

layer supporting the catalyst film. One challenge is to grow CNT on a conducting support without scarifying the CNT yield and structural quality of the grown CNTs.

Using a Co-buffer layer in-between Si-support and Fe-catalyst leads to the formation of conductive  $\text{CoSi}_2$  via CoSi by subsequent silicidation during the growth process. Herby a high yield of CNT was obtained.

$\text{CoSi}_2$  support is more promising than Ta support, but we used Ta as model system to explain all possible interactions, all occurring phases during processing by side reactions were recorded. Notable CNT yield triggered by high catalytic activity of iron at low temperatures  $\sim 550^\circ\text{C}$  was observed.

This study shows that in-situ diffraction experiments are a powerful tool to investigate catalytic reactions. The understandings of these processes are the basis of tailoring future materials.

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**Keywords:** carbon nanotubes, in-situ diffraction, synchrotron radiation

### MS.53.1

*Acta Cryst.* (2011) **A67**, C124

#### High-throughput crystallization as a part of streamlined drug development

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The pharmaceutical industry is in a challenging situation - decreasing number of new molecules reaching the market and simultaneous generic competition creates a need to identify, utilize and protect the full potential of both the new and existing active molecules. One efficient strategy is to explore the physical properties of active compound and to use the identified solid forms (salt, polymorphic, solvate, co-crystal, and amorphous) as a central part of product development. This decision-making point is extremely crucial - the best solid form candidate with optimal bioavailability needs to be identified; still keeping in mind that solid matter with ideal particulate properties ensuring robust processability and stability is needed.

Screening of pharmaceuticals early in the drug development to identify all possible solid state forms has significant impact. This aids in choosing the 'best solid form' for further development and reduces emergence of unexpected forms later on in the drug development process. A startling example of appearing new polymorphic form is the case ritonavir, a peptidomimetic drug used to treat HIV-1 infection and introduced in 1996 (Norvir). Two years after entry into the market, several lots of Norvir capsules began failing dissolution specifications. Evaluation of the failed drug products revealed that a second crystal form of ritonavir (form II) had precipitated from the formulation. At some considerable cost a new formulation of Norvir was eventually developed and launched.

Current polymorph screening practice is aiming at maximizing the number of solid forms identified as early as possible in the drug development phase. Each new solid form can be patented and by this means, the lifetime of a possible "blockbuster" drug can be optimized. There is not always enough fundamental knowledge available on crystallization and nucleation of pharmaceuticals, which underlines the need for experimental approaches in this field. Current state of art

in the field of solid form screening involves techniques and solutions originating from the field of synthetic chemistry. Labor intensive crystallizations are performed in vessels of varying size (from well plates with few microliters to bigger scale) and the resulting solid product is analyzed using suitable methods. These approaches are having one major drawback in connection to the final dosage form - they do not include the evaluation of the role of formulation and secondary manufacturing (with small molecules granulation, tableting, coating, and with protein/peptide systems freeze drying) on the solid state stability of matter. This type of processing typically involves the use of heat, pressure, and solvents, which again may affect the solid state stability of the drug product, and even introduce a new, previously unidentified polymorphic form. Performing solid form screening by combining the small scale crystallizations and the evaluation of processing induced solid state changes in miniaturized scale will provide remarkable improvement to the current practice of polymorph screening. Well-plate based approach can be used to mimic conditions during secondary manufacturing and further, role of the excipients can be investigated using both small molecule as well as protein/peptide based formulation strategies.

**Keywords:** polymorph screening, pharmaceutical, high throughput screening

### MS.53.2

*Acta Cryst.* (2011) **A67**, C124-C125

#### PROTEUS – a fully automated crystallization screening equipment at AstraZeneca

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During a period from 2002 to 2003 a team at AstraZeneca set up plans to develop a fully automated system, which could handle all sorts of small scale crystallization experiments, including polymorph-, salt- and co-crystal screening. During 2004, an agreement was made with TTP LabTech, a global developer and manufacturer of automated laboratory equipment based in the UK, to form a team with the task to develop and build such a system. In late 2008 the first of two benches was accepted and put into service and in early 2010 the system was upgraded with a second bench. The system, which is today running on a routine basis, is a medium throughput system, which can accommodate approximately 200 experiments running in parallel. It is fully automated with regard to sample preparation, crystallization, sampling and analysis. Crystallization can be performed using evaporation, cooling and anti-solvent additions and re-crystallization can be performed by means of slurry experiments. The working scale is 0.3 – 10 mL and the temperature range is  $-15$  to  $100^\circ\text{C}$ . On each bench a large number of reagents can be accessed at a given time. The analytical resources include light microscopy, Raman spectroscopy and powder X-ray diffraction-analysis.

The design of the system has been based on trying to access as much of the available design space as possible, from both a thermodynamic and a kinetic perspective. For this reason the system was designed as a highly flexible, medium throughput system, instead of as a high throughput one, with little versatility. As a result the system can work dry as well as wet, in a broad temperature range, using different compositions of binary, as well as ternary, mixtures of solvents and API, and using different rates of crystallization. The system is also designed to maintain strict control over all experimental parameters as well as recording them for later use during evaluation of the screen. All different types of experiment can run in parallel.

So far we have performed some 40 screens, identifying new salts,

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

### MS.53.3

*Acta Cryst.* (2011) A67, C125

#### 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 anhydrides [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 anhydrides 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 anhydrides 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.

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**Keywords:** screening, polymorphism, prediction

### MS.53.4

*Acta Cryst.* (2011) A67, C125

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

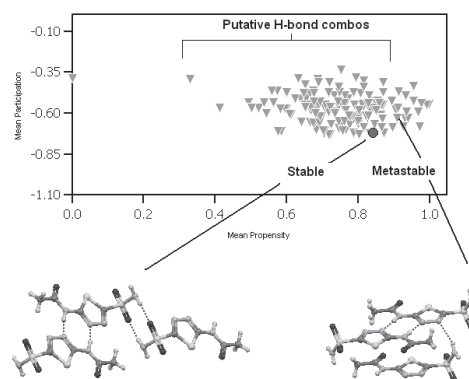
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Due to the potential for variation in physicochemical properties and new patent space, polymorphism is indeed a risk for the pharmaceutical and other fine chemicals industries where the crystalline state plays an important role. Mitigating that risk 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.



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**Keywords:** polymorphism, interaction, pharmaceutical