Early Stage Prediction of Crystal Morphology

Accelerating and de-risking drug development pathways and reducing costs

Predictive modelling may allow fast and material free risk assessment of the potential for morphology related processing issues in early development

Drivers

This case study addresses the need to accelerate and de-risk drug development pathways and reduce development costs by providing a much earlier indication of any potential issues associated with the expected crystal morphology of drug candidates. Early signalling of such issues will enable preventative work, including triggering more detailed modelling and focused experimentation, to be carried out off the development critical path.

Longer term, linking the underlying predictive capability developed with other crystallisation models will contribute to improved experimental design. Taken together, these benefits would effectively increase overall resource efficiency and hence capacity to progress a pipeline of product development projects.

Approach

Database and visualisation scripts have been developed by the CCDC to interface with and harness the morphological predictive ability of Leeds' Visual Habit software. These tools are being brought to bear on live drug candidates within Pfizer with the aim of predicting crystal morphological properties (and limited mechanical properties) from a single crystal structure.

Key Features

- A new script linking advanced predictive modelling into an existing structural database interrogation prior to pivotal clinical studies, extending its coverage to include crystal morphology
- An accessible tool and visual, easily-interpreted output for non-specialists providing a clear, early signal of potential morphology-related issues in processing

The new scripts fit with an existing interrogation of the Cambridge Structural Database (CSD) prior to pivotal clinical studies, extending its coverage to include morphological predictions. The goal is to predict and visualise crystal habit, the major crystal faces, chemical functionality and charge distribution, and roughness from a single crystal structure experiment, using best available lattice energy calculation methods developed in ADDoPT at the University of Leeds.

An ADDoPT Case Study featuring collaboration between Pfizer, the Cambridge Crystallographic Data Centre, and the University of Leeds

Building a body of visually-rich knowledge

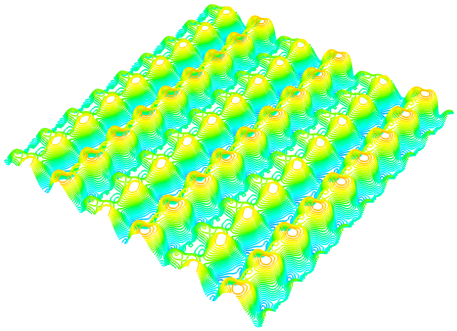
An informatics assessment is carried out based on a single-crystal structure and data from the CSD. This delivers predicted morphology in a visual report, and as data suitable for building a new knowledge bank database. The new approach provides better information earlier in development as there is no need for bulk material.

The models employed are low in computational demand and the tool is available to anyone capable of running a Mercury script, rather than being limited to experts.

The output report favours visual presentation and non-expert qualitative topological analysis without sacrificing the underlying quantitative data which is retained in the database.

Early non-expert user access to visualised morphology means a much earlier heads-up on potential challenges in formulation development, and earlier and better decision making about resources and prioritisation. Expectations of potential for problematic morphologies (*e.g.* plates, needles) can be communicated to those developing the crystallisation process stage, and similar flags could be raised for issues around filtration and flow behaviour.

Reducing the entry barriers to use of the tool through scripting will accelerate the rate at which the new database of morphological properties will build, increasing its value as a key information asset.



Visualisation of predicted crystal surface of Ritonavir

Interconnectivity nurtured across ADDoPT's technical work streams has helped deliver a user-friendly solution that will grow in value as a key information asset

Experimental verification is provided from the study of single crystals, which are face indexed and assessed for morphology. Ultimately this approach could allow a detailed understanding of particle informatics and de-risking of drug development.

Results and Benefits

The approach has been carried out successfully for one candidate compound, and could ultimately be adopted as part of Pfizer's development workflow. The morphology scripts will therefore be deployed for every project that is submitted for the informatic risk assessment to guide experimental activities.

From a single crystal structure, predicted *in vacuo* morphological characteristics will be presented in a visual format, that can be understood by formulation scientists who are not necessarily materials specialists. With time and effort, the accumulated dataset acquired over many materials could allow a set of morphology parameters to be predicted and related to performance characteristics, allowing the level of confidence in the predictions to be assessed.

Further Steps

In order to utilise this tool companies would need access to a crystal structure (which is already needed for development), the CCDC Mercury software and training in software tools, and sufficient materials/particle expertise to back up general users in data interpretation

There is a potential big data application of the tool to broader classes of materials – including non-drug-like molecules. It could be used to evaluate excipients, or applied to any database of in-house structures.

Transforming pharmaceutical development and manufacture

Addressing the pharmaceutical industry's desire to deliver medicines more effectively to patients, the ADDoPT project has developed and implemented advanced digital design techniques that streamline design, development and manufacturing processes.

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ADDoPT is a collaboration instigated by the Medicines Manufacturing Industry Partnership, and part funded under the Advanced Manufacturing Supply Chain Initiative, a BEIS initiative delivered by Finance Birmingham and Birmingham City Council.