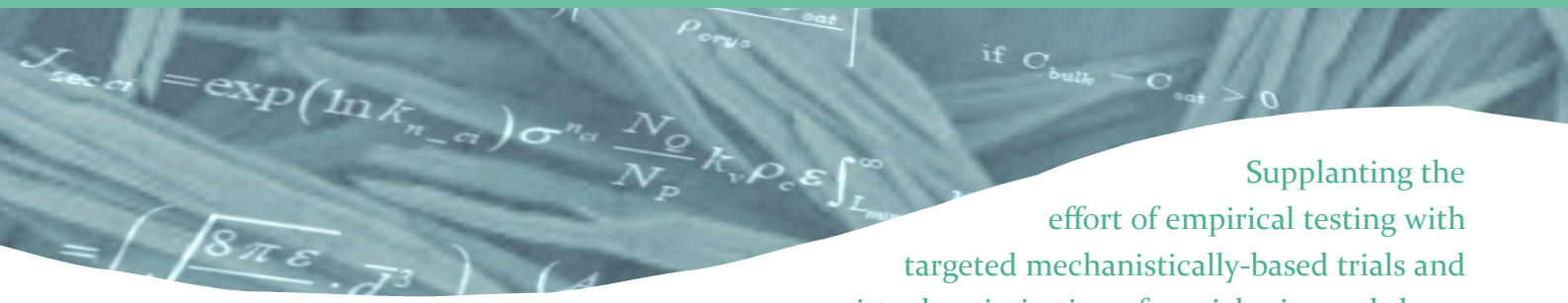
Optimising Crystallisation for API Habit and Physical Properties

Designing processes to deal more efficiently and effectively with needle-like materials



Supplanting the effort of empirical testing with targeted mechanistically-based trials and virtual optimisation of particle size and shape

Drivers

Active Pharmaceutical Ingredients (APIs) of needle-like shape tend to impact powder flowability and with industry trends towards more challenging APIs, higher drug loadings, and more continuous manufacture, are often considered as high risk and a source of difficulty in the manufacture of a pharmaceutical dosage form. As a result, the technical challenge of designing upstream processes, notably crystallisation, is important to ensure that good flow is achieved for downstream processes such as formulation. A model-based approach offers the prospect of both a more efficient optimisation workflow and improved plant utilisation by having better understood and optimised crystallisation processes.

Approach

This study addresses the challenge of dealing with APIs which tend to crystallise as long needles during simple seeded cooling crystallisation. These form cohesive powders in bulk which are extremely difficult to handle in downstream formulation processes.

Current practice involves a great deal of experimental work to develop crystallisation processes with wet milling temperature cycling which modifies the crystal size and shape to a less elongated, better flowing form. This is very time-consuming both in the development lab and when operating at scale: multiple cycles can result in overall crystallisation processing times of up to one week per batch. A modelling-based approach to design of the temperature cycling programme would save time and cost, and allow for more effective optimisation of the conditions employed, ensuring that only necessary cycles are included, and contributing to a reduction in the overall duration of the crystallisation stage.

Key Features

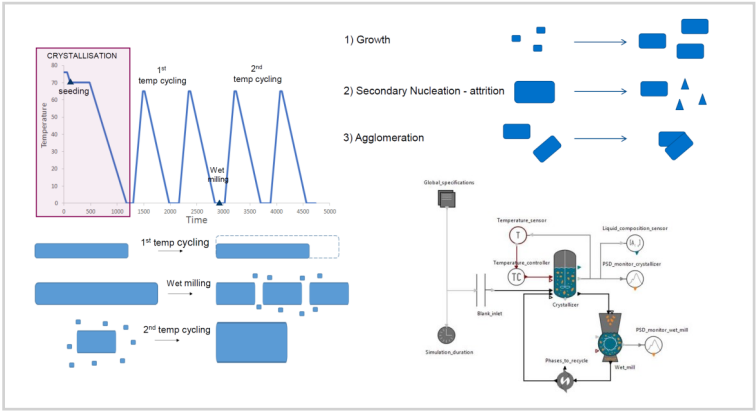
- A model-based approach to designing crystallisation processes that will deliver particles of the right size and shape for free flow in downstream processing
- Time, effort and cost savings through a more efficient optimisation workflow and improved plant utilisation

An ADDoPT Case Study featuring collaboration between PSE and AZ

Defining a fit for purpose model

A Design Brief

- A modelling-based approach to temperature cycling programme design saving experimental time, effort and cost and allowing more effective optimisation of crystallisation conditions.
- Ultimate goal is to ensure a powder Flow Function Coefficient (FFC) > 3 measured by shear cell.
- The approach could be applicable from early stage evaluation onwards to pick up on potential issues as early as possible when a needle-like morphology is identified as likely.
- Any supporting experimentation at 0.1 litre scale.
- Note that CMOs would be unlikely to have access to the relevant advanced measurement tools (e.g. Morphologi G3 particle size and shape analysis, shear cell), nor materials science expertise.



A finished 2D morphological population mass balance model implemented in gPROMS FormulatedProducts using crystallisation kinetic data may be able to predict quantitatively critical API characteristics such as particle size and shape, to better estimate flow properties around which crystallisation can be optimised.

ADDoPT has enabled AZ and PSE to work together to define the requirements for a fully 2D crystallisation model filling a gap in the current marketplace

Results and Benefits

A 2D morphological population mass balance model is under development to predict critical particle attributes like size and shape characteristics of morphologically challenging crystals. By using the model and crystallisation kinetics data, *e.g.* growth parameters, the process can be optimised to ensure that desired product with better flow properties is formed.

Virtual optimisation based on the new model would help with process development work providing information on both sensitivity of the outputs to various parameters and scale-up difficulties, and would overcome the issue of being constrained by amounts of material physically available with which to experiment.

With early, effective optimisation of the API form, formulation process developers may gear their work around this from the outset, rather than being obliged to design to cope with a challenging material.

Further Steps

After initially exploring implementation using a 1D model adjusted for particle aspect ratio, it is envisaged that the model will be ultimately delivered as a fully "built-in" 2D morphological population balance model in PSE's gPROMS FormulatedProducts suite. Once fully realised, this model will deliver the ability to better optimise crystallisation processes of particles with challenging morphology, to predict and control the final product quality, and to do so in less time and consuming less material.

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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