APM 2013

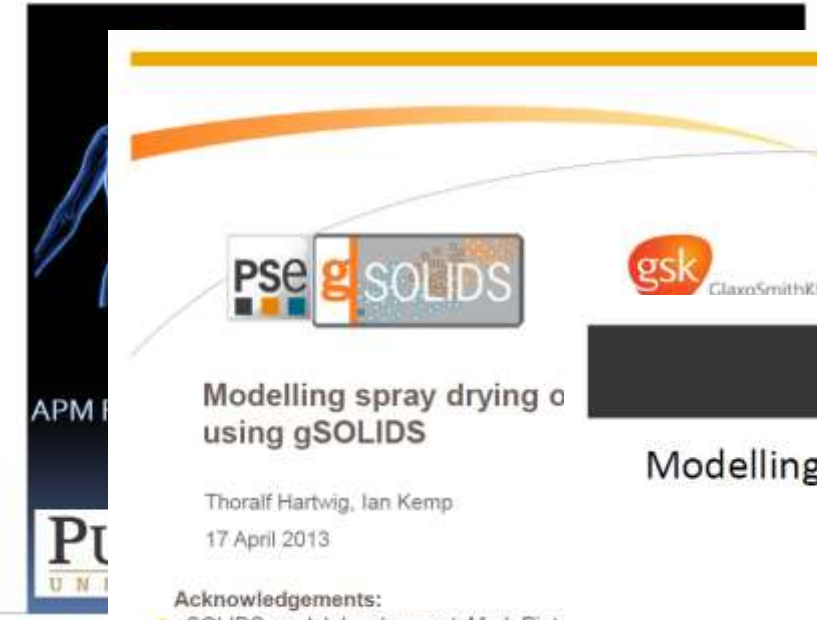
The Advanced Process Modeling Forum

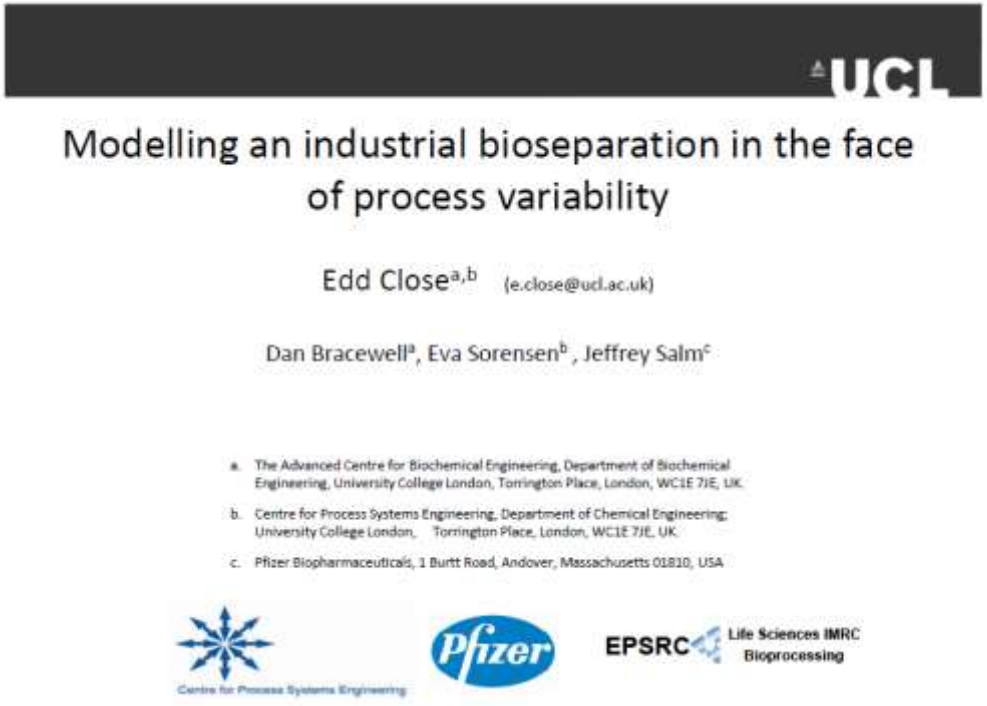
June 5–6, 2013, New York

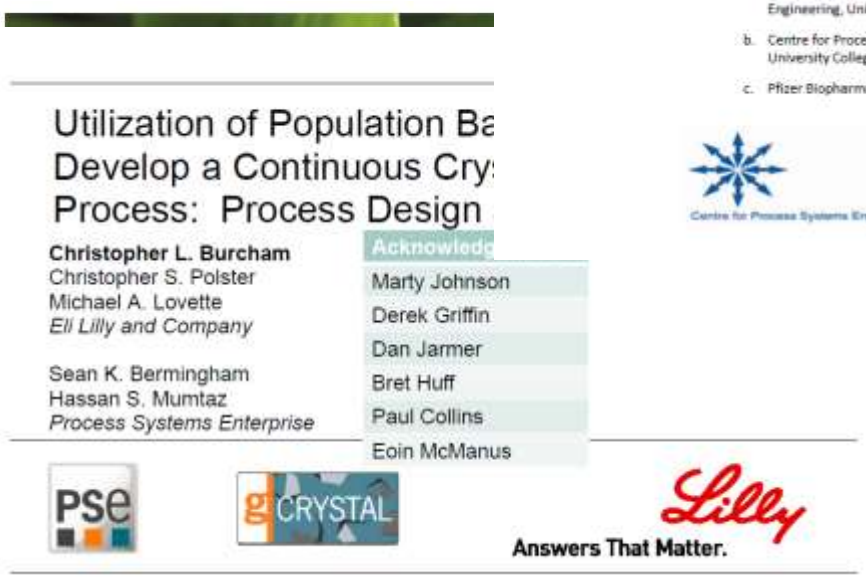
Life Sciences session introduction

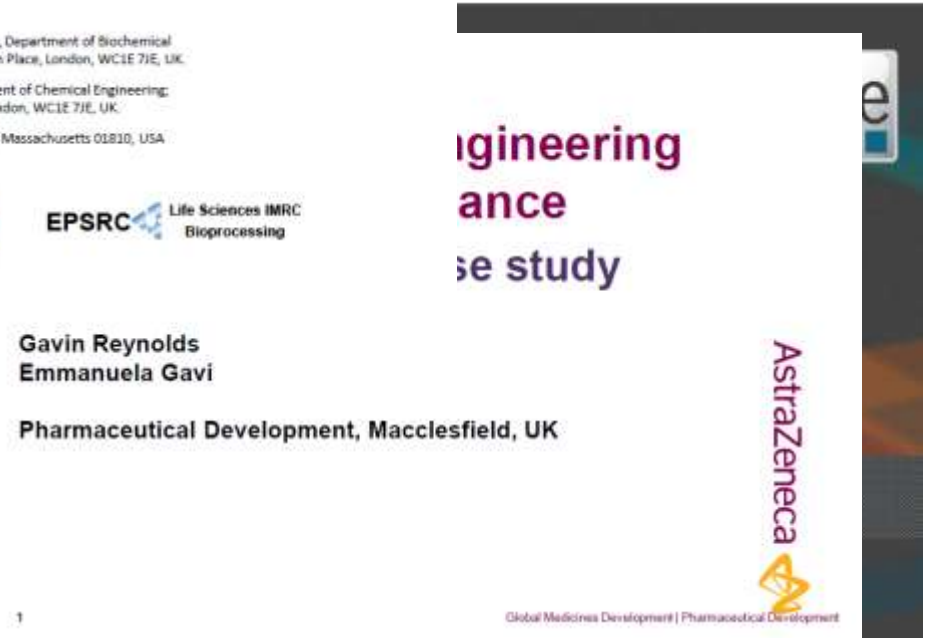
A summary of key presentations from the London APM Forum

Pat Dennin, Business Development Life Sciences
Sean Bermingham, PSE Life Sciences, Consumer Goods & Fine Chemicals

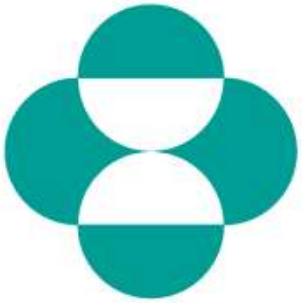









PFIZER
Pfizer
Pfizer



MERCK

Lilly

Pfizer

VERTEX™

THE SCIENCE *of* POSSIBILITY

Boehringer Ingelheim

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Life Sciences & Fine Chemicals session at APMF 2013

Modelling, simulation and optimisation of filtration processes

Filtration is an important step in pharmaceutical, fine chemical and food manufacturing. Having a detailed understanding of the determining parameters for the filtration process helps process engineers to define the design space and optimal operating conditions. DI Gursch describes how advanced process modelling helps reduce tedious experimental efforts and provides crucial tools to enable process design, optimisation and scaleup.

DI Johannes Gursch
Researcher
RCPE

Applying crystallization modelling to improve the understanding of a batch cooling process of an agrochemical active ingredient

The current production process of a Syngenta active ingredient isolates the batch by a cooling crystallization process. A major bottleneck of the process is the isolation time of the product after crystallization. In this presentation Rhea Brent describes an experimental scale-down study that was carried out to replicate the plant process and to assess whether the filtration properties could be improved by modifying the conditions in the crystallizer. Crystallization modelling using gCRYSTAL was employed to rationalise the experimental observations and to identify the key crystallization phenomena that are dominant in the process.

Rhea Brent
Senior Crystallization Scientist
Syngenta

Utilising population balance models to develop a continuous crystallization process

Due to material and time constraints, experimentation alone often cannot provide a means for the design of an optimised continuous crystallization process within the pharmaceuticals industry. In this talk, Chris Burcham describes how Eli Lilly used a combined population balance and process design software (gCRYSTAL) as a means of process optimisation for continuous crystallization. In performing this process optimisation, Eli Lilly used rate constants for nucleation and growth that were obtained from regressed experimental data using the same software. Insights regarding the implementation of process optimisation as a part of a proposed 'universal' work flow for the design of continuous crystallizations will also be presented

Christopher Burcham,
Engineering Advisor
Eli Lilly

Modelling spray drying of fine particles using gSOLIDS

Spray drying can be used to rapidly produce fine particles with narrow size distributions and low moisture contents. Thoralf Hartwig and Ian Kemp describe a model that generates temperature and droplet size histories of droplets of various sizes, showing how drying time varies with inlet droplet size. The model has been applied to a pharmaceutical spray dryer to improve process understanding and predict the effect of operating conditions on product attributes. This potentially reduces process development times and costs.

Ian Kemp
Senior Scientific Investigator, **GSK**

Thoralf Hartwig
Senior Process Engineer, **GSK R&D**

Modelling the manufacturing process and product performance of roller compacted pharmaceutical tablets

Significant progress in developing unit operation models for pharmaceutical processes has been made in recent years. A key objective for developing a pharmaceutical manufacturing process is to understand and control the product quality attributes, such as tablet content uniformity or disintegration rate. In this presentation Gavin Reynolds describes how a flowsheet model of a roller compaction immediate release tablet manufacturing process is developed. Simple models are developed to account for transformation of granule properties to tablet properties during tabletting and to describe the dissolution performance of the subsequent tablets. A virtual experimental design is performed to demonstrate the contribution and interaction of different unit operations on the tablet quality attributes in terms of tensile strength and dissolution performance.

Gavin Reynolds,
Associate Principal Scientist
AstraZeneca R&D

Flexible multipurpose continuous processing of pharmaceutical tablet manufacturing

Pharmaceutical industries are facing significant challenges from regulatory constraints, market demands, operational complexities and economical limitations. Continuous manufacturing processes have evolved as promising alternatives to traditional batch approaches because of high efficiency, better product quality, and reduced space, labour and resource requirements. However there remain challenges related to flow of solids, residence time and process buffering. Rohit Ramachandran describes how high-fidelity modelling is used to optimise and design a control system for a planned flexible multipurpose continuous tablet manufacturing process.

Rohit Ramachandran,
Assistant Professor
Rutgers University

Modelling of fluid bed drying at different scales in drug product manufacture

Empirical approach to scale up fluid bed drying is time consuming and resource intensive. Boehringer Ingelheim uses advanced process modelling to develop and validate a mechanism based fluid-bed drying model with placebo materials. The model is able to predict batch drying profiles for different initial moisture contents and granule sizes. In this presentation Dr Xiaorong He describes the process of developing and validating the lab-scale model and explains the impact and importance of internally and externally limited drying on the final results. The model is then successfully applied to simulate drying profile for a real drug product manufactured in large scale fluid bed dryer.

Xiaorong He,
Senior Research Fellow
Boehringer Ingelheim

Oral absorption modelling tool set for drug product design

PSE, with substantial input from Pfizer, is developing a detailed, mechanistic modelling framework for oral absorption of active ingredients. Some highlights of the framework are accounting for the full PSD of the API, a detailed description of intrinsic solubility and the ionic equilibria of endogenous and exogenous species in the bulk and at the surface of the various solid phases (salts and freeform), a description of transit that does not include constant volumes, mechanistic models for nucleation kinetics, and a range of permeation models. Another key feature is the openness of the model framework, which allows biopharmaceuticists to implement custom models for nucleation, dissolution/growth, permeation and transit.

Mei Wong,
Pfizer

Sean Bermingham,
VP PSE Solids
PSE

Oral absorption: simulation studies to predict drug precipitation in vivo

Modelling drug absorption is a challenging task as it depends not only on the physico-chemical properties of the drug but also on the different processes and hydrodynamic conditions in the gastro intestinal tract. While the current commercial oral absorption simulation packages successfully model most of the pharmacodynamic and pharmacokinetic processes taking place in vivo, they lack a reasonable explanation of the precipitation behavior of poorly soluble drugs in the small intestine. This talk presents a compartmental modelling approach of the GI tract with an emphasis on crystal nucleation and growth, and discusses experimental studies to extract the kinetic parameters of two poorly soluble model APIs, felodipine and dipyridamole, to be used as model inputs.

Kaoutar Abbou Oucherif,
Research Assistant
Purdue University

Design space: modelling an industrial chromatographic bioseparation in the face of process variability

In collaboration with University College London, Pfizer are using advanced process modelling to increase the robustness of chromatographic bioseparations in the face of process variability. In this presentation, Edd Close describes how they developed and validated a mechanistic model of a commercial chromatographic separation where resin lot variability can cause significant performance issues. He describes how the model was successfully applied to enable process operation further away from high risk regions, to increase the size of operating regions and improve flexibility to variations in process inputs.

Edward Close,
Postdoctoral Researcher
UCL/Pfizer

Systems-based Pharmaceutics – transforming drug manufacturing in the pharmaceutical industry

Advanced Process Modelling techniques make it possible to consider a systems-based approach to pharmaceutical manufacture, where the manufacturing steps are optimised to ensure optimal delivery of the drug in the human intestine. Sean Bermingham, VP of PSE's Solids business, explains the underlying concepts and software technology behind the vision, and recent advances in the practice.

Sean Bermingham,
VP PSE Solids
PSE

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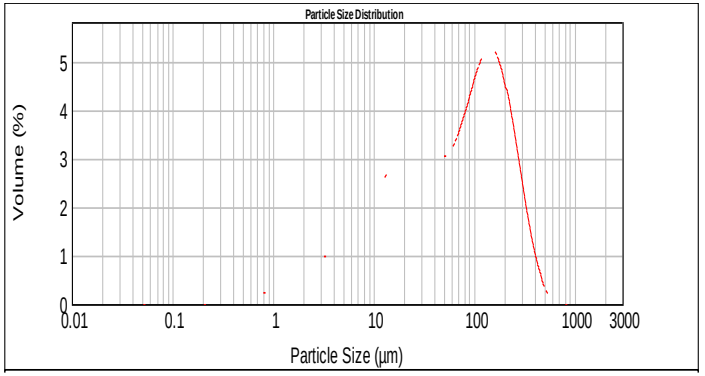
Rhea Brent, Senior Crystallization Scientist, Syngenta

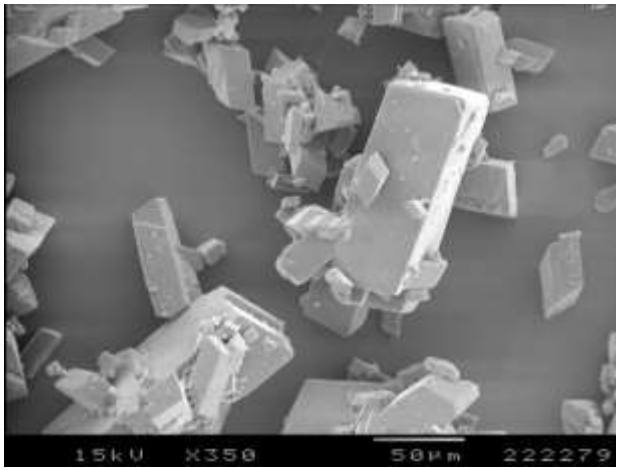
Applying crystallization modelling to improve the understanding of a batch cooling process of an agrochemical active ingredient

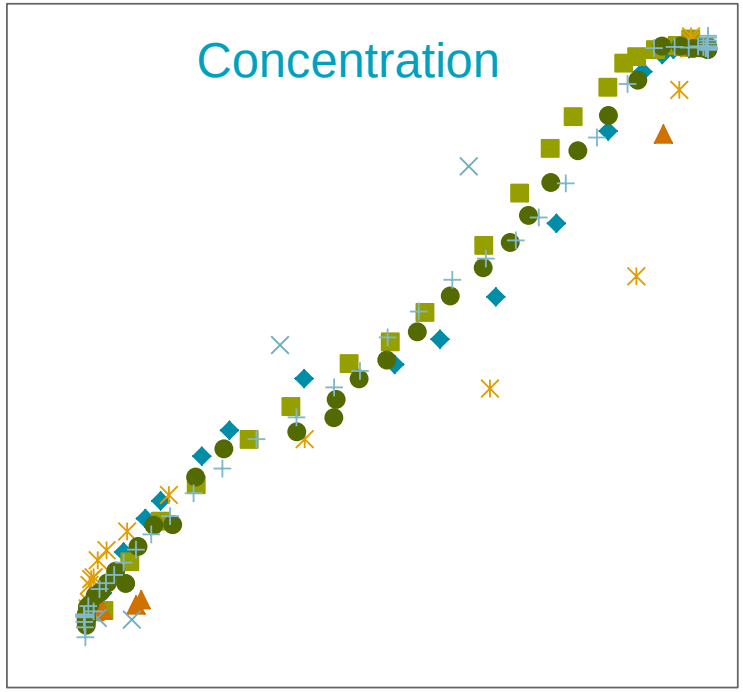
Syngenta AI-X Current Process

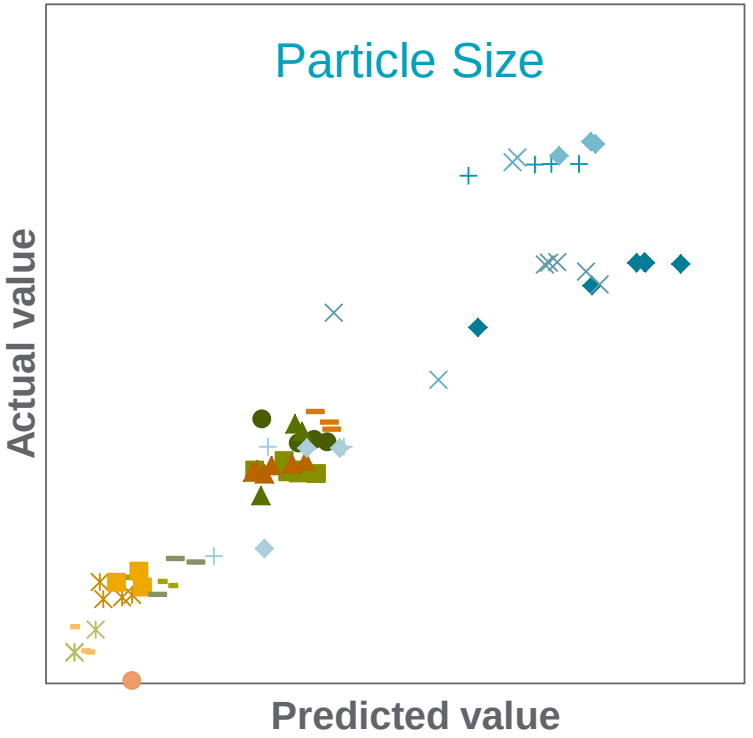
- AI-X currently manufactured and isolated by a cooling crystallisation process
- Currently isolation has batch to batch variability– in extreme cases rate decreases four-fold.
- Occasionally, subsequent batches must be held in a slurry hold vessel until the centrifuge is freed up.
- The AI is not likely to be polymorphic
- Poor filtration has been attributed to the width of the particle size distribution.



Typical particles from plant batches





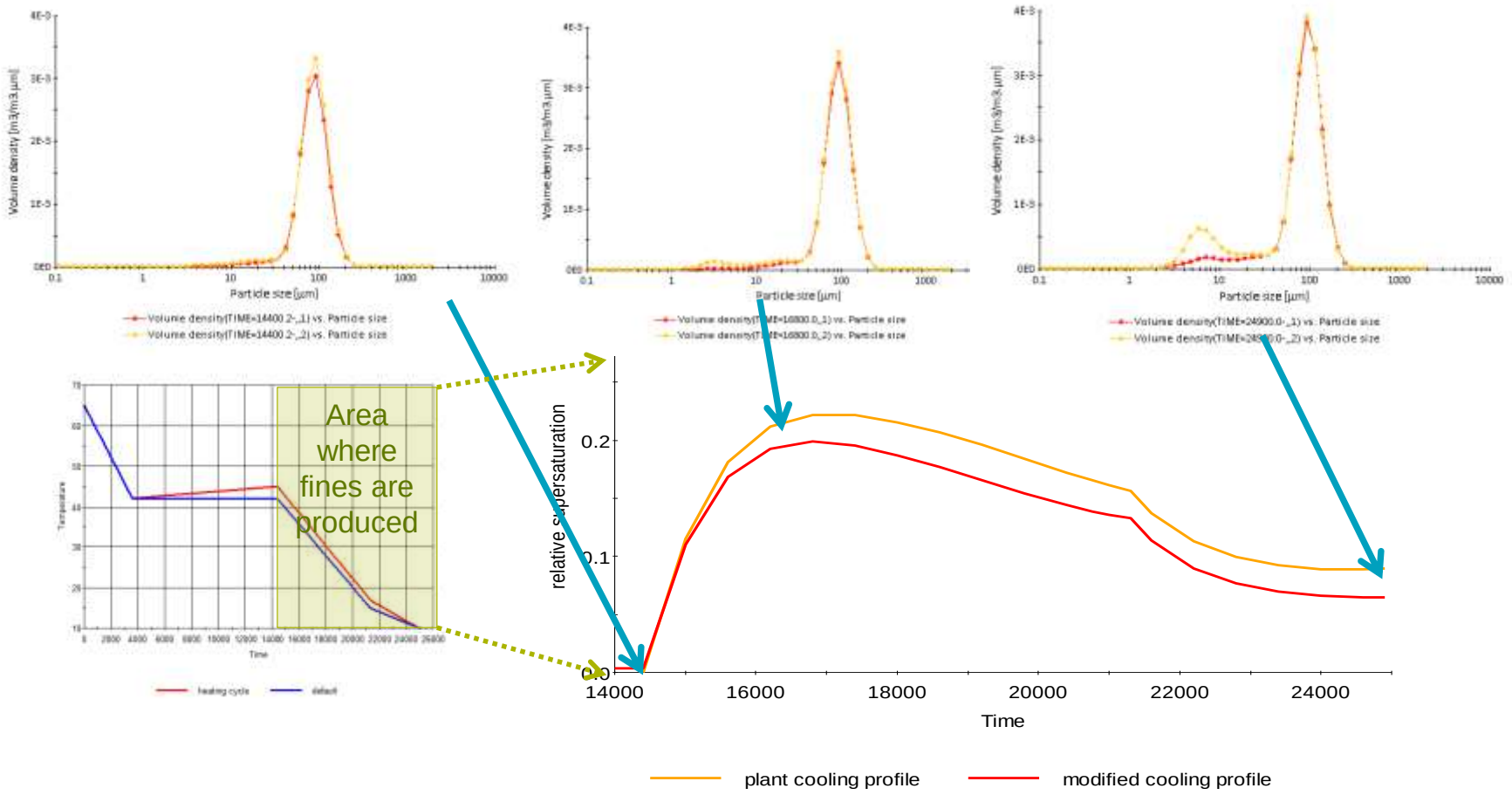


- cooling profile 1 (fastest)
- cooling profile 2 (faster)

- D50 plant profile 1
- D90 plant profile 2
- D90 plant profile 3
- D90 cooling profile 1 (fastest)

Model Fit to Experimental Data

Modelling Results: Effect of Modifying Cooling Profile with Low Loading of Seeds



Conclusions

- Lab to commercial scale batch cooling crystallisation has been successfully modelled.
- Modelling indicates that attrition is dominant in this crystallisation.
- To reduce the span of the particle size distribution the amount of attrition needs to be reduced, only apparent way is to reduce the size to which particles can grow.
- It is possible that by varying the seed amount, the PSD could be optimised.
- It is also possible that the temperature profile could be modified using temperature cycling to improve the PSD.

Christopher Burcham, Engineering Advisor, Eli Lilly

Utilisation of population balance models to develop a continuous crystallization process

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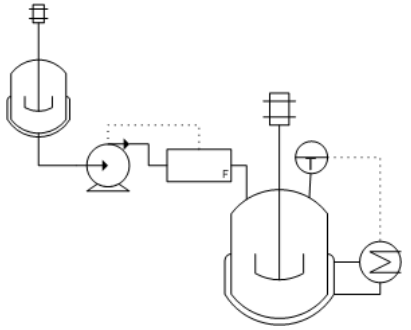
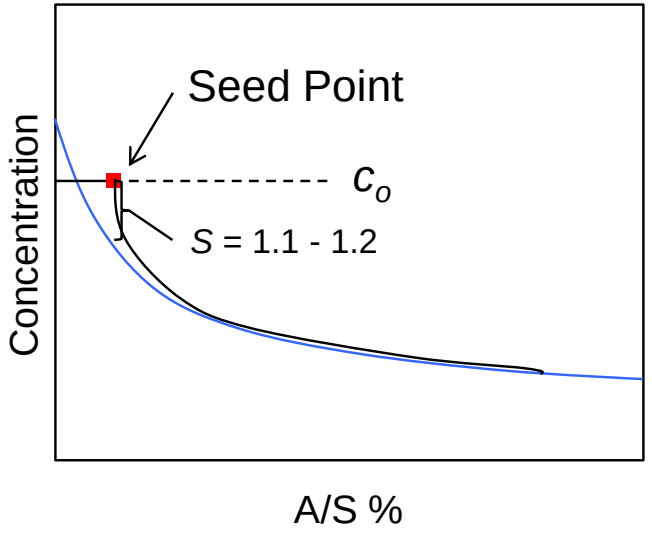
Typical Batch Crystallization Development

1) Choose solvent system
   - Solvent screening
   - Solubility modeling
2) Collect solubility data
   - Data drives choice of: thermal, A/S, combo
3) Choose seed point
   - c/c^* = 1.1 to 1.2
4) Follow solubility curve
   - *eg.* c/c^* = const
   - $c - c^*$ = const
5) Equilibrate and isolate

- Seeded, growth dominated crystallization.
- Time frame for design is accepted.



Example Crystallization



Continuous Crystallization Design

1) Choose solvent system

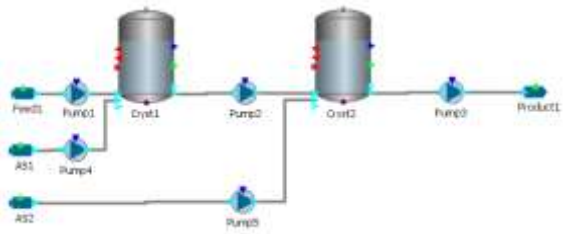
2) Collect solubility data
   - Data drives choice of: thermal, A/S, combo?

3) (startup: generate initial seed bed)

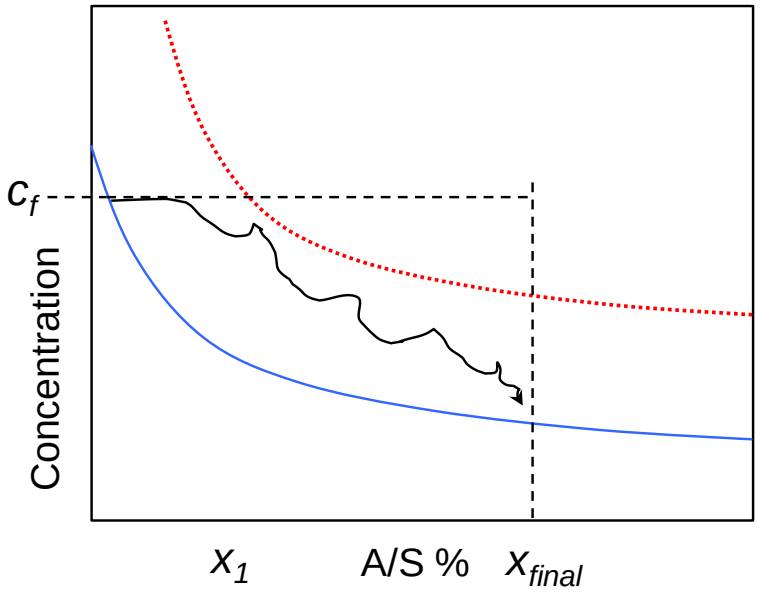
4) Traverse the solubility curve

5) Isolate

- Choose feed concentration based on prior process steps.
- Choose final composition based on yield and total solvent volumes.

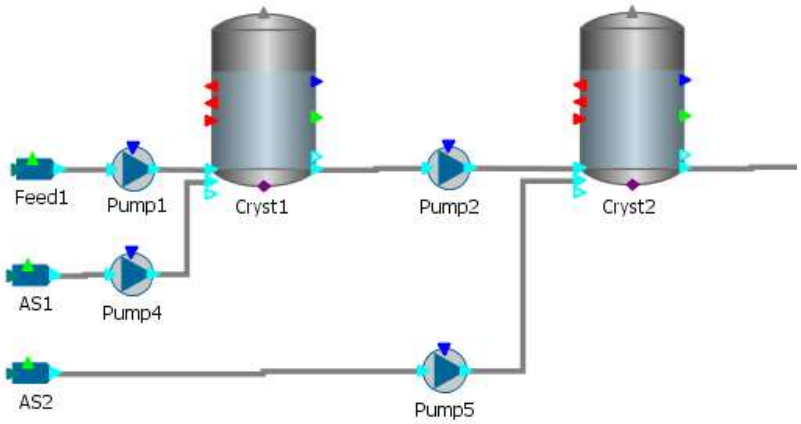


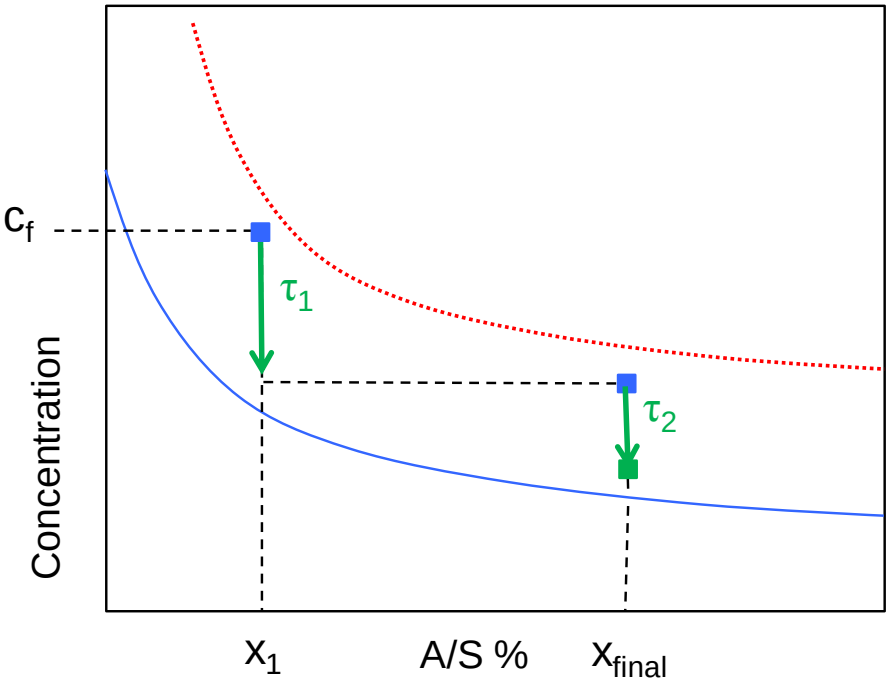
Example Crystallization



Continuous Anti-Solvent Crystallization Development Example – Two MSMPRs

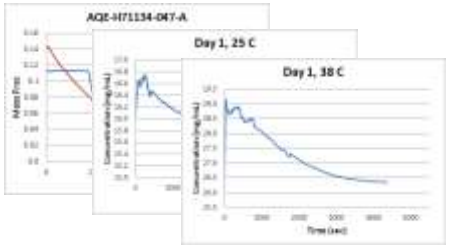
- 3 variables – τ_1, τ_2, x_1
- 3 levels, 27 total experiments, 4 experiments/wk
- ~7 weeks



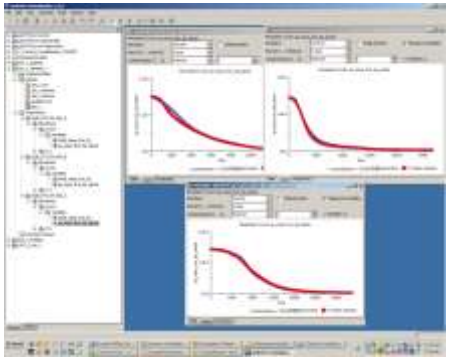


Development Cycle

Perform experiments to extract kinetics

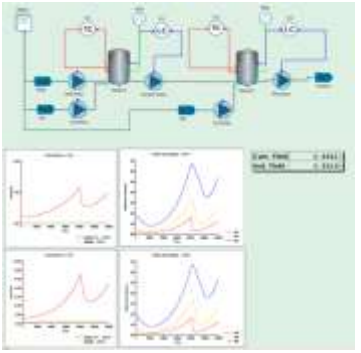


Determine growth and nucleation parameters



Apply appropriate kinetic model

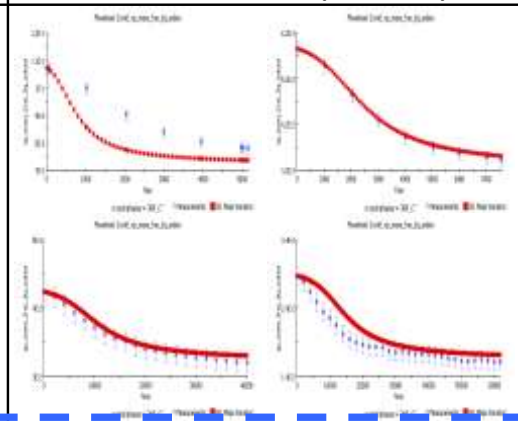
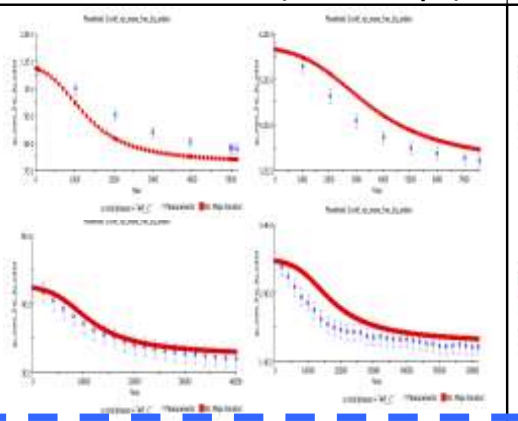
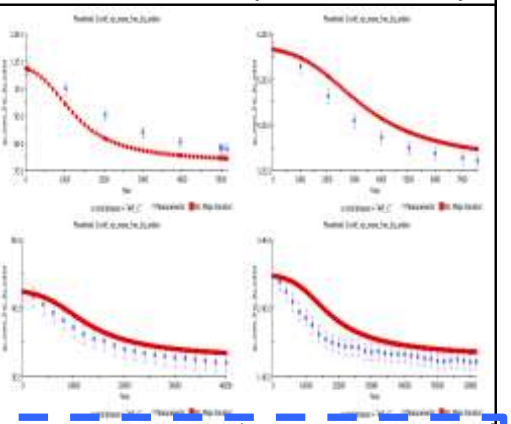
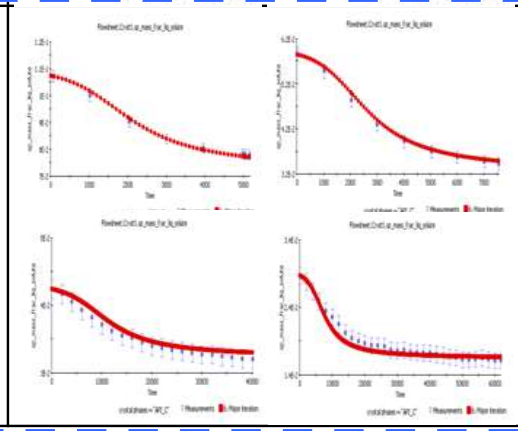
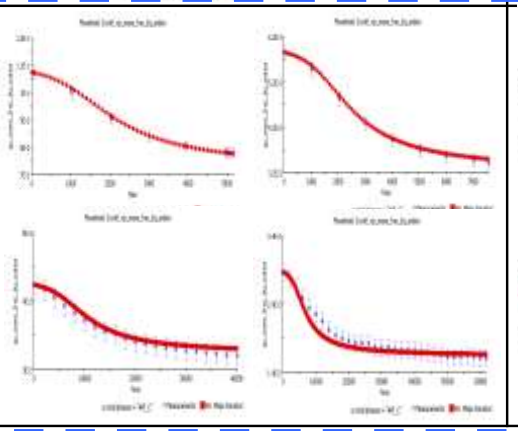
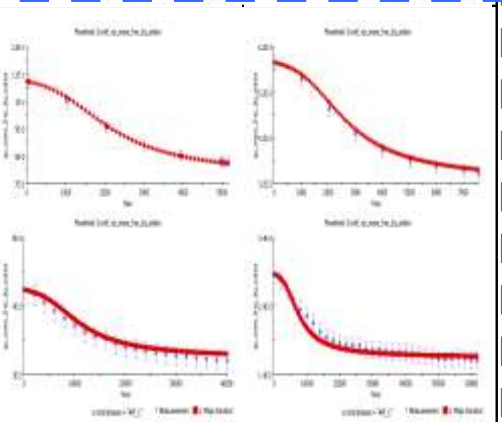
Determine optimal process conditions



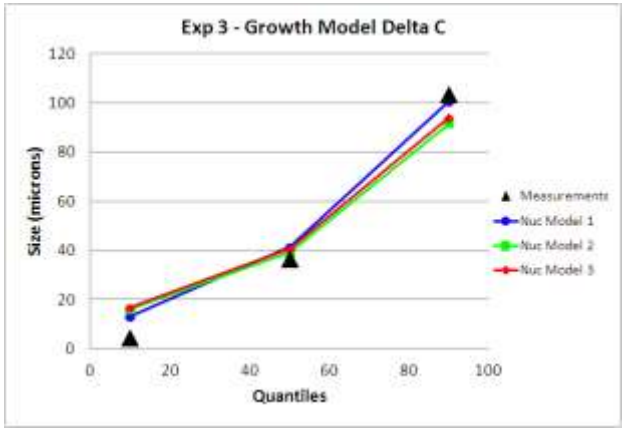
Establish steady state

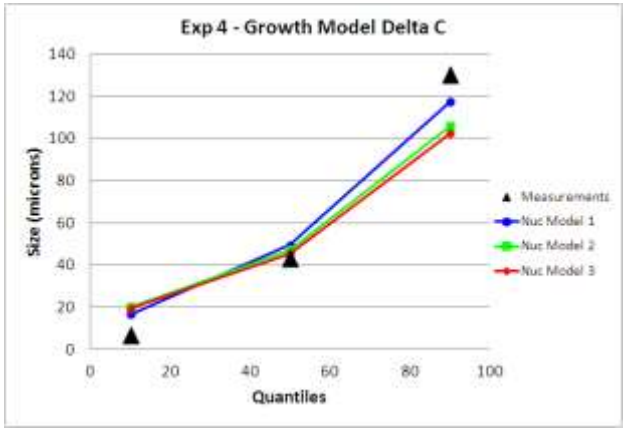
Utilize new data to update model

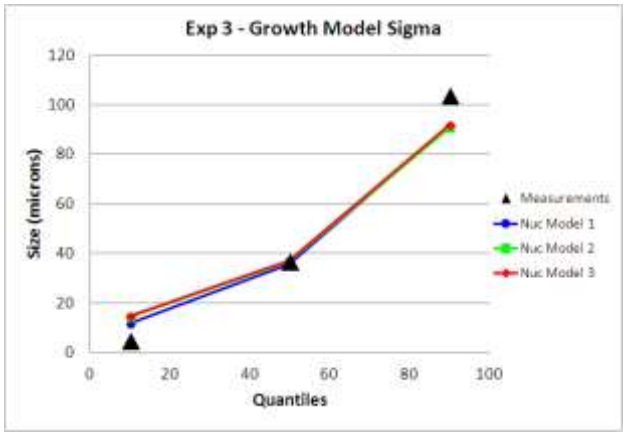
Solute Concentration vs. Time Fits

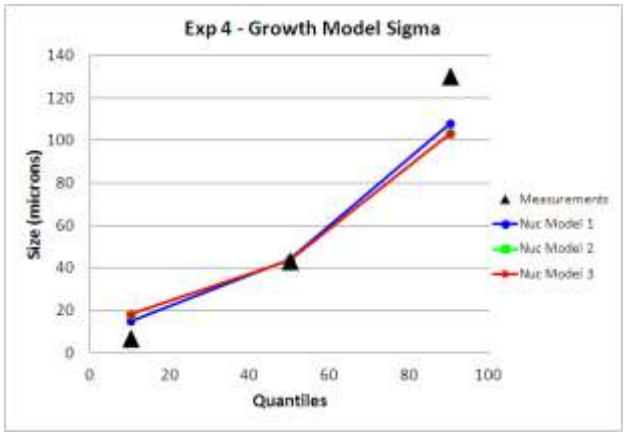
Growth Model ↓	Nucleation Model: Nuc Model 1 (Evan's)	Nuc Model 2 (w/T Dep.)	Nuc Model 3 (Power Law)
ΔC			
σ			

Particle Size Quantile Fits





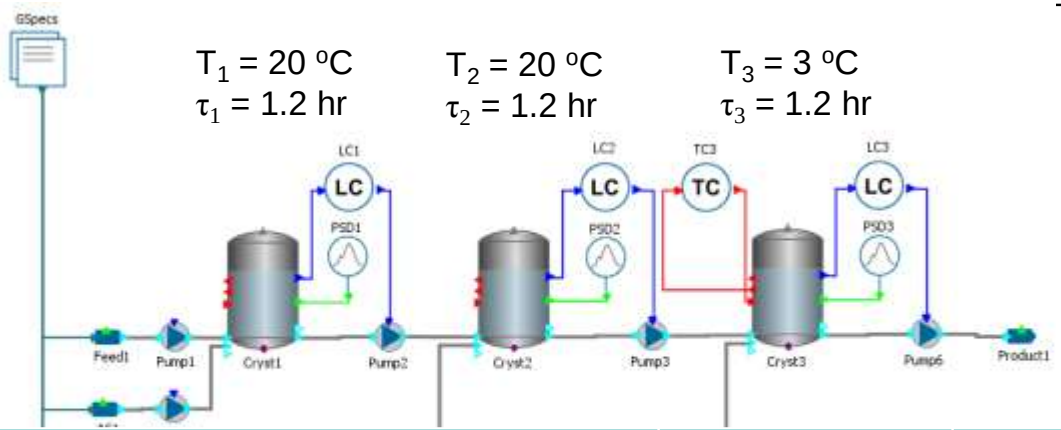




Observations

- Nucleation Model 1 predicts broader PSD (lower d10, higher d90) across the board. This is more representative of the measured values.
- Predictions using relative supersaturation growth model less dependent on nucleation model choice.
- Nucleation Models 2 and 3 predict very similar values.

gCRYSTAL Model Verification – Steady State Conditions, Iteration 1



T_1 = 20 °C
τ_1 = 1.2 hr

T_2 = 20 °C
τ_2 = 1.2 hr

T_3 = 3 °C
τ_3 = 1.2 hr

A/S_1 = 5 L EtOH/kg Solute

A/S_2 = 0.9 L H2O/kg Solute

A/S_3 = None

Value	Actual	Model 1	Model 2
Solubility MSMPR 1 (wt%)	5.7	5.7	5.7
Solubility MSMPR 2 (wt%)	1.2	1.2	1.2
Solubility MSMPR 3 (wt%)	0.76	0.73	0.73
Solute in Solution MSMPR 1 (wt%)	**7.9**	**8.2**	10
Solute in Solution MSMPR 2 (wt%)	**1.7**	**1.6**	2.0
Solute in Solution MSMPR 3 (wt%)	**0.83**	**0.86**	1.0
Rel. Supersaturation MSMPR 1 (%)	40	44	78
Rel. Supersaturation MSMPR 2 (%)	35	29	63
Rel. Supersaturation MSMPR 3 (%)	9.2	18	41

Optimization Problem Statement

Potential Objectives

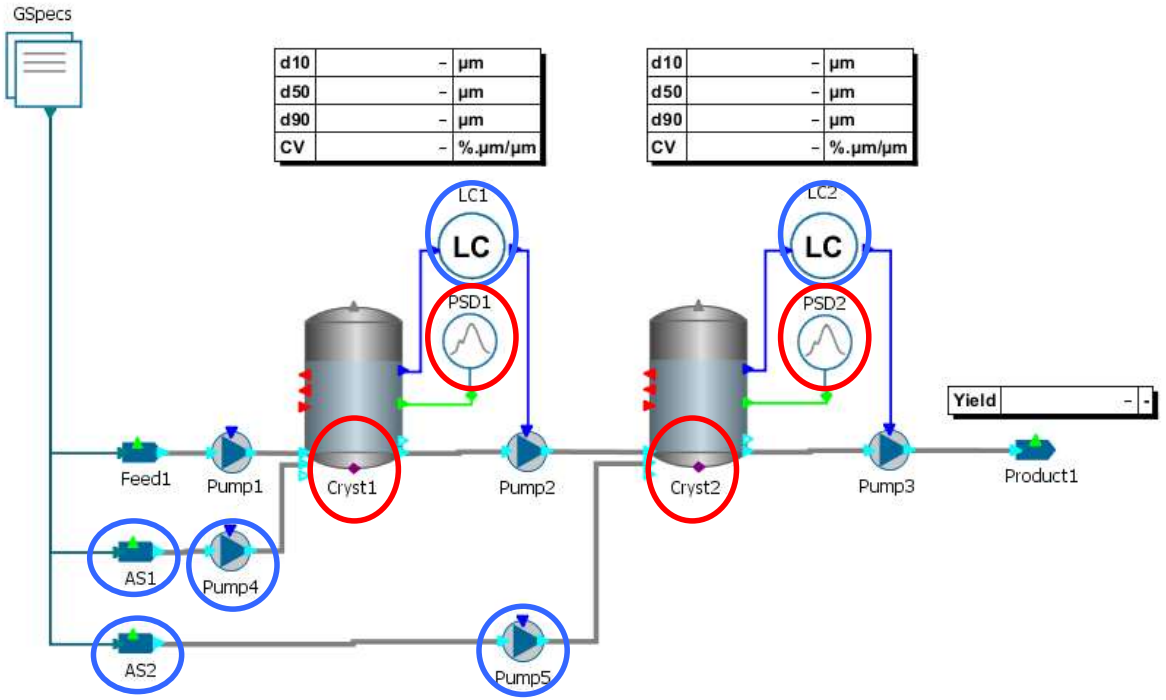
- Simple
  - Maximize Yield
  - Minimize Impurities
    - Need impurity model…
- Compound
  - Combine simple objectives
    - Maximize yield but penalize volume
    - penalize impurities
    - penalize deviation from target particle sizes
- Explicit Cost
  - Assign costs to product loss, solvent use, equipment time, etc.

Potential Constraints

- Equipment Size
- Solute Concentrations
  - Prevent process problems such as oiling, agglomeration, encrustation
- Product Properties
  - Bounds on PSD quantiles
    - d10 > x (prevent excess fines)
    - d90 < x (bioavailability)
    - d90 – d10 < x (powder flow)
  - Impurity levels
    - Need impurity models…

2-MSMPR Optimization

- Objective Function: Max[Yield – (Residence Time MSMPR1 + Residence Time MSMPR2) / Scaling Factor]
- Yield is a fractional amount, residence time is in minutes and Scaling Factor = 2000
  - (20 minutes = 1% yield)
- Controls:
  - AS1 Composition
  - AS2 Composition
  - Pump4 Rate
  - Pump5 Rate
  - LC1 Volume
  - LC2 Volume
- Constraints:
  - Cryst1 σ < 1
  - Cryst2 σ < 0.2
  - d10 > 10 µm
  - d90 < 200 µm
- Optimization maximizes yield with a penalty on equipment size
- Constraint on particle size, supersaturation.



Summary of Trade-Offs

Limit – d_{90} max (μm)	Cryst1 τ (hr)	Cryst2 τ (hr)	Total Process Volume (L/kg)	Yield (%)
200 ↓	0.78 ↓	6 ↑	14 ↑	90 ↓
190	0.75	7	17	90
175 ↓	0.70 ↓	8.3 ↑	20 ↑	87 ↓

- Particle size is tunable
- Smaller size requires:
  - Larger equipment size (residence time)
  - More anti-solvent
  - Results in lower yields.

Conclusions

De-supersaturation experiments were used to determine growth and nucleation kinetics.

Multiple models for growth and secondary nucleation considered.

- Generated significant process insight for process design and optimization.

Verification of the predictive capability of the different secondary nucleation models.

Process optimization was performed for a 2 MSMPRs.

- Resulted in much different residence times in each from initial experimental development.

Model was used to provide directional guidance on how to manipulated process variables to achieve desired results.

Utilization of population models for continuous crystallization does speed up process development time.

Ian Kemp, Senior Scientific Investigator, GSK
Thoralf Hartwig, Senior Process Engineer, GSK R&D

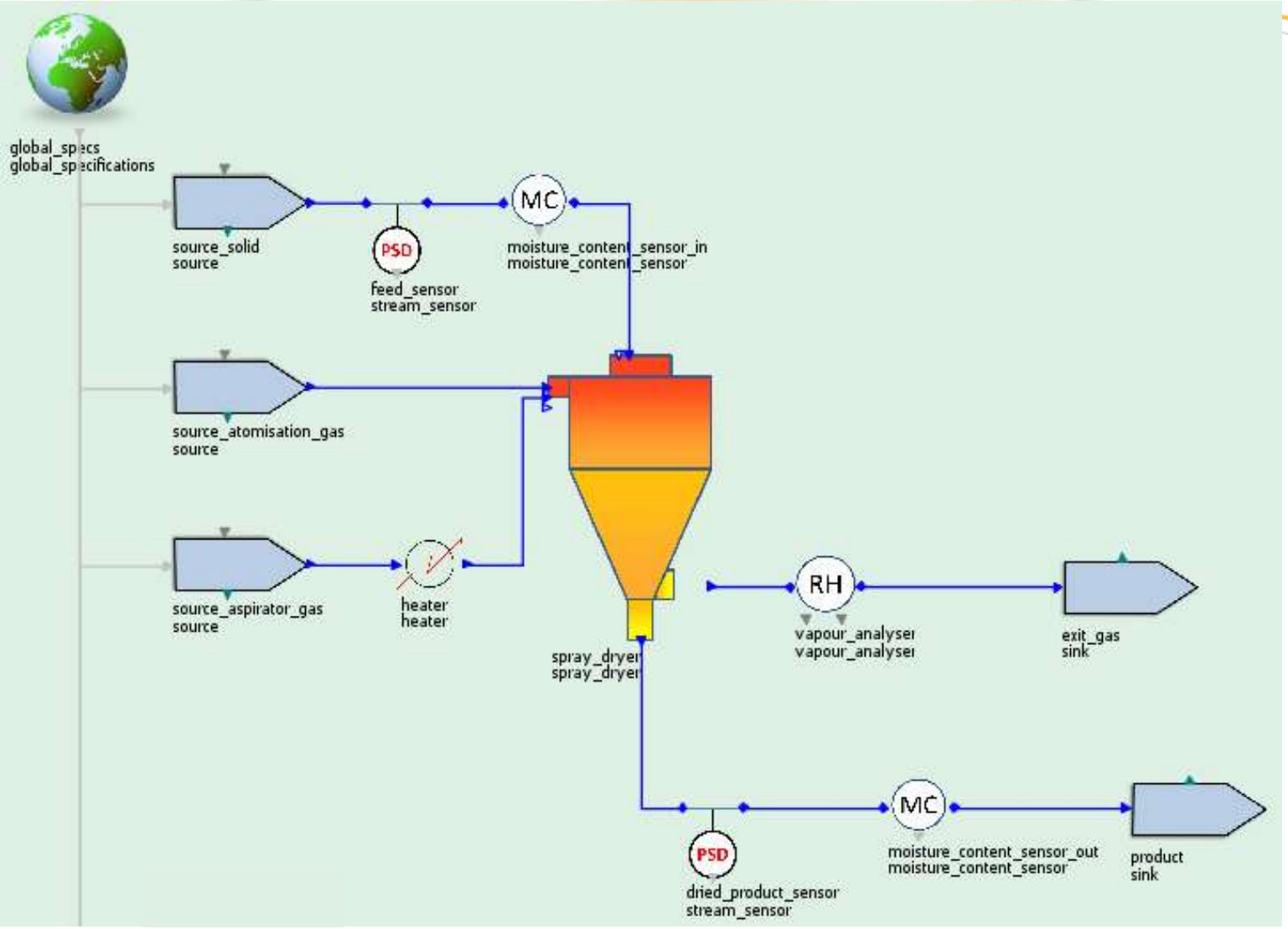
Modelling spray drying of fine particles using gSOLIDS

Strategy for spray dryer modelling

- Heat and mass balances (Levels 1 and 2) used for scale-up and production rate calculations
- Simple droplet models (Level 2) show basic relationship of final particle size to initial droplet size and solids concentration
- CFD modelling with FLUENT™ (Level 5) demonstrates flow patterns; cool fast-flowing core, hot central annulus, cool stagnant outer layer
- PSE gSOLIDS model is a one-dimensional Level 4 incremental model giving droplet and particle tracking through the spray dryer
  - Can incorporate CFD insights on multiple zones rather than assuming plug flow or CSTR
  - Much faster than CFD for “what-if” calculations to show trends and gain process understanding
  - More flexibility than CFD to vary the drying model and allow for crust formation

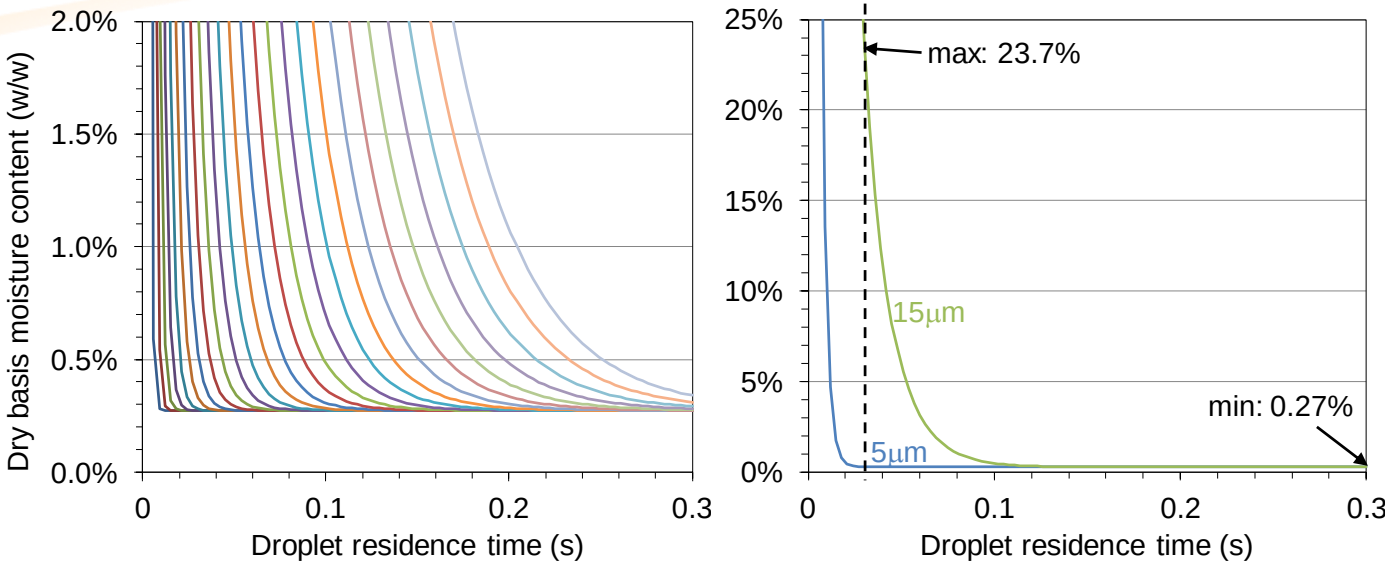
Modelling Approach in gSOLIDS

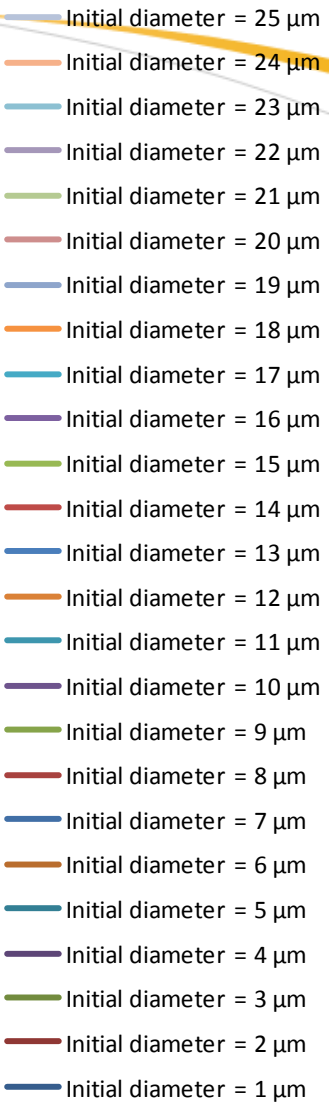
User Interface



Results

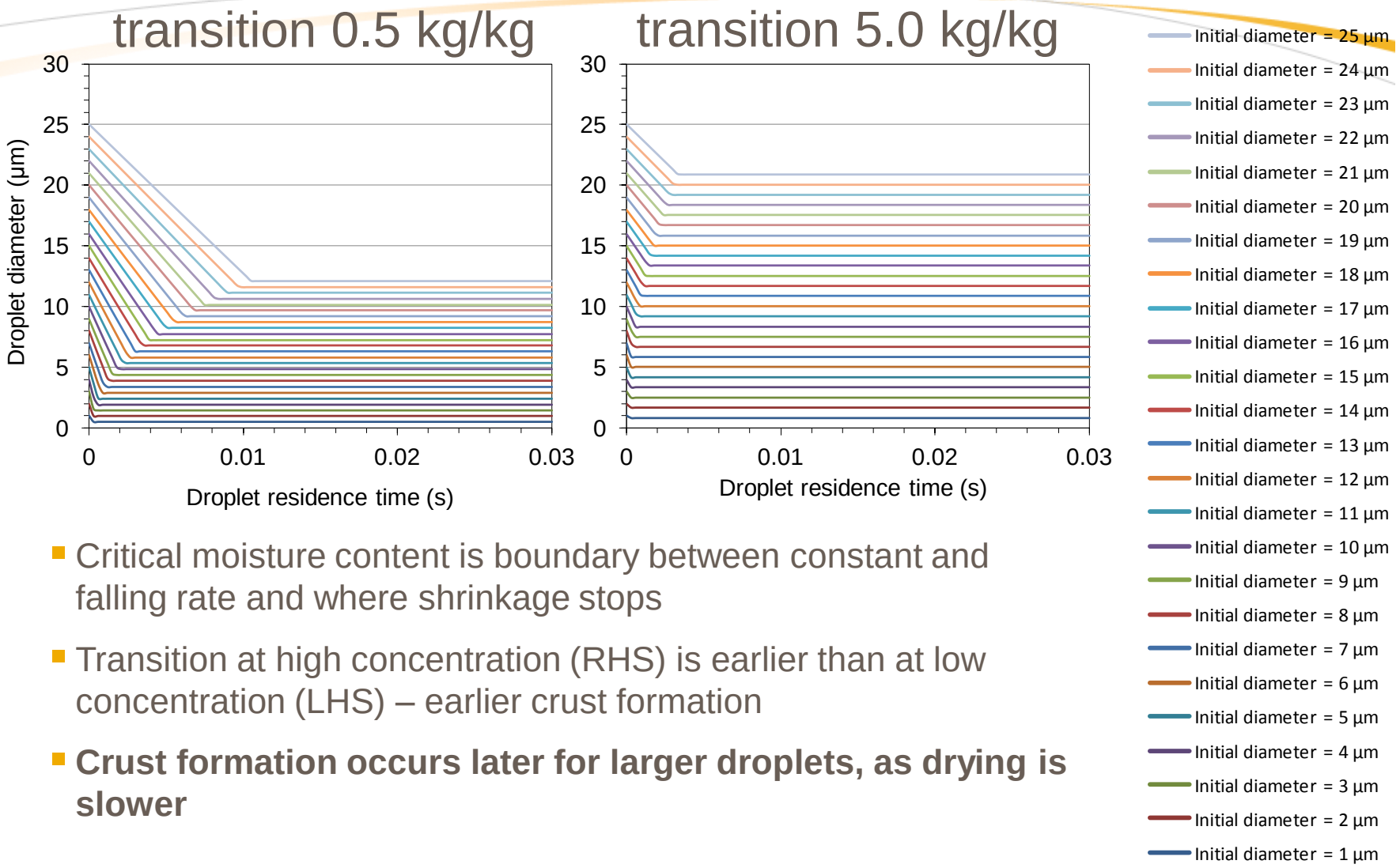
Moisture content for different residence times





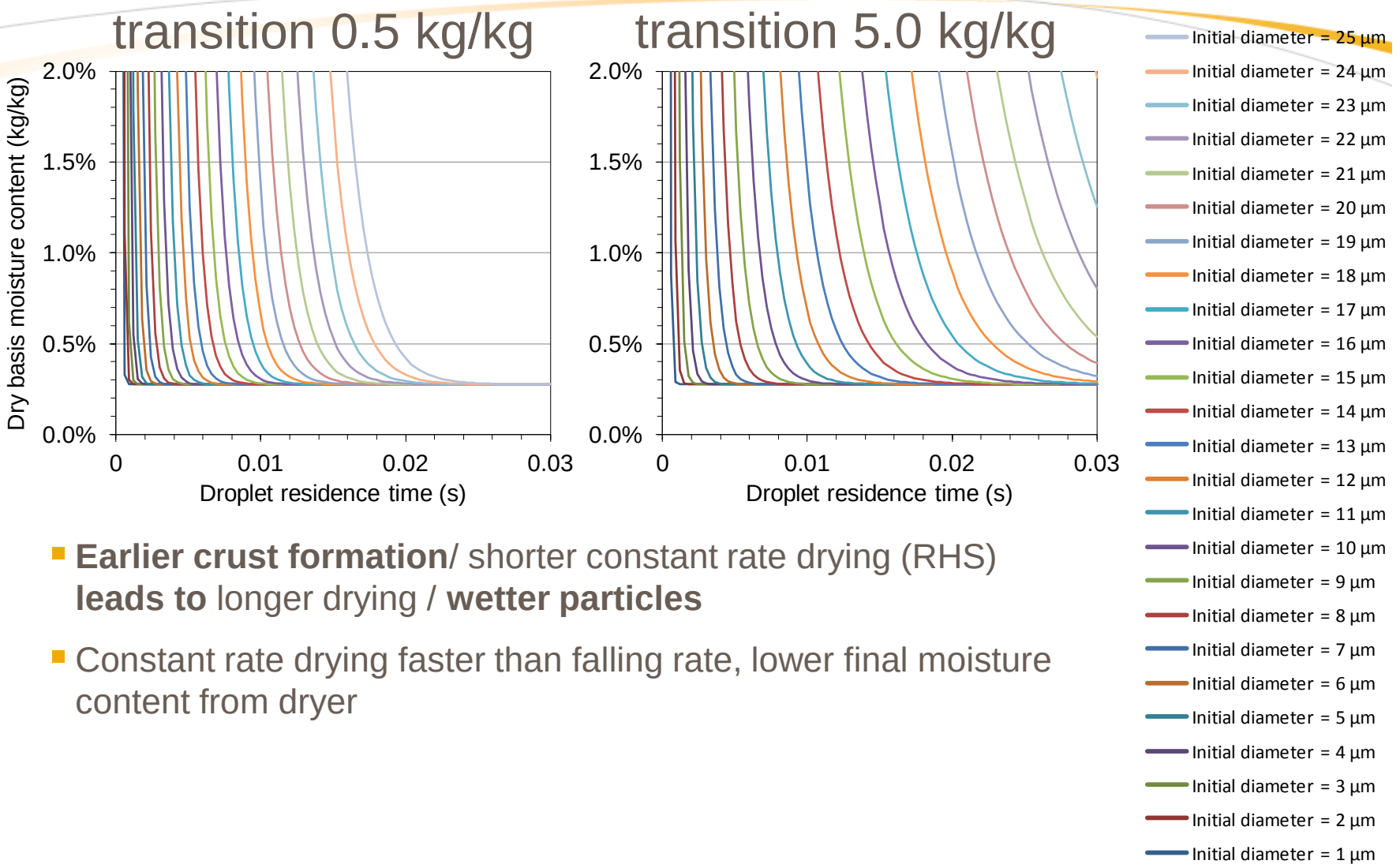
- Distribution of moisture content (here: ranging from 0.27-23.7w/w%) depending on inlet droplet size & residence time
- Highest moisture contents (and largest offload particles) for large inlet droplets with small residence time
- Average moisture content (offload particle size) depends on droplet size and residence time distribution

Constant rate with shrinkage, followed by falling rate drying with no shrinkage



- Critical moisture content is boundary between constant and falling rate and where shrinkage stops
- Transition at high concentration (RHS) is earlier than at low concentration (LHS) – earlier crust formation
- **Crust formation occurs later for larger droplets, as drying is slower**

Constant rate with shrinkage, followed by falling rate drying with no shrinkage



- **Earlier crust formation**/ shorter constant rate drying (RHS) **leads to** longer drying / **wetter particles**
- Constant rate drying faster than falling rate, lower final moisture content from dryer

Results
Sensitivity Study

- Assess impact of process parameters on output attributes
  (no / low ↑ / medium ↑ / high impact ↑) (black: model, red: experiment)
- Increase input parameters 10% from base case → study impact on output attributes

	Control parameters						
	Aspiration flowrate	Inlet temperature	Atomisation gas flowrate	Liquid feedrate	Solids conc	Inlet droplet size	Heat loss
Particle size			↓	↑	↑↑	↑	
Solvent content	↓↓	↓↓		↑↑	↓↓	↑	↑

- Inlet temperature ↑ → Heat Loss ↑
- Atomisation flowrate ↓, liquid feedrate ↑ → Inlet droplet size ↑

gSOLIDS model agrees qualitatively with experimental findings

gSOLIDS model currently models heat balance but not atomisation process

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gSOLIDS Spray Drying model
Summary & Conclusion

- Sensitivity Analysis: gSOLIDS Model predicts qualitatively correct the impact of critical process parameters on output attributes
- Different scenarios studied (shrinkage vs no shrinkage, constant vs falling rate) and results compared to experimental data
- Model assists process understanding of droplet drying
- Constant rate drying with shrinkage followed by falling rate drying without shrinkage gives consistent results
- **Predicted outlet moisture content is always very low (close to equilibrium moisture content) and below some experimentally observed values**
- **Suggests that model is overpredicting drying rates in falling rate period**
- Model uses a simple linear falling-rate method (first-order kinetics); appears to be insufficient for porous spray dried particles
- First-order kinetics works well for dryers with minutes/hours residence time, but diffusion rate in crust is probably limiting for residence times << 1 second
- Observed final particle sizes and densities are more consistent with late crust formation (< 1 kg/kg)

Xiaorong He, Senior Research Fellow,
Boehringer Ingelheim

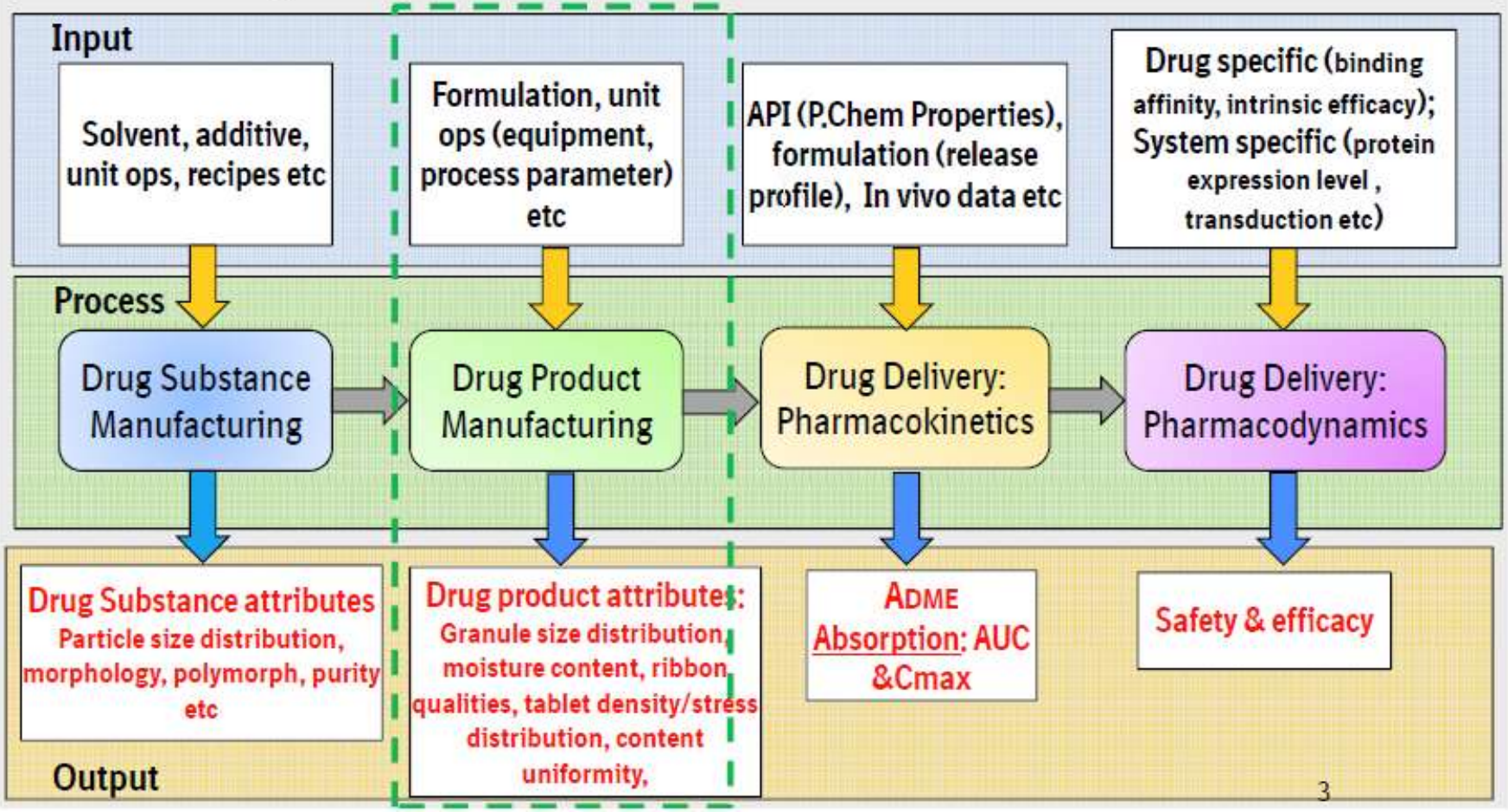
Modelling of fluid bed drying at different scales in drug product manufacture

Process Modeling for Pharmaceutical Industry

Boehringer Ingelheim

PSE

Process modeling – Use of physical, chemical, engineering, and/or biological principles coupled with computational methods to describe and simulate outcome of a process under a set of given conditions



Regulatory Expectation for Drug Product Development

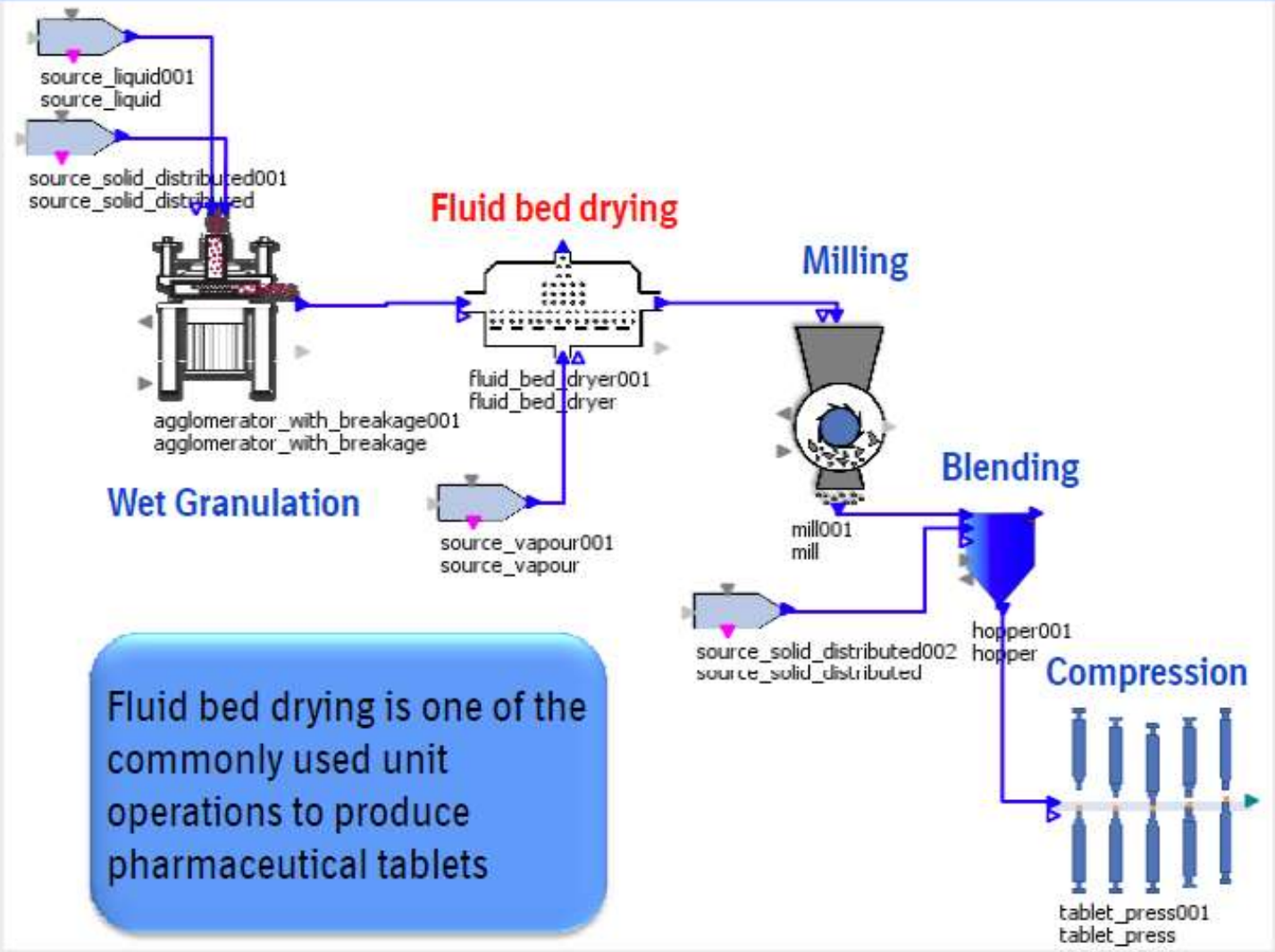
Acceptable ways to demonstrate product/ process understanding & control

"prior knowledge, experimentation, statistical & **mechanistic studies** "

- ICH Q8R2

PLEASE INSERT Presentation title

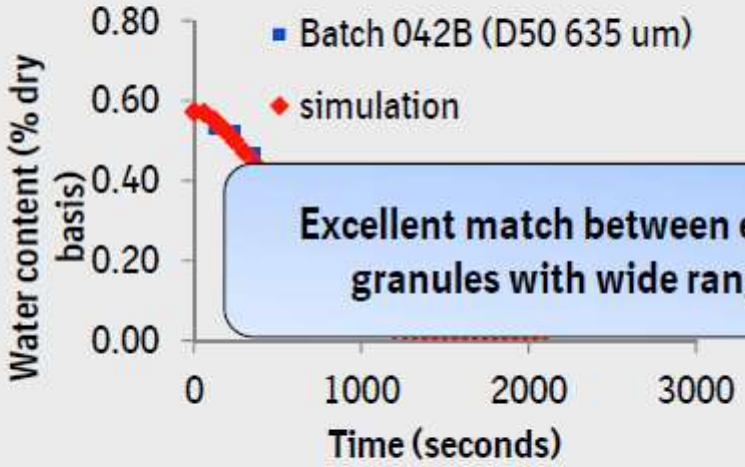
Typical Process Flow for Pharmaceutical Tablet Production

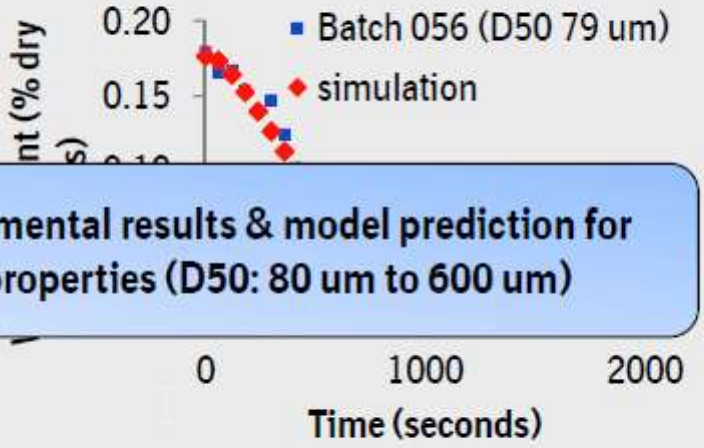


Comparison of Simulation vs Experimental Results
(Placebo granules with D 50 ranging from D50 80 um to 635um)

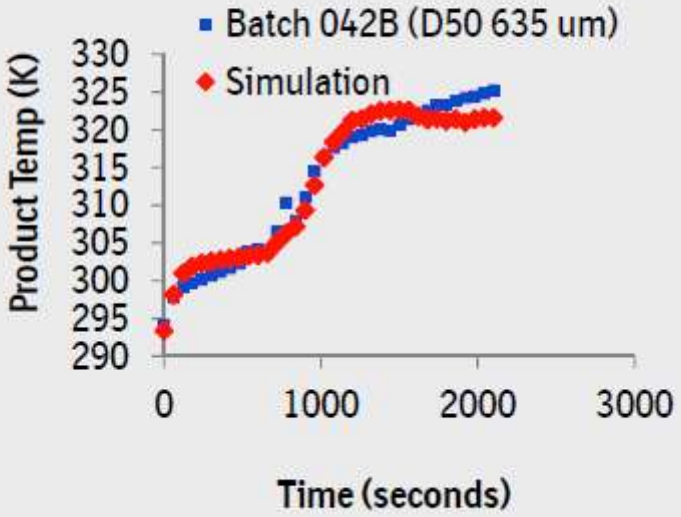
Boehringer Ingelheim

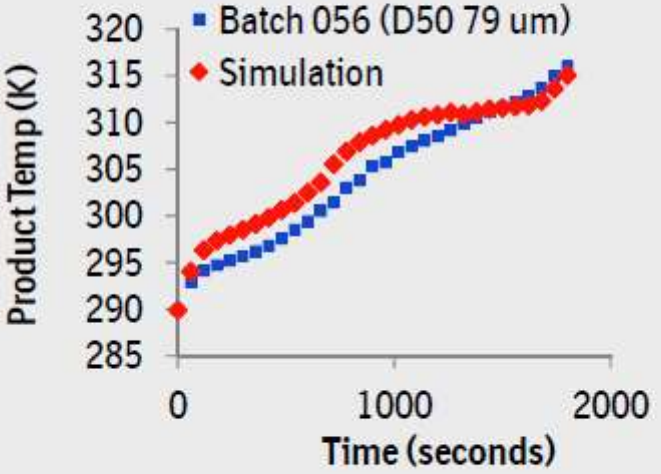
PSE



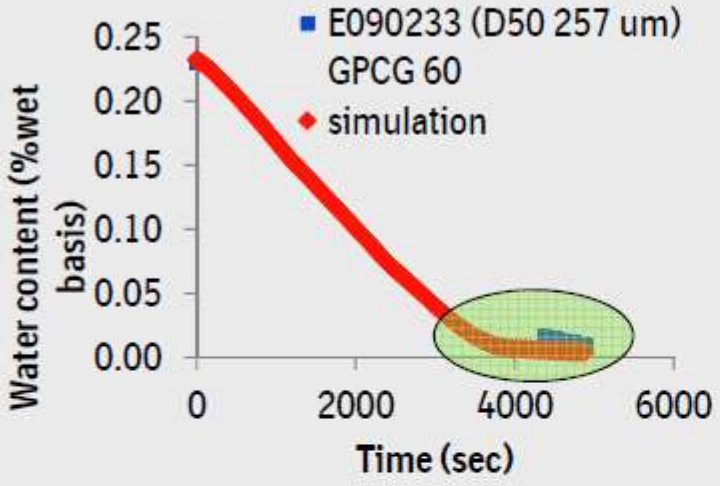


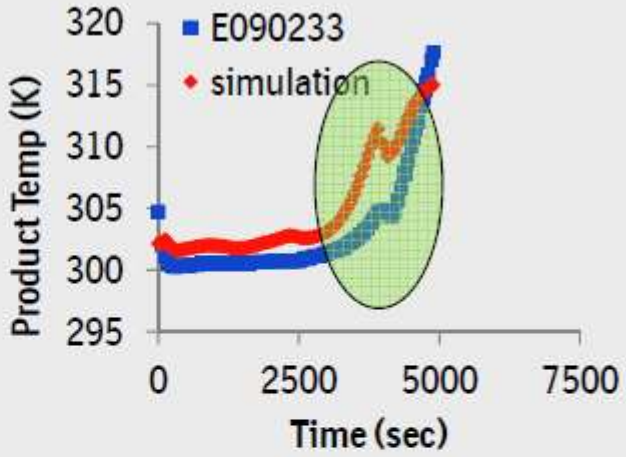
Excellent match between experimental results & model prediction for granules with wide range of properties (D50: 80 um to 600 um)

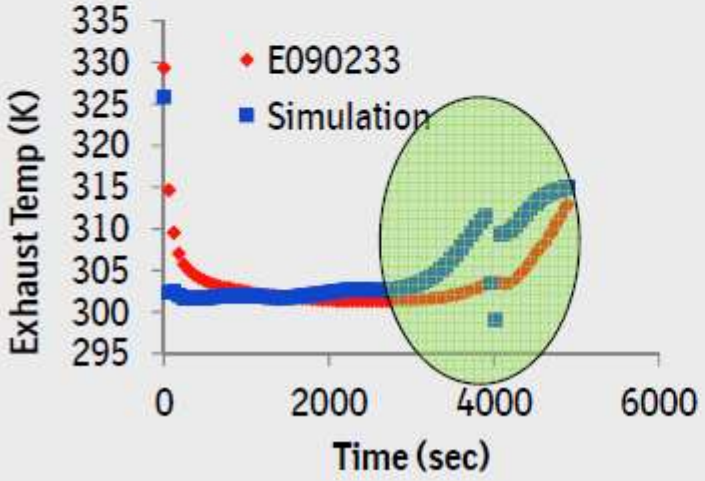




Comparison of Simulation vs Experimental Outcome (2.5 mg Granulation Full Scale GPCG 60)







- More discrepancy between model prediction & experimental values for full scale than the lab and pilot scale
- The assumption of "well mixed system" needs to be re-evaluated for large scale fluid bed dryer

Conclusions

- Fluid bed drying model was validated using three formulations at different scales
  - The model predicted experimental outcomes very well for lab & pilot scale fluid bed dryer
  - The assumption of well mixed system may not adequately describe mixing behavior in large fluid bed dryer (Glatt GPCG 60)

- Process modeling offers great potentials to gain process understanding with reduced experimental efforts – significantly saving resources & efforts

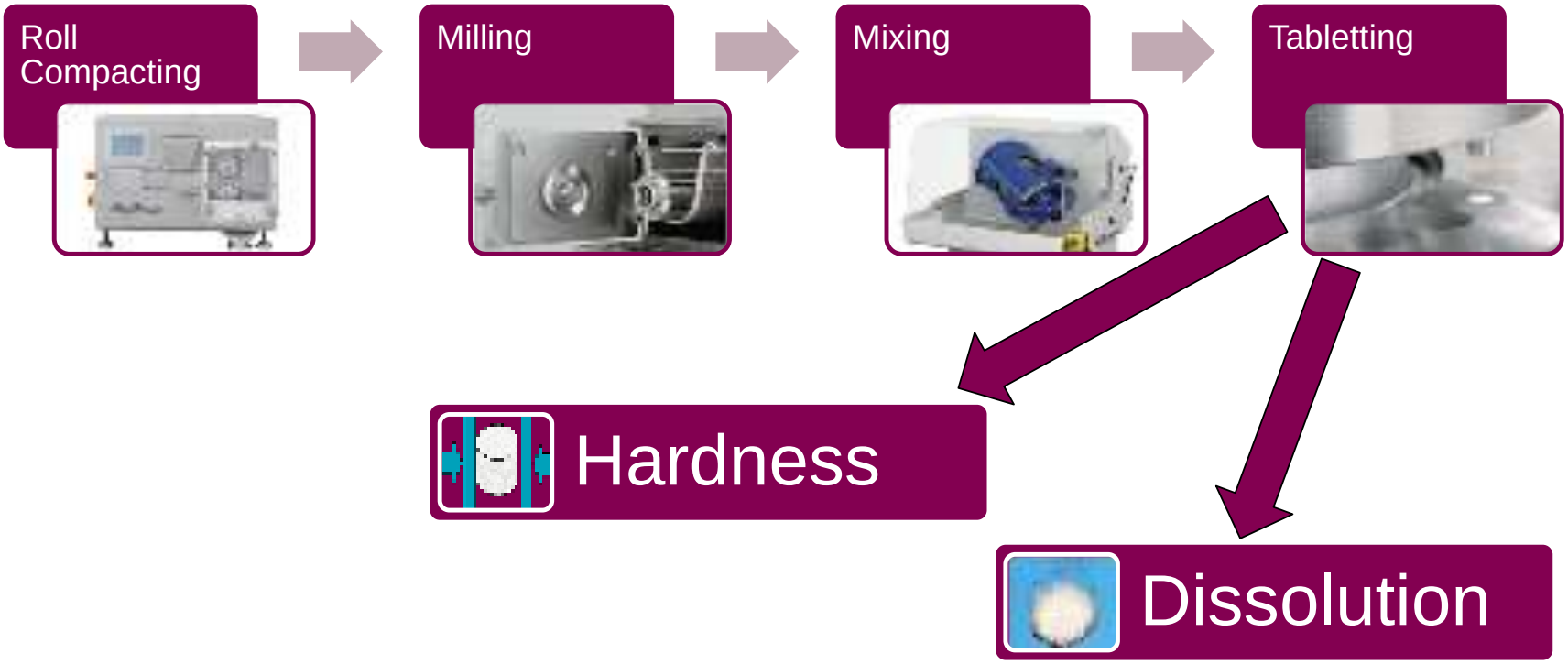
- gSOLIDS provides a user friendly platform for process modeling

Gavin Reynolds, Associate Principal Scientist, AstraZeneca R&D

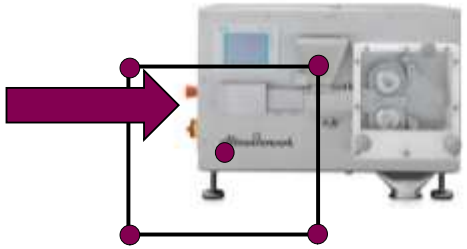
Modelling the manufacturing process and product performance of roller compacted pharmaceutical tablets

A systems-based approach

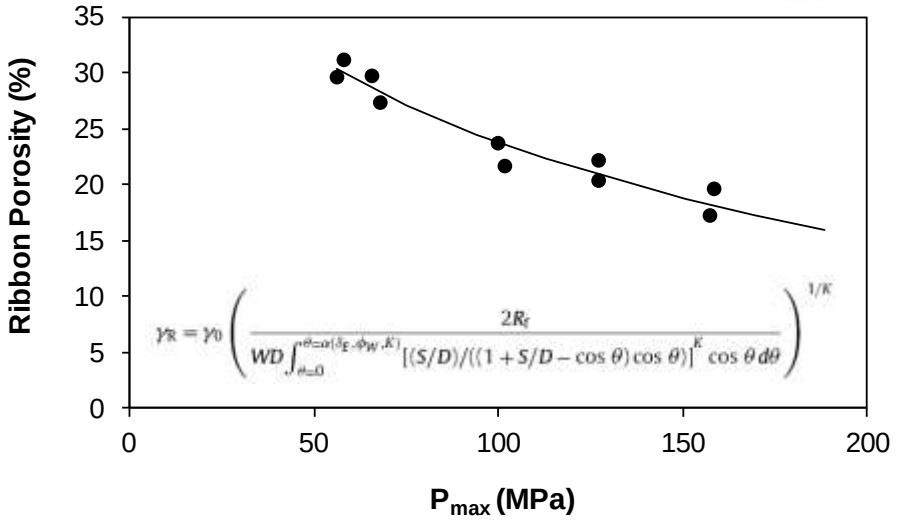
Develop unit operation models and link to product performance



Unit Operation – Roll Compactor
Calibrating a model



- The powder compaction properties are calibrated to RC experimental data.
- P_{max} is dependent on these parameters, so the model needs to be solved iteratively to determine γ_0 and K.



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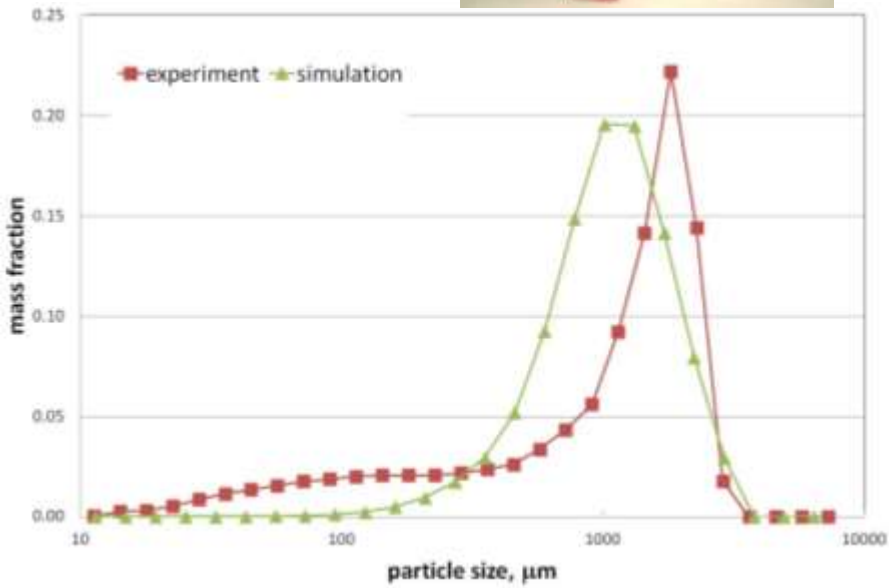
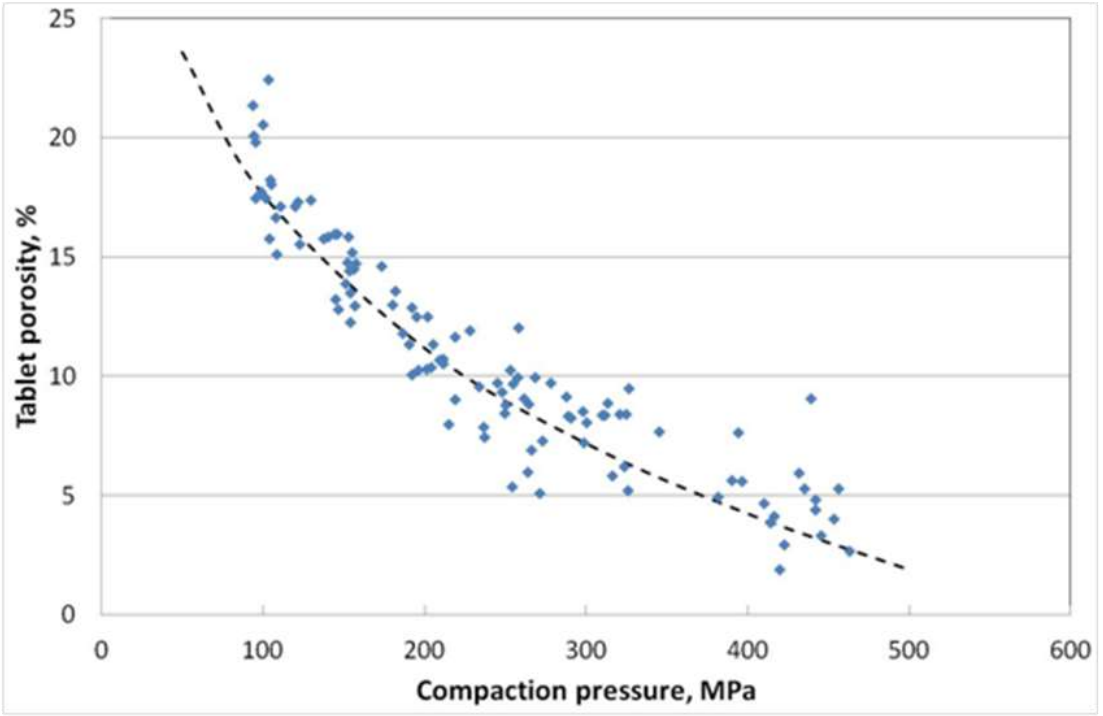
Unit Operation – Milling
Calibrating a model

- The six parameters of the breakage kernel are determined by fitting the predicted granule size distribution to experimental data.
- In this case the mill model was only able to approximate the granule size distribution
  - The sharpness of the large mode is not captured
  - No fines are predicted



Unit Operation – Tabletting
Calibrating a model

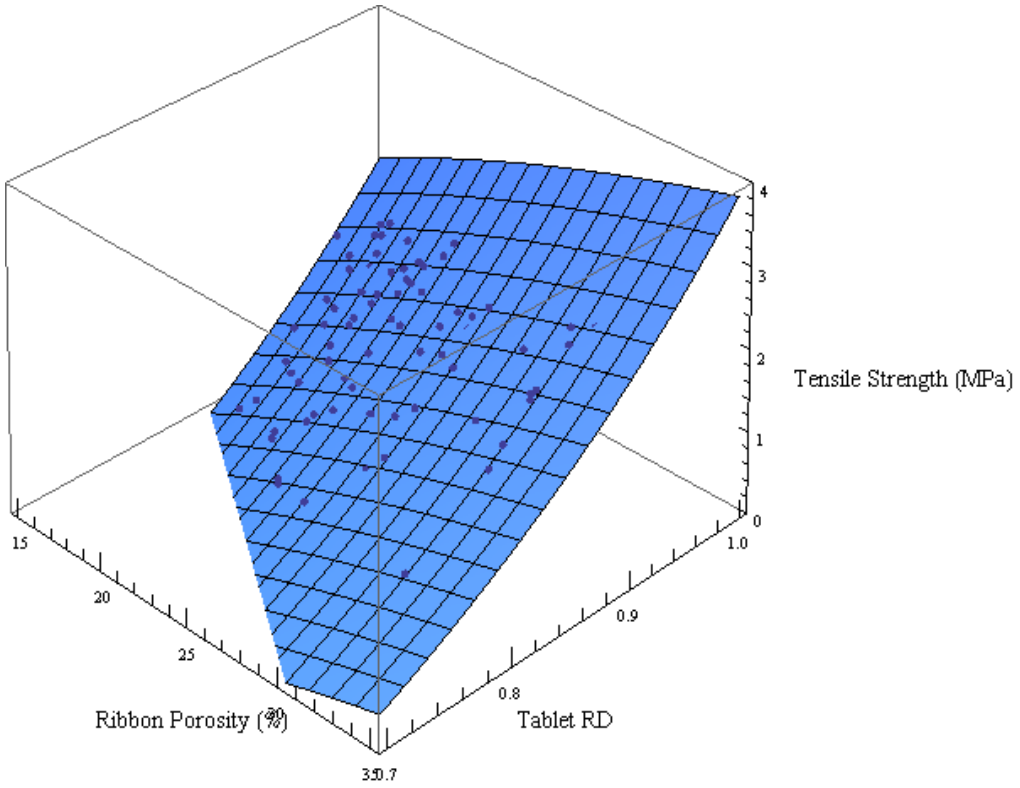


• This simple model assumes that only the formulation composition influences the relationship, and not upstream processes (e.g. roll compaction). In this case, a single relationship across all the experiments seems to be a reasonable approximation.

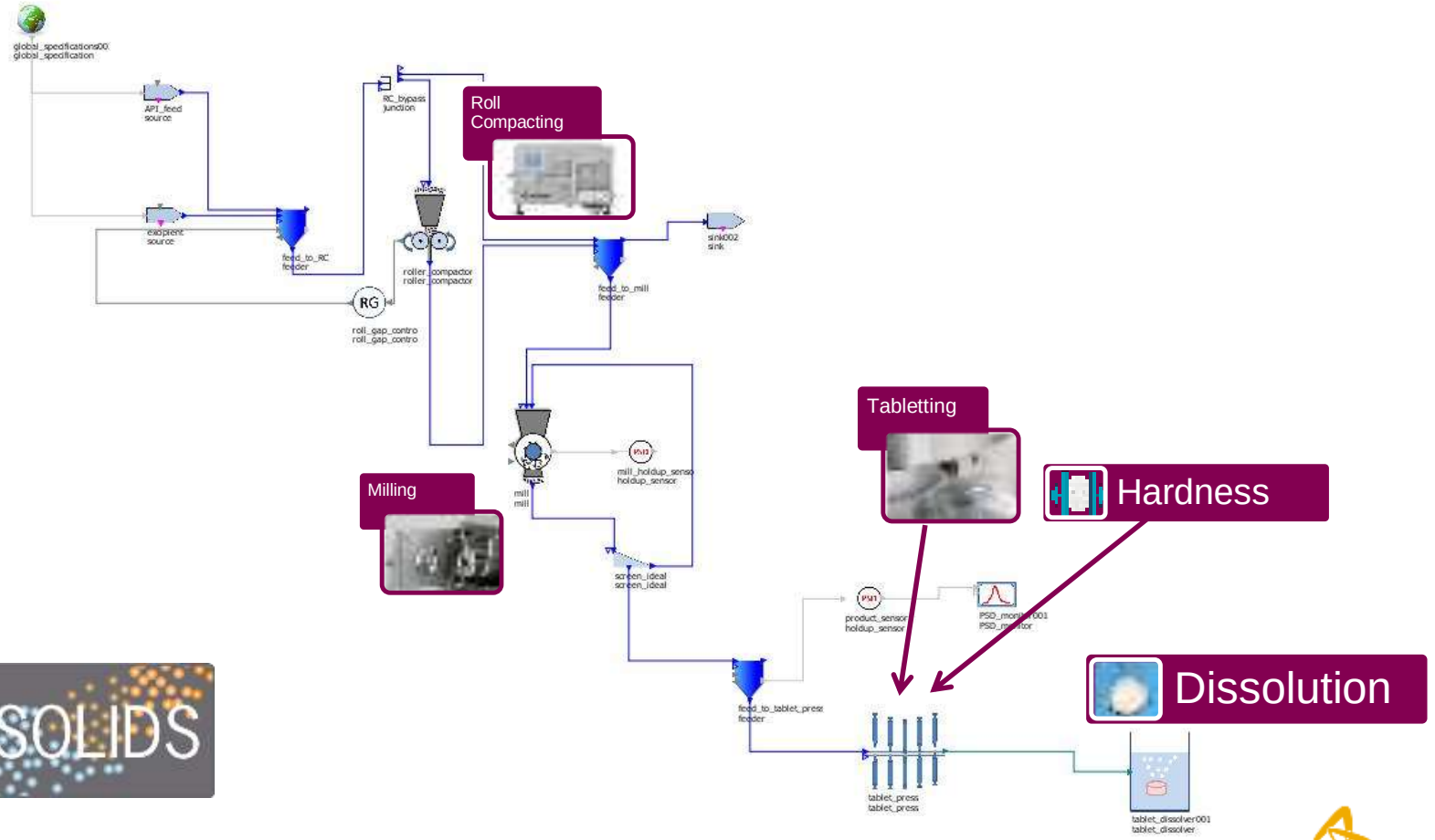
Performance – Hardness
Calibrating a model

Hardness

- A single set of material parameters was estimated by fitting the compaction model to experimental data.
- This single set of parameters were able to be used across all the process conditions (i.e. related to formulation composition rather than upstream processing such as roller compaction).

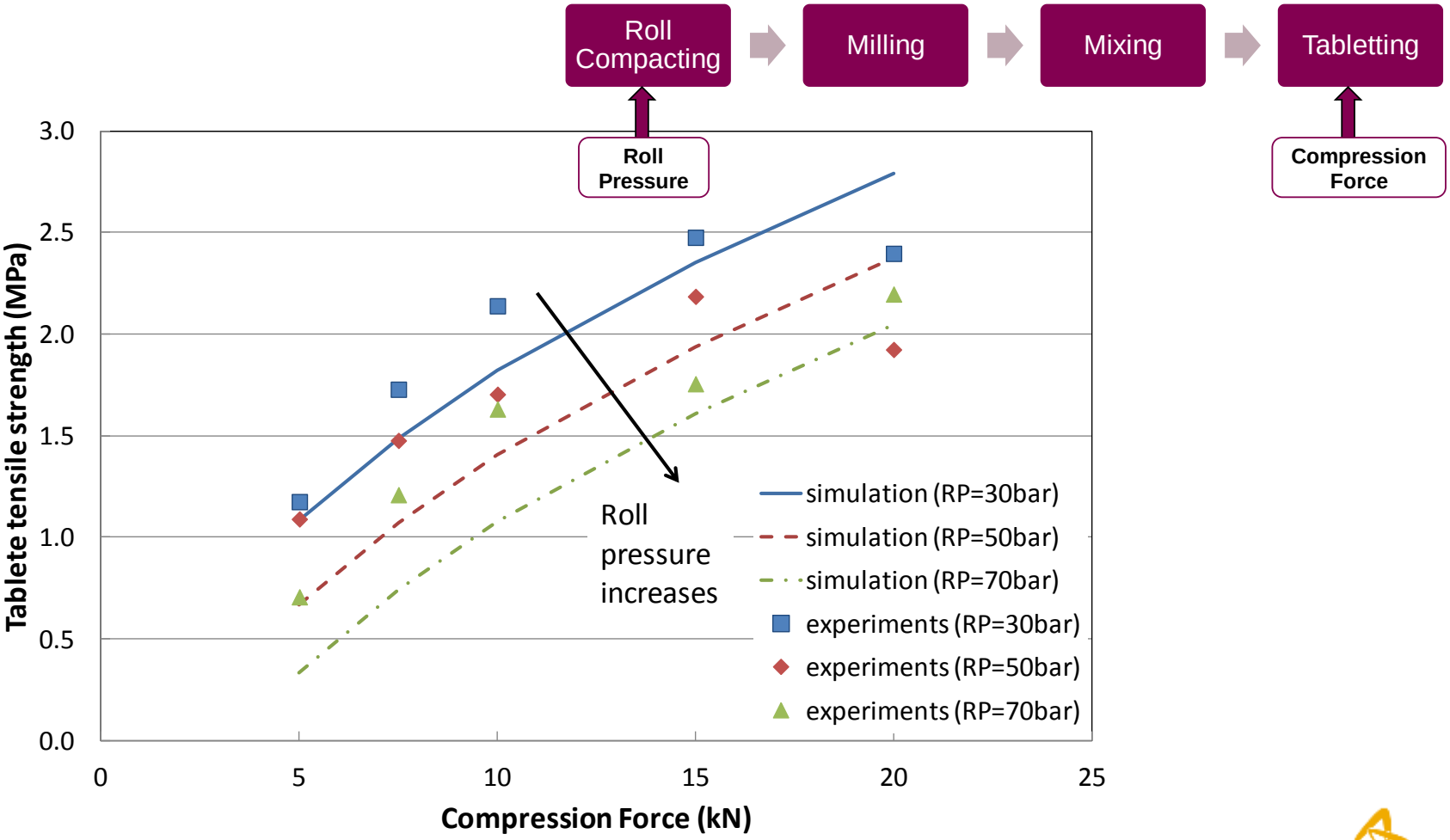


Putting it all together
Implementing the system in gSolids



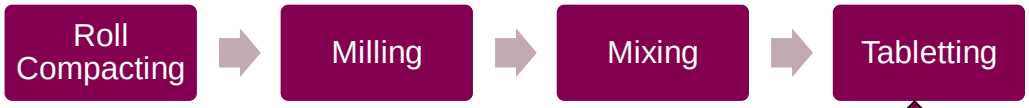
Results

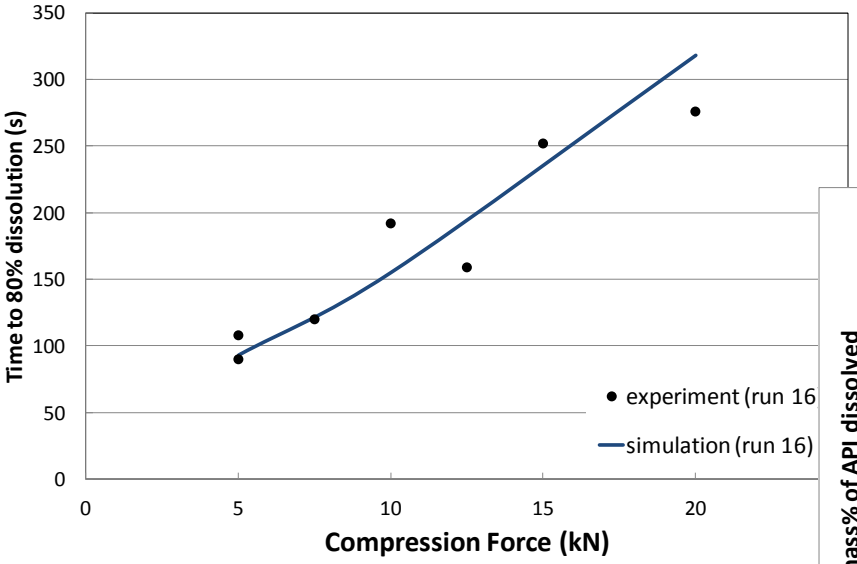
Roller Pressure and Tablet Tensile Strength

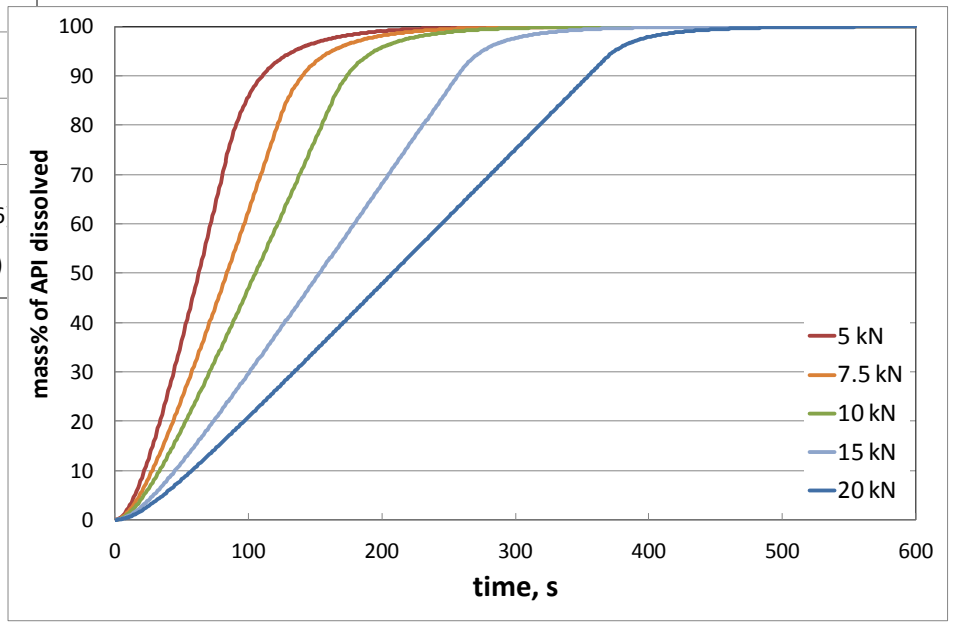


Experimental Validation

Tablet Compression Force and Dissolution





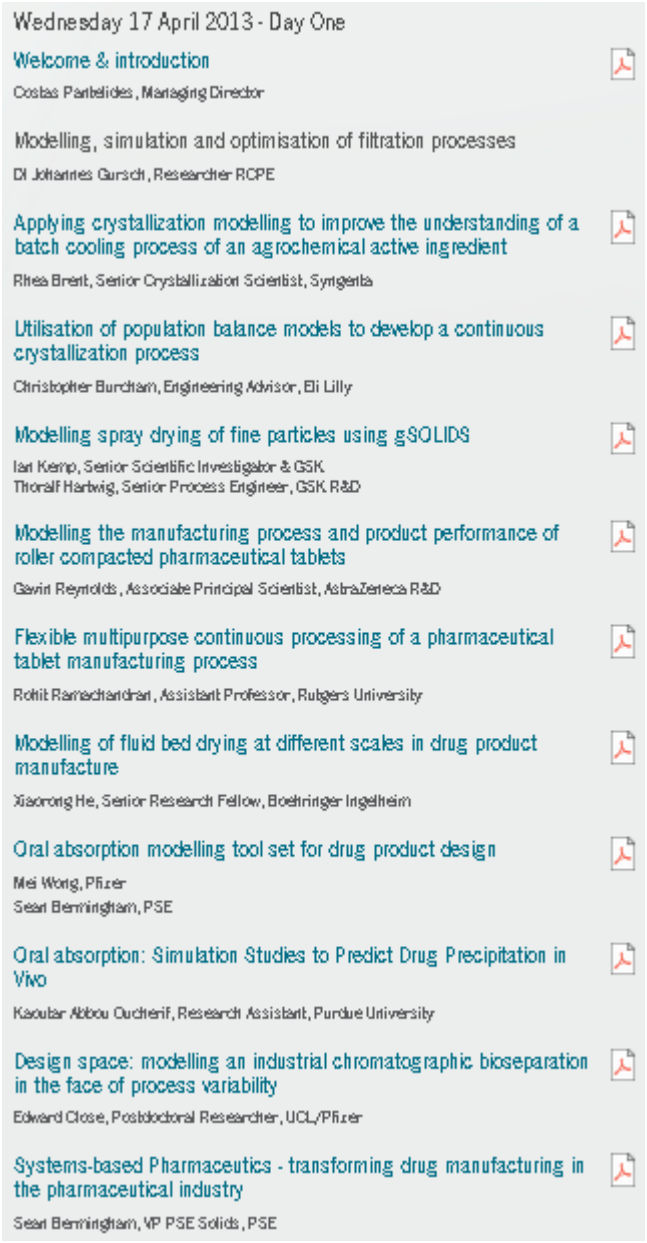


Conclusions

- **Demonstrated constructing a system model linking tablet manufacture to performance.**
- **Relatively simple unit operation models link together to provide qualitatively and in some cases quantitatively excellent predictions of effects and interactions between process parameters and product quality attributes.**
- **This provides an excellent basis for**
  - Improving product and process understanding
  - Education
  - Supporting process optimisation
  - Building control or RTRT models
  - Implementing improved unit operation or product performance models (e.g. in-vivo absorption)
  - Support a move towards continuous manufacture

All presentations are available for download to customers

http://www.psenterprise.com/events/uk/2013/apmf/presentations.html



Wednesday 17 April 2013 - Day One

Welcome & introduction

Costas Pantelides, Managing Director

Modelling, simulation and optimisation of filtration processes

Dr Johannes Gursch, Researcher RCPE

Applying crystallization modelling to improve the understanding of a batch cooling process of an agrochemical active ingredient

Rhea Brent, Senior Crystallization Scientist, Syngenta

Utilisation of population balance models to develop a continuous crystallization process

Christopher Burcham, Engineering Advisor, Eli Lilly

Modelling spray drying of fine particles using gSOLIDS

Ian Kemp, Senior Scientific Investigator & GSK
Thoralf Hartwig, Senior Process Engineer, GSK R&D

Modelling the manufacturing process and product performance of roller compacted pharmaceutical tablets

Gavin Reynolds, Associate Principal Scientist, AstraZeneca R&D

Flexible multipurpose continuous processing of a pharmaceutical tablet manufacturing process

Rohit Ramachandran, Assistant Professor, Rutgers University

Modelling of fluid bed drying at different scales in drug product manufacture

Xiaorong He, Senior Research Fellow, Boehringer Ingelheim

Oral absorption modelling tool set for drug product design

Mei Wong, Pfizer
Sean Bermingham, PSE

Oral absorption: Simulation Studies to Predict Drug Precipitation in Vivo

Kaoutar Abbou Oucherif, Research Assistant, Purdue University

Design space: modelling an industrial chromatographic bioseparation in the face of process variability

Edward Close, Postdoctoral Researcher, UCL/Pfizer

Systems-based Pharmaceutics - transforming drug manufacturing in the pharmaceutical industry

Sean Bermingham, VP PSE Solids, PSE

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Thank you!

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