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# CASE STUDY

## KEY STRATEGIES CENTRAL TO OVERCOMING POOR API SOLUBILITY

Noel Hamill, an Investigator with the Physical Sciences Group at Almac discusses various fit for purpose and cost effective routes to enable rapid progression of new drugs into clinical development.

The number of novel drug candidates with solubility limited bioavailability is increasing and this presents an industry wide challenge to effective and efficient drug development. The widespread use of high throughput screening in drug discovery, and the tendency towards targets with more lipophilic binding sites are factors that have contributed significantly to poor solubility of new active pharmaceutical ingredients (APIs)[1]. Rather than seeking a re-design of the molecule through the medicinal chemistry route, solid state chemistry and preformulation development are a fit for purpose and cost effective means of enabling rapid progression into the clinical phases.

### IMPROVING DRUG SOLUBILITY

To date, the most common means of improving drug solubility has been salt formation, with around half of all drugs in the FDA Orange Book marketed as salts[2]. Salts can increase solubility by several orders of magnitude compared to the unionized API, albeit over a specific pH range. Although salt screening is recognized as an essential part of drug development, it is often restricted to a lower priority activity for the medicinal chemist, development chemist or formulator to accomplish alongside other tasks. For those who have not had experience in this area, screening can be narrow in scope and 'risk averse', with the first crystalline 'hits' generally accepted as a successful outcome. For example, hydrochloride is not automatically the best choice for a basic molecule, as the dissolution rate and bioavailability may be retarded as a result of the common ion effect. Restricting the screening to ions which have been previously used in marketed drugs does not necessarily mitigate risk either; just because hydrobromic acid and ethylenediamine were (and are) readily used in organic chemistry labs, which means that they would be acceptable to today's regulators.

It is true that while the methodology for salt screening is not difficult, the understanding of salt formation, toxicology and solid state characterization is essential to create the best opportunity for drug improvement and avoid incorrect (or costly) selection of the 'wrong' form of an API. To this end, a tailored scientific investigation is preferable to a generic high throughput experimental screen, as several iterations with different conditions may be necessary to coax the first good quality crystals to nucleate.

Changing the salt form during the clinical phase of a drug should be avoided because this is regarded as a change in the drug substance from a regulatory point of view, which results in costly repeated toxicological ('tox') bridging studies. This implies that most effort on salt formation is applied during the synthesis of the preclinical 'tox' batch. For small and virtual pharma and biotech companies, using an integrated supplier like Almac for project management of synthesis, screening, form selection and 'tox' studies in parallel (known as rapidd™) can reduce risk and minimize spend by eliminating the extended time and loss of information from technology transfer.

The main drawback with salts is that, by necessity, the API must be an acid or base of sufficient strength to enable a stable salt to form and therefore, for a weak acid or base, only a few non-toxic,

pharmaceutically acceptable counter-ions may be available for screening. This is not the case for cocrystals, which are stoichiometric mixtures held together by hydrogen bonds, as there is no requirement for ionizable moieties and allows a much wider range of excipients to be screened. Although known about for a long time as 'molecular complexes' or 'addition compounds', cocrystals have only recently attracted attention as a tool for rescuing insoluble drug candidates from rejection. As the drug is not ionized, there is an enhancement in the 'kinetic' solubility, not a fundamental change in the thermodynamic equilibrium solubility afforded by salts at certain pH. Nonetheless, the solubility advantage can be substantial, with up to a 150-fold increase reported for carbamazepine cocrystals[3].

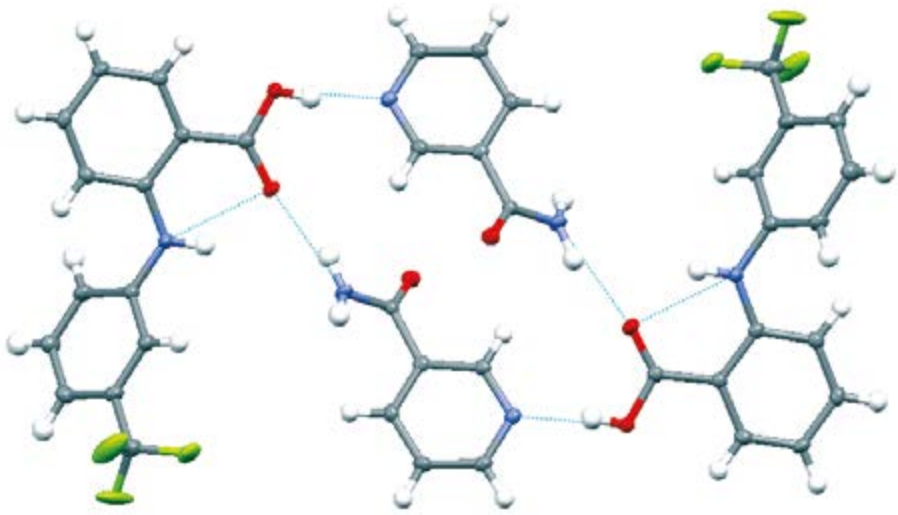
Whereas salt formation is predictable to some extent from pKa data, cocrystals are not. Formation can be inferred from known functional group interactions, such as Etter's rules[4], but these predictions are only successful in an estimated 30% of cases[5]. Even when observed, the properties of the resulting cocrystal canelude prediction. For example, in our recent study on five structurally related non-steroidal anti-inflammatory drugs (NSAIDs)[6], four formed cocrystals with nicotinamide (example in Figure 1), but the solubility and stability of the resulting cocrystals were remarkably different. As with salts, the challenge is not so much in finding cocrystals, but development of an operable scale up method. Control of purity and particle size usually requires a solution based method, for which knowledge of ternary phase diagrams and in situ crystallization development tools, such as FBRM and PVM (Figure 2) become invaluable in this regard.

Although most commonly employed for modifying aqueous solubility, salts and cocrystals modify a range of other properties, such as hygroscopicity, chemical stability, dissolution rate, crystallinity and physical stability, making them an attractive means of generating intellectual property.

## AMORPHOUS PHASES

It is worth noting that the level of solubility enhancement through the use of crystalline salt and cocrystal forms may not be sufficient for large insoluble and/or lipophilic (also known as 'brick dust' and 'grease ball') molecules. In such cases, amorphous phases may be more advantageous. The solubility enhancement possible with amorphous material has been reported as 10 to over 1000 times greater than crystalline forms in some cases[7], with 2-10 fold increases much more common in practice. However, as they are inherently more chemically and physically unstable than crystalline forms, amorphous formulations require increased investment to develop and stabilize. As a result of this need for stabilization with excipients, amorphous dispersions are traditionally the reserve of formulation specialists in late phase development. However, this huge solubility enhancement can also be used to great benefit during preclinical studies. Due to the improvements in targeted drug therapies, it is becoming increasingly difficult to demonstrate a toxic effect during ascending dose animal studies. This requires higher dosing and bioavailability quickly becomes solubility limited, due to the increasingly lipophilic character of new chemical entities. In many cases for salts, cocrystals

**Figure 1:** Flufenamic acid / nicotinamide cocrystal



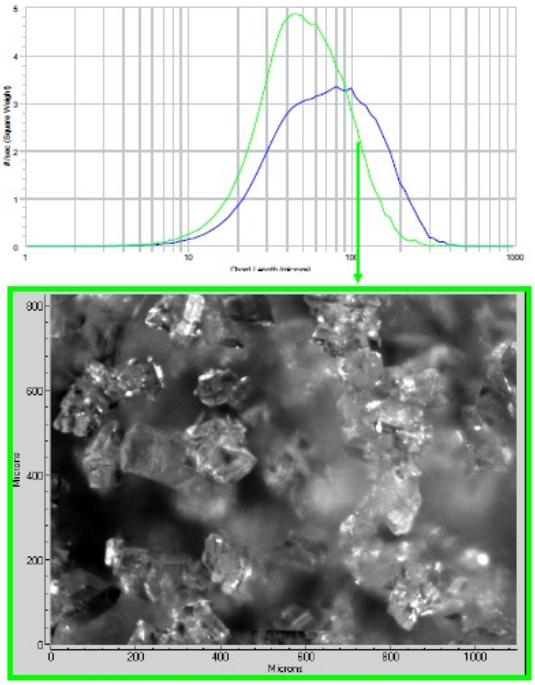



**Figure 2:** In situ PVM (particle video microscope image of a crystal suspension

and amorphous formulations, the solubility enhancement is short-lived 'kinetic' solubility, before a more stable, less soluble form precipitates in vivo. The challenge to formulators is to sustain the enhancement long enough to maximize bioavailability.

## FORMUFAST™

Almac have developed a screening platform for amorphous solid dispersions, formufast™ SD, which assesses the interaction of stabilizing polymer and API in the solution state. Stronger interactions have been linked with stability in the solid dispersion[8] and precipitation inhibition[9]. Variations on this platform have also been successfully employed for screening excipients for oral and intravenous formulations, formufast™ PO & IV, to provide a scientific rational approach to early phase formulation development. The historical approach was stepwise, with simple formulations incrementally changed until a 'hit' was achieved, much in the same way as with salt screening, as discussed earlier. This methodology is more likely to miss the best possible formulation and does not generate the deep understanding which can streamline later phase (clinical) formulation development, leading to calls for a more systematic approach[10].

The formufast™ oral and IV screens are a rapid, low cost means of systematically assessing many excipients, as combinations in different proportions or by varying the order of addition. From these small scale tests, a rational design for preclinical formulation can be identified from kinetic solubility and precipitation inhibition in aqueous media or lipidic vehicles.

Of course, there are always difficult APIs that may not form stable amorphous dispersions, or where enhancement from salts/cocrystals is still inadequate. Since poor solubility also imparts a poor dissolution rate, this implies that the bioavailability of some APIs is reduced merely because they are not dissolving fast enough in vivo. The simplest way to increase the rate is by increasing surface area through particle size reduction. The micronization of drugs is now commonplace, with jet milling and spray drying routinely carried out at manufacturers such as Almac. Micronization increases dissolution rate but tends not to influence the equilibrium solubility of a drug[11], except by disordering the crystallinity of the particle surface. Since surfaces have a higher free energy (and higher solubility) compared to the bulk, particles have to be sub-micron in size before this phenomenon can be exploited. This has led to the rise of

nanosuspensions for drug delivery in the last two decades[12]. These sub-micron colloidal dispersions of drug particles are stabilized by surfactants and enable increased bioavailability, such as the 16-fold increase reported for Danazol[13]. Some preparation techniques remain under patent protection; such is the level of commercial interest. However, research samples can be successfully scaled down and tested[14], prior to committing to these technologies at full scale.

## IN SUMMARY

As an integrated service provider, Almac can employ the full arsenal of solubility enhancement tools and brings a wealth of experience in synthetic chemistry, solid state services and formulation to provide clients with workable cost effective solutions, and allow the best candidates to progress into the clinical phase rapidly and with minimal spend.

The Almac Group provides a broad range of services from R&D, biomarker discovery and development, API manufacture, formulation development, clinical trial supply and IXRS® technology (IVRS/IWRS), to commercial-scale manufacture. Almac provides services to more than 600 companies, including all the world leaders in the pharmaceutical and biotech sectors. The company employs over 3,300 individuals and is headquartered in Craigavon, Northern Ireland. US operations are based in Pennsylvania, North Carolina and California. For more information about the Almac Group, please visit www.almacgroup.com or e-mail info@almacgroup.com.

Almac's Physical Sciences group offers the complete range of screening, development, analytical and legal support services relating to solid forms in drug substance and drug product, uniting Almac's expertise in process chemistry, operations and formulation to provide an integrated, synergistic solution to our clients' needs.

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