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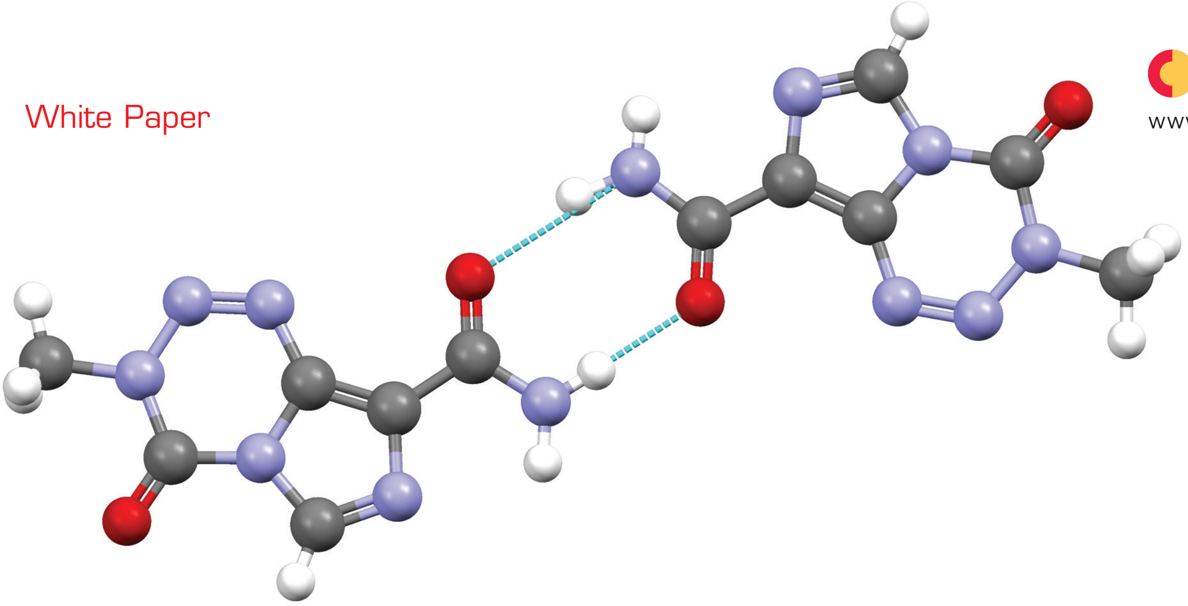

CSD Solid Form Suite: addressing Key Issues in Solid State Development

Polymorphism, Co-Crystallisation and hydrate Formation

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Abstract

We present a new tool based on Solid Form Informatics [1] developed to aid in multi-component solid form design as well as complement strategies for risk assessment of polymorphism. The tool harnesses the knowledge extracted from the millions of intermolecular interactions contained in the Cambridge Structural Database (CSD) and uses it to predict interaction outcomes in the target molecule.

The new CSD Solid Form Suite [2] includes the Hydrogen Bond Propensity method, which encodes the observed hydrogen bonding behaviour of functional groups in the crystal structures of the CSD in a statistical model. Through the model, it is possible to predict which hydrogen bonds are both likely and unlikely to occur in the solid form, and thereby assess whether polymorphism is likely, and/or if there is the possibility of a more stable form.

The method is also applicable to the prediction of cocrystal, solvate and hydrate forms. The tool facilitates the selection of feasible coformers, or the understanding of the likelihood of solvate or hydrate formation vs. a pure form.

The software provides an easy to use, step-wise interface. Presentation of the results through 3D structural visualisation, interactive tables, and as a chart provides an easily interpretable overview of the solid form landscape which aids both understanding and communication. With the knowledge accessed through the tool, experimental work in active ingredient development can be rationalized and targeted.

Introduction

Decisions made in solid form selection of an Active Ingredient (AI) for onward development can have consequences on the whole lifecycle of a crystalline product. We at the Cambridge Crystallographic Data Centre have been working with industrial partners, through our Crystal Form Consortium, to build software tools designed to both complement and enhance established screening techniques to support decision making processes in the development pipeline. This paper introduces an easy-to-use computational tool which quickly allows a deeper understanding of the solid form landscape from the earliest stage in development onwards.

The tool is part of the new CSD Solid Form Suite [2] and predicts hydrogen bonding outcomes – strong, reliable intermolecular interactions which pervade organic structures. Events in the recent past have shown that unforeseen new forms involving changes in hydrogen bonding with respect to marketed formulations (e.g. ritonavir) can be hugely problematic and costly. The introduction of additional components such as co-formers, solvent molecules or other excipients can introduce preferred interactions, yielding either unwanted forms or new opportunities with desirable physicochemical properties. Being able to identify as early as possible if and when such occurrences might exist is now readily accessible through this new tool.

Knowledge has been distilled from the millions of intermolecular interactions found in the Cambridge Structural Database (CSD), [3] the world's repository for small molecule crystal structures. The new software introduces a novel source of information to the development portfolio and, unlike other computational approaches to solid form screening, these analyses can be performed within experimental timescales and don't require knowledge of complex modeling techniques.

The tool calculates *propensity* values for hydrogen bonds in the range 0 to 1 using models which interpret how several factors of the environment affect a functional group's ability to form an interaction. The methodology has been developed and peer reviewed in several publications. [4-6] A form with high propensity values indicates optimal intermolecular bonding, whereas low propensity hydrogen bonds can indicate that alternative ways of packing might be preferable, suggesting likely polymorphism. Combining propensities with models of *how often* a functional group participates allows the *in silico* generation of all chemically reasonable possible structures. Comparing a given solid form to other possible structures in the resultant solid form landscape suggests whether a more stable form is likely or whether other competitive polymorphs might exist. Much assessment of the candidate can be done prior to the appearance of a crystalline form, and the analysis can be used, revisited and expanded to inform decisions throughout the development life-cycle.

The tool can also provide knowledge-based prediction of cocrystals, hydrates and solvates. Hydrogen bonds possible in a pure form can be easily compared with those between other molecular components (homo-molecular vs. hetero-molecular interactions) to reveal whether or not there is a preference for strong recognition between active ingredient and solvent, excipient, and/or co-former. The various applications of the new tool are now illustrated with examples where we outline difficulties typically faced, how the tool is applied, and how this knowledge can enable improved decision-making as a candidate progresses through development.

Applications and benefits

Assessing polymorph stability

The identification of the stable form of a candidate is a crucial step in the development of the active ingredient. Many experimental protocols exist to establish relative stability, however, supplementing these using structural informatics can establish a wider perspective, e.g. whether sufficient experimental screening has been carried out. A lot can be learned about the stability of a solid form by comparing it to existing structures in the CSD. If the intramolecular geometry and the intermolecular interactions are "usual" within the context of the CSD then the portfolio of evidence for the stability of the form has been significantly strengthened. Unusual intramolecular geometries or unusual hydrogen bonding interactions (c.f. form I of ritonavir) are indicators of potential stability issues. In the following examples we look at the results of an analysis carried out on drug compounds omeprazole and piroxicam using the hydrogen bond propensity methodology. Conclusions regarding the stability of the structures are drawn from the propensity/ participation charts, a convenient view on the results of the tool which allows potential variations in hydrogen bonding to be compared and explored.

For the first example we will focus on omeprazole (the structure is given in Figure 1). It is a relatively simple molecule with one hydrogen bond donor and five acceptors.

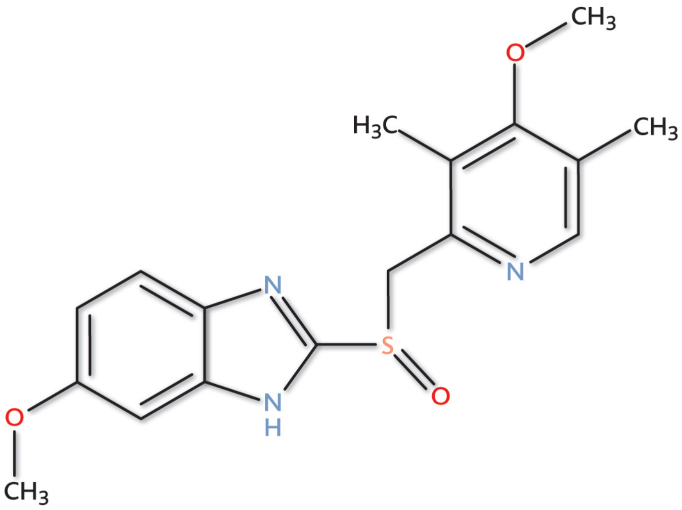


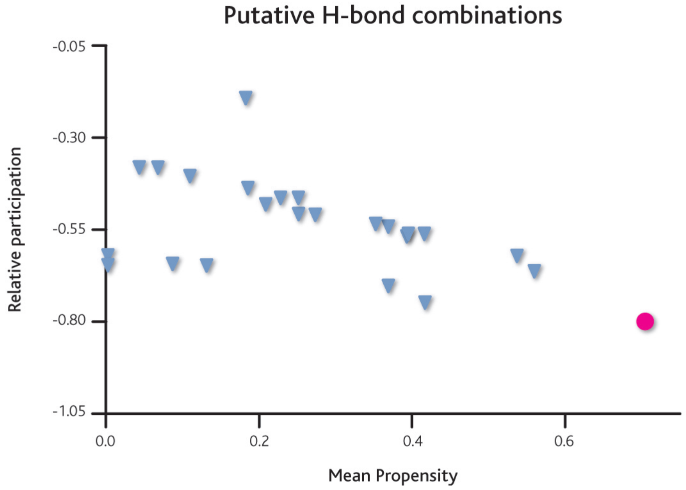
Figure 1 - Chemical diagram of omeprazole

Applying the hydrogen bond propensity methodology (see method section) generates a table of predicted donor-acceptor outcomes. Also included is a record of where the observed hydrogen bonds lie in the table of predictions. This allows a quick assessment of whether the structure is likely to be stable: high value propensities indicate expected intermolecular interactions. The results of the propensity calculations are shown in Figure 2.

Donor (D/A)	Acceptor	Propensity	Intermolecular interaction observed	Bounds +/-
N2 of amine ring	O1 Sulfinyl	0.74	Yes	(0.66, 0.81)
N2 of amine ring	N3 of amine ring	0.39		(0.26, 0.55)
N2 of amine ring	N1 of aromatic N	0.36		(0.23, 0.51)
N2 of amine ring	O3 aromatic methoxy	0.15		(0.09, 0.26)
N2 of amine ring	O2 Aromatic methoxy	0.11		(0.06, 0.19)

Figure 2 - Results of Hydrogen bond propensity calculations on omeprazole.
The observed hydrogen bond is predicted to be the most likely outcome.

The most likely hydrogen bond pairing predicted is that observed in the earliest published crystal structure of omeprazole. [7] Viewing the propensity-participation chart (Figure 3) shows that not only is the propensity (*x*-axis) for the observed hydrogen bond the best, but a high participation score (*y*-axis) is also achieved. The functional groups are therefore participating in hydrogen bond interactions in good agreement with their predicted capabilities.



Donor (D/A)	Participation		
	0	1	2
N2 of amine ring (d)	0.1106	0.8893	0.0427
N1 of aromatic N (a)	0.7081	0.2919	0.0028
N2 (a)	1.0000	0.0000	0.0000
N3 of amine ring (a)	0.5535	0.4465	0.0205
O1 of sulfinyl (a)	0.3749	0.6251	0.0000
O2 of aromatic methoxy	0.9132	0.0868	0.0000
O3 of aromatic methoxy	0.9080	0.0921	0.0000

Figure 3 - The propensity participation chart output for omeprazole. The observed structure is found to be the best in terms of both propensity and participation.
It is also well separated from other possible structures, indicating there are unlikely to be polymorphs.

The chart interface makes it easy to explore the other data points, each of which represents a unique combination of donors with acceptors. Clicking on a data point in the chart colours the participation scores (bottom right table) according to whether the groups are satisfied (green) or unsatisfied (red) and also highlights the rows in the propensity table (as in Fig. 2) corresponding to hydrogen bonds represented by that point.

Exploring the other data points with poorer scores in terms of propensity and participation shows that the alternative structures utilise less likely pairings of donor with acceptor and all involve a reluctant H-bond acceptor. The lower average propensity and participation scores for these alternate structures separates them markedly from the observed structure. Therefore we conclude that it is unlikely that a different hydrogen bonding pattern to that observed in the omeprazole structure exists in a competitive polymorph (with a single molecule in the asymmetric unit). To date, we are unaware of any alternative polymorphs of omeprazole.

For our second example we demonstrate how one might use the tool to identify potential issues with stability and is based on polymorphs of piroxicam. Piroxicam is a non-steroidal anti-inflammatory drug used to relieve the symptoms of rheumatoid and osteoarthritis, primary dysmenorrhoea and postoperative pain and its structure is shown in Figure 4.

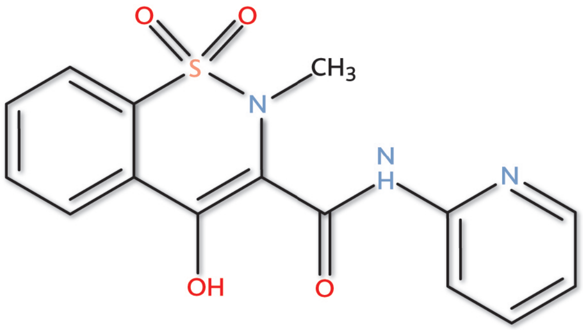


Figure 4 - Chemical diagram of piroxicam

Calculating hydrogen bond propensities for Form II of piroxicam [8] results in the chart shown in Figure 5. The presence of only an intramolecular bond in this polymorph places the structure to the left of the distribution of possible structures. There are a number of data points in the chart toward the lower right-hand side which are better propositions in terms of propensity and participation - any one of which could represent an as-yet undiscovered form. The observation of a result similar to this during drug development would indicate that the candidate is not likely to be the most stable form and further polymorphs should be sought.

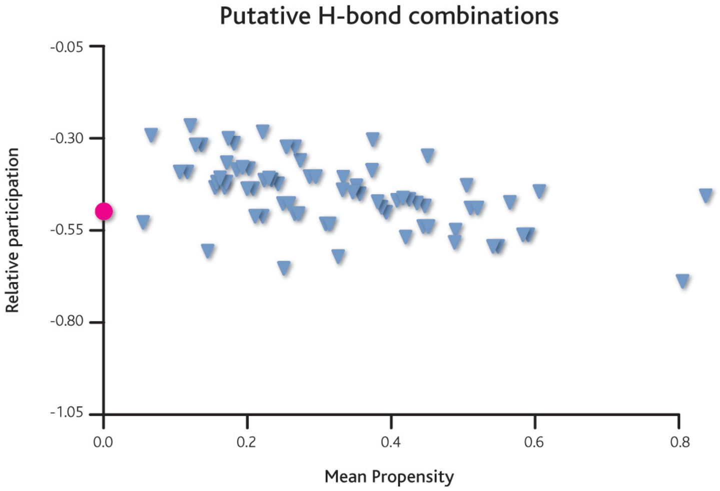


Figure 5 - The propensity/ participation chart for Form II of piroxicam. The position of the polymorph in the landscape raises questions over its stability. Is there a more stable polymorph to be found?

Looking at the results of the propensity calculations for Form I of piroxicam [9] gives a much more reassuring picture (Figure 6). The hydrogen bonding observed in this structure represents the best outcome in terms of both propensity and participation. Experimentally it is found that Form I is the most stable form.

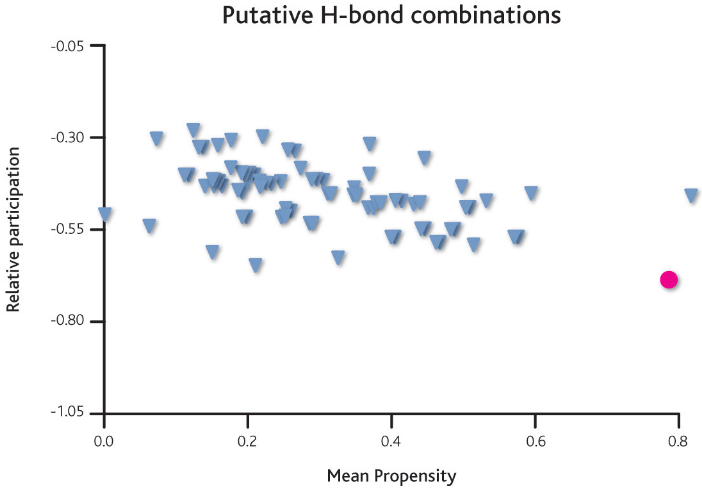


Figure 6 - The propensity-participation chart for Form I of piroxicam. The position of Form I in the chart shows the polymorph represents the best outcome in terms of propensity and participation. Confidence is provided that the stable form has been found.

Evaluating the risk of polymorphism

The ability to assess the likelihood of polymorphism as well as gain an understanding of what such polymorphic structures may look like is invaluable in active ingredient development. Such a risk assessment for polymorphism can be performed in very early development based on a 2D chemical diagram or during later stages when a crystal structure is available. In this example, we take the case of temozolomide, a drug used to treat brain tumours.

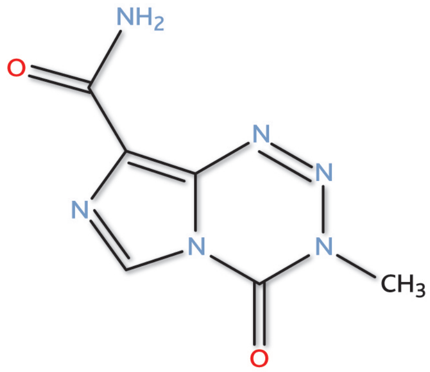
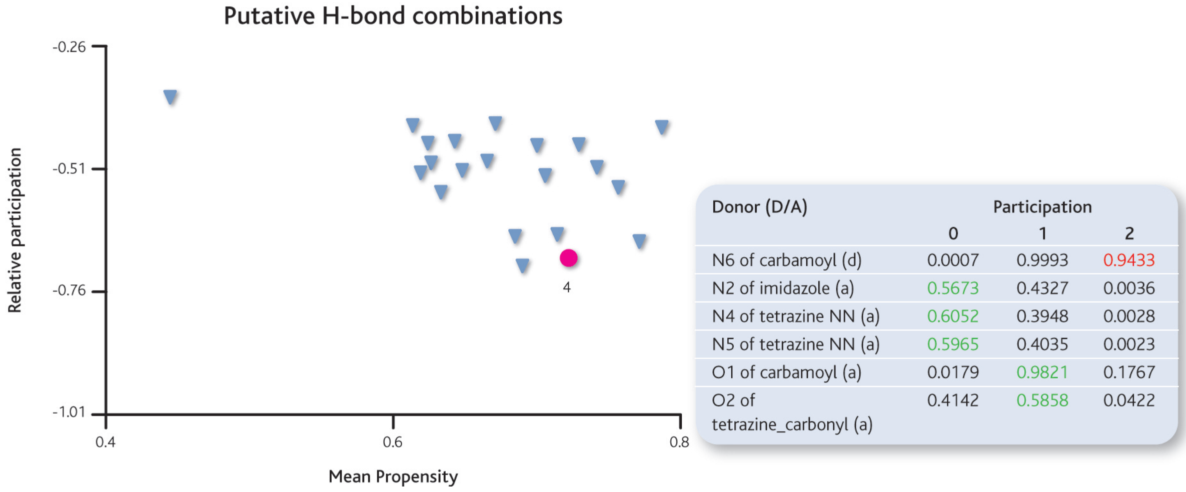


Figure 7 - Chemical diagram of temozolomide

The calculated propensity/ participation chart for temozolomide is shown in Figure 8. The chart shows the Form II crystal structure [10] (as indicated by a pink dot) is ranked well on both propensity and participation axes. However, the observed structure is not well separated from other possible structures, indicating that other hydrogen bond pairings are competitive, and which could feasibly lead to alternative, stable structures. Investigating the hydrogen bonds which contribute to the surrounding cluster of triangles shows that the amine group can donate twice comfortably, and that the other acceptors, namely the imidazole nitrogen, the carbonyl oxygen and the nitrogen atoms of the N=N group can accept without compromising the participation or propensity significantly. Indicated in the chart (Figure 8) is a reasonably stable alternative set of hydrogen bonds for temozolomide.



Donor (D/A)	Participation 0	 1	 2
N6 of carbamoyl (d)	0.0007	0.9993	0.9433
N2 of imidazole (a)	0.5673	0.4327	0.0036
N4 of tetrazine NN (a)	0.6052	0.3948	0.0028
N5 of tetrazine NN (a)	0.5965	0.4035	0.0023
O1 of carbamoyl (a)	0.0179	0.9821	0.1767
O2 of tetrazine_carbonyl (a)	0.4142	0.5858	0.0422

Figure 8 - Chart output for temozolomide. Observed form is indicated in pink. Functional groups participating in the alternative structure (highlighted with a blue circle) are shown in the participation table. The NH_2 donor of the carbamoyl group participates twice and the carbonyl group of the tetrazine accepts in addition to the carbamoyl C=O.

Looking in the CSD it is found that there are a further two polymorphs of temozolomide. Each polymorph is has two molecules in the asymmetric unit and the hydrogen bond pairings observed in these polymorphs are found to be those indicated by the cluster of triangles surrounding the original structure. In a drug development scenario the conclusion to be drawn from such a chart is that polymorphism is likely and therefore measures should be taken to minimize the risk of a polymorph appearing at a later stage in the development process.

Designing a cocrystal

Design of a co-crystal, or prediction of a successful co-former, offers an intriguing and potentially fruitful route to novel physicochemical properties and novel intellectual property. The design of the "right" experiments, however, is often a far from trivial task and even extensive screens can provide only limited results depending on the target compound. In the case of the antimalarial drug compound artemisinin, a crystallisation screen using liquid-assisted grinding against 75 potential co-formers produced only 2 hits. [11] Even for a compound that forms co-crystals readily, such as carbamazepine, the success rate can be as low as 20%. [12] This is generally due to the fact that a co-crystal form is only likely when the intermolecular interactions within the structure are stronger than the equivalent interactions within the pure crystal forms. Hydrogen-bonding statistics based on the CSD regarding specific motifs or synthons are often used to predict likely co-formers, but these approaches can break down as they frequently do not take into account aspects such as competition and molecular properties of the target compound.

The use of the H-bond propensity tool can provide more accurate statistics and predictions with regards to the relative likelihoods of the homomeric interactions compared to possible heteromeric interactions in a putative co-crystal. This can be illustrated using the case of the anticonvulsant drug lamotrigine (Figure 9), for which Cheney and co-workers have recently performed a study to discover new co-crystal forms. [13] The method in their work involved using the synthon approach with CSD data to intelligently select co-formers, resulting in the first report of lamotrigine co-crystal structures. This CSD analysis identified the best functional groups to compete with the lamotrigine heteromeric interactions to be alcohols and carboxylic acids, so molecules containing these groups were screened for possible co-crystallisation. The work reported by Cheney and co-workers also includes some information about potential co-formers that didn't work, so we can also analyse the failure

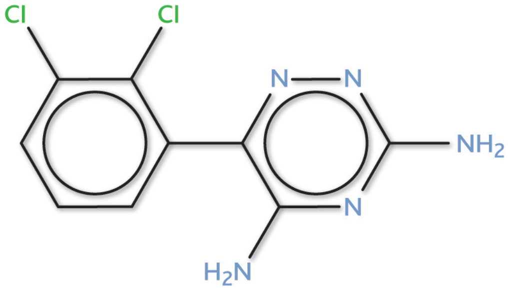


Figure 9 - Chemical diagram of the drug compound lamotrigine

Significant benefits of the H-bond propensity method include the fact that full molecules are explicitly considered in determining the interaction likelihoods, so competition effects are better dealt with, but also additional variables are considered such as the aromaticity and steric hindrance around the donors and acceptors. Let us consider two of the possible co-formers tried by Cheney *et al.,* butylated hydroxyanisole and methylparaben (Figure 10). The molecules each contain an alcohol group and a phenyl ring, but only methylparaben was a successful co-former.

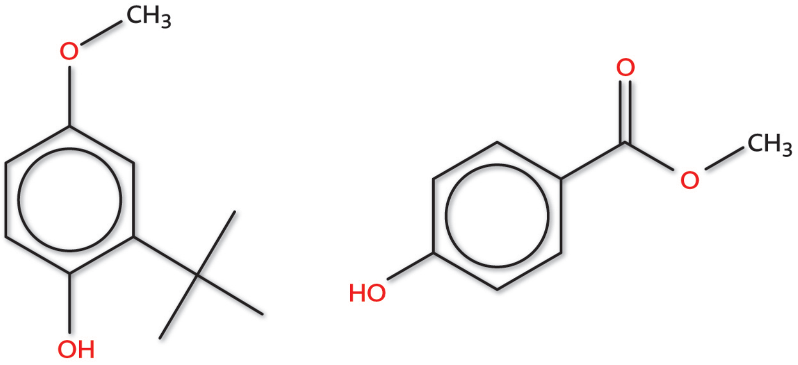


Figure 10 - Chemical diagrams of butylated hydroxyanisole (left) and methylparaben (right)

To evaluate the chance of co-crystal formation statistically we determine hydrogen-bonding likelihood predictions for both the potential molecular complexes of lamotrigine:butylated hydroxyanisole and lamotrigine: methylparaben. In the case of butylated hydroxyanisole, the observed interactions in the pure form of lamotrigine were predicted to be significantly more likely than nearly all possible heteromeric interactions. For methylparaben, however, a heteromeric interaction involving the carbonyl acceptor was found to be clearly competitive with the pure form lamotrigine interactions.

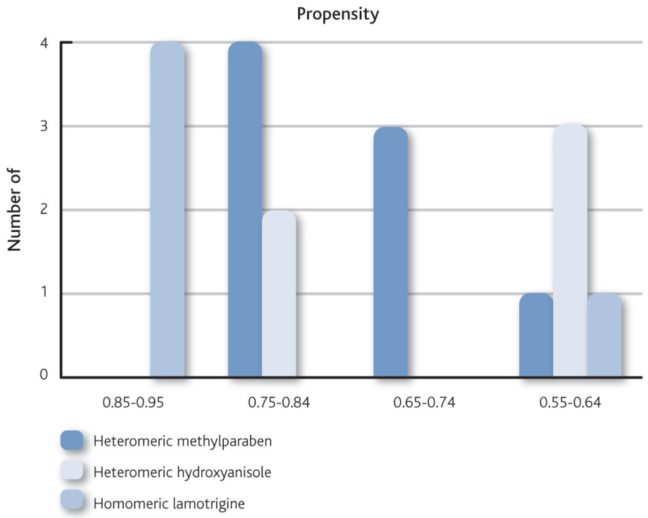


Figure 11 –Chart illustrating the comparison of propensity calculations for pure lamotrigine and hydroxyanisole and methylparben cocrystals. Predicted interactions between methylparaben and lamotrigine are more competitive with those in lamotrigine than interactions predicted for the hydroxyanisole cocrystal

The propensity prediction results match up with the experimental screening results of Cheney *et al.* indicating that a co-crystal is more likely if heteromeric interactions are seen to be competitive in terms of propensities with the homomeric interactions.

This analysis demonstrates the clear utility of the H-bond propensity method for *in silico* co-former screening by taking into account overall molecular variables of the potential co-former as well as the target molecule to determine H-bond likelihoods. Analysis of a set of potential co-formers in this way could quickly identify the most promising systems to screen experimentally for co-crystallisation.

Assessing the likelihood of hydrate formation

It has been estimated that at least a third of organic compounds and potentially up to three quarters of pharmaceutical compounds are capable of forming a hydrate [14, 15] Proceeding with a hydrate form in drug development is often seen as problematic because there may be undesired hydration or dehydration phase transitions with moderate changes in temperature or relative humidity. There have been many studies [15-18[attempting to understand the factors which influence the formation of hydrates, but as yet, it remains difficult to predict.

In a similar method to that described for co-crystal design, we can analyse the propensities predicted for hydrogen-bonds between functional groups within the molecule (homomeric propensities) compared with hydrate interactions (target:water propensities). This should provide an indication of whether a hydrate is likely or not based purely on hydrogen-bonding. The example systems presented are three drug compounds that are known to form hydrates (fluconazole, [19] paracetamol [20] and piroxicam [21]) along with two compounds that are known or believed to have no hydrate forms (rasagiline ethanedisulfonate [22] and sucrose [23]) and one compound for which no hydrate has been published (indomethacin [24]). Table 1 shows a summary of the hydrogen-bond propensities of the top three possible interactions in the pure form (including intramolecular), the highest propensity of an interaction involving a water and an indication of whether a hydrate is known or not.

Compound	Homomeric propensities	Target: water propensity	Hydrate?
Fluconazole	0.80, 0.80, 0.54	0.92	✔
Indomethacin	0.43, 0.26, 0.08	0.65	?
Paracetamol	0.41, 0.39, 0.27	0.57	✔
Piroxicam	0.91, 0.90, 0.85	0.97	✔
Rasagiline ethanedisulfonate	0.99, 0.99, 0.98	0.98	✗
Sucrose	0.89, 0.88, 0.87	0.82	✗

Table 1 - Summary of H-bond propensities for homomeric and target:water interactions for six targets

For the molecules known to form hydrates, the results suggest that an interaction involving water tends to occur as the highest propensity interaction. The two compounds believed not to form hydrates at all are seen to have a number of homomeric interactions that are calculated as having higher propensities than any involving water. Indomethacin, for which there is no published hydrate structure, would appear from the propensity predictions to have a tendency to interact with water. It is possible that a hydrate structure of indomethacin does exist, but has not been discovered or published.

Clearly there are a significant number of other factors that influence hydrate formation, but an analysis of the likelihood of a strongly competitive target:water interaction is a useful additional piece of information. Another use of the propensity method not discussed here is the evaluation of known anhydrous and hydrated forms to determine relative stability.

Future Developments

The Crystal Form Consortium (CFC) - a collaboration between the CCDC and industrial partners in the pharmaceutical and agrochemical businesses - has successfully guided the development of the software tools outlined here. This Consortium is continuing into the future and an exciting program of novel science and software development exploiting the opportunities of Solid Form Informatics is planned.

The CFC's current focus is on extending the current capabilities regarding stability risk assessment to an even wider range of organic targets. A prototype "Full Interaction Map" tool is in development which allows the quantitative assessment of the intermolecular environment, including interactions not described as hydrogen bonds.

We are also developing the Hydrogen Bond Propensity tool interface to enable automatic analysis of target compounds against libraries of commonly used solvates and coformers. A quick assessment of likely interactions between multi-component systems will be valuable to help target the large and complex space afforded by cocrystals.

An ongoing collaboration with the Institute of Particle Science and Engineering at the University of Leeds is set to deliver useful tools for the exploration of crystal surfaces, slices, slabs, morphologies and an understanding of energetic interactions at these scales. Current developments include incorporating the attachment energy model for crystal morphology prediction (as seen in the HABIT program [25, 26]) into the Solid Form Suite.

Conclusion

This paper has presented an easy-to-use, visual and interactive tool which enables a simplified, interpretable view of the solid form landscape of an Active Ingredient for use throughout the product development pipeline. The new software tool enables a rapid assessment to be made as to whether a candidate is likely to be stable and whether there are likely to be competitive pairings indicating a risk of polymorphism. Design space for alternative multiple-component formulations such as solvates or cocrystals can also be easily explored and rationalized.

At the heart of the tool is an assessment of potential hydrogen bond pairings based on the millions of interactions found in structures in the CSD. This approach offers many benefits to the AI development pipeline. It provides a complementary tool to experimental screening indicating when further screening is necessary and what interaction modes should be expected. Being based on observations in 3D crystal structures, the tool also adds a new perspective to computational modeling. Results are obtained quickly, are easily interpreted and actionable in an interface designed to integrate neatly into the lab chemist’s workflow.

The examples presented have shown applications of the tool in four problem domains: assessing polymorph stability, evaluating the risk of polymorphism, designing a cocrystal and assessing hydrate formation. The ability to *apply* hydrogen bond propensity analysis to chemical diagrams as well as crystal structures is also emphasized. This allows assessment of candidates to be performed at any stage in a development process where having a view of potential issues early on in the development lifecycle offers huge gains in efficiency and achievement of a greater understanding and control of the AI.

We finally highlight the added value that simplified, visual results provide to internal and external communications, reporting and general evidence of a fuller understanding, for example in patent applications. The encapsulation of complex but vital information through the propensity/participation chart is a valuable asset representing the resultant predicted solid form landscape. It summarizes the entire assessment of a candidate that can be supplemented and amended as information is gathered during the development process and should be considered as an essential part of pharmaceutical development reports and quality by design documentation.

Methods

Calculation of Propensities for Hydrogen bond formation

In the hydrogen bond propensity method4 we ask a question of every potential hydrogen bonding interaction in a molecule: will this interaction form in the crystal structure or not? The question, posed so simply, is formulated as a two-state outcome, well characterised by a dichotomous probability distribution function (PDF). With the chosen PDF we can model what is termed a *propensity* for each H-bond to form.

The technique used to fit such a model function is logistic regression which has become widely used for the analysis of discrete state systems. The H-bond propensity PDF is built using variables describing the local chemical environment of the functional groups in a training set extracted from the CSD. The model is trained using the response variable, the presence/absence of H-bonds between the functional groups of molecules in the training set. The variables are 1- & 2-dimensional by nature allowing the method to be truly predictive from, for example, a 2D chemical diagram. An important feature of the tool is that maximum flexibility over structures as part of the training set is given, enabling only the most relevant data to be used during model training. Once the model has been built, it can then be applied to the target molecule, producing a quantitative measure of the likelihood of hydrogen bond pairings.

The modeling of the participation of functional groups in hydrogen bonds

The goal here is to describe probabilistically the expected number of H-bonds a given donor or acceptor might form. This behaviour has previously been termed H-bonding capacity or donating/accepting ability [27, 28]. For example a water molecule might be expected to form two H-bonds with each donor hydrogen and 2 H-bonds at both acceptor lone pairs. Thus the likelihood of forming 4 H-bonds should be comparatively high. Our formulation allows the user to query the likelihood of a donor or acceptor forming any integer number of bonds, and hence the most likely number is quickly apparent. We term our model the H-bond *participation* model and it too is built using a logistic PDF, like propensity. Again, there is a two state outcome: group X is either forming x or more H-bonds or not (where x is 0, 1, 2…4). Clearly the participation is dependent on both the donor and acceptor capacity of an atom, and is quite different for different atoms and chemical environments.

Building putative structures and the combination of propensity with participation

In order to assess where a target structure sits within a landscape of potential polymorphs we need to be able to "build" possible alternative structures. Putative structures are represented by unique subsets of H-bonds that we can construct using hydrogen donor and acceptor atoms found in the molecule (but with no reference to 3D geometry). In a crystal structure, the symmetry irreducible set of H-bonds can range from the null set (no H-bonds) to a set containing a potentially infinite combination of pairings. Clearly we need an upper limit on the number of allowed unique donor-acceptor pairings, which is enabled by the participation models described above. Possible structures are built with combinations of donor and acceptor pairs, but only structures that utilize the functional groups in-line with the modeled participation are retained.

For each set of possible hydrogen bonds we assess the mean propensity for the H-bonds, and the mean participation. These values denote the likelihood of the H-bond pairings and the H-bonding efficiency (*viz*. extent of usage of the available donor/acceptor sites) for the putative structure.

We plot the putative structure set as a chart (Figure 12) with the horizontal axis as mean propensity and the vertical as the (negative) mean participation. The combination of propensity and participation is a powerful one – possible structures are generated and ranked allowing the evaluation of the potential polymorph landscape. The hypothesis is that both good participation and good propensity indicates a stable set of H-bond pairings. These are quickly identified in the lower right-hand-side of the display. Putative structures which contain more unlikely hydrogen bonds are also quickly picked out toward the upper left. If a 3D structure is supplied as a target, this is plotted in pink.

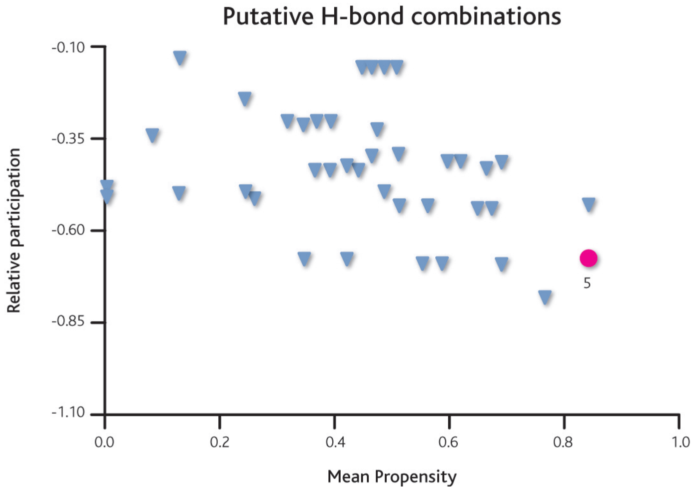


Figure 12 - The unique donor-acceptor pair combinations possible for 4-aminobenzoic acid, represented as grey triangles. A known polymorph in the CSD, AMBNAC04 [29], is represented as a pink dot.

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