Harnessing The Power of Solid Form and Particle Engineering to Overcome Solubility and Bioavailability Challenges

An Interview with Veranova's Craig Grant

Persistent challenges in poor solubility and low bioavailability have long impeded the pharmaceutical development pipeline, presenting ongoing hurdles for drug companies. As the industry grapples with increasingly complex new chemical entities, the need for innovative solutions to overcome these challenges becomes more urgent.

To delve into this issue, explore current strategies for advancing poorly soluble drugs through the clinical pipeline, and uncover best practices for formulating drugs with solubility issues, IPI Journal spoke with Veranova's Craig Grant, VP and General Manager, Cambridge.

With over two decades of solid form expertise, Craig is a founding figure behind Pharmorphix®, Veranova's dedicated brand for solid form and particle engineering.

Q: It's estimated that up to 40% of marketed drugs, and between 70 and 90% of drug candidates in the development stage, exhibit poor solubility.[1] Could you explain why solubility and bioavailability continue to be such big issues in bio/pharmaceutical drug formulation?

A: In the pharma and biotech industries, the need for effective therapeutics is continually driving the discovery and development of novel active pharmaceutical ingredients (APIs) and new chemical entities (NCEs). This has resulted in the development of increasingly complex drug scaffolds, often with one or more chiral centres and which routinely possess high molecular weight. Though these drugs offer improved stereoselectivity, target specificity and activity, their complexity often causes them to be poorly soluble, which can cause a wide variety of knock-on issues, most notably poor bioavailability with low drug absorption in the body, resulting in such molecules being assigned to BCS Class II (high permeability, low solubility).[2]

Moreover, at the candidate selection stage, developers are more likely to focus on potency or efficacy, meaning the downstream developability of NCEs is often overlooked during early-stage development. This can lead to significant challenges further down the development pipeline, leading to costly delays and resource wastages.

Q: As increasingly complex drug molecules enter the development pipeline, how do you see solubility challenges evolving in future?

A: With small molecules becoming increasingly more complex, solubility challenges are here to stay. This is even more relevant when considering current pharmaceutical trends, with increased prevalence in existing modalities such as peptides, which, depending on size and/or complexity, straddle the boundary between small and large molecules. The emergence of new "small molecule" modalities such as PROTACs (PROteolysis TArgeting Chimeras) also bring substantial solubility and developability challenges. PROTACs are a subset of TPD (targeted protein degraders), an emerging therapeutic modality used to treat previously difficult or undruggable targets. Unlike traditional protein inhibition methods, PROTACs are two-pronged molecular entities designed to seek out and degrade disease-causing proteins within the cell. However, due to their size and flexibility, PROTACs typically pose crystallisation and solubility challenges during solid form studies. PROTACs are just one example of how molecular complexity is likely to continue to present difficulties going forward.

Q: What are the most common approaches to overcoming solubility/bioavailability issues during development? Which do you think are the most effective?

A: Obtaining the optimal solid form is pivotal in developing a drug product with good solubility and bioavailability as well as many other required or desirable physical properties. For crystalline materials, optimal usually refers to the thermodynamically stable polymorph of the parent API, salt or cocrystal thereof. Metastable forms have their place too but the key to developing these is a rigorous understanding of the solid form landscape and interconversions that may take place to progress stable, developable forms.

Salts make up the majority of all marketed drugs and are typically the first port of call when attempting to improve aqueous solubility. Crucially, by conducting salt screening and identifying the optimal salt, it is possible to tune the physical properties of the drug in development. If there are no accessible ionisable centres and producing a salt is not possible, cocrystal screening and selection is an increasingly popular alternative.

Arguably less obvious to make, but just as attractive in their ability to modify physical properties as salts, cocrystals allow formulators to preserve the therapeutic benefits of an API but offer the potential to improve solubility and bioavailability. Unlike salts where acid-base chemistry is at play between the API and corresponding acid or base, interactions between an API and coformer are weaker and typically hydrogen bonding-driven. Despite an increase in regulatory approvals over the years, cocrystals still appear somewhat underutilised within the pharma industry, yet our understanding of how to effectively screen, select and scale developable cocrystals offers a significant opportunity.

Then, once the optimal salt, cocrystal or parent version of the API has been selected, it is necessary to carry out full polymorph screening. In fact, it is prudent to perform a preliminary polymorph assessment as part of salt or cocrystal screening, as this is likely to guide selection. Understanding the polymorphism behavior of an API is important for multiple reasons. It not only develops an understanding of the solid form landscape of the molecule in question, but solid forms are also patentable and, crucially, understanding polymorphism for an API is a regulatory requirement.

Beyond modification of the crystal lattice as per methods already outlined, particle-size reduction methods including micronisation are commonplace in the industry, although typically in a "top down" approach. Methods for achieving ever smaller "nano" sized particles are becoming increasingly popular.

Exploring a variety of excipients and surfactants can also provide valuable uplifts in solubility during the early stages of formulation development. It may even be prudent to develop such an "enabling formulation" for toxicology studies, facilitating API progression whilst other crystal or particle engineering methods are pursued for the longer term. Either way, the method of choice needs to consider both the route of administration and the final dosage form to ensure effective formulations are designed with the end in mind.

Amorphous materials, being the most metastable of forms, also offer attractive solubility and bioavailability benefits, though this usually comes at a price. Such materials, where "unprotected", are more unstable chemically and from a solid form perspective than their crystalline counterparts. Stabilisation via incorporation into an appropriate polymer matrix to give a developable Amorphous Solid Dispersion (ASD) is one solution, however. In summary, there is no 'one-size-fits-all' approach, and the process will often be different for each drug molecule.

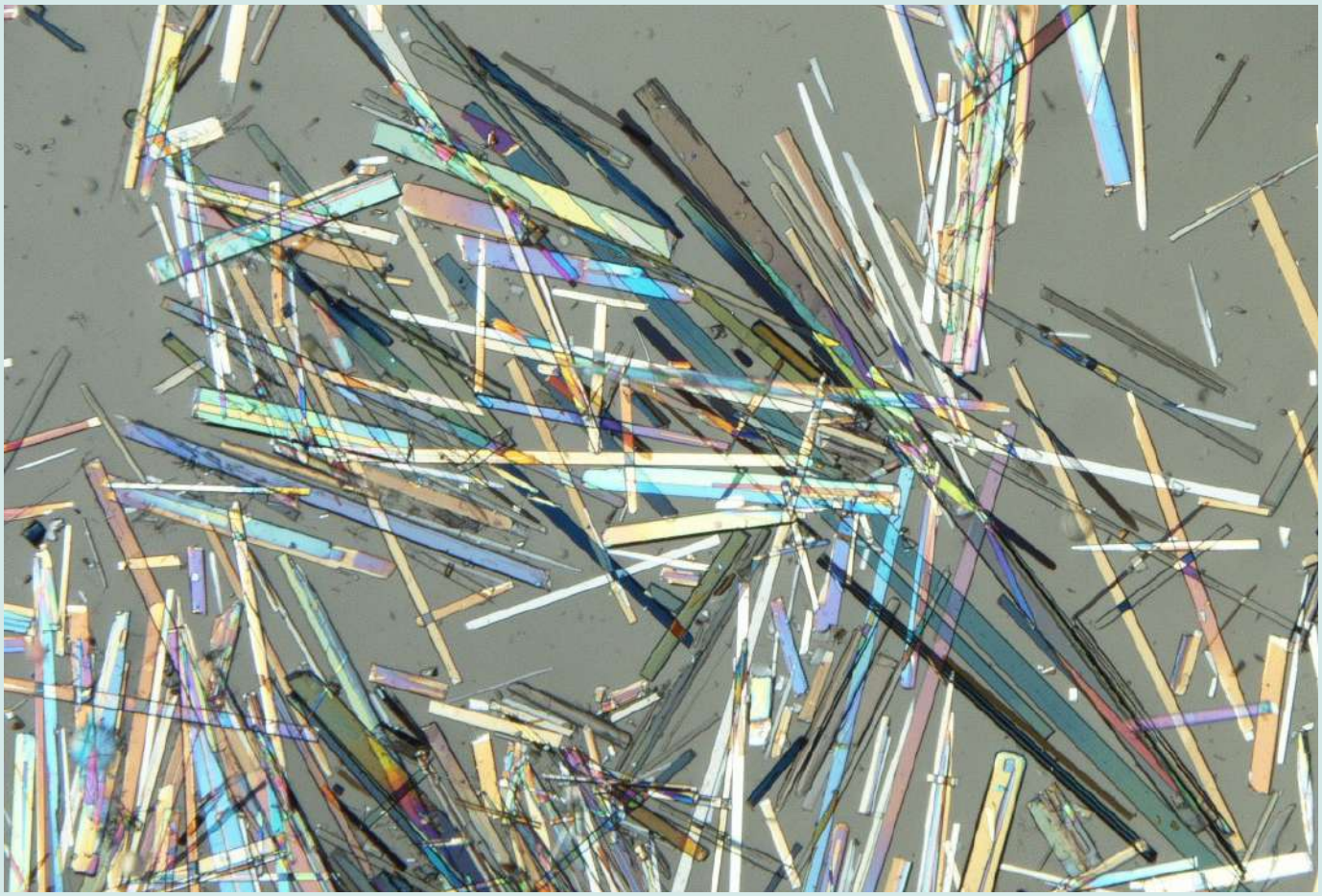
Q: Why is it so important to address solubility issues early in the drug development pipeline?

A: The further an API progresses down the development pipeline, the larger the ramifications will be if a problem is discovered. The main aim of performing solid form studies early is therefore to 'de-risk' future development. Scientists must gain a deep understanding of the physical properties of the drug candidate as early as possible. Typically, solid form studies are performed in preclinical development, but you could argue that understanding the physical characteristics of molecules should be applied in late-discovery/lead-candidate selection. Issues uncovered at this early stage may even promote the selection of an alternate lead candidate but ultimately one that is developable! Solid form and particle engineering studies are vital in ensuring speed to market – by taking all possible precautionary steps, the development process will be streamlined and its efficiency maximised.

Q: Have there been any recent technological advances that you think will have a significant impact on aiding solubility and bioavailability in the development pipeline?

A: Looking to the future, it is likely that predictive AI technologies will see increasing use in parallel with experimental work to help scientists conduct more pertinent experiments earlier on. Modelling tools are already used increasingly in the work we do spanning physicochemical and solubility predictions to crystallisation development. These along with other developments in polymorph prediction will all play their part in helping scientists get to the answer quicker.

Due to convenience and ease of manufacture, oral dosage forms continue to be one of the most preferable delivery routes, and improvements in the methods used to monitor their dissolution in the



gastrointestinal (GI) tract have been invaluable. Small-scale in situ dissolution studies have helped improve our understanding of the solubility and bioavailability of BCS Class II compounds, which are highly permeable in the GI tract but exhibit poor solubility.

There have also been some advancements in the use of porous excipients, such as mesoporous silica, often formulated as lipid nanoparticles to boost the solubility and bioavailability of known compounds. There have been no FDA-approved drugs utilising these technologies yet, but research in this area will likely advance in the coming years.

Q: Could you provide some best practices for formulators when dealing with poor solubility/bioavailability?

A: When dealing with poorly soluble APIs, the aim is always to get it right the first time. It is therefore vital for formulators to obtain as much information about the end goals of a novel drug product as early as possible. Factors such as the route of administration, drug target, and so on can impact the type of experimental design and yield the best value-added data.

Successfully overcoming solubility and bioavailability issues also requires the implementation of robust scale-up processes – for any solid form to have value, it must be scalable. Modelling tools are routinely employed as we design and build robust crystallisation processes, enabling the development of one that will require minimal intervention as it is scaled up.

Should a company decide to collaborate with an outsourcing partner, it is important to carefully consider the requirements and complexity of the project in question. This ensures they select the right expertise for their drug candidate. At Veranova, we adopt a hierarchical approach, following a drug candidate at all stages of development and collecting as much data as possible. Nevertheless, a developer will likely need to draw on a wide range of expertise when managing difficult issues such as solubility, so it is important to fully consider the demands of their drug moiety.

Q: In what ways can a CDMO partner help pharmaceutical companies overcome solubility and bioavailability challenges during formulation?

A: CDMOs can provide pharmaceutical companies struggling with solubility and bioavailability with invaluable guidance. Using specialised technology and expertise, they can develop a tailored approach to each drug molecule, helping companies overcome development hurdles at every stage. A reliable and experienced CDMO company will have the capacity to react to challenges in both a proactive and reactive manner, ensuring that all bases are covered and that the project is brought to completion as efficiently as possible.

Though solubility and bioavailability challenges are central to drug development today, CDMOs can help pharmaceutical companies identify and overcome the full scope of problems associated with a particular drug moiety, from stability to hygroscopicity. By fully understanding the chemistry and selecting the optimal solid form of a drug candidate, CDMOs can help develop robust scalable processes, establish a robust IP position, and ultimately accelerate the therapeutic to market.

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Craig Grant is Veranova's Vice President and General Manager in Cambridge, UK. He heads up the solid form and particle engineering team. Craig has a Ph.D. in structural inorganic chemistry from the University of Edinburgh and has over 20 years' experience in the health and pharmaceutical industry. He has worked across a range of service-based companies, including Cambridge Combinatorial, Exova and Solid Form Solutions, as well as pharma companies, such as Millennium. In 2003, Craig co-founded Pharmorphix® Ltd which was acquired by Sigma-Aldrich in 2006, later by Johnson Matthey in 2015 and is now part of Veranova, a standalone CDMO with a global footprint and particular expertise in the development and manufacture of highly potent and controlled substances. Under the Pharmorphix® brand, Veranova offers one of the most comprehensive arrays of integrated solid form, pre-formulation, particle engineering and chemical development capabilities available to the pharmaceutical and biotechnology industries.