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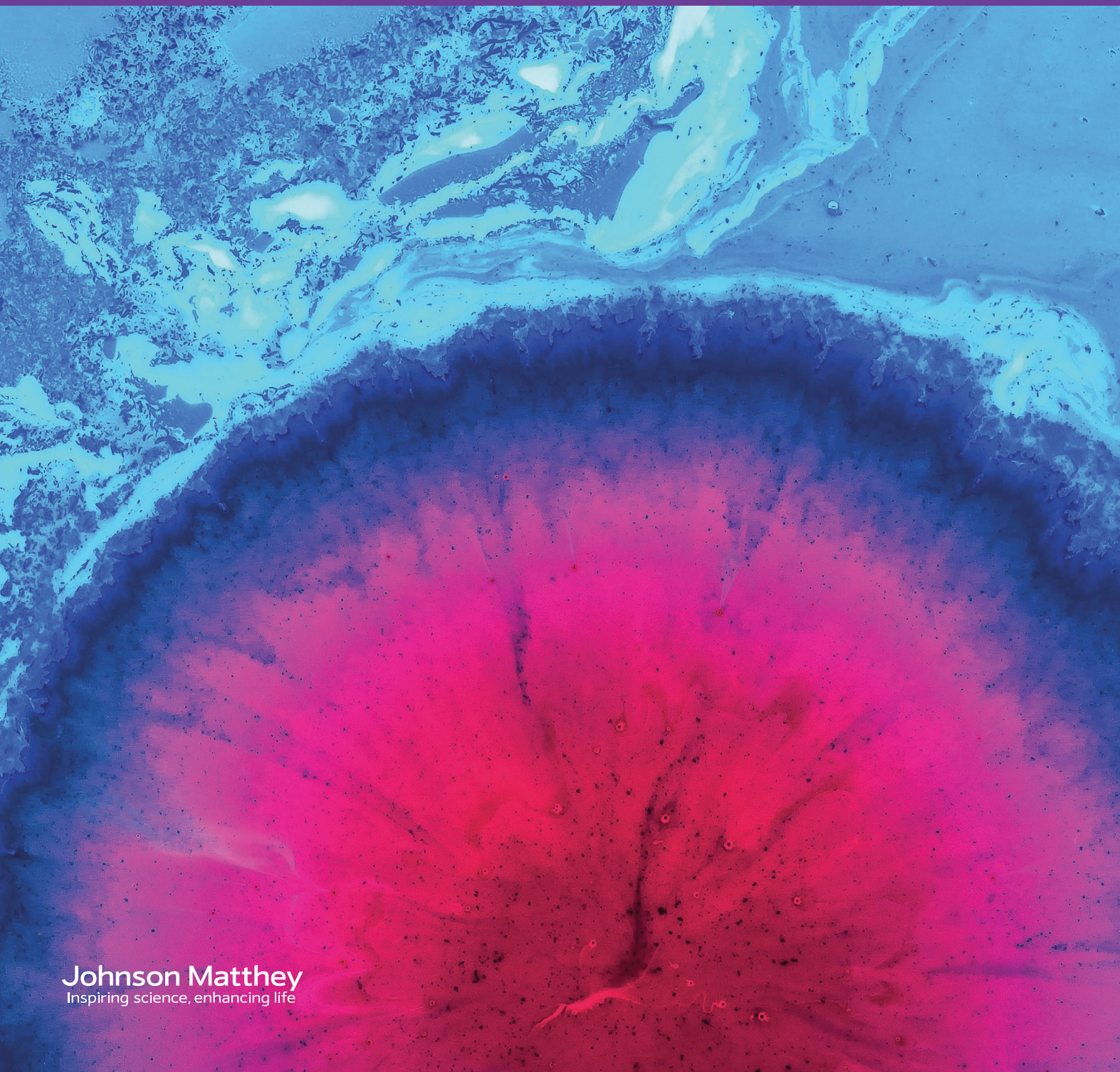
White paper

Early form screening strategies to accelerate candidate selection



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Prof. Chris Frampton. Biography

Professor Chris Frampton obtained his B.Sc in Chemistry and his Ph.D in Inorganic Chemistry from the University of Essex in 1981 and 1985 respectively. After completion of his Ph.D research he took up a postdoctoral position in the laboratory of Professors Tom Birchall and Ron Gillespie at McMaster University Hamilton, Ontario, Canada, researching into the correlation of crystal structure data with Mössbauer spectroscopic parameters of high-oxidation state main-group compounds. He subsequently took up the management position of the single-crystal X-ray facility at McMaster University. Prior to his more recent academic positions, Professor Frampton is a cofounder and Chief Scientific Advisor of Nuformix (2009), a company devoted to the exploitation of cocrystal technology to improve the pharmaceutical characteristics and generate new IP for new and existing drug products, as well as cofounder and Director of Pharmorphix Ltd. (July 2003-May 2014), providing consultancy and solid-form research services to the pharmaceutical and biotechnology sectors. He joined Pharmorphix full time in January 2005 as Chief Scientific Officer. Pharmorphix was acquired by SAFC Pharma, A Sigma-Aldrich Company Ltd. in August 2006 and more recently by Johnson Matthey PLC, October 2015.

He held the position of Director of Strategic Marketing at Bruker AXS where he was responsible for new technology in the bio-market. He joined Bruker AXS after 9 years at Roche Discovery Welwyn, a UK-based semi-autonomous research and development division of F. Hoffman La-Roche AG, with the primary responsibility for the establishment of a single crystal X-ray diffraction laboratory to support both medicinal chemistry and the pre-clinical Pharmaceutical Development Department. This included participating in research projects that led to the successful market launch of drugs such as the influenza neuraminidase inhibitor Tamiflu® (oseltamivir phosphate) and a first-generation HIV protease inhibitor Invirase® (saquinivir mesylate). He is the author and co-author of over 30+ patents and over 140 peer-reviewed research publications which have appeared in many high-impact journals. He is a member of the editorial board of for the IUCr journal Acta Crystallographica, Sect. C.

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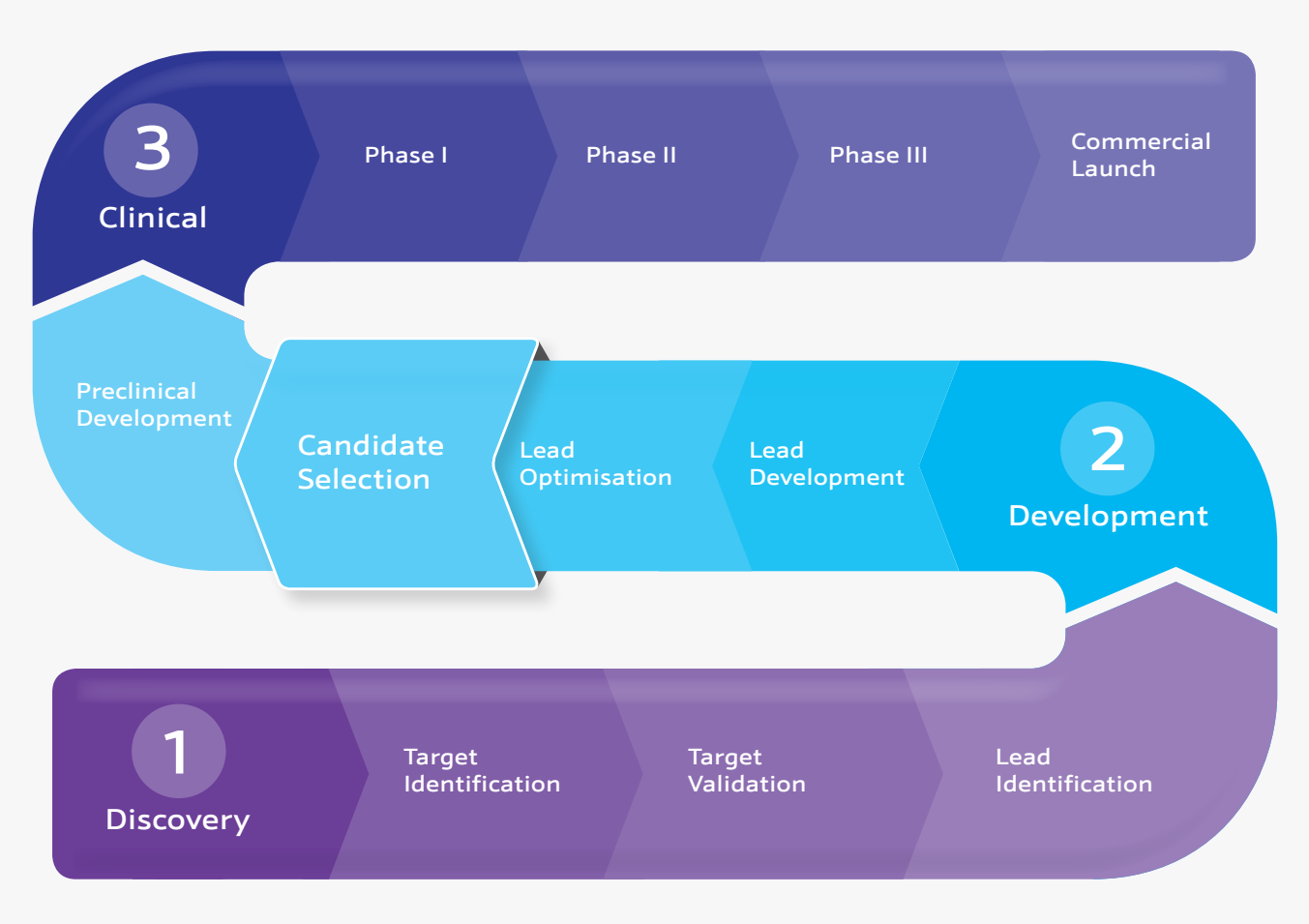
Early form screening strategies to accelerate candidate selection

The development of a new drug often begins with a hypothesis. In particular, researchers are interested in understanding how an individual biological molecule, such as an enzyme or protein receptor, can be targeted to regulate its function and affect the disease process. The route to new medications follows a well-recognised drug discovery pathway (depicted below) which begins with the target identification and ends with the commercial launch of the drug product.

This route to drug discovery, development and manufacture is a notoriously lengthy process, and can often take over a decade from discovery to launch. Additionally, there can be many challenges and pitfalls that need to be addressed along the way. As the process moves forward, there comes a point at which the selection of a particular candidate and perhaps one or two backup candidates to go forward into the clinical phase is reached, this is termed clinical candidate selection.



Pathway diagram

Candidate selection

The process of lead candidate selection is possibly the most crucial of all the steps in the drug discovery and development pathway, as the ultimate goal of the commercial launch of a successful therapy will be solely dependent on the performance of that selected candidate through the clinic. Due to the importance of a selected candidate or candidates' ability to overcome the challenges that lie ahead during the development phase, there are many factors that that must be taken into consideration. This includes

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pharmacokinetic, safety and efficacy data, all of which need careful analysis before any decision can be made. Failure to select a successful candidate can be expensive in terms of both time and money. Indeed, the clinical development success rate for obtaining approval has been shown to be only around 10% for all indications outside oncology, with the main reason for failure being given as poor or even non-existent efficacy.

Overcoming the challenges

So, what can be done to increase the chances of success for a particular candidate? Candidate selection is a far more complex procedure than just pursuing the most active lead compound. Before any decision can be made the candidates should be subjected to a full range of preclinical safety, toxicology and performance assessments, including a full physicochemical profiling package, oral bioavailability assessment, a full understanding of the DMPK and ADME models and also an understanding of the possible downstream formulation issues, for both an enabling and final form. It is also worthwhile keeping in mind at this stage the possibility for solid-form modifications such as polymorph selection to overcome a potential instability, for example hygroscopicity or light. Salt and cocrystal forms may also be considered for potential solubility enhancements. Current research estimates that approximately 40% of NCEs currently being developed demonstrate little or no aqueous solubility.[1]

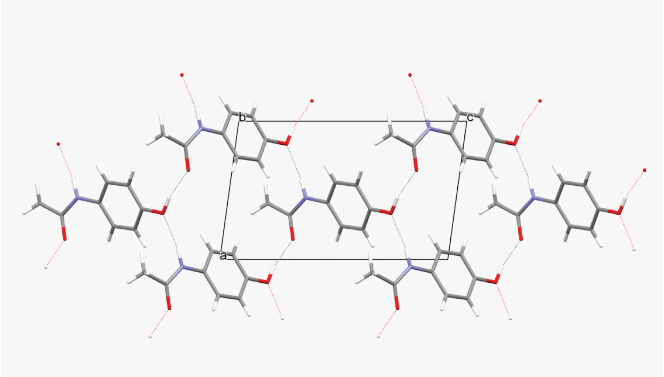

Figure 1: Crystal structure of form 1 of acetominophen.

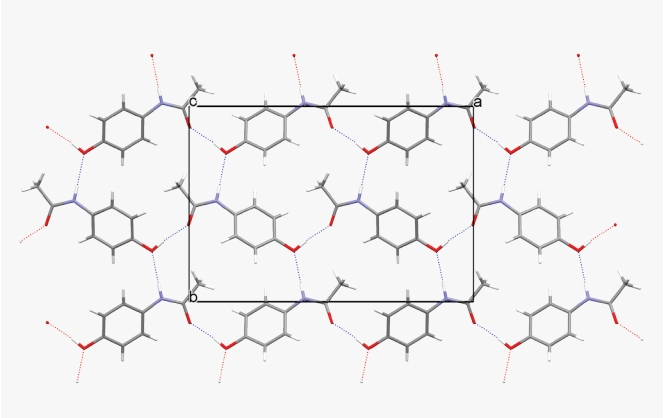

Figure 2: Crystal structure of form 2 of acetominophen.

When compiling the data for each drug candidate, it is essential to maintain a level playing field. This helps to ensure that the final selection decision is made in a rational and unbiased manner. For example, unintentional bias towards a particular candidate can occur when comparing the pharmacokinetic results before understanding whether the materials are crystalline or amorphous. In general, amorphous materials demonstrate better solubility behaviour than their crystalline counterparts. This is seen when monitoring the pharmacokinetic properties in acetaminophen (see figure 1 and figure 2). The difference in solubility between the two crystalline polymorphs of acetaminophen is only ~5mg/ml whereas the solubility of amorphous acetaminophen is about an order of magnitude greater than that. Such significant differences in solubility between the amorphous form and crystalline forms of an API and the modest differences observed between the individual crystalline polymorphs are typical for any given API. This solubility difference will have a marked downstream impact on the observed pharmacokinetic behaviour which in turn frequently leads to the conclusion that a particular candidate is a better choice when in fact it is an amorphous form. Once the amorphous candidate crystallises, its performance may be equivalent or perhaps even worse than its already crystalline competitors. It should be kept in mind, however, that there may be instances in development where an amorphous dispersion or even a kinetically stable crystalline form is the preferred choice over the thermodynamically stable crystalline form to achieve a satisfactory pharmacokinetic profile.

Crystallise, Crystallise, Crystallise

In order to avoid this pitfall, an early solid-form screening study on all the potential candidates is useful to ensure that all are in an equivalent, preferably crystalline, physical form. This ensures a level playing field when considering the pharmacokinetic data. A further screening benefit is the early detection of potential solid-form issues, such as multiple crystalline forms or the presence of solvates. This provides developers with a degree of insurance for the future with relatively little investment at this early stage.

When approaching lead identification and lead optimisation, many of the candidates are isolated as amorphous forms. To gain a more realistic pharmacokinetics result it would be worthwhile to crystallise materials that are deemed important or potential clinical candidates. There are a number of factors that can influence the ability of an amorphous form to crystallise, such as chemical and conformational purity, torsional flexibility, chirality, solvation/ hydration and molecular interaction.

Within the pharmaceutical industry, the need for chemical purity is well known. The presence of even small amounts of impurities can prevent the crystal growth process occurring by inhibiting vital molecular interactions in particular growth directions. However, the necessity for conformational purity is not so obvious. A good way to think about this is to consider the cyclohexyl and cyclopentyl substituents as shown in figure 3. There are two well-defined conformations that exist for the cyclohexyl group, the chair and the boat, along with two intermediate conformations, the half-chair and twist-boat. The energy requirement to go from the chair to boat or from the boat to chair conformation is approximately 41.8 kJ mol^{-1} since it has to go through both intermediates. The conformations of the cyclopentyl group, the envelope and the half-chair; however, are not so well defined and the energy barrier between them is quite low being only 2.1 kJ mol^{-1} such that the overall conformation is quite fluxional.

1 Acta Pharm Sin B. 2015 5(5): 442–453.

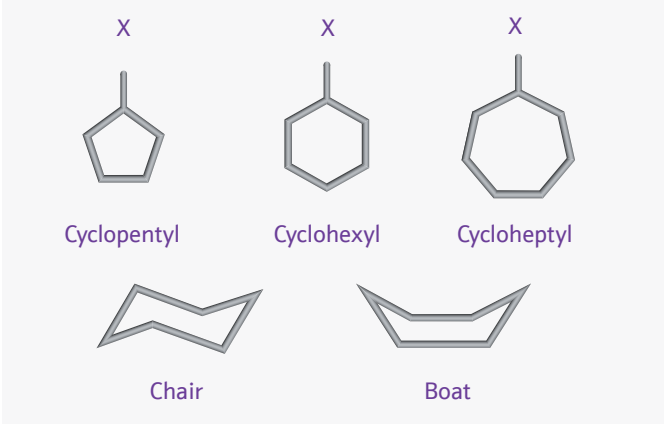

Figure 3: Conformations of cyclohexyl group. The energy requirement to go between chair and boat conformation is approximately 41.8 kJ mol^{-1}.

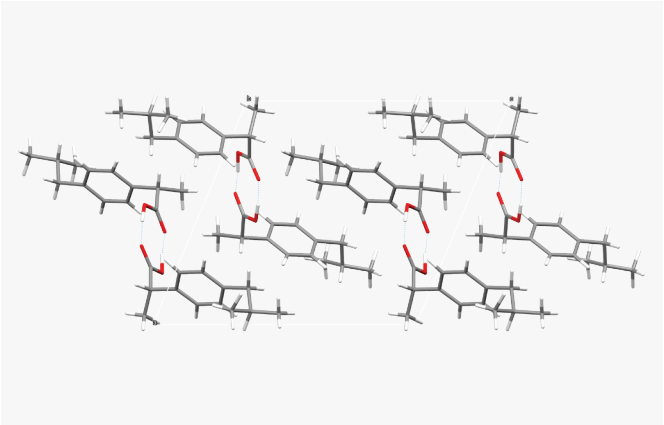

Figure 4: Crystal structure of S-ibuprofen highlighting common supramolecular hydrogen bonding interactions.

The impact of the fluxional behaviour of the cyclopentyl group on crystallisation is borne out by an analysis of the number of crystal structures that contain this group that have been deposited in the Cambridge Structural Database. For the cyclopentyl group, there are only 800 entries out of a current total of 1,023,814 structures which represents just 0.078% of the database and of these structures, 42.6% are disordered. The situation is quite different for the cyclohexyl group where there are 11561 entries, (1.13%), and of these only 32% are disordered. It is this fluxional behaviour that can inhibit crystallisation of molecules because to build the crystal and confer long range order on the structure, the molecules have to come together in precisely the same conformation in three dimensions.

This is also the case for molecules that have a large number of degrees of torsional flexibility. These materials often contain long mobile side chains that can take time to stabilise during a crystallisation process and effectively pose the same challenges as discussed above. One method of effectively crystallising these mobile fluxional materials is to maturate them over long periods of time using very slow cooling rates, thus allowing the mobile conformations to settle into the lowest energy form and give the crystallisation process the best possible chance of succeeding. If possible, it may be useful in these cases to select crystallisation solvents that have very low freezing points so that much lower temperature regimes may be accessed.

The molecules have to come together in precisely the same conformation in three dimensions.

Chirality can also impact the crystallisation process. Enantiomerically pure chiral molecules can only crystallise in chiral crystallographic space groups. These are groups that do not possess a centre of inversion, glide or mirror plane symmetry operations. This puts a limitation on the number of available space groups for the materials to crystallise in at 65 out of a possible 230. A common supramolecular hydrogen bond interaction utilised in crystallisation is the homo dimer carboxylic acid or amide interaction as shown in figure 4. This interaction is usually formed through the inversion symmetry operation; however, for a chiral molecule this cannot occur and this interaction is then formed by a process of pseudo-inversion creating asymmetric units with Z′ > 1, where Z′ is the number of individual molecules in the asymmetric unit of the crystal structure and as such these chiral materials will also benefit from slow maturation and ripening crystallisation processes.

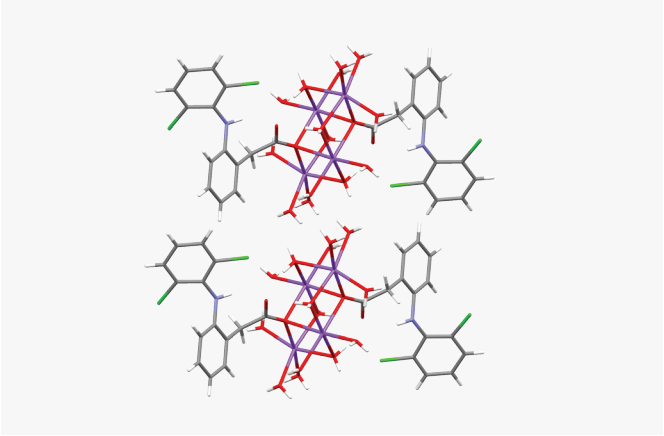

Figure 5: Crystal structure of sodium diclofenac 3.5 hydrate showing the interaction between water molecules and the crystalline structure.

Solvation and hydration are often needed for molecules that form voids or channels. A common example is that of group I and II salt forms, for example sodium. Sodium, if present in a crystal structure, requires its coordination shell to be filled. If it cannot obtain enough oxygen atoms to fulfil this requirement from the molecule itself, it will pull in oxygen from elsewhere, i.e. the atmosphere, in the form of water. This is one reason why these salts typically demonstrate higher levels of hygroscopicity over other materials. When crystallising these forms, it is beneficial to have a small amount of water available to fill these coordination sites as shown in figure 5.

Conclusion

Crystalline materials generally provide more robust solid forms for drug development and delivery. Throughout the pathway, unbiased candidate selection is an important process that can help to accelerate time to market and reduce the associated costs. To ensure impartial candidate selection, it is important that drug developers compare the results obtained with crystalline forms whenever possible. Additionally, it is vital to understand that amorphous forms will give results that appear more promising, owing to their more favourable solubility profiles.

In striving for crystalline forms, some inherent molecular characteristics can make it more challenging (chemical and conformational purity, torsional flexibility, chirality, solvation/hydration and molecular interaction) and appropriate crystallisation strategies can assist in the generation of crystalline phases for these materials. However, prudent candidate selection maximises chances of clinical efficacy. Finally, some understanding of a compound's solid form landscape and characteristics can streamline its process and formulation development, all in all providing significant benefits from understanding your pharmaceutical materials better at the stage of candidate selection.

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