polymorphs and also crystallizing compounds, which would have been laborious using traditional methods. This has led to increased confidence that we have identified the correct forms and has therefore saved much time in the drug development process.

Keywords: crystallization, polymorphism, salt

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Does computational work help in solid form screening?

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This was tested on three pharmaceutical building blocks, 2,4- and 2,5-dihydroxybenzoic acid (DHB) and phloroglucinol (PhG) by combining extensive experimental screens and computational search methods.

Our manual polymorphism screen approach covered crystallization from solution (evaporation, cooling, slurry conversions), sublimation, crystallization from the melt, thermal and moisture dependent studies and desolvation methods. Thermodynamic and kinetic stabilities of the forms were ascertained by thermoanalytical methods and solvent-mediated transformation studies. It is impractical to cover the whole range of experimental techniques that have been shown to produce new polymorphs [1] and to guarantee that all possible forms are found. Therefore, the practical screens were complemented by computing the crystal energy landscapes.

The experimental screen of 2,4-DHB found a second polymorph, two stoichiometrically different hydrates (hemi- [2] and new monohydrate) and five novel solvates, with dioxane (2:1, acid: solvent ratio), acetic acid (1:1), dimethyl formamide (4:3 and 2:1) and dimethyl sulfoxide (2:1). For 2,5-DHB we found two anhydrates [3] and four novel solvates with dioxane (2:1 and 1:1), acetic acid (1:1) and dimethyl formamide (1:1). The anhydrate [4] and dihydrate, [5] as well as novel methanol and dimethyl sulfoxide solvates were identified during the PhG screen.

The computational studies found all five unsolvated and three hydrated structures at or close to the global minimum in the crystal energy landscape. Comparing the crystal energy landscapes of hydrates with anhydrates and ice correctly predicts that PhG and 2,4-DHB will form hydrates of known stoichiometry and rationalizes why no hydrate was found for 2,5-DHB. Furthermore, the calculations provided rational explanation for features in the more challenging forms, i.e. confirmed proton disorder in the meta- or para-OH proton position of the high temperature DHB anhydrates and PhG dihydrate, the diffuse scattering effects of PhG dihydrate and proposed a structure for the short-lived 2,4-DHB monohydrate. [6,7]

Even with this combined approach it appears impractical to guarantee that no additional metastable forms can be found. Nevertheless, the consistency of experimental and computational results adds confidence that the practically most important solid forms have been found and structurally characterized.

[1] J. Aaltonen, M. Alleso, S. Mirza, V. Koradia, K.C. Gordon, J. Rantanen, *Eur. J. Pharm. Biopharm.* **2009**, *71*, 23-37. [2] V. Horneffer, K. Dreisewerd, H.C. Ludemann, F. Hillenkamp, M. Lage, K. Strupat, *Int. J. Mass Spectrom.* **1999,** *187*, 859-870. [3] D.E. Cohen, J.B. Benedict, B. Morlan, D.T. Chiu, B. Kahr. *Cryst. Growth Des.* **2007**, *7*, 492-495. [4] K. Maartmann-Moe, *Acta Crystallogr.*, **1965**, *19*, 155-157 [5] S.C. Wallwork, H.M. Powell, *Acta Cryst.*, **1957**, *10*, 48-52. [6] D.E. Braun, P.G. Karamertzanis, J.B. Arlin, A.J. Florence, V. Kahlenberg, D.A. Tocher, U.J. Griesser, S.L. Price, *Cryst. Growth Des.* **2011**, *11*, 210-220. [7] D. E. Braun, P.G. Karamertzanis, S.L. Price, *ChemCom*. **2011**, doi: 10.1039/c1cc10762c.

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The polymorph time bomb: a new knowledge-based tool for risk mitigation

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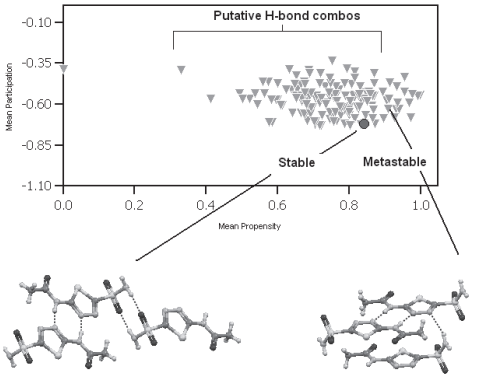
Due to the potential for variation in physicochemical properties and new patent space, polymorphism is indeed a risk for the pharmaceutical and other fine chemicals industries where the crystalline state plays an important role. Mitigating that risk is the role of solid form screening and selection. A challenge is to identify risks of alternative forms as early as possible along the development pipeline. The discovery of new polymorphs late on can be disastrous and hugely costly, as in the well-known case of Ritonavir [1], and more recently Rotigotine [2].

In the case of Ritonavir, subsequent analysis of the different hydrogen-bonding patterns in the two forms identified a weakness with regards to the interactions in the first form, indicating alternative crystal packing might be a possibility. A method has now been developed at the CCDC to quantify the propensity of a given hydrogen bond to form. This Logit Hydrogen-bonding Propensity (LHP) method [3-5] uses probability models built on the knowledge-base of existing structures in the Cambridge Structural Database (CSD) [6] and sets of relevant chemical or topological descriptors.

Software incorporating this method is being developed under the aegis of the Crystal Form Consortium (CFC); a partnership between the CCDC and eleven pharmaceutical and agrochemical companies. Current work is driving the software towards assessment of the full hydrogen-bonding landscape for a crystal and thus assessment of the risk of polymorphism.

Here we will illustrate the use of the method in assessing the risk of polymorphism and show the latest improvements in visualisation and analysis of the data.



[1] J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter, J. Morris, *Pharm. Res.* **2001**, *18*, 859-866. [2] S. Cajigal, *Neurology Today* **2008,** *8*, 1 & 8. [3] P.T.A. Galek, L. Fábián, F.H. Allen, W.D.S. Motherwell, N. Feeder, *Acta Cryst.* **2007**, *B*63, 768-782. [4] P.T.A. Galek, F.H. Allen, L. Fábián, N. Feeder, *CrystEngComm* **2009**, *11*, 2634-2639. [5] P.T.A. Galek, L. Fábián, F.H. Allen, *CrystEngComm* **2010**, *12*, 2091-2099. [6] F.H. Allen, *Acta Cryst.* **2002**, *B*58, 380-388.

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