the potential for an undesired hydrated form posed a potential risk. The ICH class 3 alcohols (which are defined as solvents with low toxic potential) showed really high

solubility. Methanol, as a class 2 solvent (defined as solvents to be limited), also showed good solubility but offered some disadvantages compared with ethanol and isopropyl alcohol (IPA, propan-2-ol), such as in the areas of toxicity and its thermal window. Heptane and methyl tert-butyl ether (MTBE) were identified as antisolvents, with heptane being preferred as a class 2 solvent with a higher boiling point than MTBE.

Experiments were then undertaken to gather metastable zone width measurements. There are a variety of ways to obtain these using a range of different tools; such as focused beam reflectance measurement (FBRM), turbidity probes, Crystal16™ and the recent BlazeMetrics™ probes. In this case, a cooling crystallization was used and the metastable zone width measured in a variety of different solvent systems. This data can be used to assess potential recovery and the metastable zone width measurements, as well as to give early indication of particle size, morphology and other properties. The ethanol-heptane system gave the widest metastable zone width, which allowed greater flexibility over seeding point, cooling profile and therefore desupersaturation rates. The crystal form produced from these experiments was also checked and found to be the desired form 1, even without the use of seeds.

Once the solvent system has been identified – and in this case, ethanol:heptane looked ideal – the crystallization should be optimized with an in situ, real-time analysis of the process. Using a BlazeMetrics™ probe, particles were monitored as they were produced and this provided a wealth of information on the formation, growth, morphology and size distribution. The large particles obtained filtered very rapidly, dried easily and ultimately gave a high-quality product and a process that could easily scale to a vessel size in excess of 1,000 liters.

Online Raman spectroscopy was not required, as use of a non-aqueous solvent system reduced the risk of hydrate formation. However, it could be used to observe the formation of an undesired crystal form or, more importantly, confirm that there was no change in form occurring in the vessel as the crystallization process proceeded.

Conclusion

Undesired hydrates can appear at any stage in R&D, and manufacturing operations and specific steps can be utilized to avoid them. Obviously, understanding the science behind the relationship between the anhydrous and hydrated forms is critical. In both of the case studies described above, the formation of potentially disastrous hydrated forms were successfully avoided; and in both examples the final morphology returned solids that filtered efficiently and handled well.

Understanding the different crystal forms that a material can produce can speed up the development of an API, reduce risk in the development and manufacturing of both the drug substance and drug product, as well as adding intellectual property to the portfolio. Working with an expert team that has a deep understanding of the solid state will help the progression of a development program, and help deliver new, efficacious medicines to the patients.

References/Sources

[1]Cambrex Marketing & Intelligence; (2019)
[2]CrystEngComm; 8 (2006) 11-28