ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

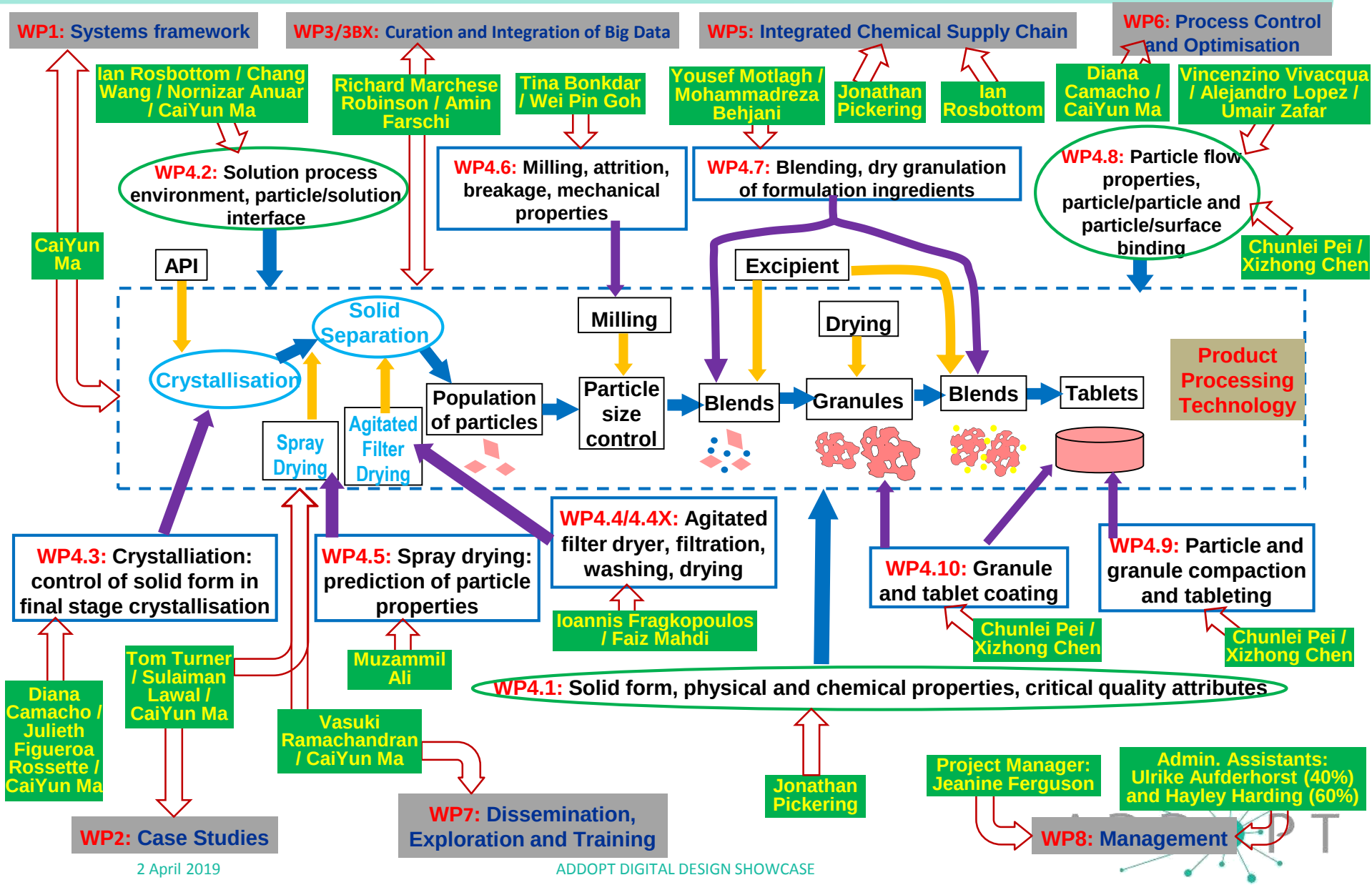
First Principles Models for Particle and Process Design

Kevin J. Roberts

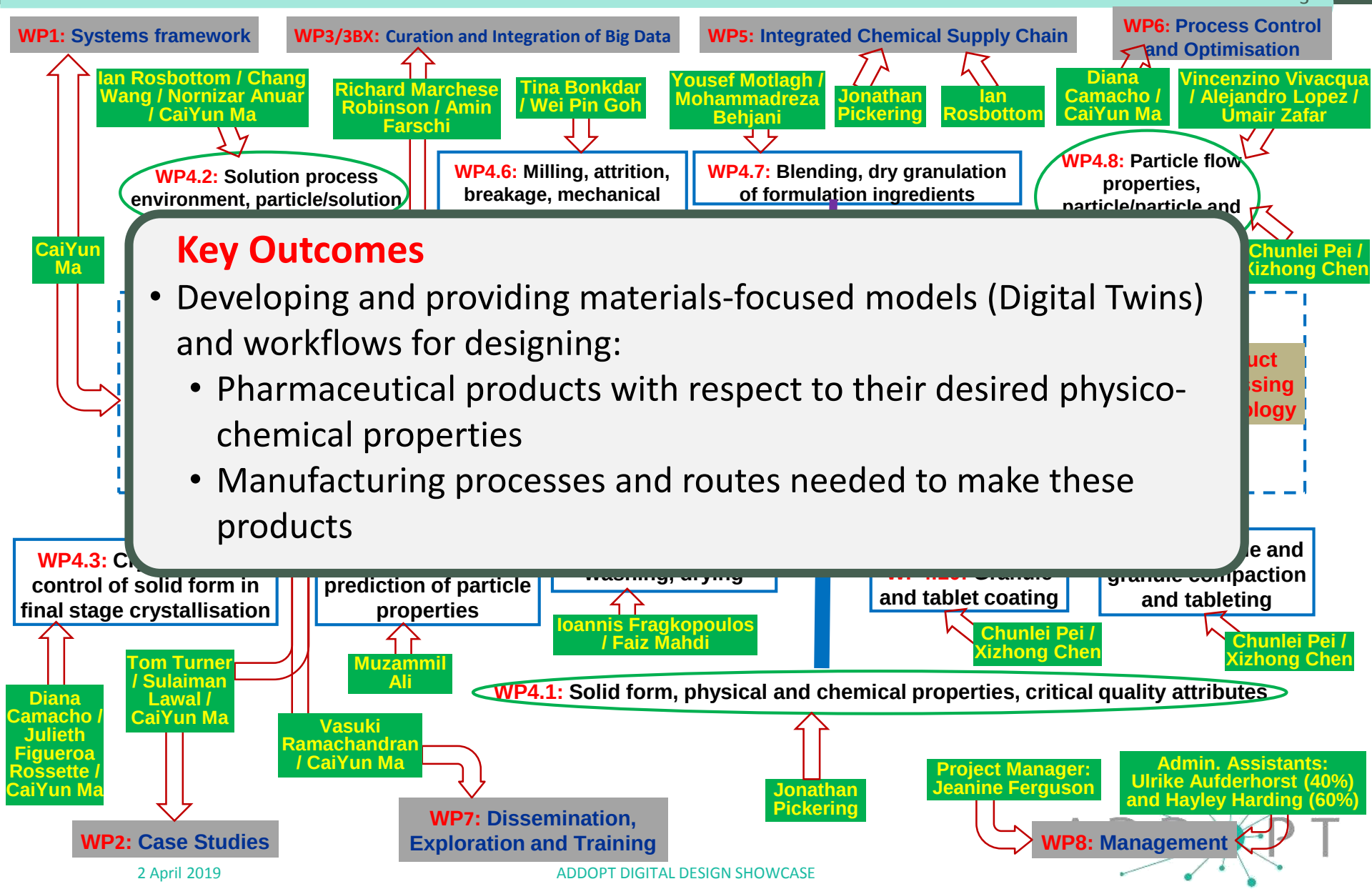
School of Chemical and Process Engineering

University of Leeds

Work Programme 4: Development of 1st Principles Models for Pharmaceutical Materials (24 researchers in total)



Work Programme 4: Development of 1st Principles Models for Pharmaceutical Materials (24 researchers in total)



VisualHabit: Predicting the Morphology of α-Lactose

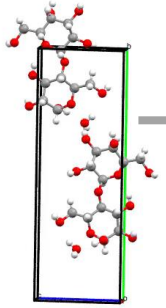
WP 4.1: J. Pickering, I. Rosbottom, H. Nguyen, R. Hammond and K. Roberts

- VisualHabit a platform for calculating the lattice energy of organic crystals, predicting their morphology, and investigating the synthons generating the morphology.

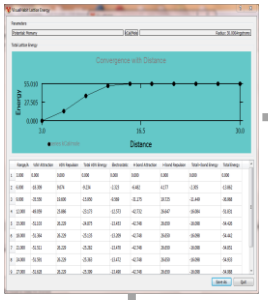
Workflow

Crystal Structure File/Database (CCDC) → Lattice Energy Prediction (VisualHabit) → Morphology Prediction (VisualHabit) → Investigation of Primary Synthons (VisualHabit)

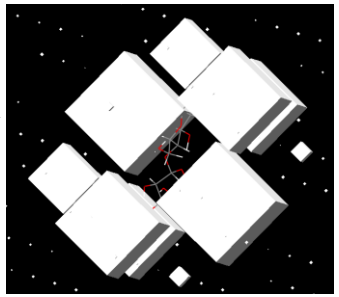
Unit Cell



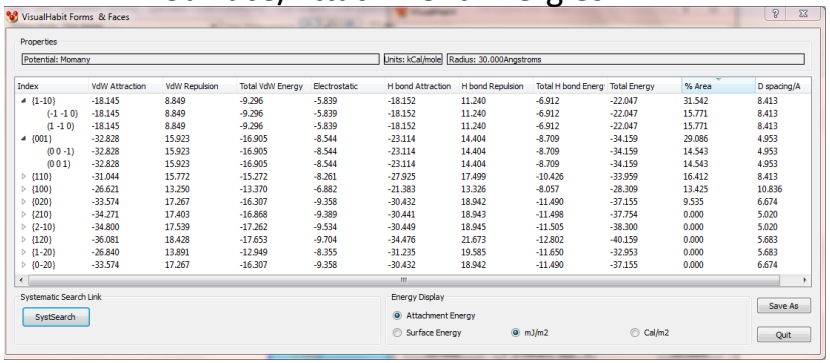
Lattice Energy



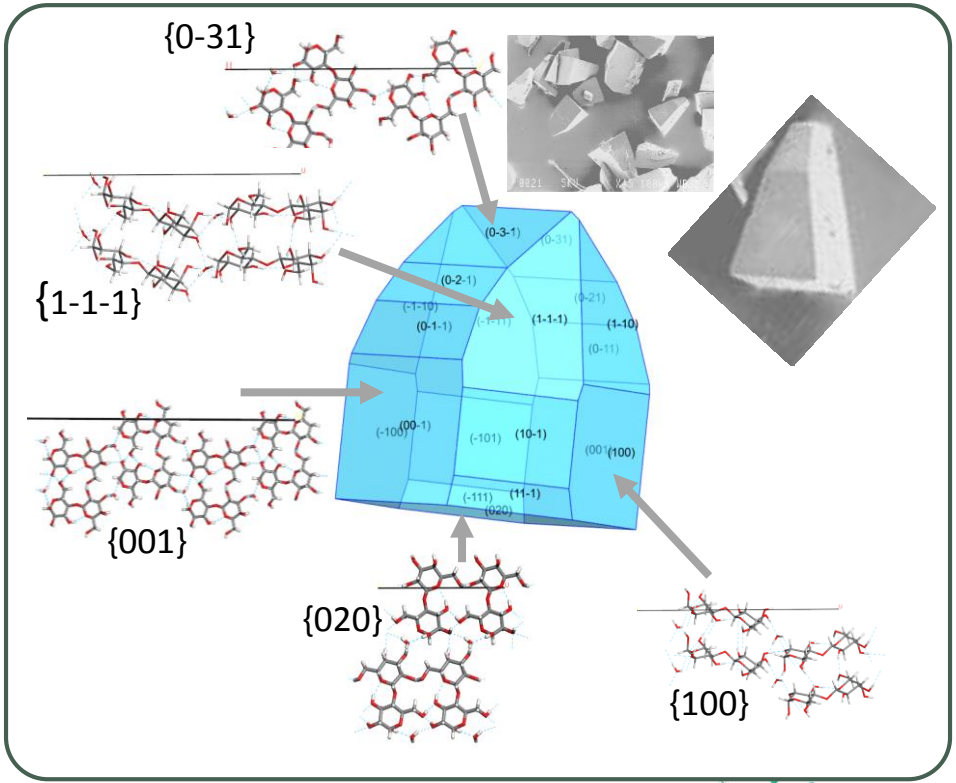
Synthon Analysis



Surface/Attachment Energies



Index	VdW Attraction	VdW Repulsion	Total VdW Energy	Electrostatic	H bond Attraction	H bond Repulsion	Total H bond Energ	Total Energy	% Area	D spacing/A
{1-10}	-18.145	8.849	-9.296	-5.839	-18.152	11.240	-6.912	-22.047	31.542	8.413
(-1 -1 0)	-18.145	8.849	-9.296	-5.839	-18.152	11.240	-6.912	-22.047	15.771	8.413
(1 -1 0)	-18.145	8.849	-9.296	-5.839	-18.152	11.240	-6.912	-22.047	15.771	8.413
{001}	-32.828	15.923	-16.905	-8.544	-23.114	14.404	-8.709	-34.159	29.086	4.953
(0 0 -1)	-32.828	15.923	-16.905	-8.544	-23.114	14.404	-8.709	-34.159	14.543	4.953
(0 0 1)	-32.828	15.923	-16.905	-8.544	-23.114	14.404	-8.709	-34.159	14.543	4.953
{110}	-31.044	15.772	-15.272	-8.261	-27.925	17.499	-10.426	-33.959	16.412	8.413
{100}	-26.621	13.250	-13.370	-6.882	-21.383	13.326	-8.057	-28.309	13.425	10.836
{020}	-33.574	17.267	-16.307	-9.358	-30.432	18.942	-11.490	-37.155	9.535	6.674
{210}	-34.271	17.403	-16.868	-9.389	-30.441	18.943	-11.498	-37.754	0.000	5.020
{2-10}	-34.800	17.539	-17.262	-9.534	-30.449	18.945	-11.505	-38.300	0.000	5.020
{120}	-36.081	18.428	-17.653	-9.704	-34.476	21.673	-12.802	-40.159	0.000	5.683
{1-20}	-26.840	13.891	-12.949	-8.355	-31.235	19.585	-11.650	-32.953	0.000	5.683
{0-20}	-33.574	17.267	-16.307	-9.358	-30.432	18.942	-11.490	-37.155	0.000	6.674



Ramachandran, V. et al., Mol. Pharmaceutics 12, 1, 18-33
Clydesdale, G. et al., Journal of Pharmaceutical Science. 1997. 86.135-141

VisualHabit: Predicting the Morphology of α-Lactose

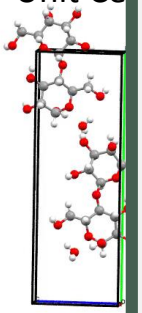
WP 4.1: J. Pickering, I. Rosbottom, H. Nguyen, R. Hammond and K. Roberts

- VisualHabit a platform for calculating the lattice energy of organic crystals, predicting their morphology, and investigating the synthons generating the morphology.

Workflow

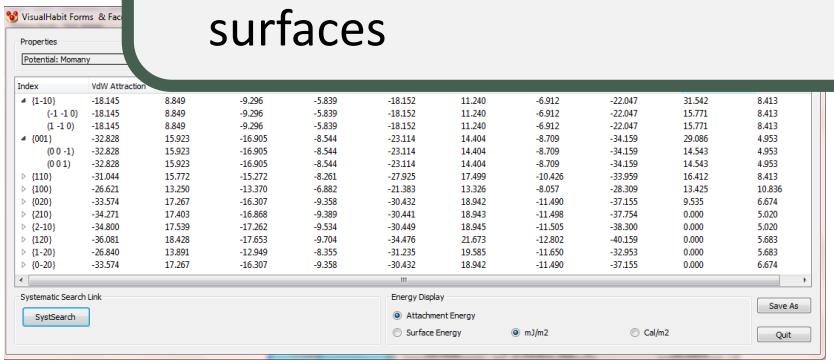
Crystal Structure File/Database (CCDC) → Lattice Energy Prediction (VisualHabit) → Morphology Prediction (VisualHabit) → Investigation of Primary Synthons (VisualHabit)

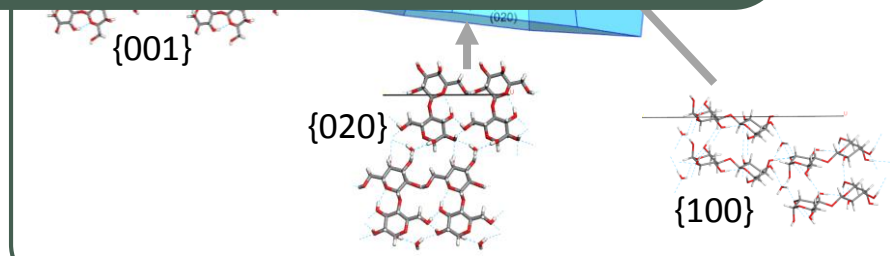
Unit Ce



Key Outcomes

- Lattice energy calculated from crystallographic structure, using an interatomic potential
- Calculations of the attachment/surface energies, generating a energy based morphology prediction
- Investigation of the primary synthons in the bulk and on the surfaces





Ramachandran, V. et al., Mol. Pharmaceutics 12, 1, 18-33
Clydesdale, G. et al., Journal of Pharmaceutical Science. 1997. 86.135-141

Predicting Solvent Mediated Morphology of Ibuprofen

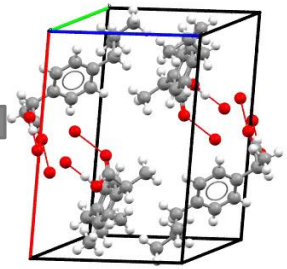
WP 4.1: J. Pickering, I. Rosbottom, R. Hammond and K. J. Roberts

- VisualHabit/SystSearch a platform for facetted crystal particle design

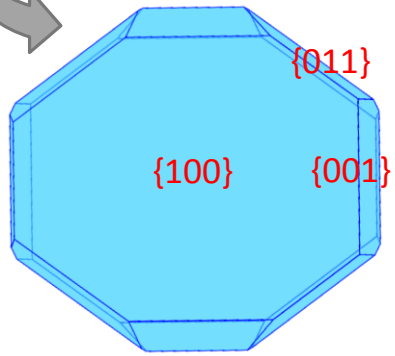
Workflow

Crystal Structure File/Database (CCDC) → Morphology Prediction (VisualHabit) → Characterize the surface chemistry (SystSearch) → Solvent Selection for Optimal Morphology

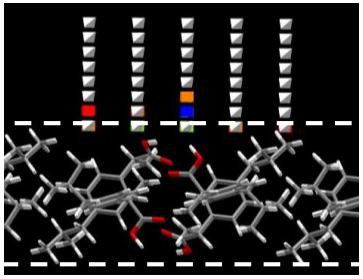
Unit Cell



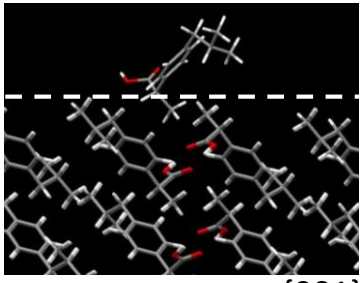
Morphology



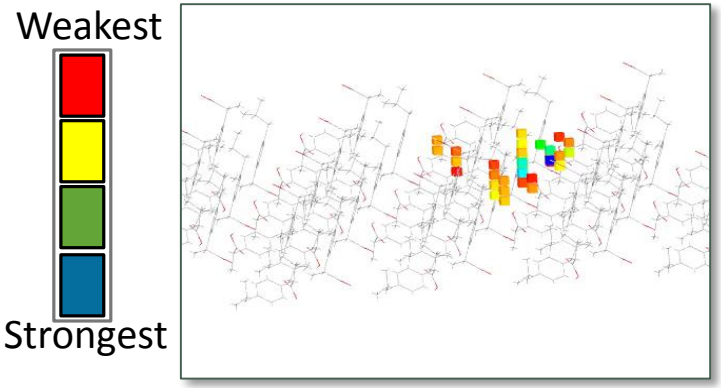
Search Grid



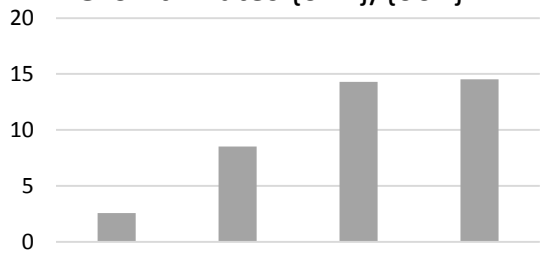
Probe on Surface

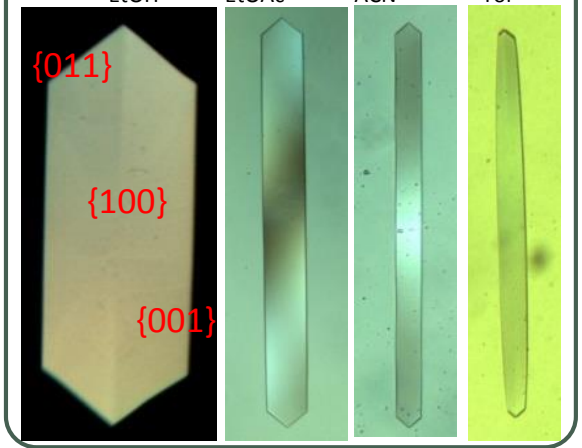


Energy Map of Surface {11-1}



Ratios of Calculated Growth Rates {011}/{001}





Rosbottom I, Pickering J, Etbon B, Hammond R and Roberts K, "Examination of inequivalent wetting on the crystal habit surfaces of RS-ibuprofen using grid-based molecular modelling", Physical Chemistry Chemical Physics, 2018, Vol. 20, Num. 17, DOI: 10.1039/c7cp08354h

Predicting Solvent Mediated Morphology of Ibuprofen

WP 4.1: J. Pickering, I. Rosbottom, R. Hammond and K. J. Roberts

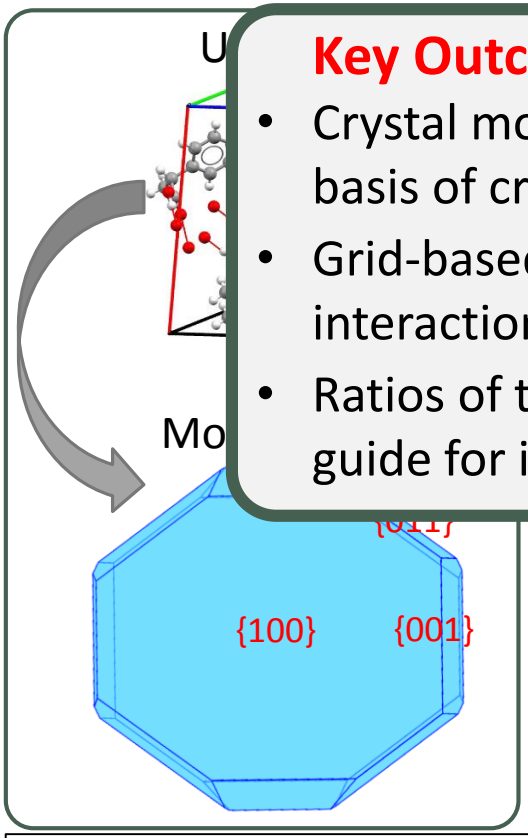
- VisualHabit/SystSearch a platform for facetted crystal particle design

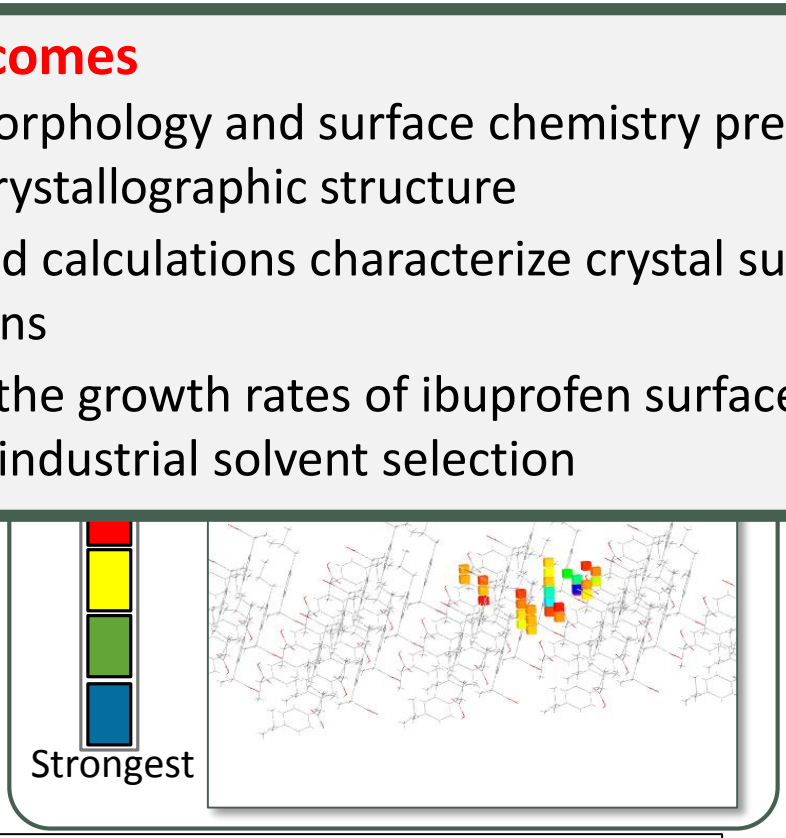
Workflow

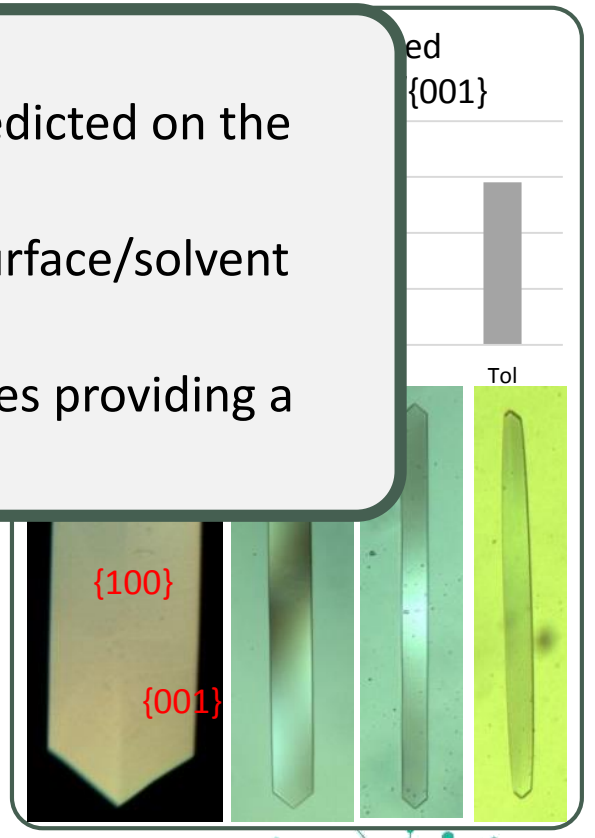
Crystal Structure File/Database (CCDC) → Morphology Prediction (VisualHabit) → Characterize the surface chemistry (SystSearch) → Solvent Selection for Optimal Morphology

Key Outcomes

- Crystal morphology and surface chemistry predicted on the basis of crystallographic structure
- Grid-based calculations characterize crystal surface/solvent interactions
- Ratios of the growth rates of ibuprofen surfaces providing a guide for industrial solvent selection







Rosbottom I, Pickering J, Etbon B, Hammond R and Roberts K, "Examination of inequivalent wetting on the crystal habit surfaces of RS-ibuprofen using grid-based molecular modelling", Physical Chemistry Chemical Physics, 2018, Vol. 20, Num. 17, DOI: 10.1039/c7cp08354h

Tablet Compaction: Prediction of Mechanical Properties

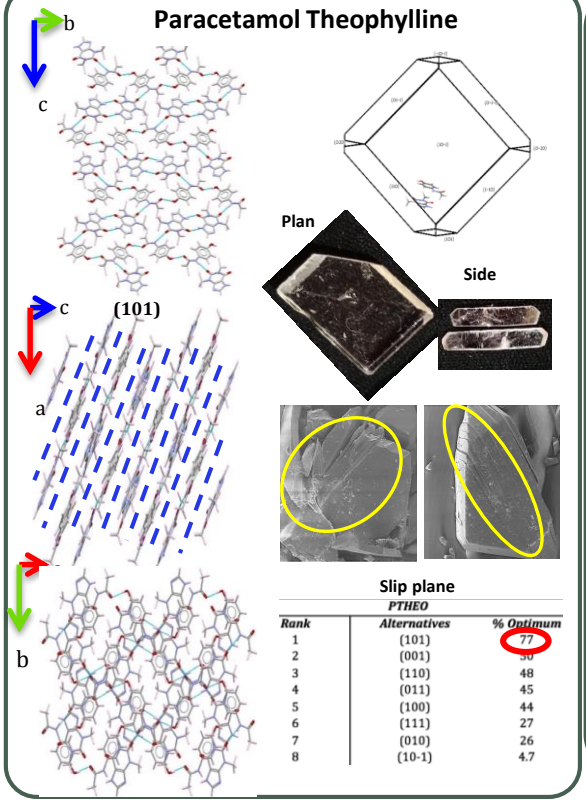
WP 4.1: S. F. Ibrahim, J. Pickering, V. Ramachandran, K. J. Roberts

- Enabling solid form design for direct compression through crystallographic structure analysis for prediction of API mechanical properties

Workflow

Molecular Level Modelling; Lattice Energetics, Rugosity, Elastic Energy, Dislocation → Statistical Consideration; Multiple Attributes Decision Making (MDAM) → Prediction of Dislocation Slip Systems

Paracetamol Theophylline

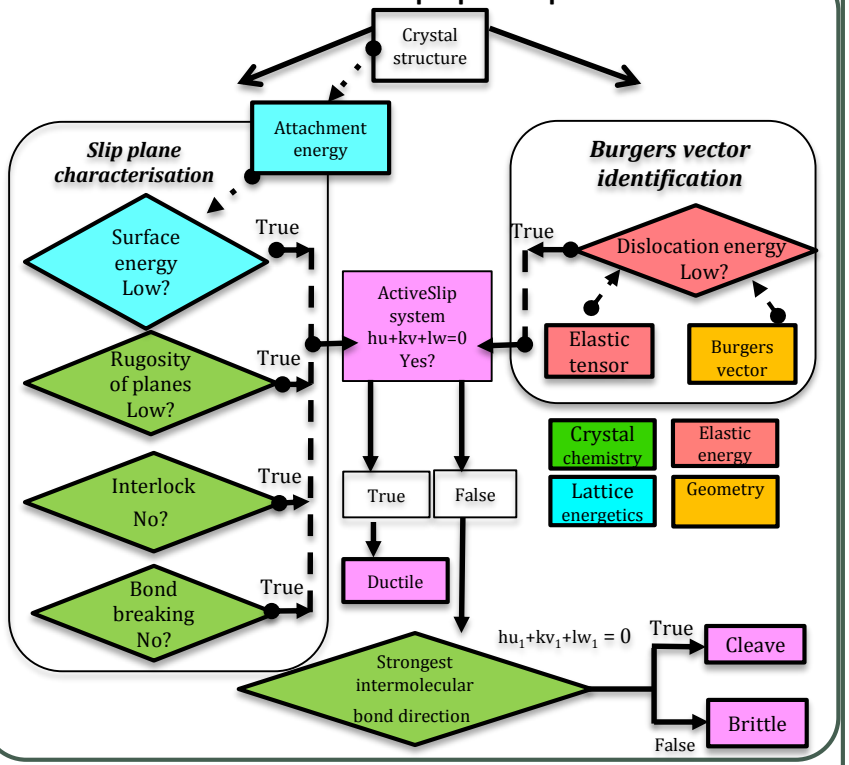


Slip plane

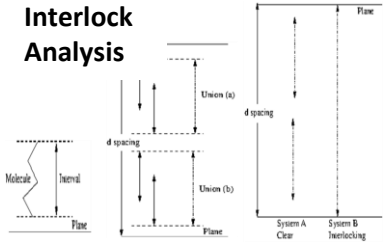
PTHEO

Rank	Alternatives	% Optimum
1	(101)	77
2	(001)	50
3	(110)	48
4	(011)	45
5	(100)	44
6	(111)	27
7	(010)	26
8	(10-1)	4.7

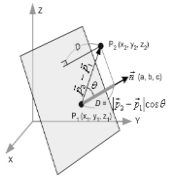
Molecular level mechanical properties prediction model



Interlock Analysis



- **Distance between each molecule atom in unit cell with respect to potential slip plane**



- **Rugosity: atomic scale roughness of slip plane**
- **Degree of molecular interlock: interval analysis of extents of molecules in unit cell**

Tablet Compaction: Prediction of Mechanical Properties

WP 4.1: S. F. Ibrahim, J. Pickering, V. Ramachandran, K. J. Roberts

- Enabling solid form design for direct compression through crystallographic structure analysis for prediction of API mechanical properties

Workflow

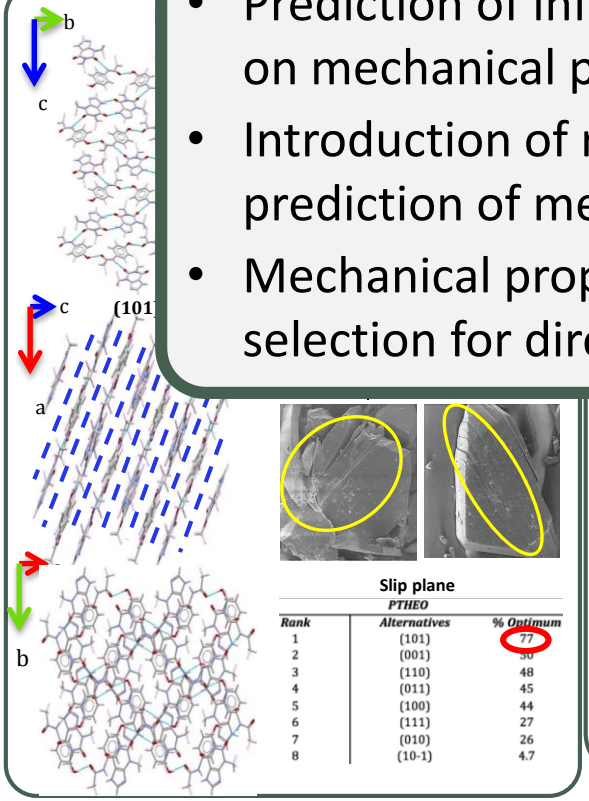
Molecular Level Modelling; Lattice Energetics, Rugosity, F

→ Statistical Consideration; Multiple Attributes

→ Prediction of Dislocation Slip ms

Key Outcomes

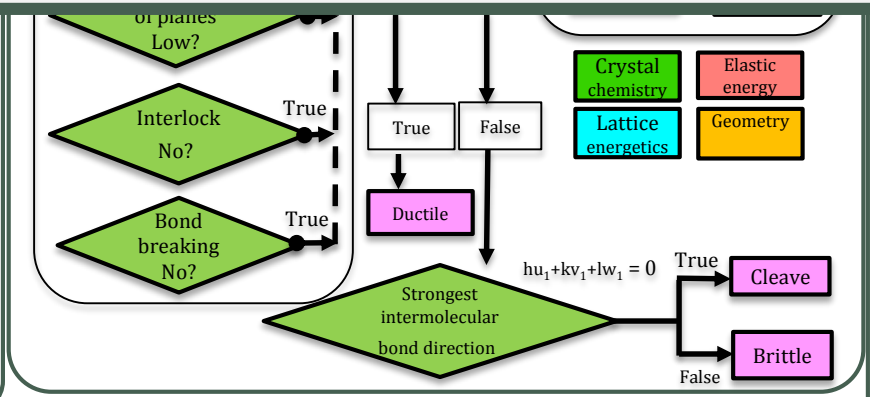
- Prediction of influence of molecular and crystallographic structure on mechanical properties of crystals
- Introduction of rugosity and interlocking of planes to enhance prediction of mechanical properties
- Mechanical properties based design tool useful in solid-form selection for direct compression

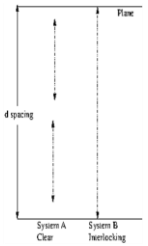


Slip plane

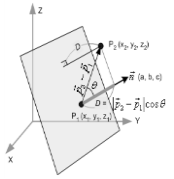
PTHEO

Rank	Alternatives	% Optimum
1	(101)	77
2	(001)	50
3	(110)	48
4	(011)	45
5	(100)	44
6	(111)	27
7	(010)	26
8	(10-1)	4.7





…en each …n in unit cell with respect to potential slip plane



- **Rugosity: atomic scale roughness of slip plane**
- **Degree of molecular interlock: interval analysis of extents of molecules in unit cell**

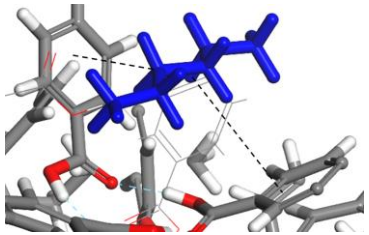
Interplay between Solution and Solid-State Interfacial Chemistry

WP 4.2: I. Rosbottom, C. Yong, D. Geatches, J. H. Pickering, R. B. Hammond, I. Todorov and K. J. Roberts

- Characteristic interactions between solute-solute, solute-solvent and solvent-solvent in the solid-state, solution-state and at crystal/solution interfaces

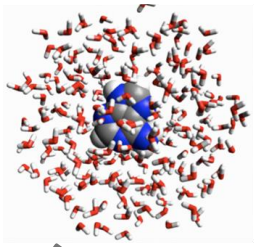
Workflow

Crystal and Surface Structure (Visual HABIT) → Solution and interfacial State (DL_POLY, Grid Search) → Solvent Directed Physical Properties

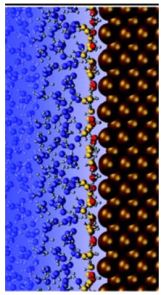


Intermolecular interactions from MD simulations to examine benzoic acid and PABA solution chemistry

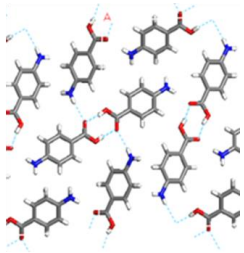
Molecules in Bulk Solution



Solid/Liquid Interface

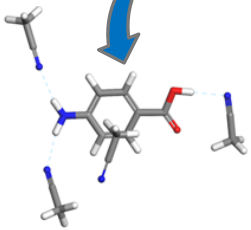


Solid-State Structure

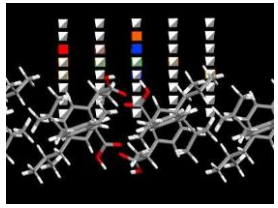


Bulk and surface synthonic modelling to understand alpha PABA morphology in mixed solvents

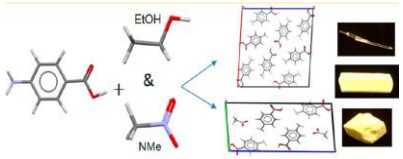
DL_Software



Grid-based modelling to build solvated clusters of p-aminobenzoic acid



Synthonic Engineering Tools

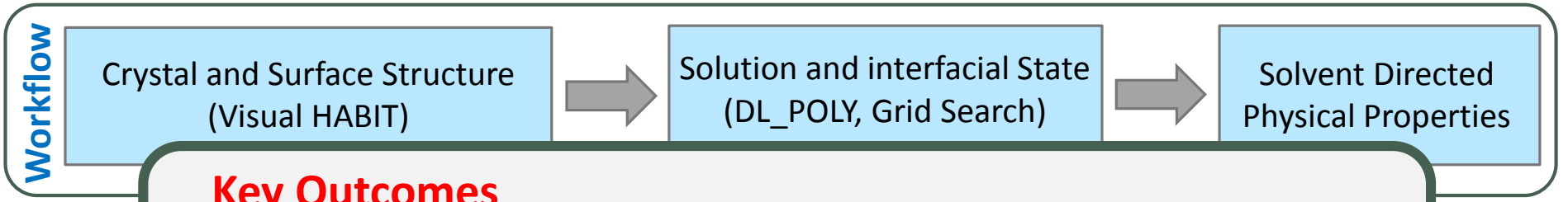


Surface grid-based modelling to examine solvent effect on ibuprofen morphology

Interplay between Solution and Solid-State Interfacial Chemistry

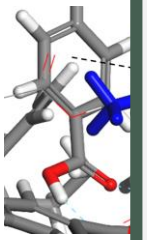
WP 4.2: I. Rosbottom, C. Yong, D. Geatches, J. H. Pickering, R. B. Hammond, I. Todorov and K. J. Roberts

- Characteristic interactions between solute-solute, solute-solvent and solvent-solvent in the solid-state, solution-state and at crystal/solution interfaces



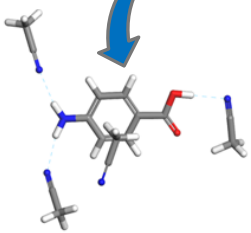
Key Outcomes

- Visual HABIT/SystSearch developed for predicting effect of solvent on physical and chemical properties of crystals
- Molecular dynamics platform for modelling intermolecular (synthonic) interactions in solution state
- Workflow for understanding inter-connectivity between intermolecular structure in the solution and solid-states



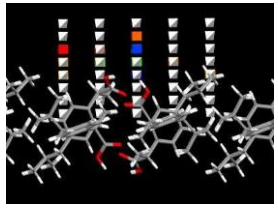
Intermolec
interaction
simulations
benzoic aci
solution ch

e synthonic
derstand
phology in

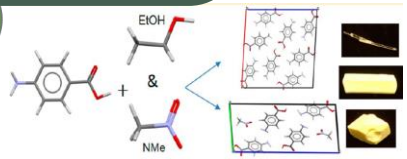


DL_Software

Grid-based modelling to build solvated clusters of p-aminobenzoic acid



Engineering Tools



Surface grid-based modelling to examine solvent effect on ibuprofen morphology

Optimisation of API particles attributes in batch crystallisers

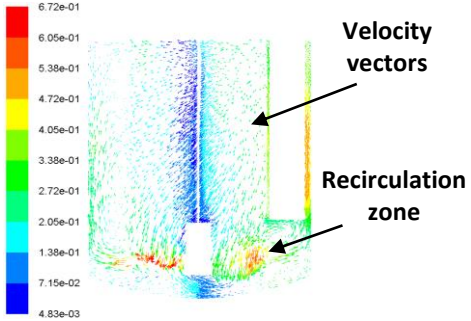
WP 4.3: D. M. Camacho, J. A. Figueroa Rosette, C. Y. Ma, T. Mahmud and K. J. Roberts

- Models were developed to assess hydrodynamics and evolution of CSD in a 20-Litre jacketed crystalliser with a retreat impeller and a single baffle

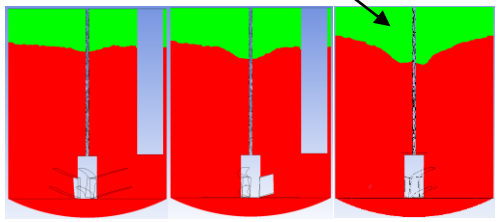
Workflow

CFD Methodology Development → Fully Coupled Multiphase CFD Modelling with Population Balance Model (PBM) (Fluent) → Zonal Modelling (gCRYSTAL)

Hydrodynamics



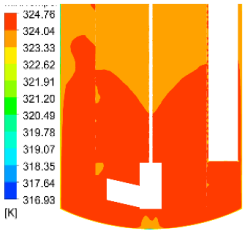
Vortex Formation



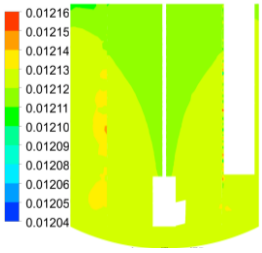
100 rpm 150 rpm 250 rpm

CFD Simulations of Cooling Crystallisation of L-glutamic Acid (LGA) in Aqueous Solution

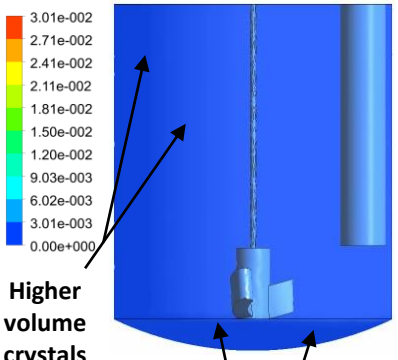
Temperature distribution



Mass fraction distribution

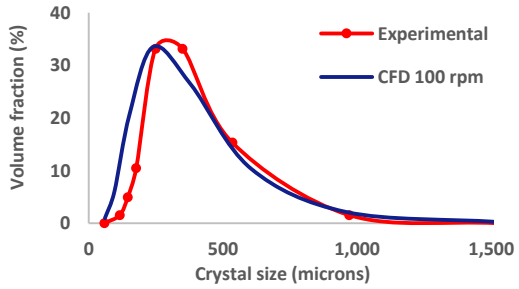


Evolution of solid volume fraction with time

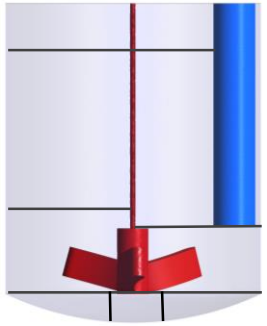


CFD simulation at 100 rpm impeller speed

Particle size distribution



Zones Schematic



Particle morphology
Particle size distribution

Optimisation of API particles attributes in batch crystallisers

WP 4.3: D. M. Camacho, J. A. Figueroa Rosette, C. Y. Ma, T. Mahmud and K. J. Roberts

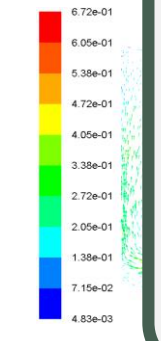
- Models were developed to assess hydrodynamics and evolution of CSD in a 20-Litre jacketed crystalliser with a retreat impeller and a single baffle

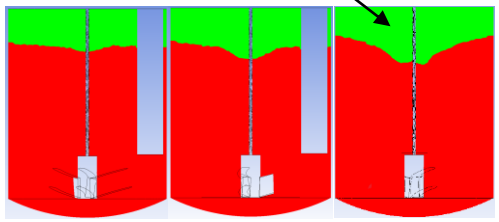
Workflow

CFD Methodology Development → Fully Coupled Multiphase CFD Modelling with Population Balance Model (PBM) → Zonal Modelling (CRYSTAL)

Key Outcomes

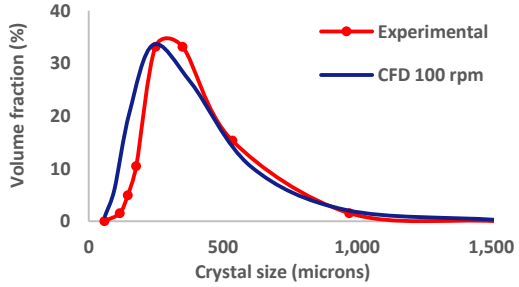
- Models predict effect of operating conditions on hydrodynamics in conventional pharmaceutical crystalliser
- 3D CFD-PBM predicts the evolution with time of CSD in batch cooling crystallisation
- CFD modelling results can be used into multi-zonal modelling software for process optimisation

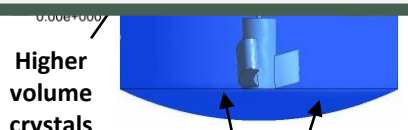




100 rpm 150 rpm 250 rpm

Particle size distribution



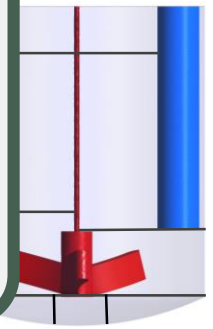


Higher volume crystals

small volume crystals

CFD simulation at 100 rpm impeller speed

s Schematic



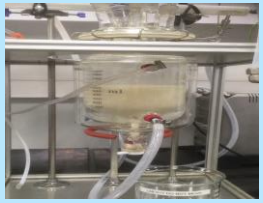
Particle morphology
Particle size distribution

AFD: Prediction of Filtration and Drying Performance

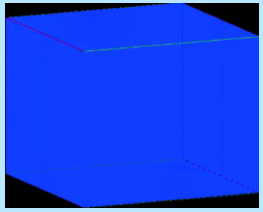
WP 4.4: I. Fragkopoulos, T. Mahmud, P. J. Heggs, A. E. Bayly and F. Muller

Workflow

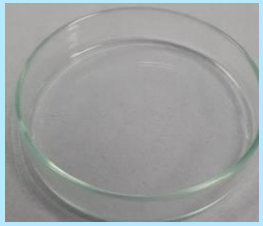
Suspended Crystals



Crystal Bed



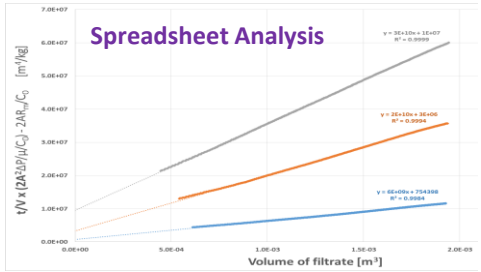
Crystal Powder



Filtration

Lab Scale: Parameter Estimation

Partial Settled Bed Filtration Model

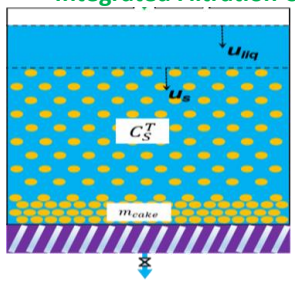


α Specific cake resistance

R_m Medium Resistance

Process Scale: Prediction

Integrated Filtration-Sedimentation Model



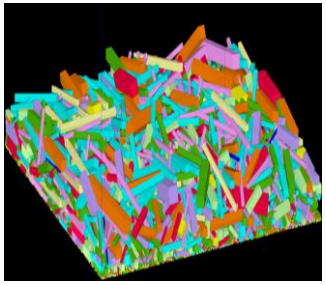
U_S

U_{Liq}

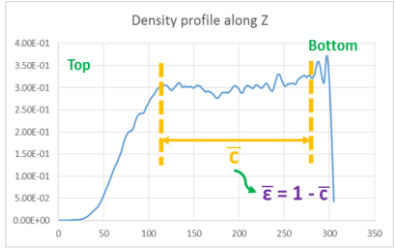
Prediction of Filtration Rate based on particle settling velocities (U_S) and filtrate flowrate (U_{Liq})

Bed Structure

DEM Simulation

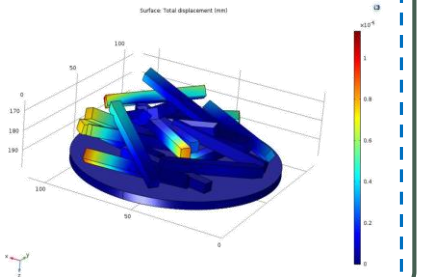


Bed Properties



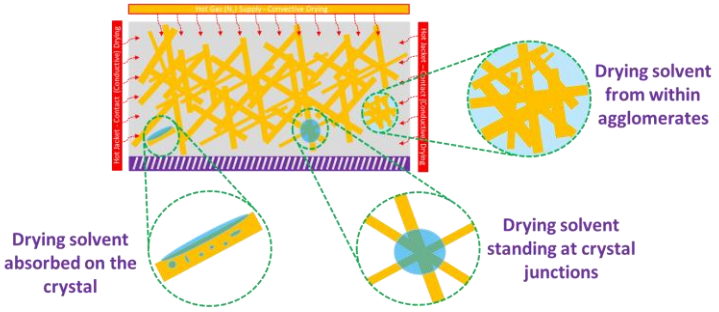
and

FEM/Breakage



Drying

Mass Transfer Resistances in Series Model



Parameter Estimation (Lab)

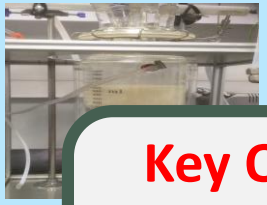
Scaled-up Prediction

AFD: Prediction of Filtration and Drying Performance

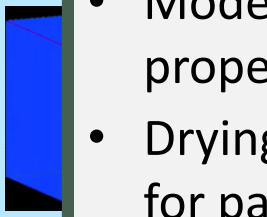
WP 4.4: I. Fragkopoulos, T. Mahmud, P. J. Heggs, A. E. Bayly and F. Muller

Workflow

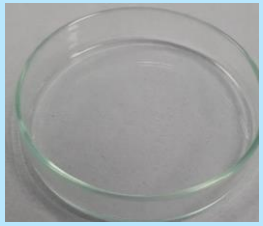
Suspended Crystals



C



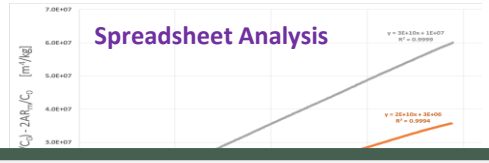
Crystal Powder



Filtration

Lab Scale: Parameter Estimation

Partial Settled Bed Filtration Model

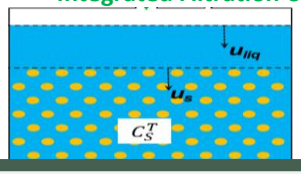


α

Specific cake resistance

Process Scale: Prediction

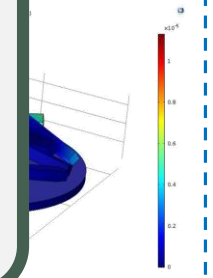
Integrated Filtration-Sedimentation Model



U_S

Prediction of Filtration Rate based on particle settling velocities (U_S) and filtrate flowrate (U_{Liq})

akage

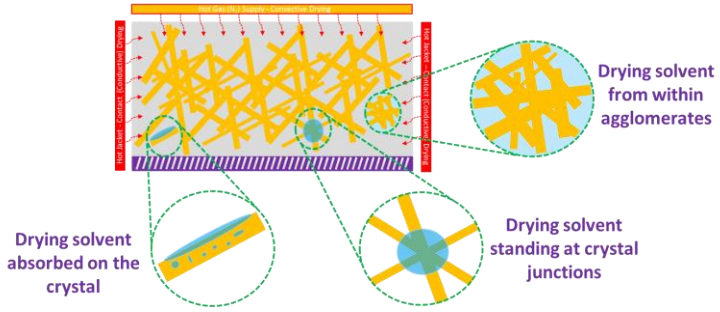


Key Outcomes

- Filtration models used for parameter estimation at lab-scale and the prediction of performance at process scale
- Modelling the packed bed structure (DEM) to predict bed properties and particle breakage (FEM)
- Drying models with a mass transfer resistances in series to be used for parameter estimation and prediction

Drying

Mass Transfer Resistances in Series Model



Parameter Estimation (Lab)

Scaled-up Prediction

ADDOPT

Investigation of Crystal Breakage during Pressure Filtration

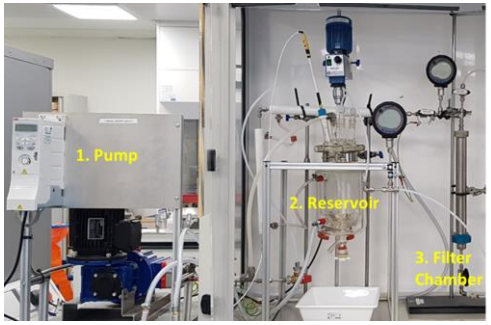
WP 4.4X: F. Mahdi, I. Fragkopoulos and F. Muller

- To validate a Crystal Breakage Model, three methods have been developed for investigating the crystal breakage experimentally: continuous pressure percolation, AFM and XRT scan

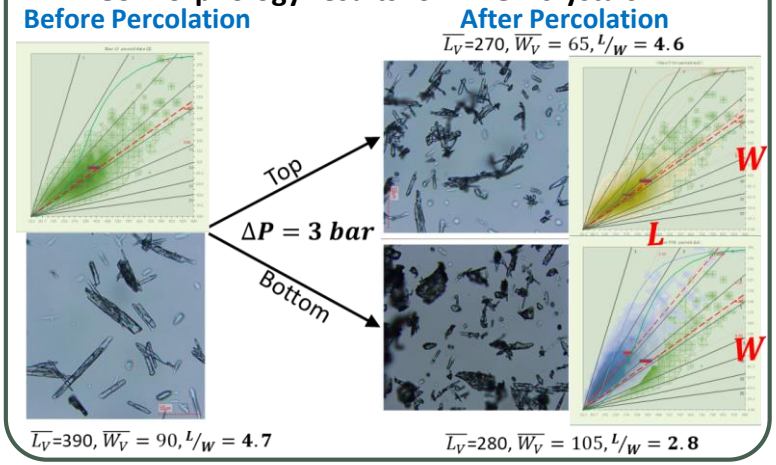
Workflow

Effect of Pressure on Particle Size Distribution and Shape Continuous Pressure Percolation	Mechanical Properties Atomic Force Microscope (AFM)	X-Ray Tomography James Carr, Henry Royce Institute, Manchester Amira-Avizo (3D software)

Continuous Pressure Percolation

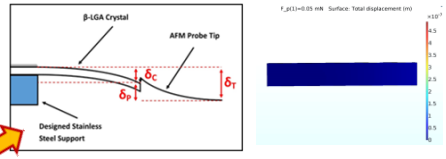


G3 morphology results for B-LGA crystals

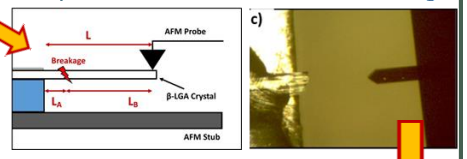


1 Atomic Force Microscope (AFM)

2. Crystal and AFM Probe Deflections

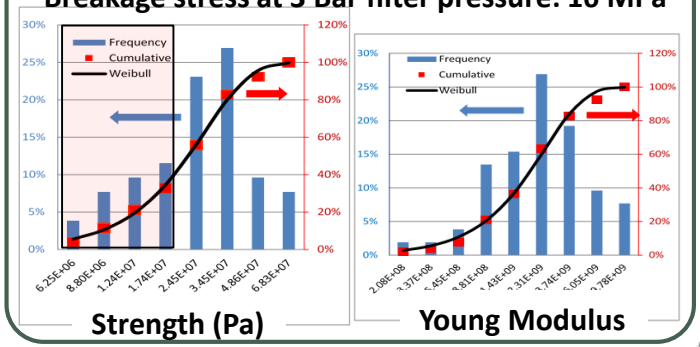


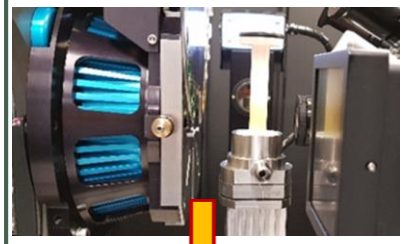
3. Crystal Dimensions Before and After Breakage



AFM Results for 52 Crystals of Beta-LGA

Breakage stress at 3 Bar filter pressure: 16 MPa

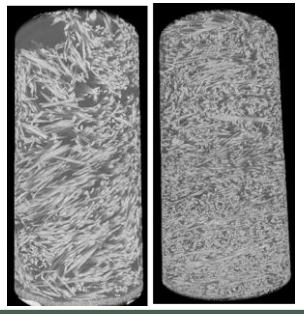




3D imaging data

Alpha-PABA Crystals Bed

0.25 bar **5.5 bar**



Investigation of Crystal Breakage during Pressure Filtration

WP 4.4X: F. Mahdi, I. Fragkopoulos and F. Muller

- To validate a Crystal Breakage Model, three methods have been developed for investigating the crystal breakage experimentally: continuous pressure percolation, AFM and XRT scan

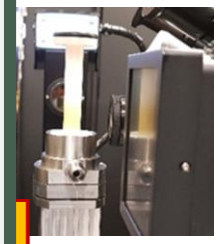
Workflow

Effect of Pressure on Particle Size Distribution and Shape	Mechanical Properties Atomic Force Microscope	X-Ray Tomography James Carr, Henry Royce Institute,
Cont		ftware)

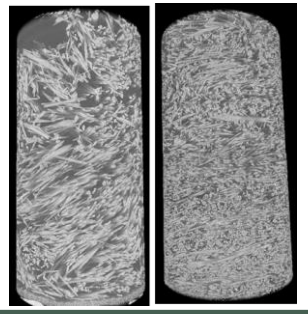
Key Outcomes

- Effect of pressure Filtration/Percolation on high aspect ratio crystals
- Mechanical properties of single organic crystals using AFM to calculate Tensile strength and Young's modulus
- Visualisation of packed bed structure of organic crystals to validate a 3D DEM Packed Bed Structures

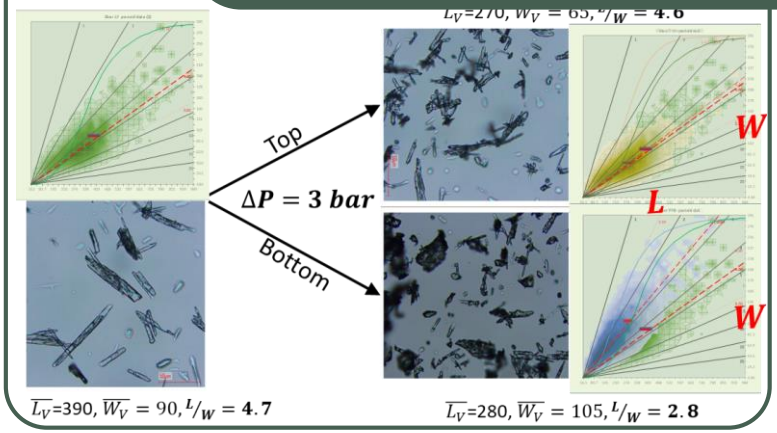
Continu
Pressu
Percolat



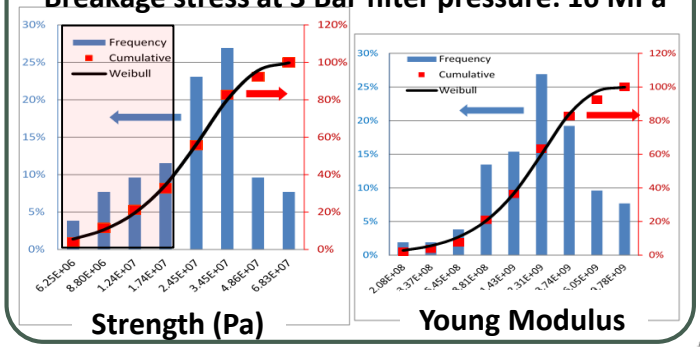
ing data
Crystals Bed
0.25 bar
5.5 bar



G3 mor
Before Percola



AFM Results for 52 Crystals of Beta-LGA
Breakage stress at 3 Bar filter pressure: 16 MPa



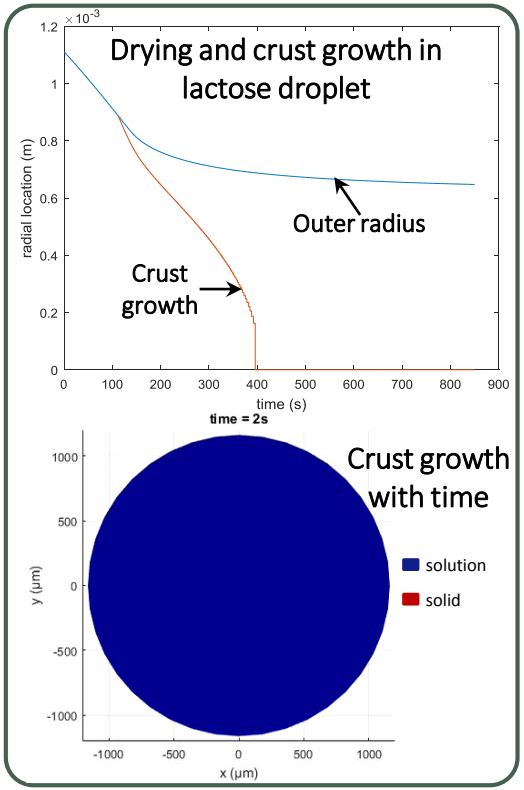
Spray Drying: Prediction of Particle Properties

WP 4.5: M. Ali, T. Mahmud, P. J. Heggs and A. E. Bayly

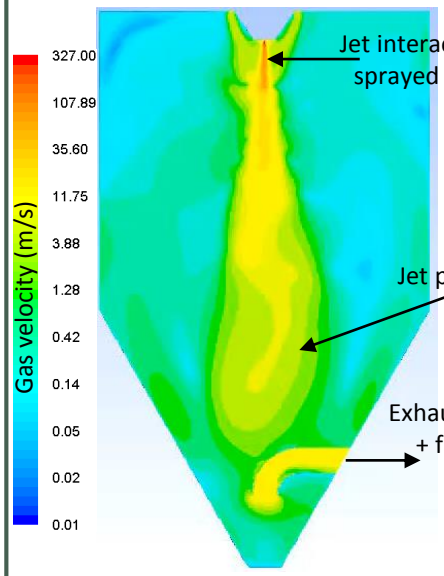
- Droplet drying models were developed and coupled with CFD models to gain better understanding of spray drying pharmaceutical materials

Workflow

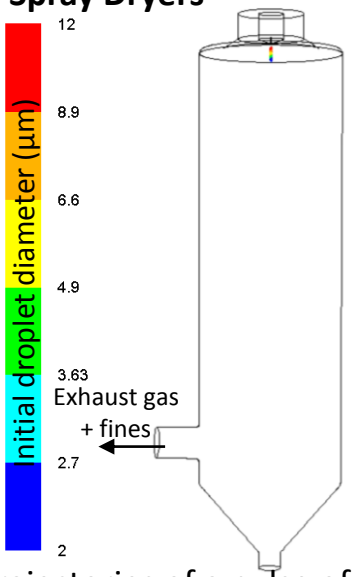
Single Droplet Drying Models for Amorphous and Crystalline Materials → Multiphase CFD Modelling of Lab and Pilot-Scale Dryers (Fluent) → Zonal Modelling (gSOLIDS)



Multiphase CFD Simulations of Spray Dryers

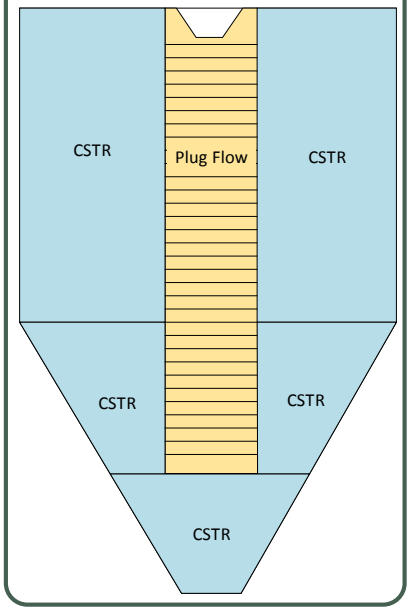


Simulated gas velocity in a pilot-scale dryer



Trajectories of a pulse of injected droplets in a lab-scale dryer

Zones Schematic



Spray Drying: Prediction of Particle Properties

WP 4.5: M. Ali, T. Mahmud, P. J. Heggs and A. E. Bayly

- Droplet drying models were developed and coupled with CFD models to gain better understanding of spray drying pharmaceutical materials

Workflow

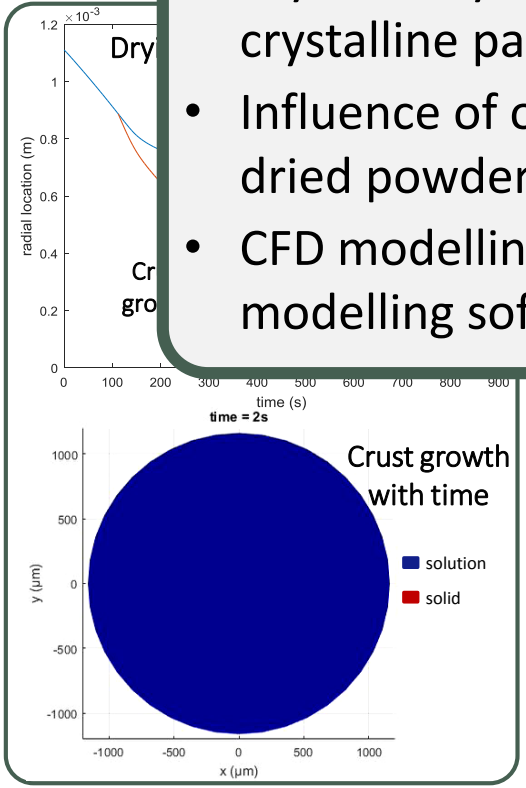
Single Droplet Drying Models for

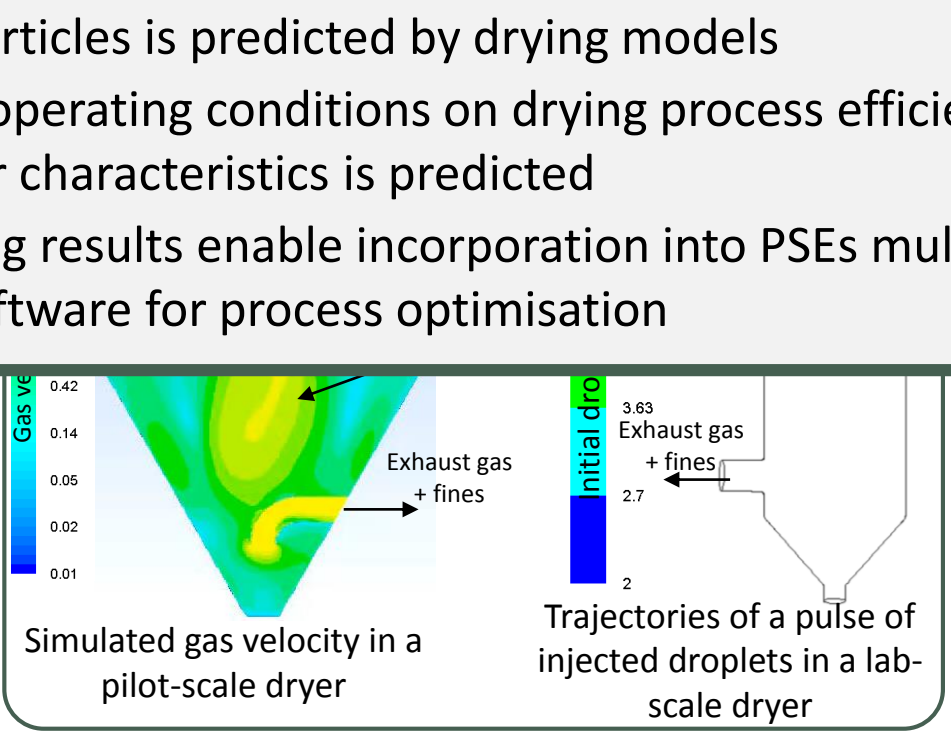
Multiphase CFD Modelling of

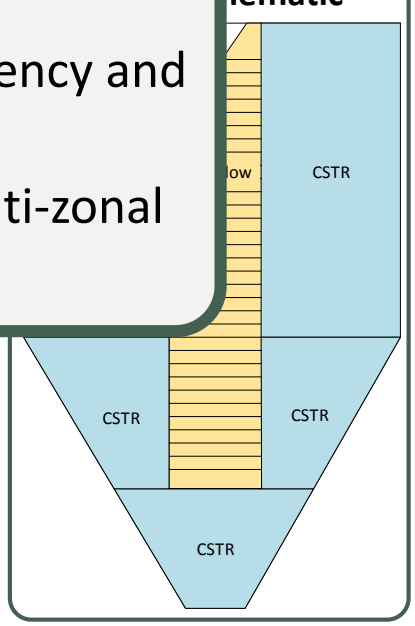
Zonal Modelling DS)

Key Outcomes

- Crystallinity in amorphous and crystal size distribution in crystalline particles is predicted by drying models
- Influence of operating conditions on drying process efficiency and dried powder characteristics is predicted
- CFD modelling results enable incorporation into PSEs multi-zonal modelling software for process optimisation







Breakability Assessment of Pharmaceutical Materials

WP 4.6: W. P. Goh, T. Bonakdar and M. Ghadiri

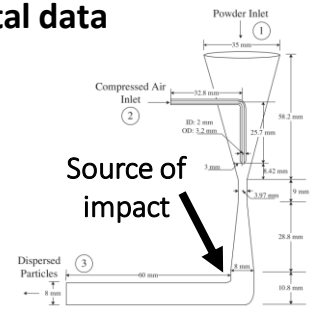
- Novel method was developed to assess the breakability of pharmaceutical materials using aerodynamic dispersion technique

Workflow

Particle size analysis at different dispersion pressures using Scirocco disperser → Fitting of the experimental data using a modified impact breakage model → Breakability Assessment Tool (BAT) (gSOLIDS)

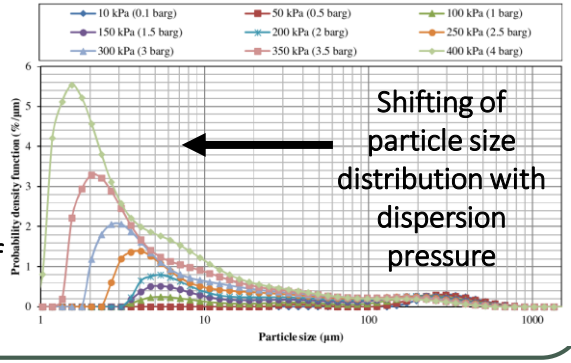
Experimental data

Malvern Mastersizer 2000 (commercial)



Scirocco Disperser Unit

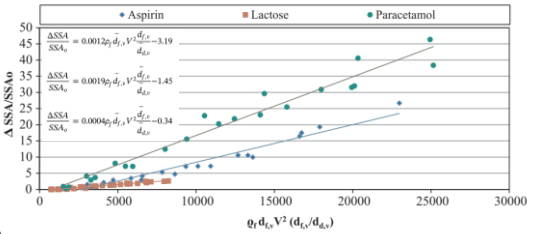
Particles are dispersed at different dispersion pressure, causing different degrees of breakage



Shifting of particle size distribution with dispersion pressure

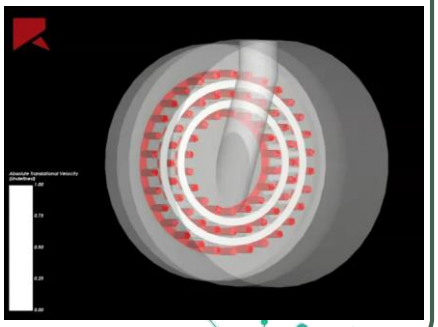
Breakability Assessment

- Breakage is expressed in terms of shift of specific surface area
- Slope of the fitted line, $\alpha H/K_c^2$ gives a measure of the breakability of the material
- Breakage Kernel gives a measure of how much energy is required to induce certain degree of breakage and that information can be used to analyse the breakage behaviour in the DEM simulations



DEM Simulation

- Real particle shape is used to simulate pin milling of pharmaceutical materials
- Faceted Polyhedron with 26 faces
- Breakage model available and the parameters can be calibrated using the breakage kernel



Breakability Assessment of Pharmaceutical Materials

WP 4.6: W. P. Goh, T. Bonakdar and M. Ghadiri

- Novel method was developed to assess the breakability of pharmaceutical materials using aerodynamic dispersion technique

Workflow

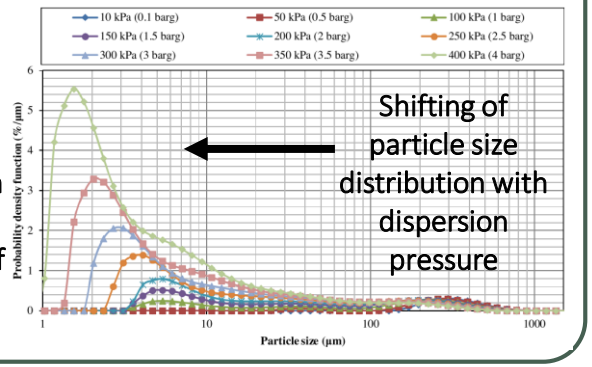
Particle size analysis at different dispersion pressures using Sympatec disperser → Fitting of the experimental data using a modified impact breakage model → Breakability Assessment Tool (BAT) (gSOLIDS)

Key Outcomes

- Model predicts the breakability of materials
- BAT model has been implemented in gPROMs, simplifying the analysis of the experimental data
- The performance of pin mill is simulated and investigated using DEM

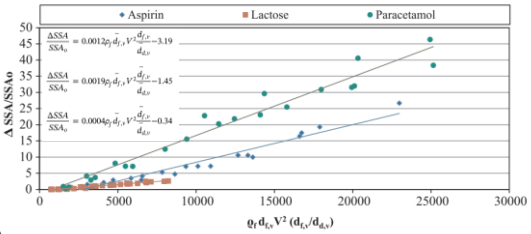
Malvern Mastersizer (commercial)

Particles are dispersed at different dispersion pressure, causing different degrees of breakage



Shifting of particle size distribution with dispersion pressure

Information can be used to analyse the breakage behaviour in the DEM simulations

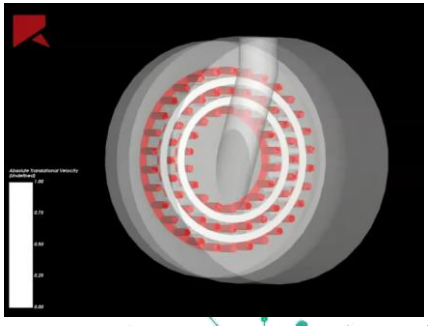


…lation

…be is used …illing of …materials

…on with

…vailable and …be calibrated …age kernel



Continuous Blending: Prediction and Assessment

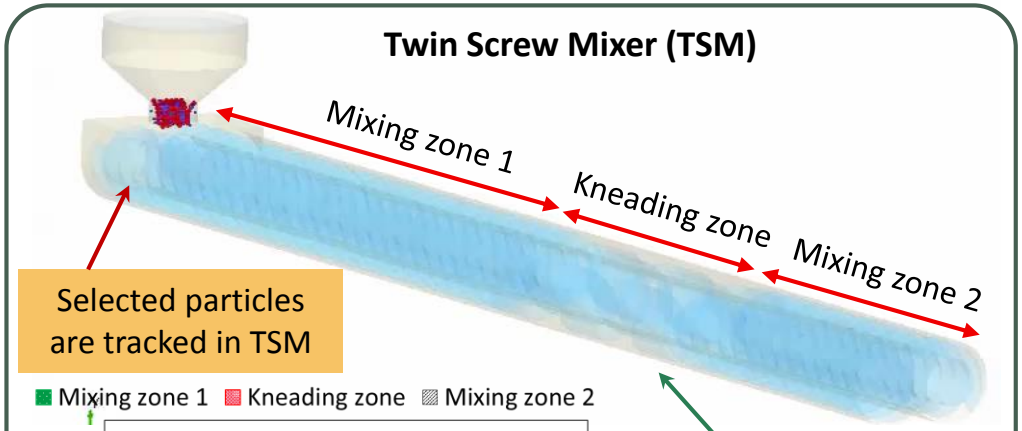
WP 4.7: M. A. Behjani, A. Hassanpour and A. E. Bayly

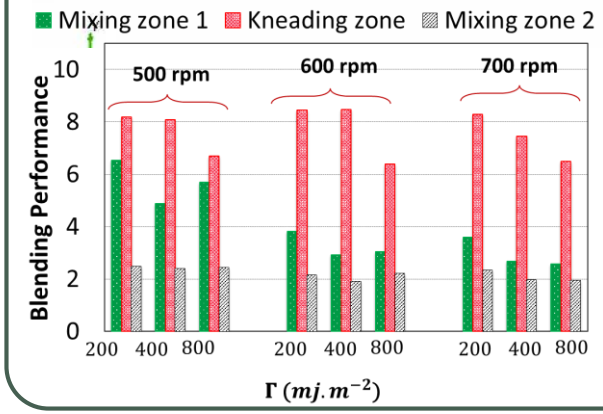
- Discrete Element Method (DEM) is used to predict continuous blending of pharmaceutical powders and optimise the process design

Workflow

Particle Characterisation → Calibration of DEM Input Parameters → Blending Simulation and Sensitivity analysis → Process Design Optimisation (gSOLIDS)

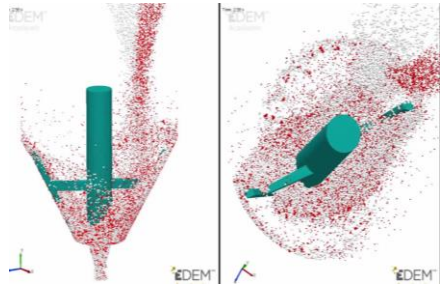
Twin Screw Mixer (TSM)

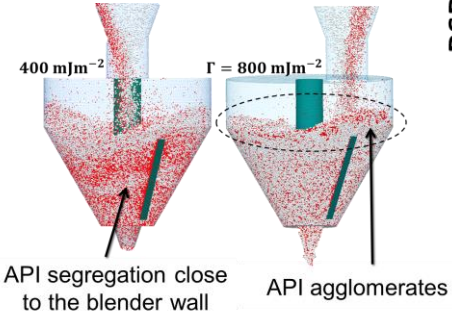


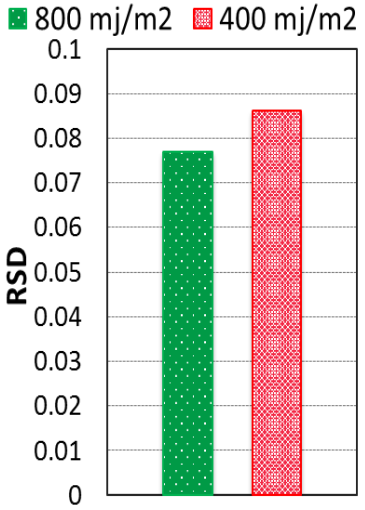


API agglomerates form in the mixing zone 1 and break in the kneading zone

Continuous Mixing Technology (CMT)







Continuous Blending: Prediction and Assessment

WP 4.7: M. A. Behjani, A. Hassanpour and A. E. Bayly

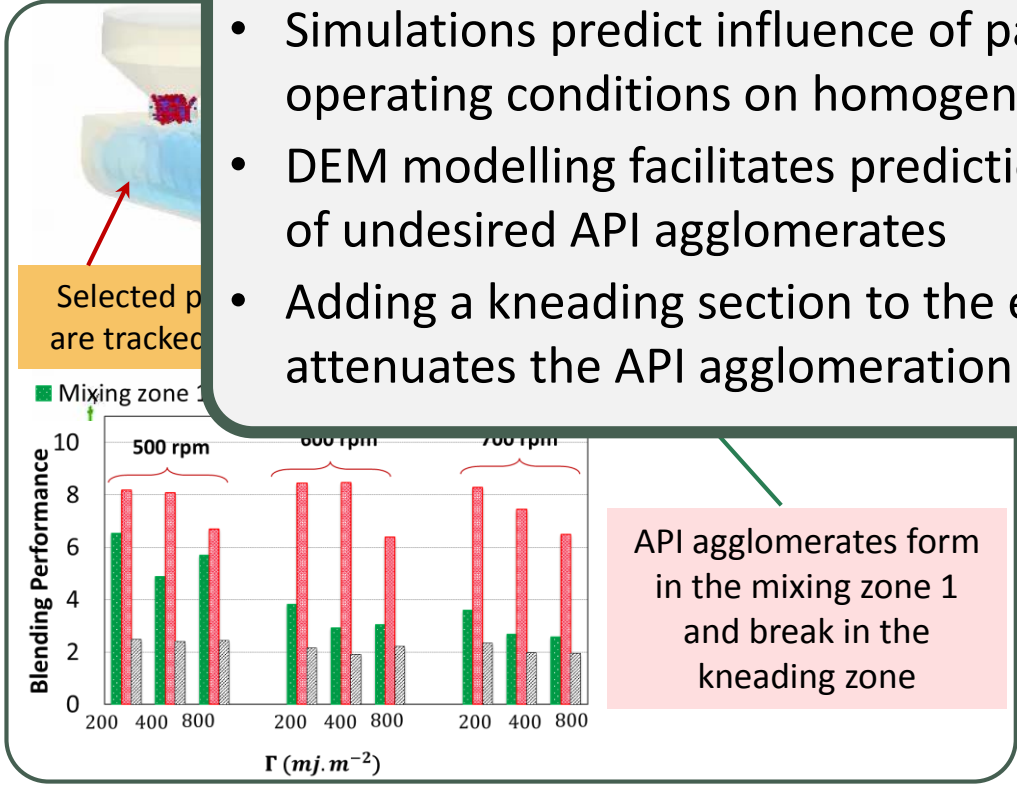
- Discrete Element Method (DEM) is used to predict continuous blending of pharmaceutical powders and optimise the process design

Workflow

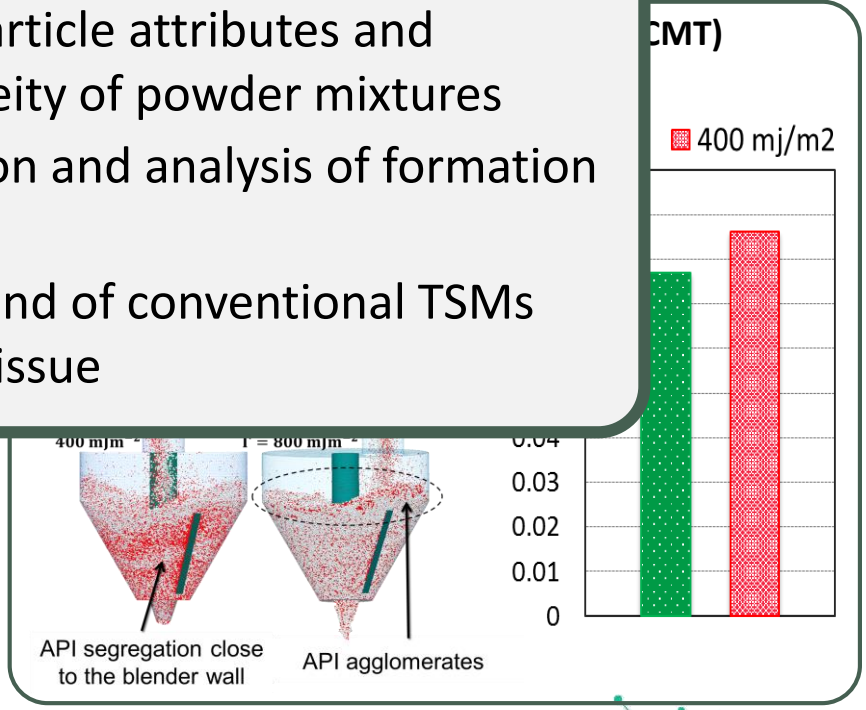
Particle Characterisation → Calibration of DEM Input Parameters → Blending Simulation and Sensitivity → Process Design Optimisation (…OLIDS)

Key Outcomes

- Simulations predict influence of particle attributes and operating conditions on homogeneity of powder mixtures
- DEM modelling facilitates prediction and analysis of formation of undesired API agglomerates
- Adding a kneading section to the end of conventional TSMs attenuates the API agglomeration issue



API agglomerates form in the mixing zone 1 and break in the kneading zone



Prediction of Cohesive Powder Flow under Dynamic Conditions

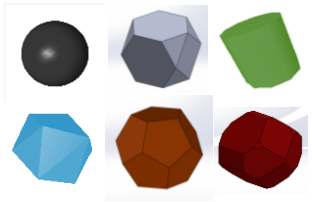
WP 4.8: U. Zafar, , A. Lopez, V. Vivacqua, R. Hammond and M. Ghadiri

- Numerical simulation by DEM is used to develop a unified rheological description of flow of cohesive and faceted particles in Freeman Technology FT4 rheometer and screw feeder

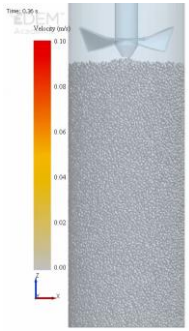
Workflow

DEM Modelling: Shape | Cohesion | Strain rate → Experimental Validation of the Model → Rheological Description (gPROMS)

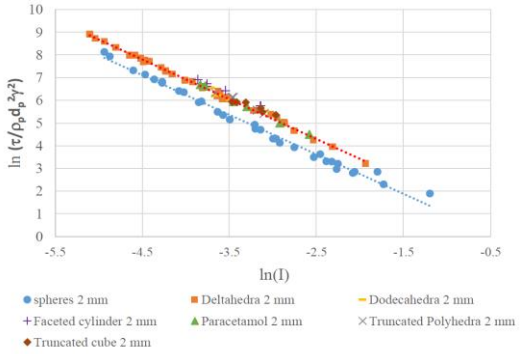
- Cohesive faceted particles have been derived from DEM simulations.



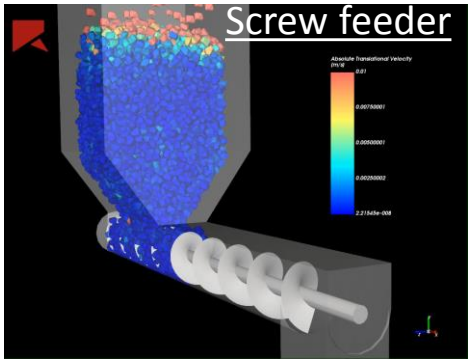
- Two different equations have been developed for dynamic powder flow behaviour.

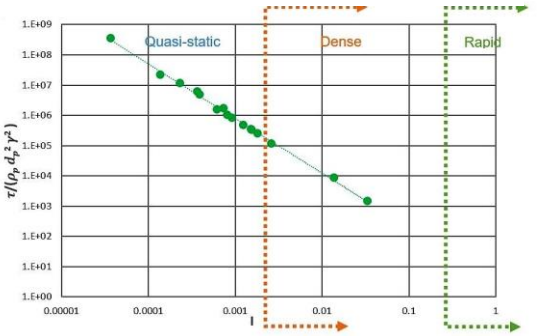


FT4 rheometer



Screw feeder

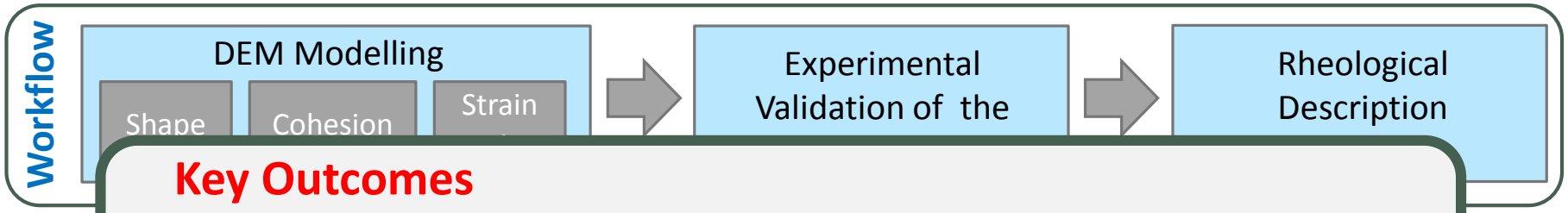




Prediction of Cohesive Powder Flow under Dynamic Conditions

WP 4.8: U. Zafar, , A. Lopez, V. Vivacqua, R. Hammond and M. Ghadiri

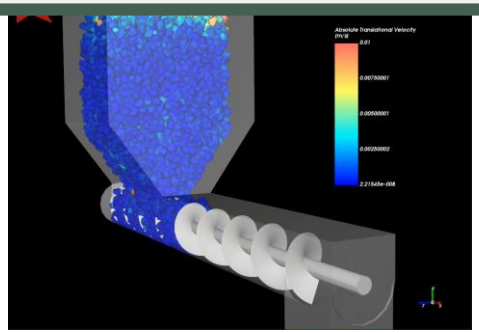
- Numerical simulation by DEM is used to develop a unified rheological description of flow of cohesive and faceted particles in Freeman Technology FT4 rheometer and screw feeder

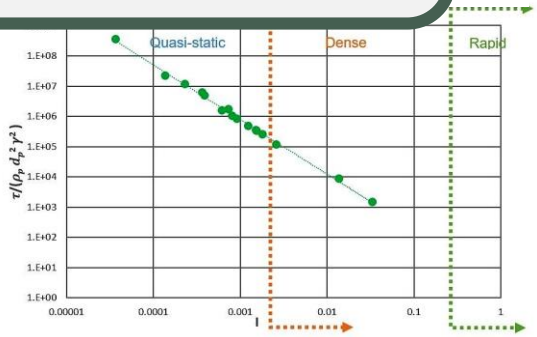


Key Outcomes

- The ability to predict accurately how a new API will flow in the devices used for its processing to minimize manufacturing issues
- The research will impact the powder processes and design of new processes for the pharmaceutical industry
- The research can be merged in commercial software (PSE) and improve the current models used for predicting powder flow

- Two different equations have been developed for dynamic powder flow behaviour.





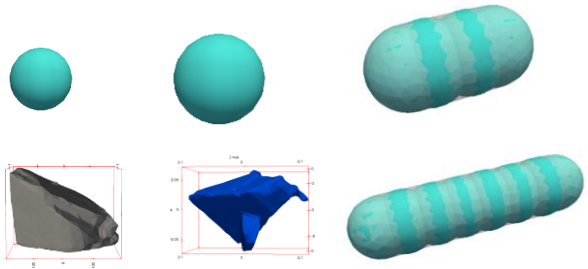
Mechanistic Powder Flow Models: Flowability Prediction

WP 4.8: C. Pei, X. Chen and J. Elliott

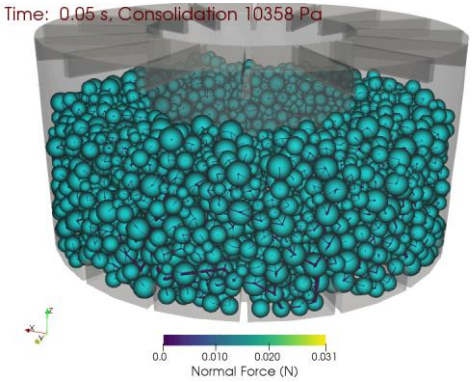
- Aim: to combine DEM and DoE to understand of the effect of changing particle shape and/or cohesive interactions on flowability of pharmaceutical powders

Workflow

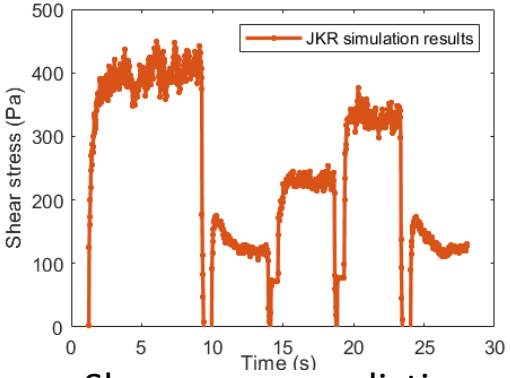
Design of experiments: flowability responses on particle size, shape, elasticity and surface energy → Discrete element modelling of particle dynamics in ring shear cell tester → Reduced model/relationship for flowability, bulk cohesion



Particle properties

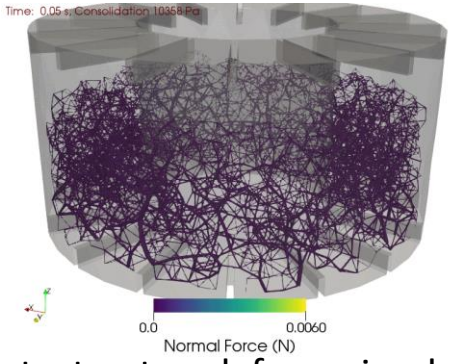


DEM simulation of ring shear cell

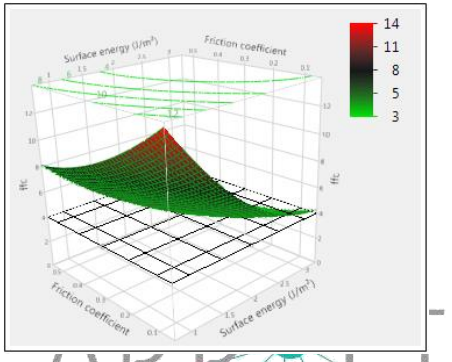


Shear curve prediction

Schulze ring shear cell test



Contact network from simulation



Flowability (ffc) prediction

Mechanistic Powder Flow Models: Flowability Prediction

WP 4.8: C. Pei, X. Chen and J. Elliott

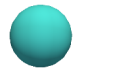
- Aim: to combine DEM and DoE to understand of the effect of changing particle shape and/or cohesive interactions on flowability of pharmaceutical powders

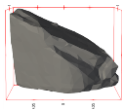
Workflow

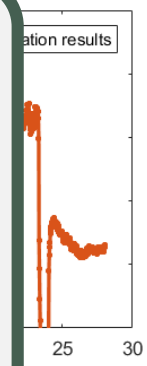
Design of experiments: flowability responses on particle size, shape, elasticity and surface energy → Discrete element modelling of particle dynamics in ring shear cell tester → Reduced model/relationship for flowability, bulk cohesion

Key Outcomes

- Powder flowability was characterized by the ring shear test and predicted using discrete element method
- The effects of powder shape, size, friction, surface energy, on flowability and internal friction angle were studied
- Simplified models for flowability, internal friction angle and bulk cohesion were built for process optimization



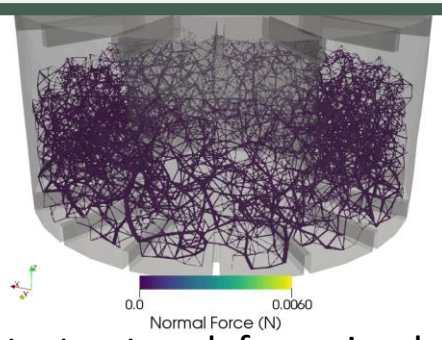




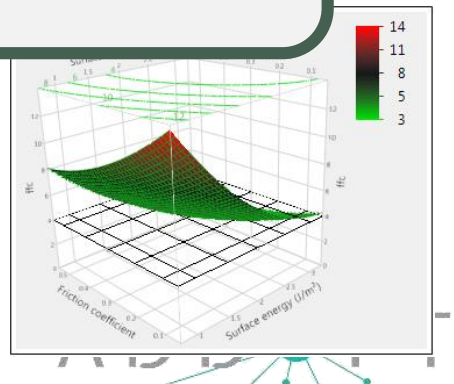
Part

ction

Schulze ring shear cell test



Contact network from simulation



Flowability (ffc) prediction

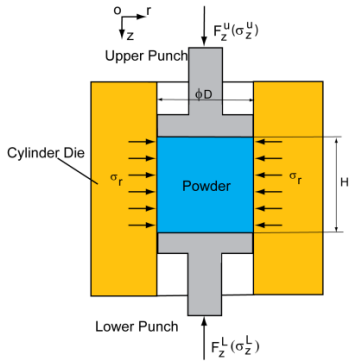
Granule Compaction and Tabletting Models

WP 4.9: C. Pei, X. Chen and J. Elliott

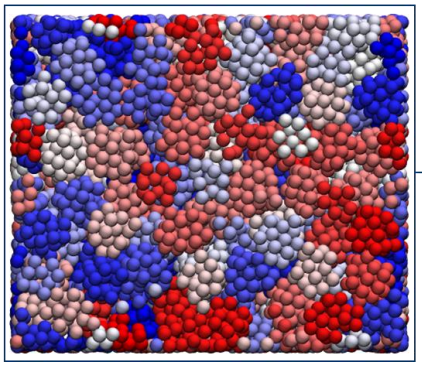
- Aim: to translate data from compaction simulator into FEM/DEM for tablet compaction and understand the ability of both blended and granulated powders to form stable compacts

Workflow

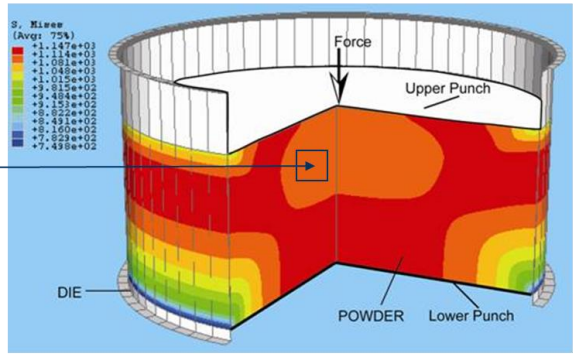
Measure material properties and compaction behaviour from instrumented die → Discrete element modelling/ Finite element modelling of tabletting → Stress concentration and failure mechanism of tabletting process



Instrumented die for tabletting

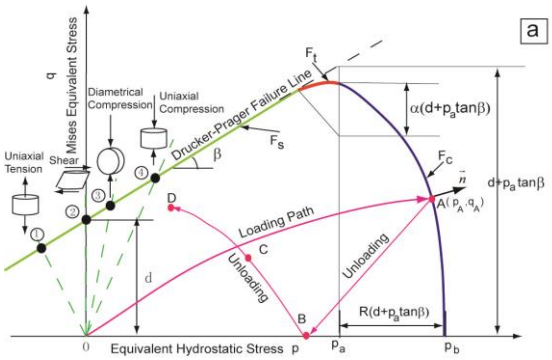


Bulk powder represented by DEM

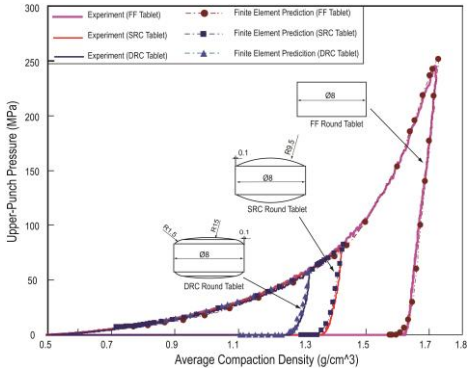


Tablet geometry represented by FEM

Huxley Bertram Servo-Hydraulic Compaction Simulator



Density-Dependent Drucker-Prager Cap Plasticity Model



FEM prediction of loading-unloading curves during tableting

Granule Compaction and Tabletting Models

WP 4.9: C. Pei, X. Chen and J. Elliott

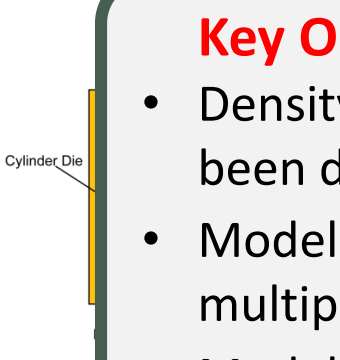
- Aim: to translate data from compaction simulator into FEM/DEM for tablet compaction and understand the ability of both blended and granulated powders to form stable compacts

Workflow

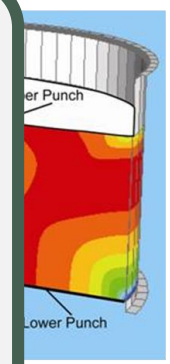
Measure material properties and compaction behaviour from instrumented die → Discrete element modelling/ Finite element modelling of tabletting → Stress concentration and failure mechanism of tabletting process

Key Outcomes

- Density dependent and density independent models have been developed and can be used in FEM package
- Models were parametrised with flat face and tested with multiple materials
- Models can be supplied for implemented and used for blends and potentially combine excipients

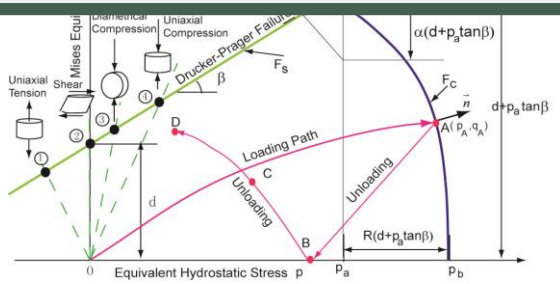


Instru

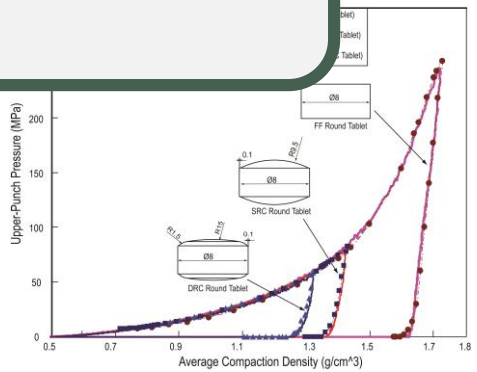


d by FEM

Huxley Bertram Servo-Hydraulic Compaction Simulator



Density-Dependent Drucker-Prager Cap Plasticity Model



FEM prediction of loading-unloading curves during tableting

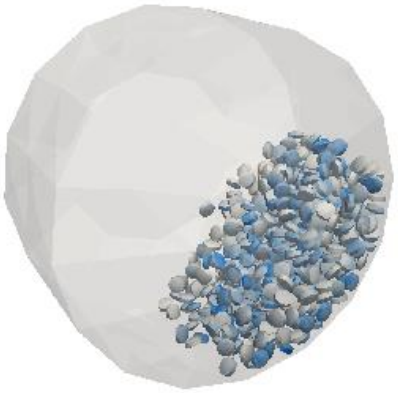
Tablet Coating : Variability and Process Optimization

WP 4.10: C. Pei, X. Chen and J. Elliott

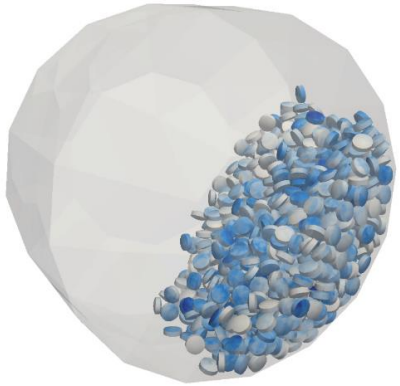
- Aim: to better understand the causes of coating variability and move towards reduced processing times and manufacturing process for spray coating

Workflow

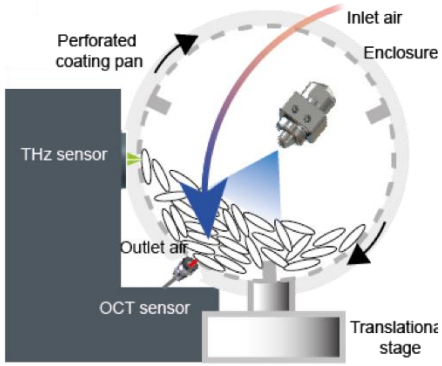
Simulation of the tablet bed mixing using the discrete element method → Spray coating investigated by terahertz pulsed imaging (TPI), ray tracing and image analysis → Inter/intra particle coating variability prediction tools



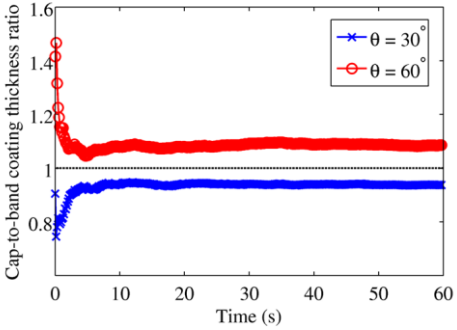
A: tablet flow/ coating uniformity (DEM)

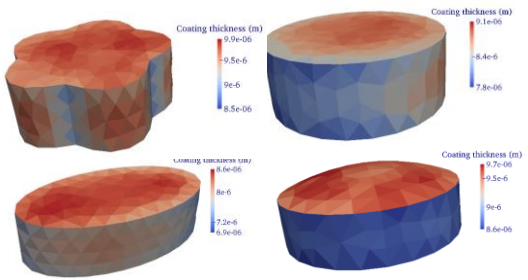


B: spray coating (ray-tracing/image analysis)

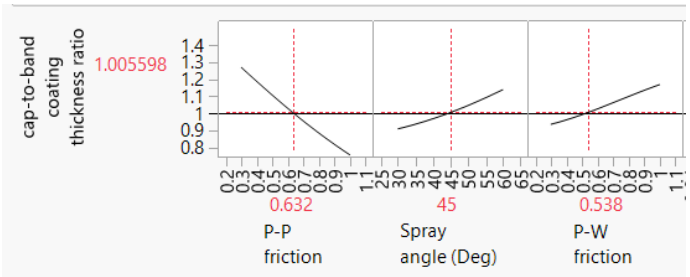


C: In-line sensing simulation (ray-tracing)





Inter/intra tablet coating variability prediction



Process optimization tools

Tablet Coating : Variability and Process Optimization

WP 4.10: C. Pei, X. Chen and J. Elliott

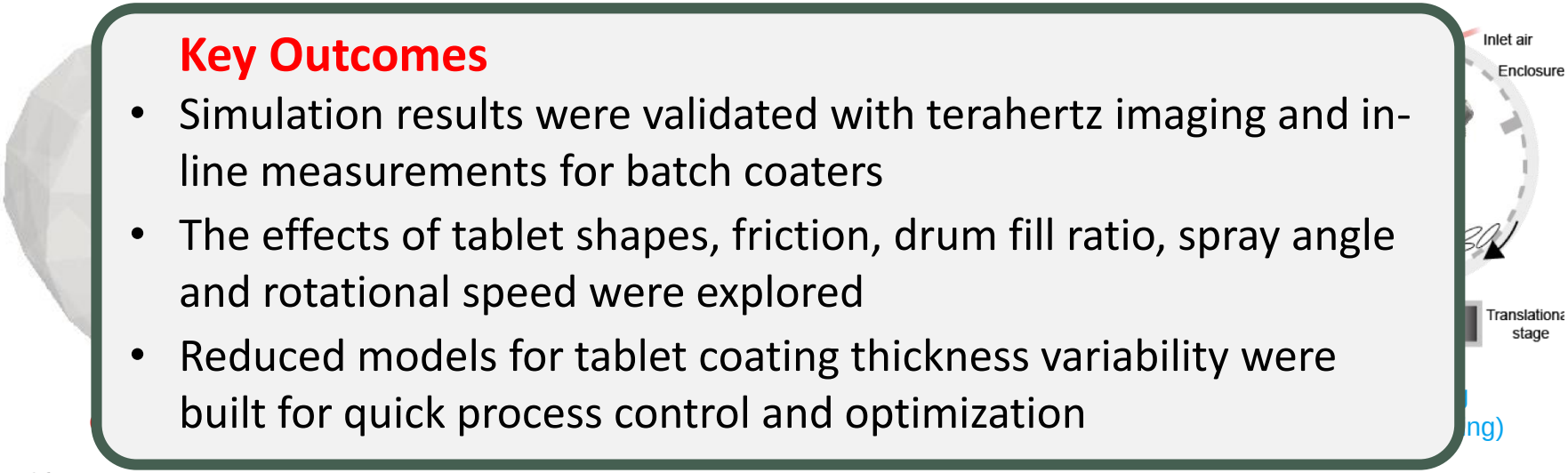
- Aim: to better understand the causes of coating variability and move towards reduced processing times and manufacturing process for spray coating

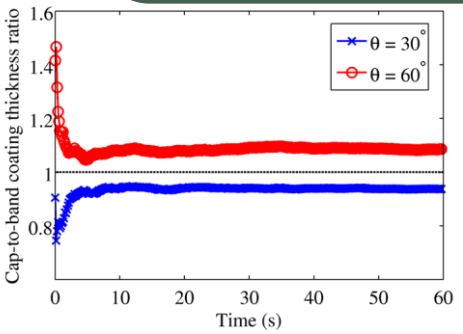
Workflow

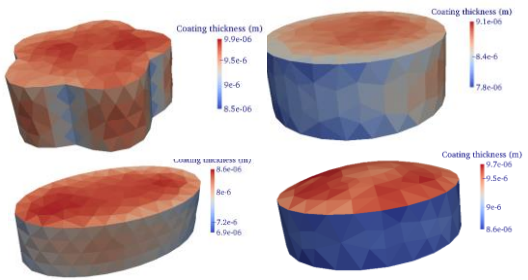
Simulation of the tablet bed mixing using the discrete element method → Spray coating investigated by terahertz pulsed imaging (TPI), ray tracing and image analysis → Inter/intra particle coating variability prediction tools

Key Outcomes

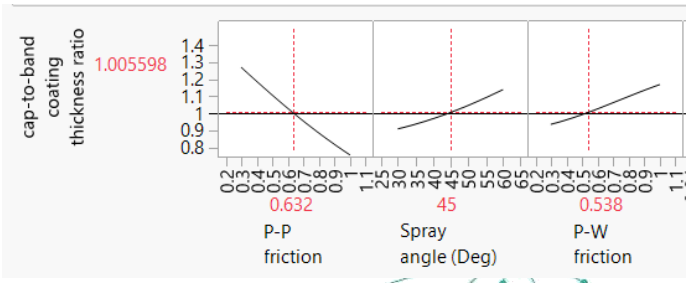
- Simulation results were validated with terahertz imaging and in-line measurements for batch coaters
- The effects of tablet shapes, friction, drum fill ratio, spray angle and rotational speed were explored
- Reduced models for tablet coating thickness variability were built for quick process control and optimization







Inter/intra tablet coating variability prediction



Process optimization tools

Morphological Population Balance (MPB) for Particle Design

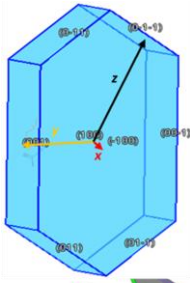
WP 4.1/4.2/4.3: C. Y. Ma and K. J. Roberts

- Integrating facet material properties and process kinetics with MPB modelling for shape/size evolution, process control and digital twins – Precision particles

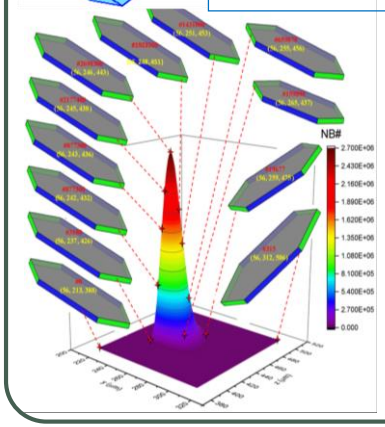
Workflow

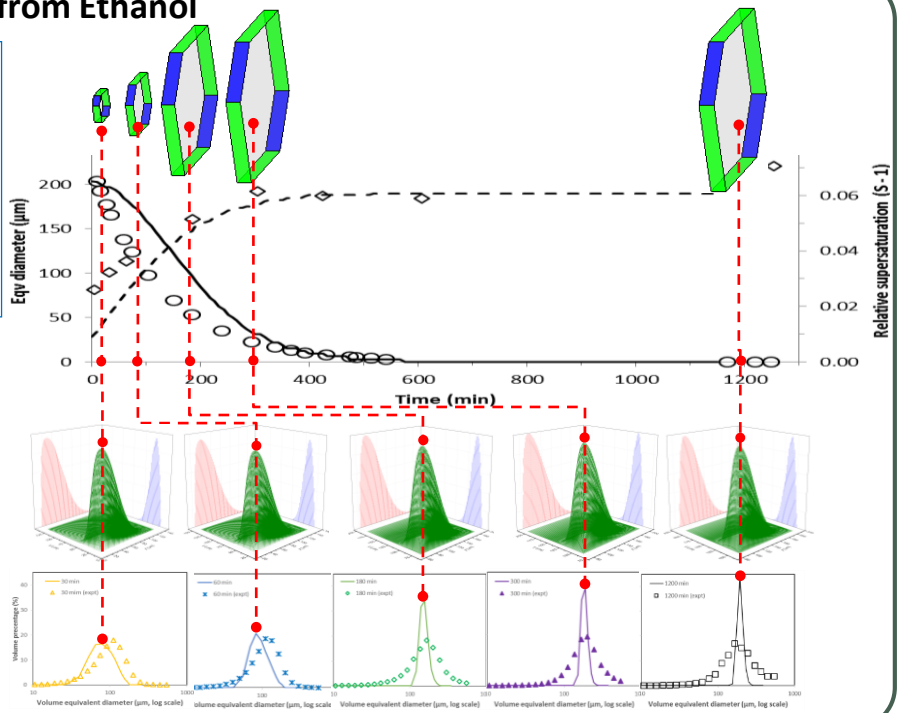
Facet properties, kinetics (shape, nucleation, growth, …) via VH and experiment and operating conditions → Multi-dimensional MPB equation and Particle shape/size analysis → Precision particle manufacture via process control/digital

Ibuprofen Crystallised from Ethanol



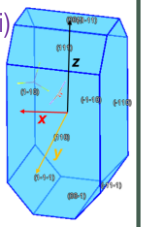
Operating parameters: Cooling rate = 0.1 °C/min; Seeds loading = 0.5%; Seeding T =20°C





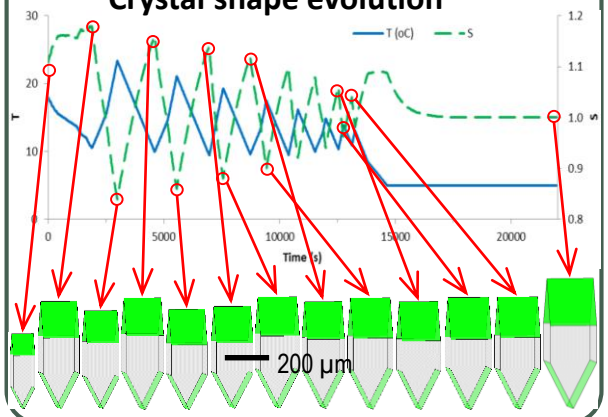
Urea Crystallisation with heating/ cooling cycles

Collaboration with Pfizer (T Izumi and A Rizvi)



Operating parameters: Cooling rate = 0.5°C/min; Seeds loading = 0.1%; Seeding T = 20°C; Cooling/heating cycles as below

Crystal shape evolution

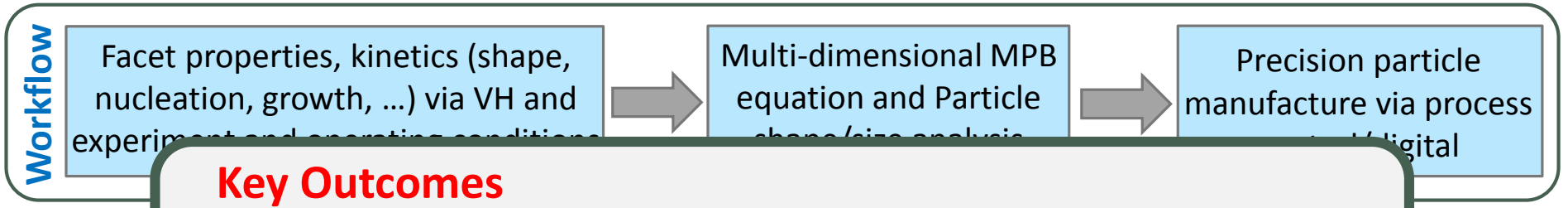


CY Ma, KJ Roberts, *Ind Eng Chem Res*, 2018, 57(48):16379-16394

Morphological Population Balance (MPB) for Particle Design

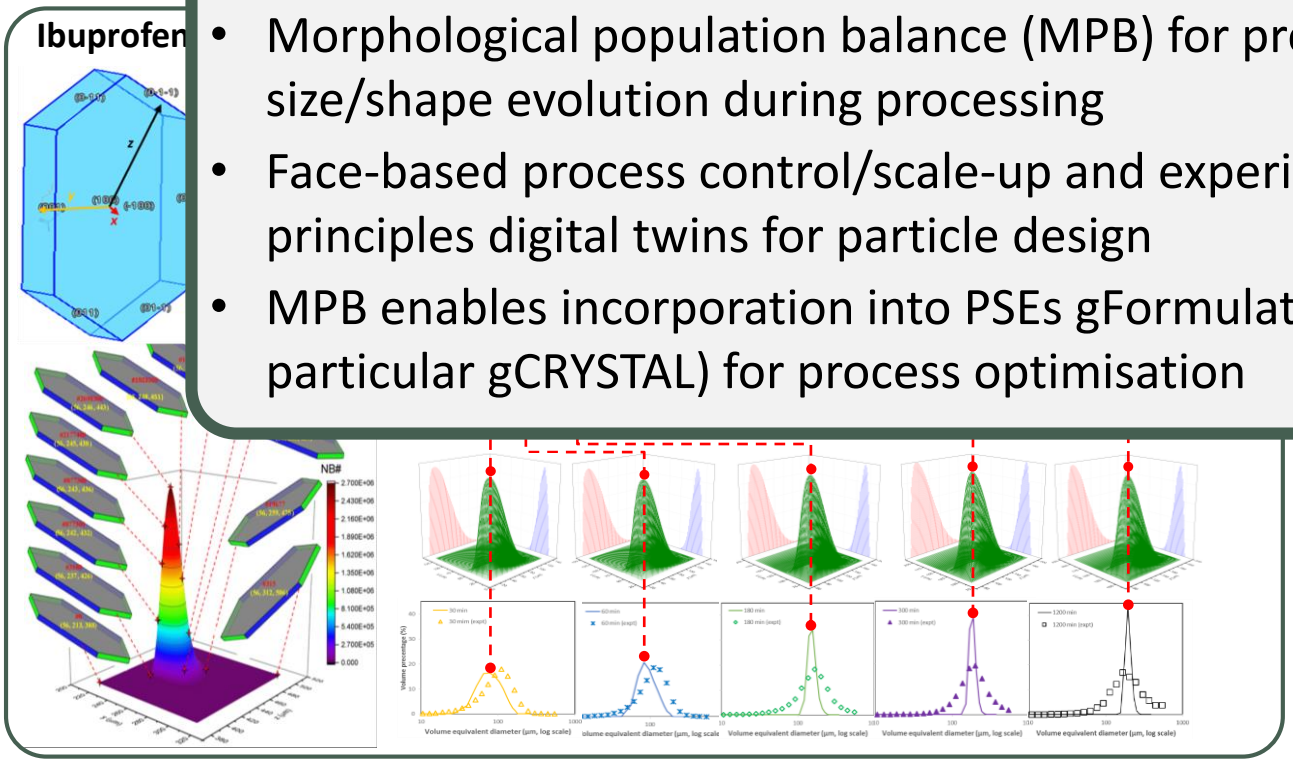
WP 4.1/4.2/4.3: C. Y. Ma and K. J. Roberts

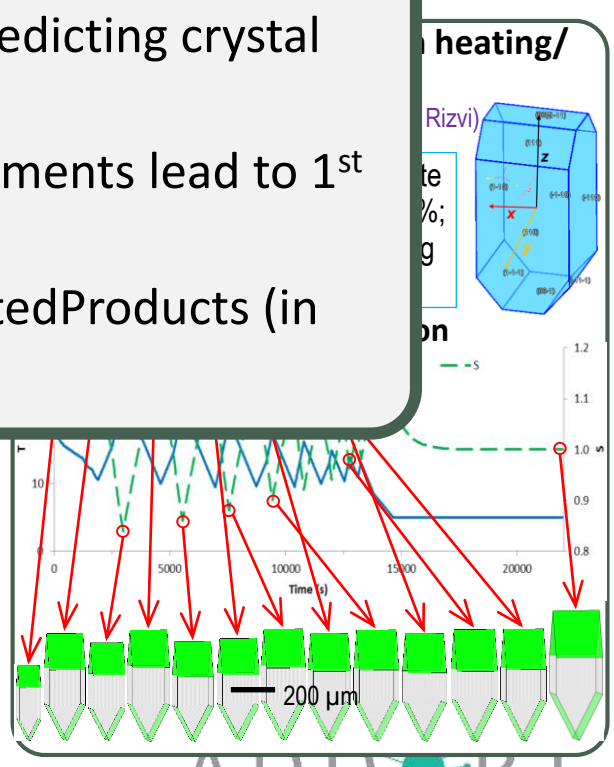
- Integrating facet material properties and process kinetics with MPB modelling for shape/size evolution, process control and digital twins – Precision particles



Key Outcomes

- Morphological population balance (MPB) for predicting crystal size/shape evolution during processing
- Face-based process control/scale-up and experiments lead to 1st principles digital twins for particle design
- MPB enables incorporation into PSEs gFormulatedProducts (in particular gCRYSTAL) for process optimisation





CY Ma, KJ Roberts, *Ind Eng Chem Res*, 2018, 57(48):16379-16394

Temperature Dependent Solubility: Statistical Models

WP 4.2/3.C: R. M. Robinson, E. Martin and K. J. Roberts

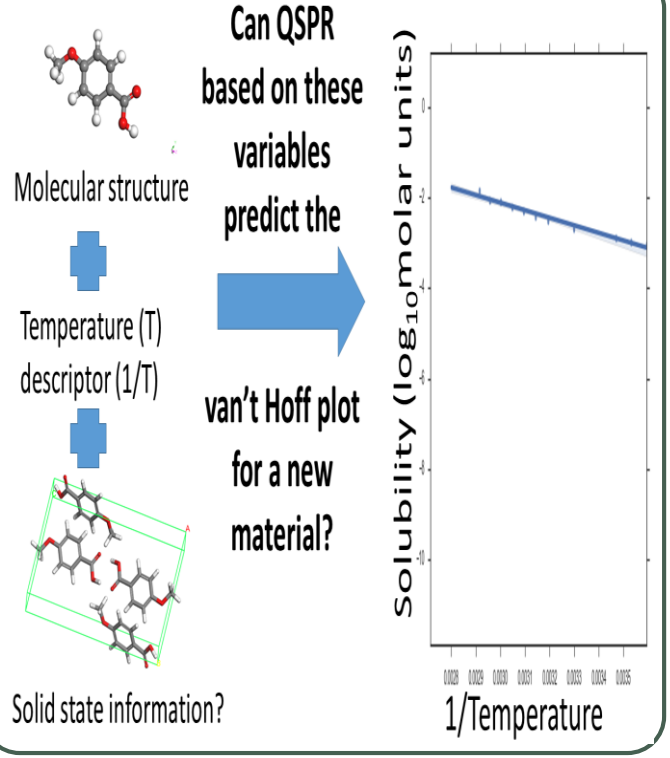
- QSPR models of temperature dependent solubility profiles support digital design of cooling crystallization and wet granulation

Workflow

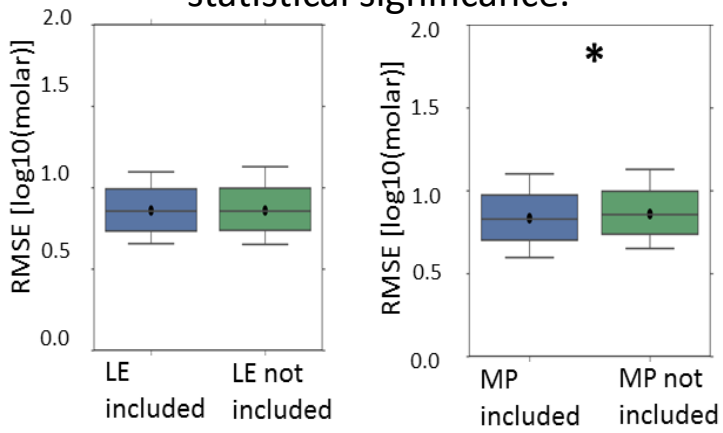
Curate hundreds of solubility datapoints (different solutes, solvents, temperatures) → Calculate variables from temperature (T), molecular and/or crystal structures and/or melting points (MP) → Machine Learning

Data curation

- 4,000 solubility values
- 5 – 95 °C
- 400 solutes
- 50 solvents
- **MP** for 309 solutes
- Crystal **lattice energies (LE)** calculated for 129 solutes



Small change in unbiased validation RMSE (log_{10}molar) values of best aqueous models upon adding lattice energy (LE) or melting point (MP) descriptors. * = statistical significance.



Temperature Dependent Solubility: Statistical Models

WP 4.2/3.C: R. M. Robinson, E. Martin and K. J. Roberts

- QSPR models of temperature dependent solubility profiles support digital design of cooling crystallization and wet granulation

Workflow

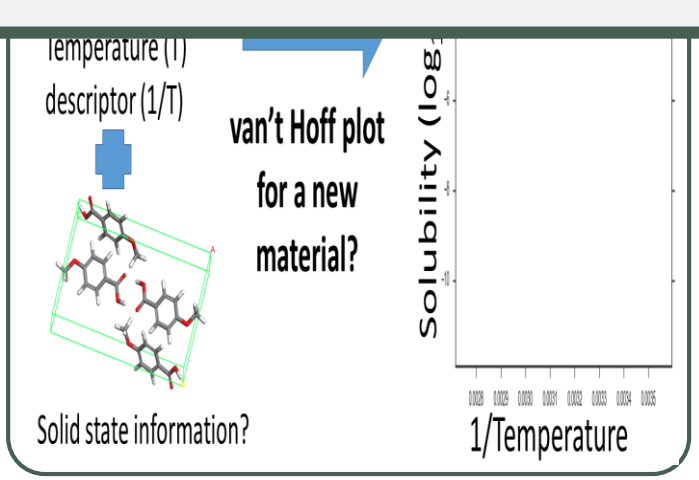
Curate hundreds of solubility datapoints (different solutes, solvents, temperatures) → Calculate variables from temperature (T), molecular and/or crystal structures and/or … → Machine Learning

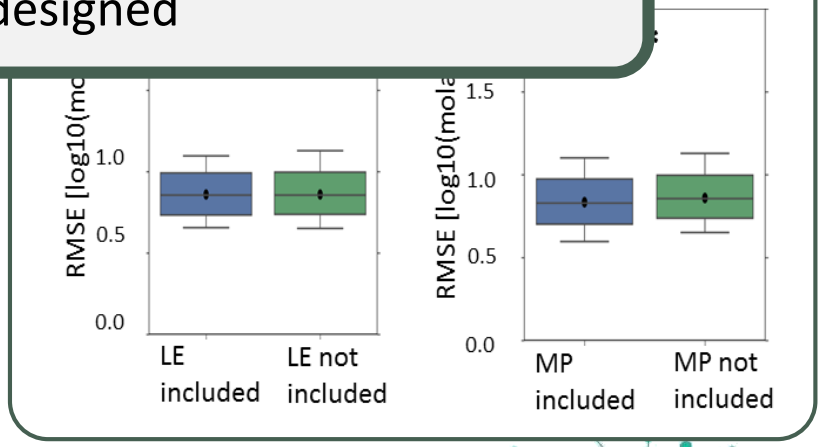
Data cur…

- 4,000 solubi… values
- 5 – 95…
- 400 so…
- 50 solvents
- **MP** for 309 solutes
- Crystal **lattice energies (LE)** calculated for 129 solutes

Key Outcomes

- Aqueous temperature dependent solubility predicted to within one log unit on average
- Reliable models can be built without solid-state information
- Novel unbiased validation protocol designed





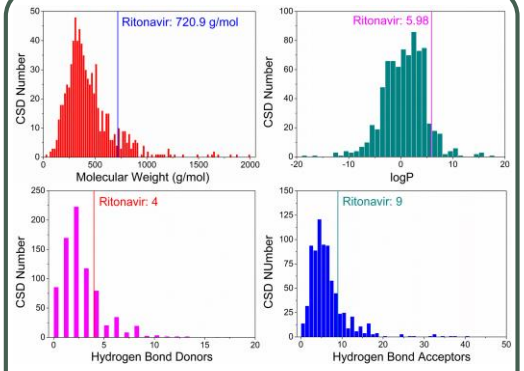
Influence of Conformational Polymorphism on Particle Properties: Ritonavir

WP 4/WP 2: Chang Wang, Ian Rosbottom, Thomas Turner and Kevin Roberts

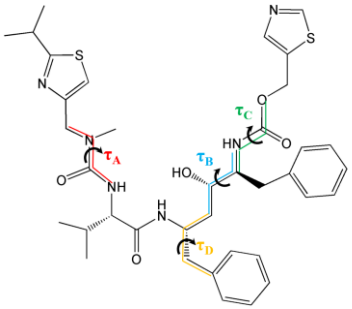
- Relative balance between molecule conformation and lattice energies characterised and related to particle properties

Workflow

Molecular Conformational Analysis → Solid-State Particle Properties → Relation to Polymorphism → Physical and Chemical Properties

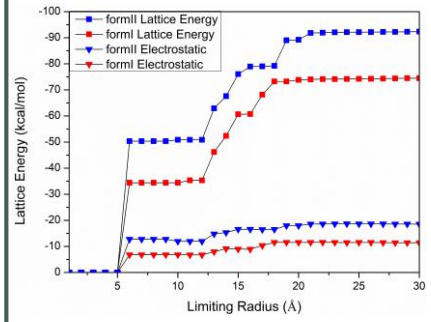


Molecular properties

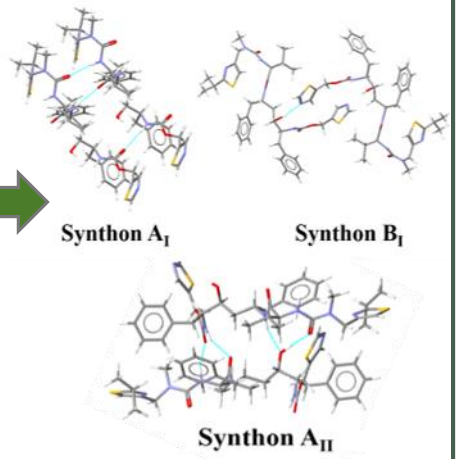


Main torsion angles of ritonavir

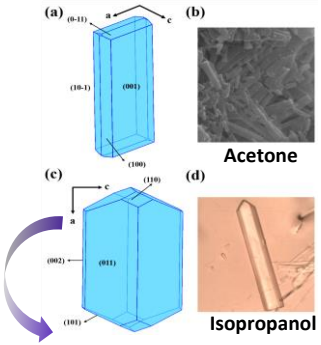
Stable conformation, denser packing and unstable lattice of form I



Lattice energy of forms 1 and 2



Polymorphs	Relative Conformational Energy (kcal/mol)	Packing Coefficient	Lattice Energy (kcal/mol)
Form I	0	0.80	-74.48
Form II	5.25	0.74	-92.33

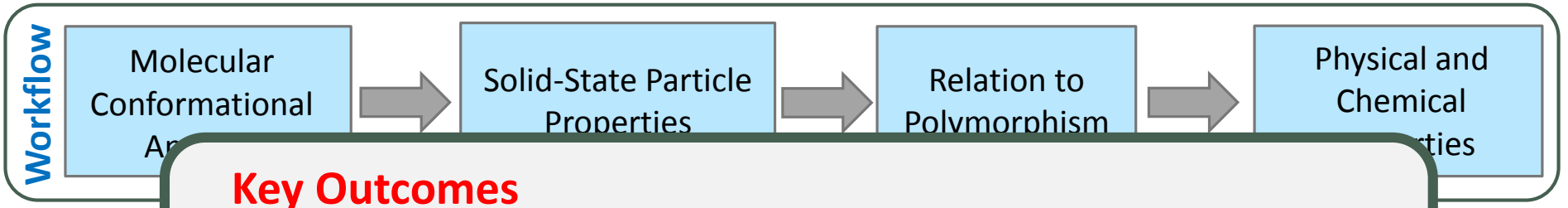


Crystal Surface (hkl)	Degree of Surface Saturation %	Extrinsic Growth Synthons
From I		
(0 0 1)	86.75	E_{vdW}
(0 1 1)	25.64	$A_{H\text{-bond}}$, $B_{H\text{-bond}}$,
(1 0 -1)	70.21	D_{vdW}, E_{vdW}
(1 0 0)	70.07	C_{vdW}, D_{vdW}, E_{vdW}
(1 1 -1)	19.59	$A_{H\text{-bond}}$, D_{vdW}
Total	74.75	
Form II		
(0 1 1)	70.75	C_{vdW}
(0 0 2)	68.34	B_{vdW}, D_{vdW}, E_{vdW}
(1 0 1)	54.04	$A_{H\text{-bond}}$
(1 1 0)	45.13	$A_{H\text{-bond}}$, C_{vdW}
Total	65.28	

Influence of Conformational Polymorphism on Particle Properties: Ritonavir

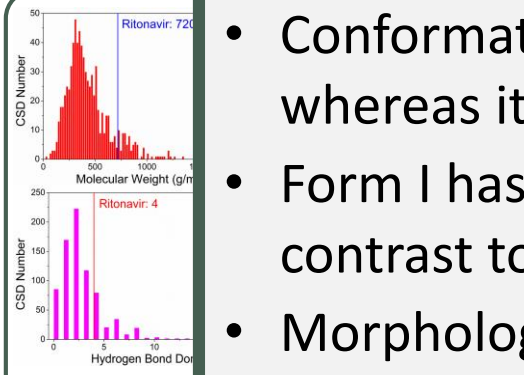
WP 4/WP 2: Chang Wang, Ian Rosbottom, Thomas Turner and Kevin Roberts

- Relative balance between molecule conformation and lattice energies characterised and related to particle properties

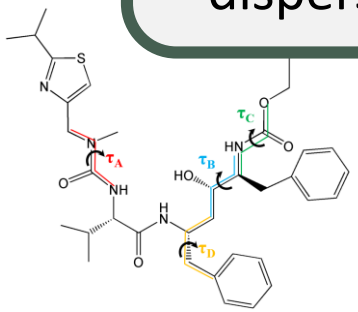


Key Outcomes

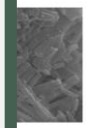
- Conformation of form I more stable and efficiently packed whereas its lattice energy is much less stable than form II
- Form I has greater contribution from vdW interactions in contrast to form 2 where H-bonding dominates
- Morphology of forms I and II are both needle-like, with dispersive equatorial planes and H-bonded capping faces



Mole



Main torsion angles of ritonavir



etone

ropanol

Polymorphs	Relative Conformational Energy (kcal/mol)	Packing Coefficient	Lattice Energy (kcal/mol)
Form I	0	0.80	-74.48
Form II	5.25	0.74	-92.33

Synthon A_{II}

		Extrinsic Growth Synthons
		E_{vdW}
(0 1 1)	25.64	$A_{H\text{-bond}}$, $B_{H\text{-bond}}$,
(1 0 -1)	70.21	D_{vdW}, E_{vdW}
(1 0 0)	70.07	C_{vdW}, D_{vdW}, E_{vdW}
(1 1 -1)	19.59	$A_{H\text{-bond}}$, D_{vdW}
Total	74.75	
Form II		
(0 1 1)	70.75	C_{vdW}
(0 0 2)	68.34	B_{vdW}, D_{vdW}, E_{vdW}
(1 0 1)	54.04	$A_{H\text{-bond}}$
(1 1 0)	45.13	$A_{H\text{-bond}}$, C_{vdW}
Total	65.28	

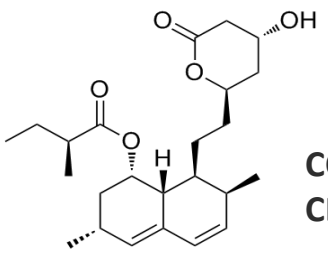
Workflow for Controlling Needle-Like Crystals: Lovastatin

WP2/4: T. Turner, L. Hatcher, C. Wilson, K. J. Roberts

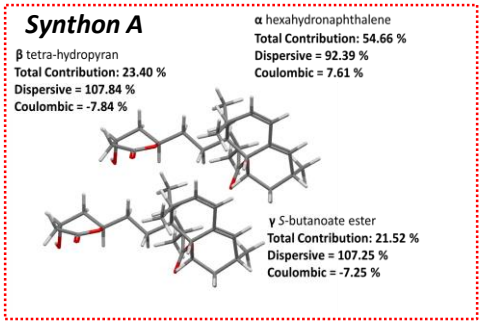
- Synthon based workflow developed to identify key inter-molecular interactions and surface chemistry which lead to the formation of needle-like particles

Workflow

Inter-Molecular Synthon ID and Energetic Characterisation → Morphology Prediction and Surface Chemistry ID → Matched Solvent / Additive Chemistry

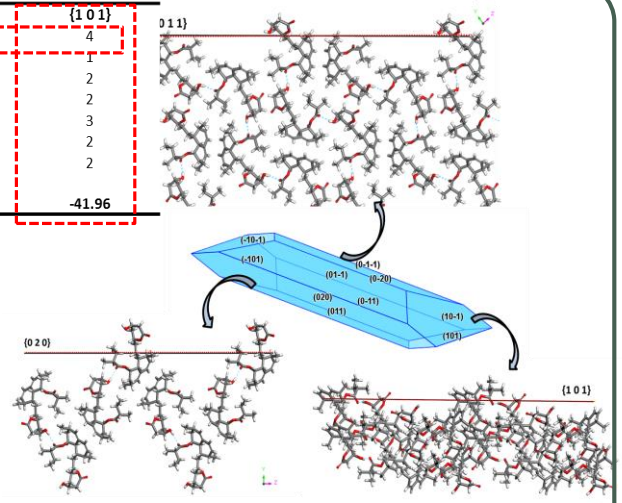


CCDC: CEKBEZ01



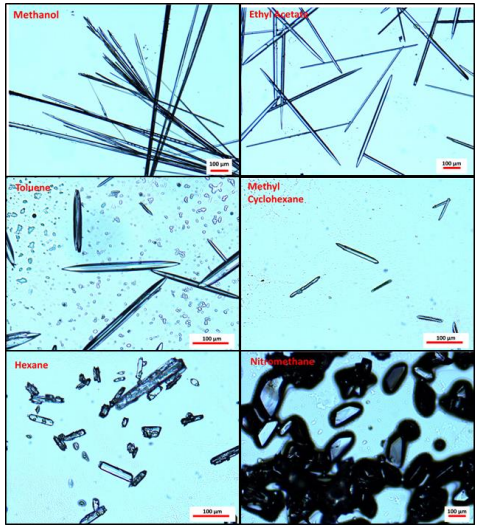
Dispersive stacking type synthon strongest in lovastatin

Synthon	{0 1 1}	{0 2 0}	{1 0 1}
A (-6.46)	0	0	4
B (-2.98)	2	4	1
C (-2.56)	2	4	2
D (-2.12)	2	4	2
E (-1.96)	2	4	3
F (-1.05)	2	0	2
G (-0.92)	2	0	2
E_{total} / kcal mol^{-1}	-18.76	-29.32	-41.96



Morphology prediction and visualisation of surface chemistry

Dispersive synthon A contributes positively to growth along needle axis



Matched to dispersive recrystallization solvent; significant reduction in aspect ratio

T.D.Turner, L.E. Hatcher, C.C.Wilson, K.J.Roberts, J. Pharm. Sci. 2018 Dec 24. pii: S0022-3549(18)30811-6. doi: 10.1016/j.xphs.2018.12.012

Workflow for Controlling Needle-Like Crystals: Lovastatin

WP2/4: T. Turner, L. Hatcher, C. Wilson, K. J. Roberts

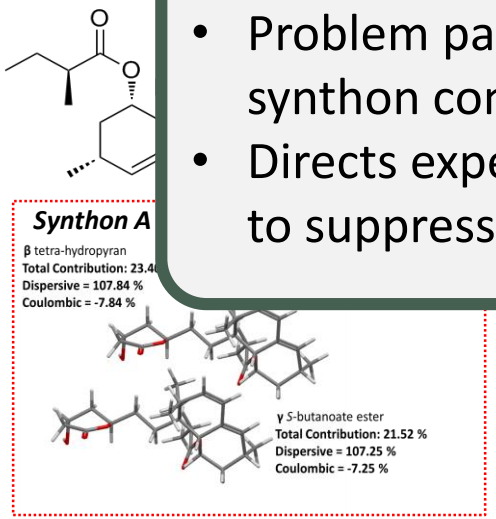
- Synthon based workflow developed to identify key inter-molecular interactions and surface chemistry which lead to the formation of needle-like particles

Workflow

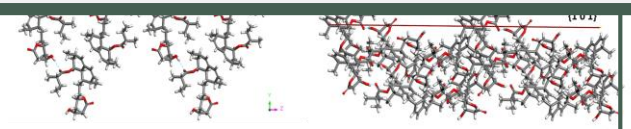
Inter-Molecular Synthon ID and Energetic Characterisation → Morphology Prediction and Surface Chemistry ID → Matched Solvent / Additive Chemistry

Key Outcomes

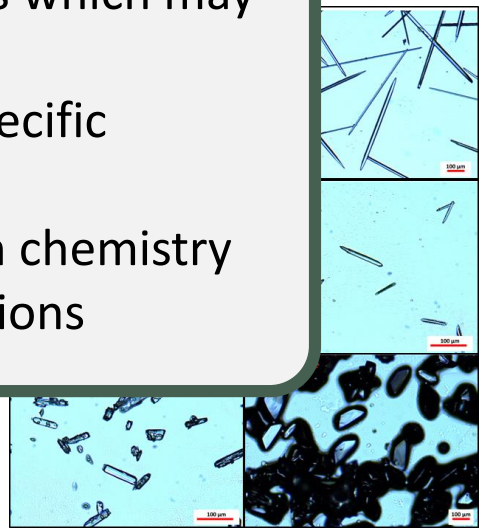
- Workflow identifies key inter-molecular interaction/s which may cause needle-like particles
- Problem particle surface chemistry identified and specific synthon contribution to growth quantified
- Directs experimental effort towards suitable solution chemistry to suppress these particular inter-molecular interactions



Dispersive stacking type synthon strongest in lovastatin



Morphology prediction and visualisation of surface chemistry
Dispersive synthon A contributes positively to growth along needle axis



Matched to dispersive recrystallization solvent; significant reduction in aspect ratio

T.D.Turner, L.E. Hatcher, C.C.Wilson, K.J.Roberts, J. Pharm. Sci. 2018 Dec 24. pii: S0022-3549(18)30811-6. doi: 10.1016/j.xphs.2018.12.012

Acknowledgements

Leeds

Muzammil Ali
Nornizar Anuar
Ulrike Aufderhorst
Andrew Bayly
Mohammadreza Behjani
Tina Bonakdar
Diana Camacho
Amin Farschi
Jeanine Ferguson
Ioannis Fragkopoulos
Mojtaba Ghadiri
Wei Pin Goh
Robert Hammond
Ali Hassanpour
Hayley Harding
Peter Heggs
Sulaiman Lawal
Alejandro Lopez
Cai Yun Ma
Faiz Mahdi
Tariq Mahmud
Yousef Motlagh
Frans Muller
Jonathan Pickering
Vasuki Ramachandran
Richard Marchese Robinson
Kevin Roberts
Ian Rosbottom
Julieth Figueroa Rosette
Thomas Turner
Vincenzino Vivacqua
Chang Wang
Umair Zafar

Cambridge

James Elliott
Xizhong Chen
Chunlei Pei

STFC, Hartree Centre

Dawn Geatches
Ilian Todorov
Chin Yong

CCDC

Ian Bruno
Mathew Bryant
Andrew Maloney

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

Acknowledgements

Leeds

Muzammil Ali
Nornizar Anuar
Ulrike Aufderhorst
Andrew Bayly
Moham
Tin
Dia
Ar
Jean
Ioanni
Moj
W
Robe
Ali Hassanpour
Hayley Harding
Peter Heggs
Sulaiman Lawal
Alejandro Lopez
Cai Yun Ma
Faiz Mahdi
Tariq Mahmud
Vincenzino Vivacqua
Chang Wang
Umair Zafar

Cambridge

James Elliott
Xizhong Chen
Chunlei Pei

Centre

ches
rov
g

no
Mathew Bryant
Andrew Maloney

Key Outcomes

- First principles models for particle and process digital design developed
- Digital workflows for product and process R&D developed and tested through industry case studies
- Brief overview given here with further details available through the demonstration and poster presentations

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