# Digital Twins for Drug Product Design and Manufacture

Creating virtual medicines and medicines manufacturing systems to ensure they are effective and efficient before creating them in the real world

The ADDoPT project has developed and implemented advanced digital design techniques that streamline drug design, development and manufacturing processes

## The ADDoPT Vision

The ADDoPT vision is the creation of virtual medicines and medicines manufacturing systems - products and processes - to make sure that they are effective and efficient before creating them in the real world. The key element in the digital design workflow is the creation of a virtual representation or "Digital Twin" of a product or process based upon a mathematical model that predicts its performance. This allows a vastly more efficient and effective design process.

Traditional practice involves an iterative design cycle consisting of building a physical prototype and its real-world testing. Through repetition of the cycle, a workable solution is reached and the product is developed, without knowing whether more robust and/or more efficient solutions exist. In ADDoPT, Digital Twins have been developed on the basis of predictive science (mechanistic models) with data analytics used to address gaps in the mechanistic understanding. Once calibrated, using greatly reduced physical experimentation, these Digital Twins can predict the performance of products or processes across a far greater design space than was used in calibration and with respect to a much wider range of material attributes and process parameters to identify those which are truly critical. Consequently, performance of the Digital Twin can be evaluated without the continual need for the production and testing of a physical prototype (efficiency gains) and robustness can be more comprehensively evaluated and optimised with respect to raw material and physiological variability. Rapid iteration of the digital design test cycle then leads to an optimum virtual product that can be replicated with confidence in the real world. Eliminating the physical make-test cycle is inherently much more efficient in material, time and cost. Our ability to model physical and biophysical properties of tablets such as hardness or bioavailability without making prototype formulations demonstrates the potential of digital approaches to vastly improve the efficiency of drug development.

## Benefits to Patients and Industry

Digital design has the potential to significantly improve the speed and efficiency of Pharmaceutical product and process development. This is important given current industry trends.

ADDoPT

Our ability to model physical and biophysical properties of tablets without making prototype formulations demonstrates the potential of digital approaches to vastly improve the efficiency of drug development

Until now clinical trials have typically been lengthy and are often unsuccessful. The advent of more targeted precision medicines allows for smaller trials and improved chances of success. Whilst in the past clinical development was almost always on the critical path to launch and commercialisation, we are now seeing more examples where development of the commercial product and its manufacturing process are the rate limiting steps on the path to market. The efficiency of Digital Design offers pharmaceutical product and process development groups a way of addressing this emerging challenge.

An implication of Precision Medicines is that more products will need to be developed: better targeted medicines will improve efficacy for specific patient populations but will reduce the size of population that each medicine will serve. In order to meet the needs of the overall population more products will have to be developed overall, and the demands on product and process development groups will increase in an already resource and cost constrained environment. Digital Design offers these groups the opportunity to achieve a step change increase in productivity in order to address this challenge.

The primary benefits of Digital Design are increased speed and efficiency of development however other benefits are apparent over traditional heuristic and purely data driven techniques currently widely used in development to underpin Quality by Design. Digital Design techniques generally need fewer experiments as the scientific knowledge captured in mechanistic models acts as *a priori* information. This leads to experimental and material efficiencies. Additionally, mechanistic modelling techniques allow for a more rigorous assessment of robustness and key sources of quality variability, enabling a more holistic approach to addressing raw material variability. Typically process optimisation work is done with input materials of fixed quality or limited material variability. The use of Digital Design and process modelling allows for an evaluation of the impacts of input product variability on product performance as part of the modelling process.

*The benefits of Digital Design to industry flow through to patients in the form of faster access to and enhanced availability of new medicines and better assured supply*

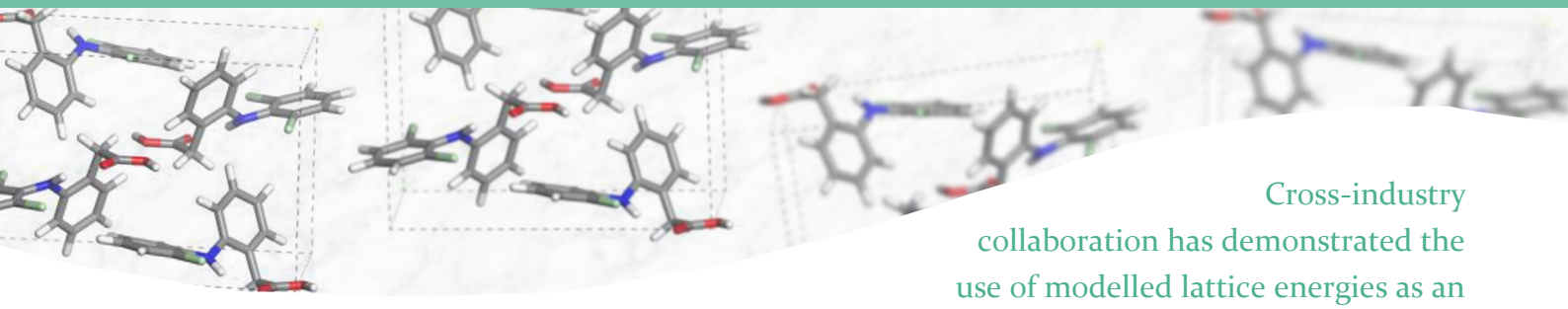
## From Digital Design to Digital Operations

The fruits of Digital Design will be most fully reaped through an integrated Digital Operations approach to manufacture. Having a calibrated digital twin of the manufacturing system and equipment that identifies and predicts the key relationships between material characteristics, process parameters and product performance allows medicines manufacturers to identify readily the manufacturing and control systems that are needed to assure product quality. Subsequently, the digital twin can streamline process optimisation, accelerate technology transfer and underpin both advanced process monitoring (inferred measurements for quality attributes that cannot be reliably measured in-line or at-line) and model predictive control to ensure the robustness of ongoing manufacture.

The following case studies demonstrate that a shared ambition to achieve step-change improvement in pharmaceutical product and process development has led to examples of improvement that are already bringing real benefits to industry and patients today

# Lattice Energy Prediction using Big Data Approaches

A step towards understanding and predicting API solubility early in the development cycle



Cross-industry collaboration has demonstrated the use of modelled lattice energies as an early indicator of API solubility

## Drivers

The sophistication of modern therapies has driven drug discovery towards higher molecular weight, lower solubility compounds. Understanding and predicting solubility early in the development cycle using lattice energy as an indicator property can provide business advantage by streamlining candidate selection, and linking up thinking between medicinal chemistry and drug development.

A new modelling tool allows lattice energies to be predicted for the crystalline form of a range of molecular variants. This gives an indication of the likely solubility directly from 2D structure, allowing candidates to be ranked with no need for experimentation.

## Approach

Solubility of any crystalline material is the result of a balance of solvation and solid state packing effects, so effective modelling needs to consider solid-state as well as molecular properties. Work done under ADDoPT has affirmed the importance of the solid-state contribution to solubility and provided a practical model to account for them.

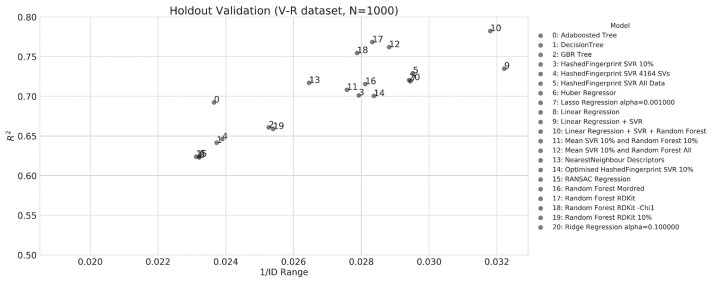
## Key Features

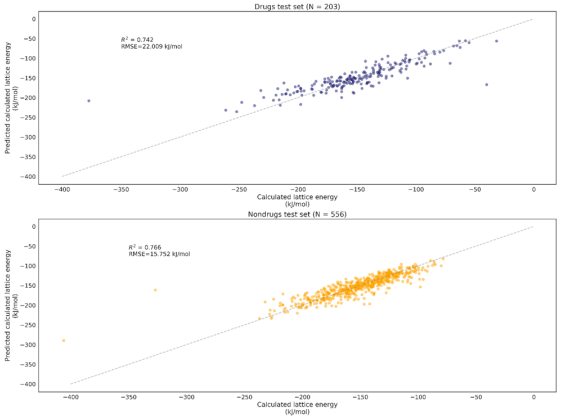
- The ability to predict lattice energies (a good indicator of solubility) from 2D structure alone developed and validated in an industry-relevant molecular space
- A big data, cross-industry approach maximizing the ability of model to cope with future evolution of drug development space
- Bridging the gap between medicinal chemistry and drug development

Fifty thousand molecules in the CSD database with known crystal structures have been analyzed using machine learning to relate 2D molecular descriptors to their lattice energies. The scarcity of directly measured lattice energies has been overcome by using calculated values derived from single crystal structure experiments, using best available lattice energy calculation methods developed in ADDoPT at the University of Leeds.

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

## *Model validation and testing*




After training, each model was validated on a validation dataset for comparative purposes (above). A combined model was the best performing, performing well on both drug and non-drug test data (right). As expected, performance was slightly better on a nondrug test set as the training data was composed of all non-drug molecules.

This may be understood as the necessary thorough groundwork to enable what will ultimately be a simple and streamlined routine workflow: the user feeds in a 2D structure and receives a lattice energy prediction as a marker of likely solubility, to guide further experimentation.

# Educating medicinal chemists in the importance of the solid state to likely solubility of candidate molecules, and aligning ways of thinking within drug development

## Results and Benefits

Material scientists at Pfizer have evaluated and further developed the new predictive model, applying it to 1500 drug structures within the area of chemical space of interest to them. Results show good correlation between model-derived and crystal structure-calculated lattice energies.

Beyond showing that the predictive model is sufficiently robust to perform in the chemical space of specific interest to Pfizer, ADDoPT has enabled the combination of diverse expertise (at Leeds for lattice energy calculation and Hartree for data analysis) to uniquely build and analyse a data set with overarching coverage of the full chemical space of crystalline materials, and demonstrate its ability to perform in the focused space of drug-interest.

By educating and informing medicinal chemists of the importance of the solid state upon the likely solubility of candidate molecules, the model helps align thinking within, and "bridge the gap" into, drug development. The ultimate benefit of this work will be a more streamlined and accelerated development timeline.

## Further Steps

Awareness raising of this new development is already underway in the medicinal chemistry community.

Ultimately, this is the first step towards achieving a vision of connected development where 2D structures are used to predict 3D crystal properties, crystal properties predict particle properties, and particle properties in turn predict bulk powder properties.

## 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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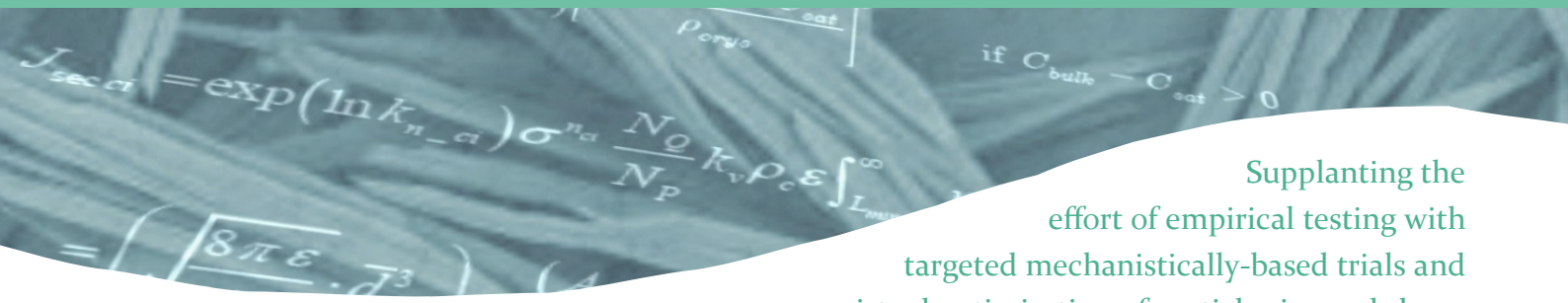
# Optimising Crystallisation for API Habit and Physical Properties

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

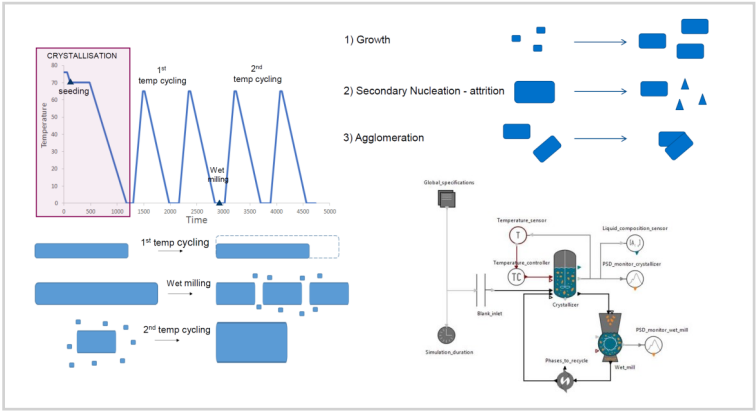
- A model-based approach to designing crystallisation processes that will deliver particles of the right size and shape for free flow in downstream processing
- Time, effort and cost savings through a more efficient optimisation workflow and improved plant utilisation

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.

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# 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*

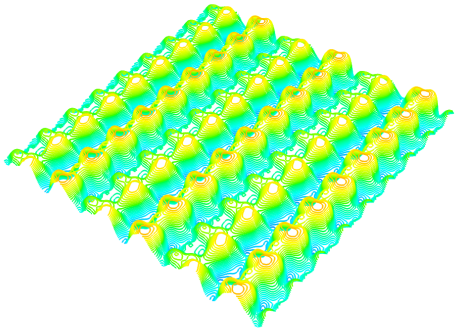
An informatics assessment is carried out based on a single-crystal structure and data from the CSD. This delivers predicted morphology in a visual report, and as data suitable for building a new knowledge bank database. The new approach provides better information earlier in development as there is no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

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# Understanding Powder Flow for Continuous Processing

Earlier and better decision making about how to formulate APIs successfully

Working together to understand how to use particle fundamentals to inform an earlier choice of formulation platform for new materials

## Drivers

The manufacture of solid oral dose pharmaceutical forms is underpinned by the need for good powder flow. Most Active Pharmaceutical Ingredients (APIs) are formed as very fine solids and do not inherently flow freely, and so additional treatment by wet or dry granulation is frequently needed to render freely flowing blends.

Industry trends towards more complex APIs and continuous processing further increase the need for a better grasp of the links between measurable particle properties and resultant flow behaviour, and the means to predict one by the other as early as possible in the development workflow.

## Approach

This work has taken place in parallel with and in the context of the development of a Manufacturing Classification System[1], modelled on the FDA Biopharmaceutics Classification System. This will allow materials to be classified for processability according to the API powder properties and the level of drug loading. A material's position in the classification then informs the choice of processing route, or whether further particle engineering is required.

## Key Features

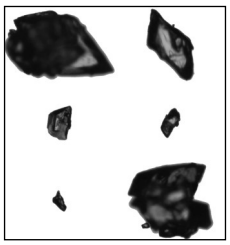
- A cross-industry collaboration to measure fundamental API properties and use the links to resultant powder flow along with drug loading in a Manufacturing Classification System
- More informed and productive dialogue between formulators and material developers
- More effective use of resources in drug product and process development

Using an agreed and standardised best practice approach to measure powder properties which elucidates flow behaviour, the partners have undertaken a study of around one hundred real APIs. The resultant data set is an order of magnitude larger than anything similar to date and uniquely, it represent the full range of performance characteristics encountered in practice: FFCs from 10—1 encompassing free down to badly flowing APIs.

An ADDoPT Case Study featuring collaboration between BMS, AZ, GSK, Pfizer, and the STFC Hartree Centre

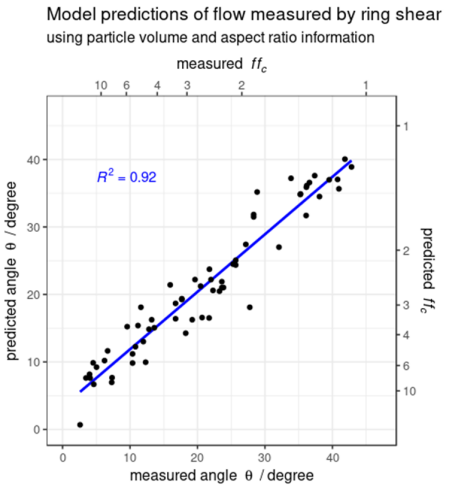
1. MCS Working Group (2018): *Manufacturing classification system in the real world*, Pharmaceutical Development and Technology, DOI: 10.1080/10837450.2018.1534863

## *Building a common language of key parameters*



After initial discussions to share ideas on which particle properties had the most potential to shed light upon flow, the partners agreed to standardize measurements upon the Malvern Morphologi G3 particle size analyzer. This provides rapid, automated particle imaging for thousands of individual particles, enabling visual and statistical data acquisition and interpretation. The result is a rich, multiparameter-based data set describing both particle size and shape distributions for a representative sample of the powder, rather than a single point D50 average particle size.

With the resultant models it has been possible to predict, for the first time across a range of pharmaceutically relevant materials, which systems would be likely to have the necessary flow characteristics to deliver the required performance in a loss in weight feeder. Importantly, this could be applied not only to pre-existing materials but also used to create material profiles, the properties of which (*e.g.* size, shape) could realistically be made, allowing the formulator to direct manufacturing colleagues to make, procure and specify suitable materials capable of performing in continuous direct compression.




# Identifying the "parameters that matter" and measuring them in a concerted way for maximum information richness and insight

## Results and Benefits

The rich, multiparameter based data set generated, which describes both particle size and shape distributions for the range of materials studied, can be broken down by multi-variate analysis into a set of key descriptors. From this a material "fingerprint" may be constructed, to provide a better understanding of the links between the fundamental characteristics of the particles and their resultant flow properties measured in a shear cell.

Ultimately, with as little as 50mg being enough to provide the crucial material property fingerprint, the MCS enabled by this work will allow

- formulators to give meaningful feedback to those producing materials and specifications for right-first-time manufacture of particles
- choice of manufacturing technology platforms to be based on science rather than preconceptions or assumptions
- developers to identify the degree of fit of new materials with a given technology platform early in the development cycle.

## Further Steps

The MCS is at its heart a means of facilitating a meaningful, actionable conversation between API development and drug product formulation functions in an organisation. The lower are the boundary walls between these two key functions and the closer they work together the better.

A modelling tool will be implemented in gPROMS FormulatedProducts to facilitate specification of the critical powder parameters for flow performance.

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# Mechanistic Modelling of Powder Feeding

Predicting flow performance and mitigating process impacts for new materials

A useful, user-friendly tool for predicting powder feeder performance has been developed with the potential for further development

## Drivers

Powder feeders are an integral part of many pharmaceutical industry solid dosage form processing trains and are particularly critical in continuous processing equipment, where any fluctuation in the rate of delivery risks being propagated into downstream blending. Managing feeder performance is often less than straightforward when dealing with active pharmaceutical ingredients (APIs) in particular, due to their challenging flow properties.

An accessible predictive model of feeder performance would enhance both drug product development and manufacture, increasing the speed of development, reducing the associated costs, and improving process robustness.

## Approach

A model based upon the best currently available in the public domain literature for powder flow[1] has been incorporated into a user-friendly interface suitable for use by "super-users" (scientists primarily focused on pharmaceutical materials but with some degree of comfort in the use of modelling tools), and by subject matter expert modelling specialists.

## Key Features

- A state of the art mechanistic model implemented on an industry compatible, user-friendly, flowsheet based platform
- Material and time-consuming experimentation avoided by adopting a digital workflow for feeder optimisation
- Faster and less costly risk assessment and mitigation approaches for materials with marginal flow properties

The model as currently configured works well for powders with good flow properties, and there is potential for future development so that it can be used for the prediction of feeder performance for less free flowing materials.

[1] *Yu, Y. and Arnold, P.C. (1997) Theoretical modelling of torque requirements for single screw feeders, PowderTechnol. 93, 151-162.*

An ADDoPT Case Study featuring collaboration between PSE and Pfizer

## *Establishing a 'modelling-first' culture*

*Lead Users*

There is a strong strategic move within Pfizer towards using computational tools for the sort of development task shown in this case study, and there is already a healthy subject matter expert community in place to develop the necessary models.

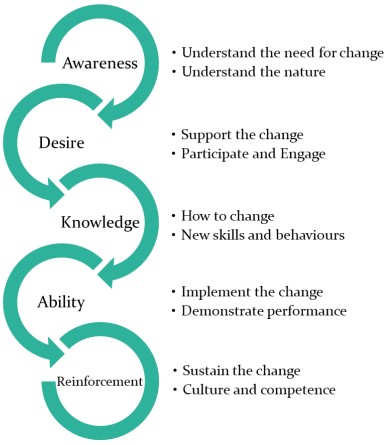
There is still a need to cultivate and grow the base of "super-users" - people with a practical/project-based background but with an early-adopter attitude towards using digital models. Ultimately this will aid the shift of the broader, perhaps somewhat more sceptical, general user base.

*Trusted Models*

A key success factor is the quality of the models: if a model "works" it will be trusted and used more widely and readily. Users have a learning, and confidence building, curve to travel on with any new model. Awareness raising actions, such as the development of bespoke digital workflows (piloted in ADDoPT via Britest technical facilitation), and helping potential users see the value of new models are helping to overcome the barriers to adoption, for example demonstrating that the amount of time that could be routinely saved employing a digital model more than outweighs the time taken to learn how to use it.

*Leadership*

Looking more broadly, the Medicines Manufacturing Industry Partnership's early instigation of digitalisation through ADDoPT resonates with companies who are now making prominent senior leadership appointments to roles entitled "Chief Digital Officer" or similar. This augurs well for positive leadership towards adoption of digital modelling approaches.




*ADKAR Change Model, Hiatt, J. M., Prosci Learning Center (2006)*

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## Results and Benefits

The Yu and Arnold model has been implemented in the screw feeder module within PSE's gPROMS FormulatedProducts platform. This implementation makes the model available via a software platform upon which Pfizer are building end to end process flowsheet models.

The main advantage in using this model is in development. Current best practice is to optimise experimentally at small scale on a benchtop feeder. Typically, to test whether a material would flow at a given throughput would require around 1kg of API at a stage where not only is material extremely expensive but also scarce.

Use of the feeder model will deliver benefits of speed and cost in assessing and mitigating the risks associated with flow for materials which are intermediate between free flowing (no problem) and highly cohesive (no chance).

## Further Steps

The focus to date has been to render the current state of the art in a user-friendly form. This is a precursor to further internal customisation of the tool within Pfizer for proprietary materials of direct interest.

Uptake by expert users for thorough model validation will be supported by a map indicating where the model performs and expected levels of confidence.

Further development in the underpinning science will be needed to generate models for less free flowing, cohesive powders. Here there is a potentially interesting correspondence with work elsewhere in ADDoPT exploring statistical relationships between particle properties and resultant flow.

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# A Process Model for Twin Screw Granulation

Using models to optimise implementation of new technology platforms

A cutting-edge modelling approach can dramatically reduce experimental burden without sacrificing process understanding

## Drivers

Twin screw granulation offers a flexible and effective continuous formulation route, but the near-infinite potential variations in screw elements and set-up that provide such useful configurability also make it highly challenging to cover all the options in a solely practically-based approach to platform optimisation.

The purpose of this case study was to see to what extent modelling could be used to reduce the number of practical trials needed without sacrificing the amount of process understanding obtainable across the full range of design space. A lower experimental burden (cost of materials and time spent in experimental design, execution and analysis) equates to increased efficiency in development and cost reduction.

## Approach

An early version of an advanced mechanistic model using a population balance based approach to describe the complex set of simultaneous rate processes occurring within a twin screw granulator was implemented within a worksheet environment by PSE for evaluation to see how close it was to utility as part of a normal AZ development workflow.

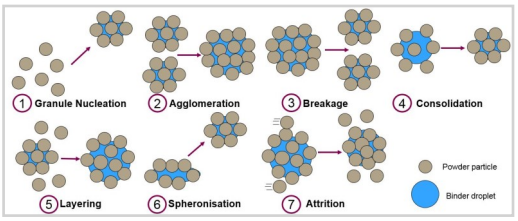
## Key Features

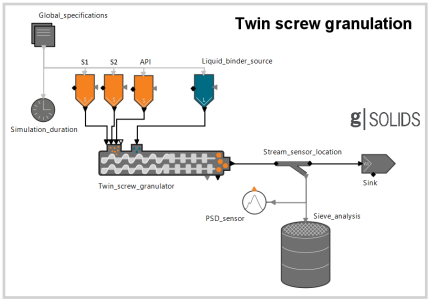
- An advanced mechanistic model has been evaluated in a flowsheet environment facilitating rapid, virtual experimentation in place of expensive and time-consuming practical experimentation
- A sufficiently predictive model was achieved using just 5 trials instead of 24
- The study demonstrates the potential for early, virtual process platform optimisation

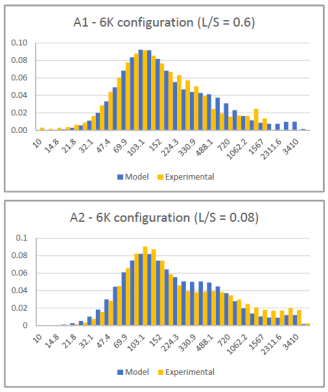
The tool was used on a retrospective example to assess the potential for reduced experimental requirements. Whilst the case study was fairly limited in scope - a practical design space including two screw configurations was used to predict behaviour in a third – a sufficiently successful demonstration would be a significant step forward and a good indicator of future utility in further process understanding work.

An ADDoPT Case Study featuring collaboration between PSE and AZ

*Mechanistic Modelling*




Many rate processes occur simultaneously during granulation. A population balance model implemented in PSE's gPROMS FormulatedProducts platform has been used to model the changing properties of the granules as the net result of these mechanisms. The model uses a combination of feed material properties (densities, size), equipment set-up (screw configuration and elements), and process settings (solid and liquid feed rates) as inputs and predicts the output granule particle size distribution.

Up to 80% fewer trials were needed to calibrate the predictive model, and similar economy in pilot validation would be expected

## Results and Benefits

Use of the modelling tool reduced dramatically the experimental requirements in the system studied. What was previously a 24 trial practical design of experiments needed just 5 trials to build a sufficiently predictive model for use in further work - exploring parameters in a fuller virtual design space, or helping researchers better target further regions of design space likely to be of most interest.

Using the model to conduct sensitivity analysis, the experimenter is directed towards regions of operating space which are (a) most informative in terms of which are the most influential parameters, and (b) most likely to allow production of tablets which can be used to establish if CQAs can be met.

A particular advantage arises if an organisation can model a technology in which it lacks an extensive "platform history" to use as a starting point (as is the case with TSG in AZ). By helping experimentalists reduce a potentially huge parameters space down to something more tractable, substantially more rapid and less costly early stage process design and development may be envisaged.

## Further Steps

This case study has provided useful insight into how such a model-based approach could be applied more generally to other relatively new formulation technology platform introductions, such as continuous direct compression. There is growing business recognition that modelling to allow "sparser" experimentation is a necessity to make a success of such technologies because of the prohibitive costs of the required full experimentation.

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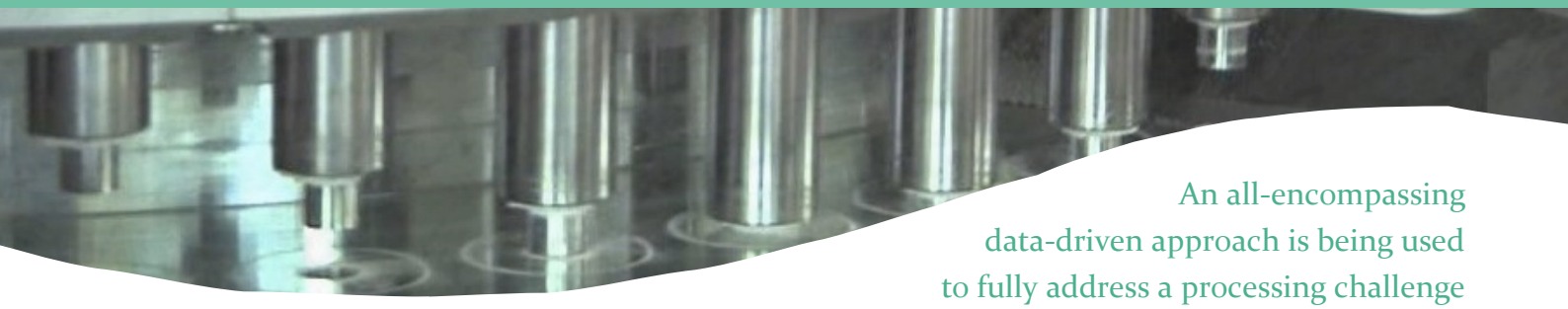
ADDoPT is a collaboration instigated by the Medicines Manufacturing Industry Partnership, and part funded under the Advanced Manufacturing Supply Chain Initiative, a BEIS initiative delivered by Finance Birmingham and Birmingham City Council.

# Using Big Data to Resolve Tablet Sticking Issues

Holistically mapping material attributes to a challenging manufacturing KPI



An all-encompassing data-driven approach is being used to fully address a processing challenge intractable to routine problem-solving methods

## Drivers

Material sticking in the die head of a tablet press is a common issue in the manufacture of pharmaceutical tablets. This leads to significant downtime in manufacturing due to stoppages and the need to clean equipment. Better prevention and management of sticking issues would enhance both the commercial and development phases of the pharmaceutical lifecycle. The negative impact of sticking extends beyond the batches directly affected due to interruption of the manufacturing schedule. Estimated losses of around 700 hours a year on a fairly typical production line can be attributed to the implications of sticking.

## Approach

What is needed is a framework and methodology that allows pharmaceutical scientists to examine large data sets and evaluate relationships between processing parameters, material attributes and key process performance characteristics.

Innovatively, this study combines Big Data sets from Drug Substance and Drug Product, material attributes and process parameters from multiple process steps, and is developing relationships from this data to manufacturing KPIs.

## Key Features

- A structured and holistic framework approach to problem analysis and resolution
- Insight from statistical and mechanistic approaches providing links between processing parameters, material attributes and manufacturing performance KPIs
- Transferable learning on how to tackle other issues and opportunities

Tablet sticking is the first performance characteristic to be tackled in this way but other issues could be tackled similarly with a framework established.

This all-encompassing approach is necessary to fully address what is self-evidently not a “simple” cause and effect relationship between one material attribute and the phenomenon of sticking, since it has proven intractable to more routine problem-solving approaches.

An ADDoPT Case Study featuring collaboration between Pfizer and the University of Leeds

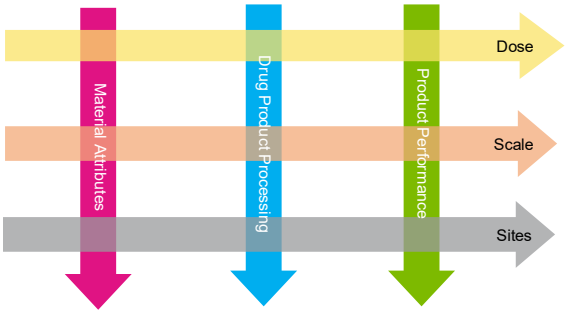
## *Mapping material attributes to manufacturing performance*

When you're looking for direction, a map is helpful, but it needs to cover the right territory at the right level of detail. By compiling big data that captures characteristics from across the materials supply and manufacturing landscape, and "surveying" it in a thorough and structured way, Pfizer have opened up the possibility of mapping routes to more effective solutions to common manufacturing issues.

The characterisation of input materials goes far beyond CoA-defined attributes, and cuts across the multi-stage processes involved. It includes traditional and advanced analytical techniques (particle size distribution by multiple methods, particle shape, flow properties, compressibility and sticking measurements of isolated materials and intermediate mixtures), and product characterisation (*e.g.* chemical imaging of tablet composition). A quantitative analysis of manufacturing KPIs (number of stops for cleaning, process yield – number of bad tablets per batch) has been recorded at the manufacturing site.

This structured and holistic framework approach to problem analysis and resolution will also allow validation of development "Science of Scale" tools: for example by linking manufacturing data with small-scale tablet press models, the former can provide validation of the latter.

Characterisation Data Architecture




ADDoPT has acted as a catalyst, encouraging the resource commitment needed to secure a sufficiently holistic data set and structured approach

## Results and Benefits

Data has been assembled for 144 measurements, made across 4 drug product process steps for 49 drug product batches made from 9 different Active Pharmaceutical Ingredients (APIs) and 7 excipients variants. Many of these measurements are multi-point, spectral, or image based. Taken together they constitute a meaningfully "big" data set, providing unprecedented coverage of a full and business-relevant materials and processing space.

Structured data analysis is underway. Although the primary goal is to draw out empirical, statistical correlations and relationships, linkages to understanding the role of surfaces in sticking provided by the mechanistic modelling software VisualHabit are also anticipated.

Ultimately this will provide a technique for better interpretation of manufacturing data relative to key outcomes in order to develop more effective solutions to common manufacturing issues. By better understanding the full range of causal relationships, it should be possible to prioritise which material attributes to monitor most closely for enhanced process control.

## Further Steps

Beyond the current study, it is hoped to bring the insight gained to bear more generally upon the pharmaceutical sector's product development cycles. Similarly, beyond the immediate goal of resolving a specific sticking issue, the learnings made should be applicable elsewhere, for instance to elucidate other steps concurrently studied in the same process and further products.

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