Modelling of Fluid Bed Drying at Different Production Scales in Pharmaceutical Manufacture

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Boehringer Ingelheim

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Process Modeling for Pharmaceutical Industry

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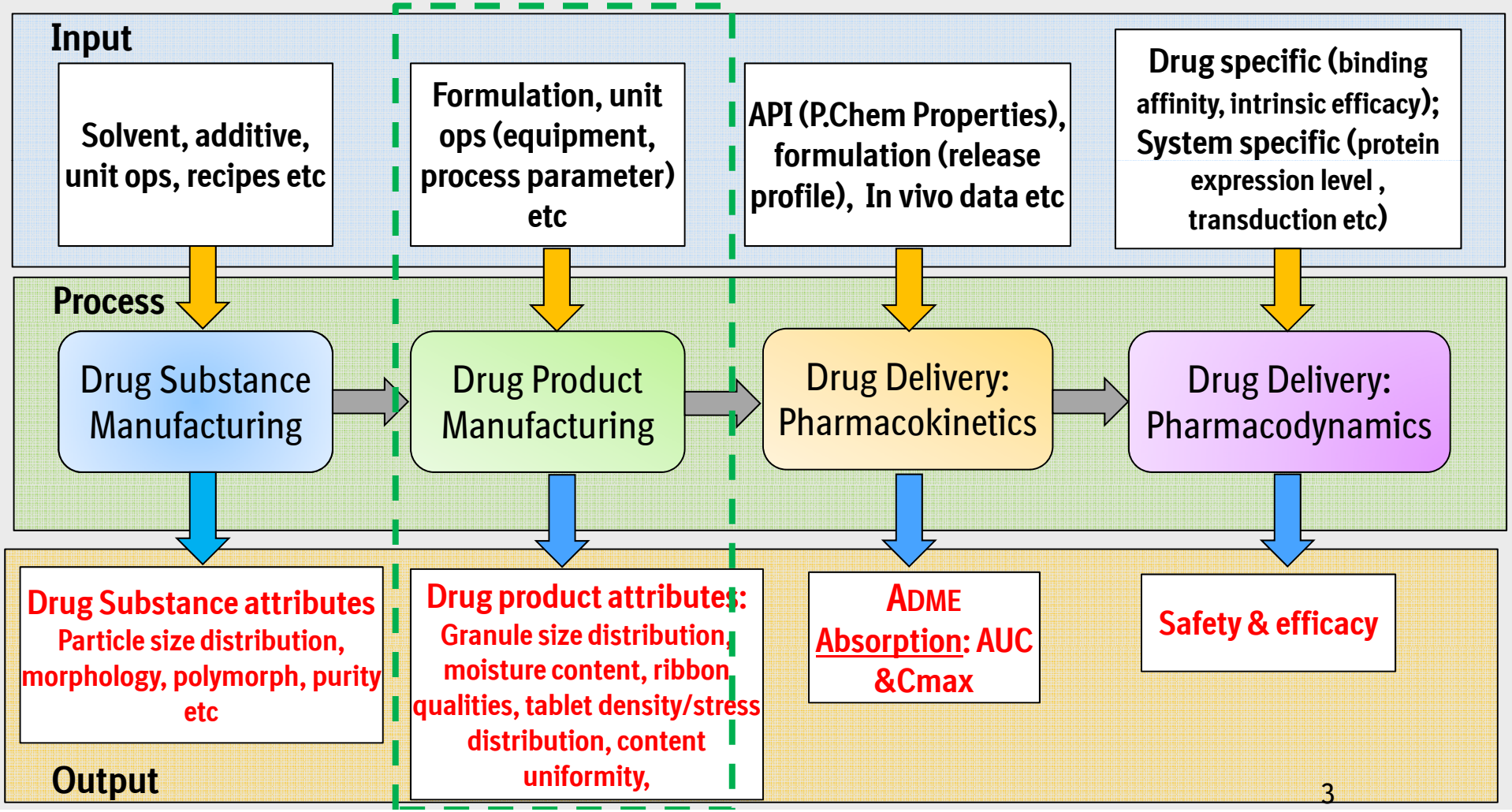
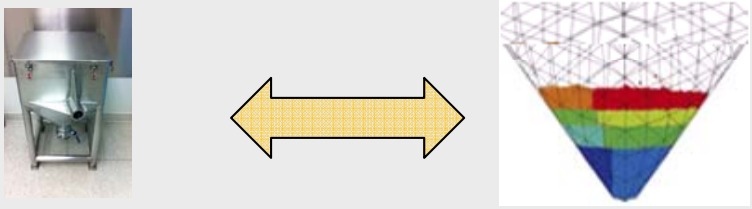
Process modeling – Use of physical, chemical, engineering, and/or biological principles coupled with computational methods to describe and simulate outcome of a process under a set of given conditions



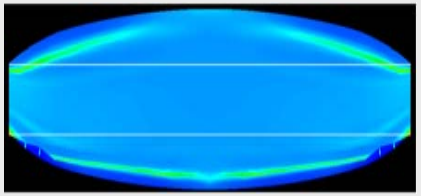
What Does Process Modeling Do?

- **Descriptive – Describe behaviors and track what happen during process**
  - **Example:** use of discrete element modeling to simulate powder mixing

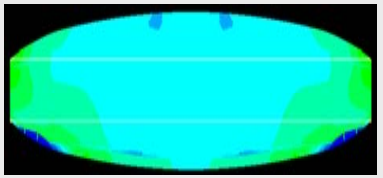


- **Prescriptive – Prescribe recipe or guidelines to achieve desired performance**
  - **Example:** Define target process parameters for fluid bed drying process

- **Explanatory – Explain or identify underlying rationale for phenomenon**
  - **Example:** use of compaction simulation (finite element modeling) to understand root cause for tablet capping

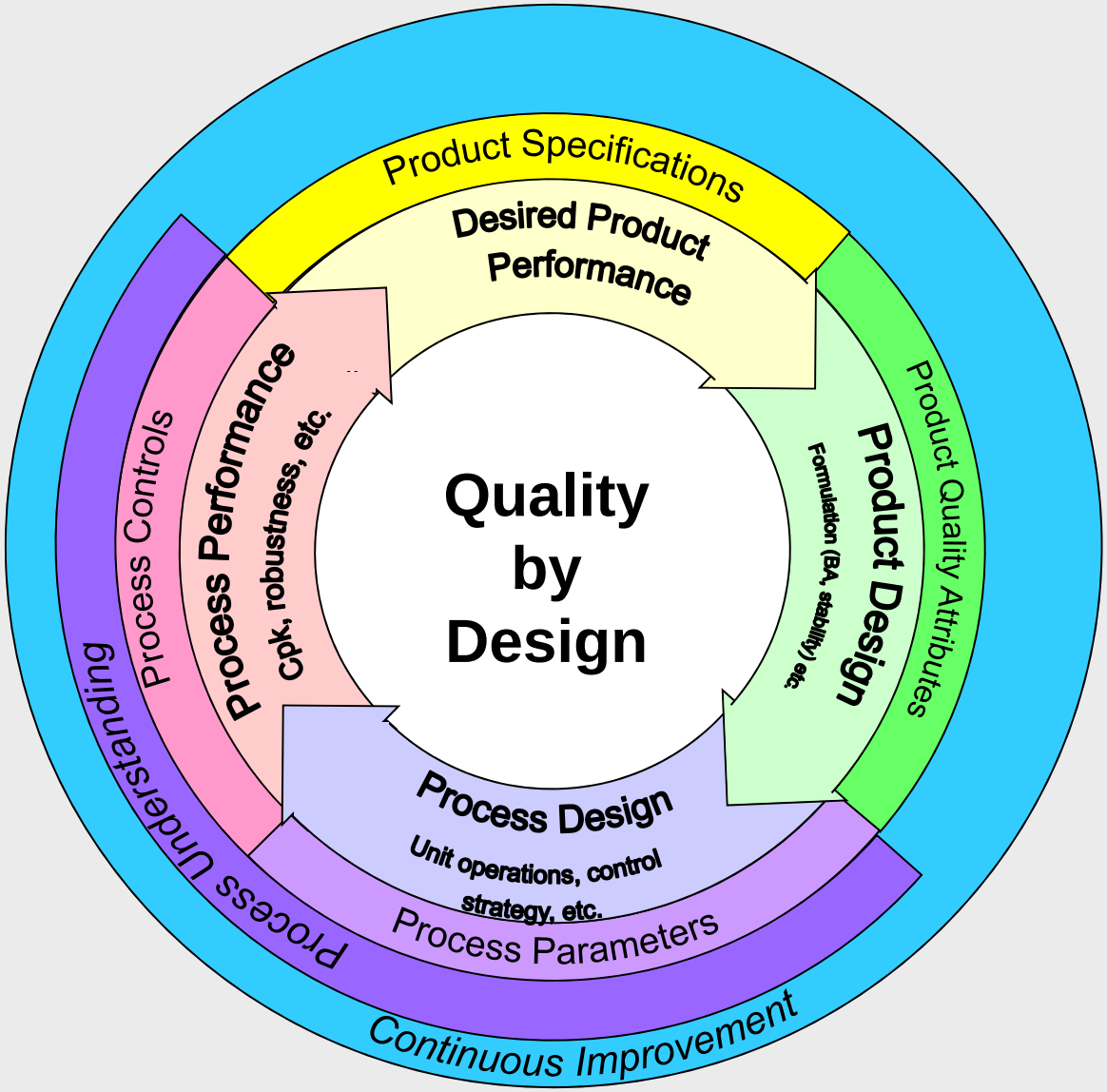


High pre-compression
Capping



No pre-compression
No capping

Regulatory Expectation for Drug Product Development



Acceptable ways to demonstrate product/ process understanding & control

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

- ICH Q8R2

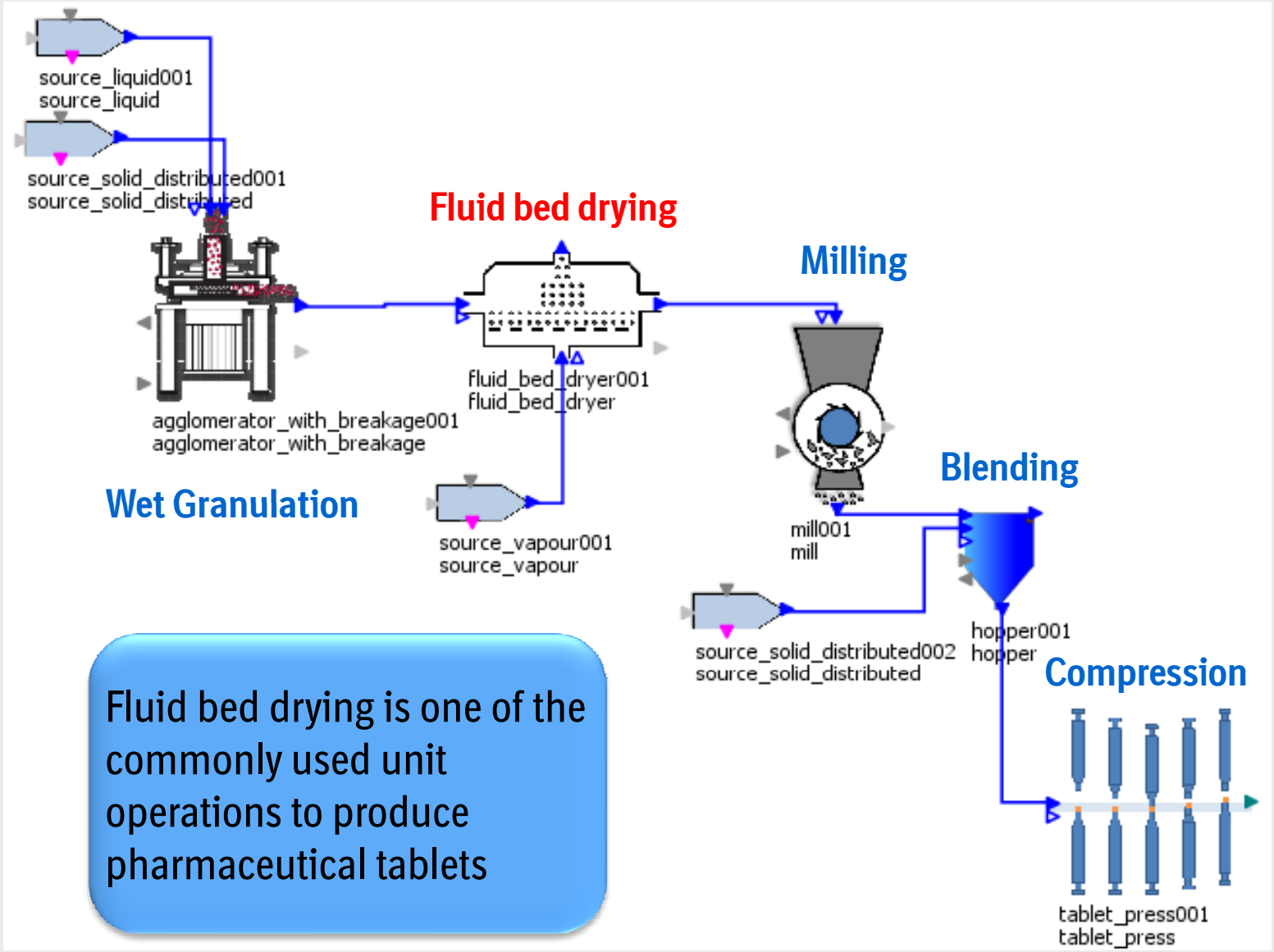
Rationale for Process Modeling

- **Perform targeted experiments**
  - Much fewer batches needed to develop and validate mechanism based model than traditional empirical approach

- **Develop better process understanding**
  - Able to extract significantly more information from lab/plant data

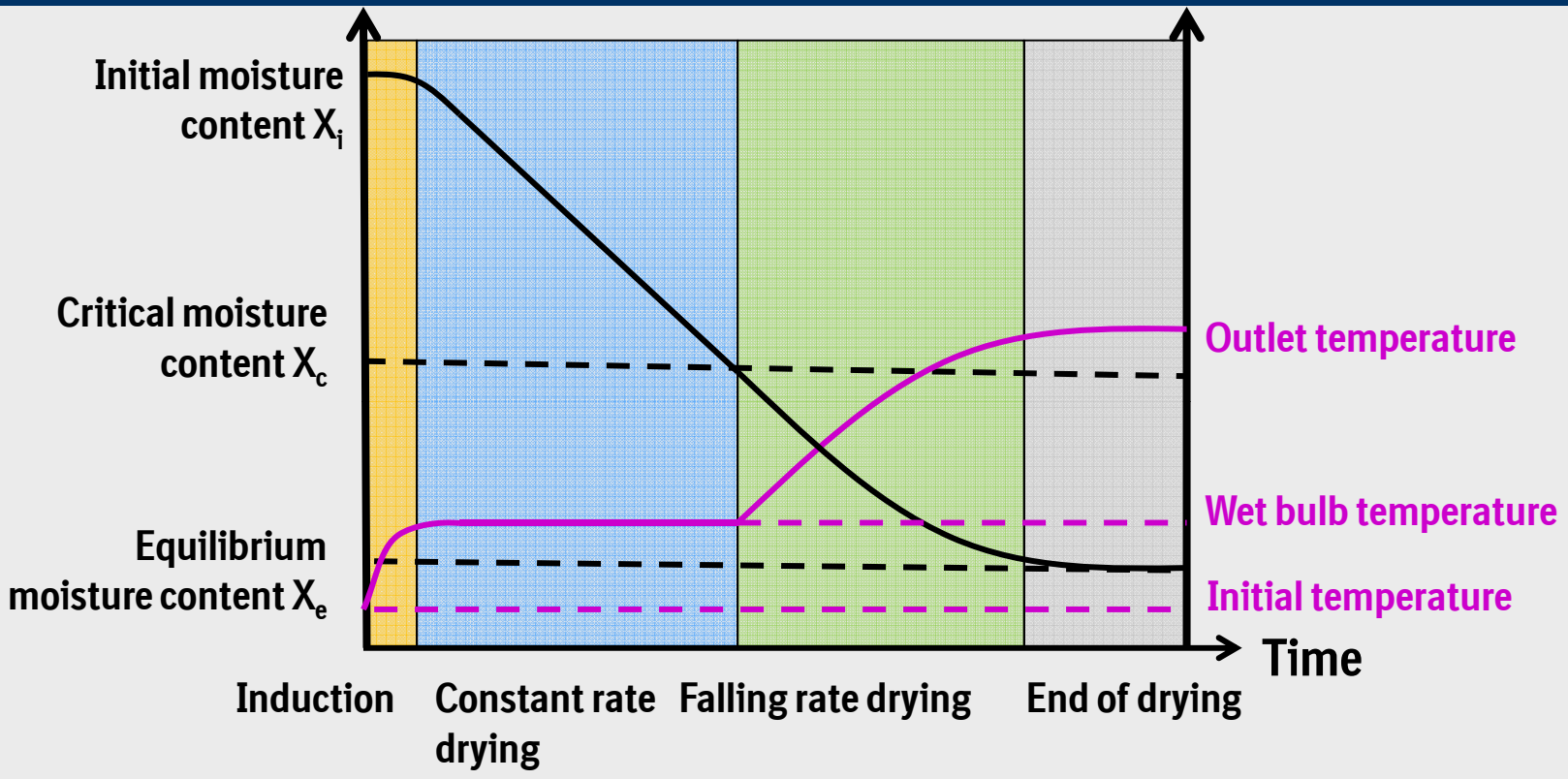
- **Reduce development cost & risk**
  - Predict process parameter space to achieved desired material attributes
  - Can extrapolate with lower risk than statistical DOE
  - Reduced experimental efforts saves API and development resources

Typical Process Flow for Pharmaceutical Tablet Production



Fluid bed drying is one of the commonly used unit operations to produce pharmaceutical tablets

Fluid Bed Drying Principles



Heat transfer to solid surface and vapor diffusion are rate limiting

Moisture diffusion from inside the granules to surface is rate limiting

Modelling Fluid Bed Drying in gSOLIDS

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Model implemented based on literature model

- J Burgschweiger, E Tsotsas (2002) Experimental investigation and modelling of continuous fluidized bed drying under steady-state and dynamic conditions. Chem. Eng. Sci. 57, 5021 – 5038

Key assumptions

- Bed and vapour are assumed to be perfectly mixed
  - Assumption will hold for smaller scales, for larger scales particle RTD, gas variations need to be considered, this extension is in progress
- Drying rate in falling rate regime is governed by either user specified drying curve or universal drying curve
- Elutriation is calculated based on Geldart correlations
  - Elutriation can be neglected if all fines are recirculated to bed

Transfer Correlations in gSOLIDS Model

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Different transfer correlations are available

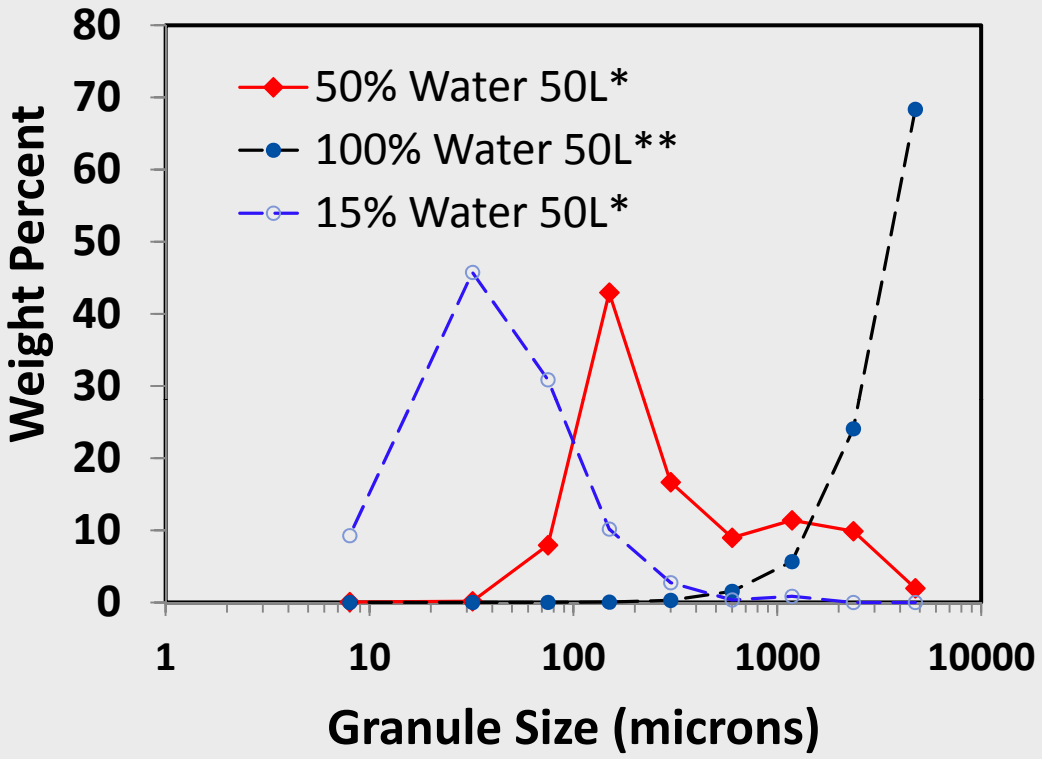
- Burgschweiger & Tsotsas (2002)
  - Takes into consideration difference between “apparent” and “real” Sherwood/Nusselt numbers
  - “Apparent” Sherwood/Nusselt number determined only by laws of momentum and mass/heat transfer around a single particle
  - “Real” Sherwood/Nusselt number also considers influence of back mixing of suspension gas
- Rhodes (1998)
  - Valid for particle Reynolds number < 50
- Internal limitation
  - Transfer rates limited by diffusion from inside the particle to particle surface
  - Particularly applicable for large particles

Objectives

- Model validation
  - Placebo formulation (lab scale – Glatt GPCG 5)
  - Product A (pilot & full scale – Glatt GPCG 30 & 60)
- Process understanding
  - Identify critical process parameters which may impact process outcome

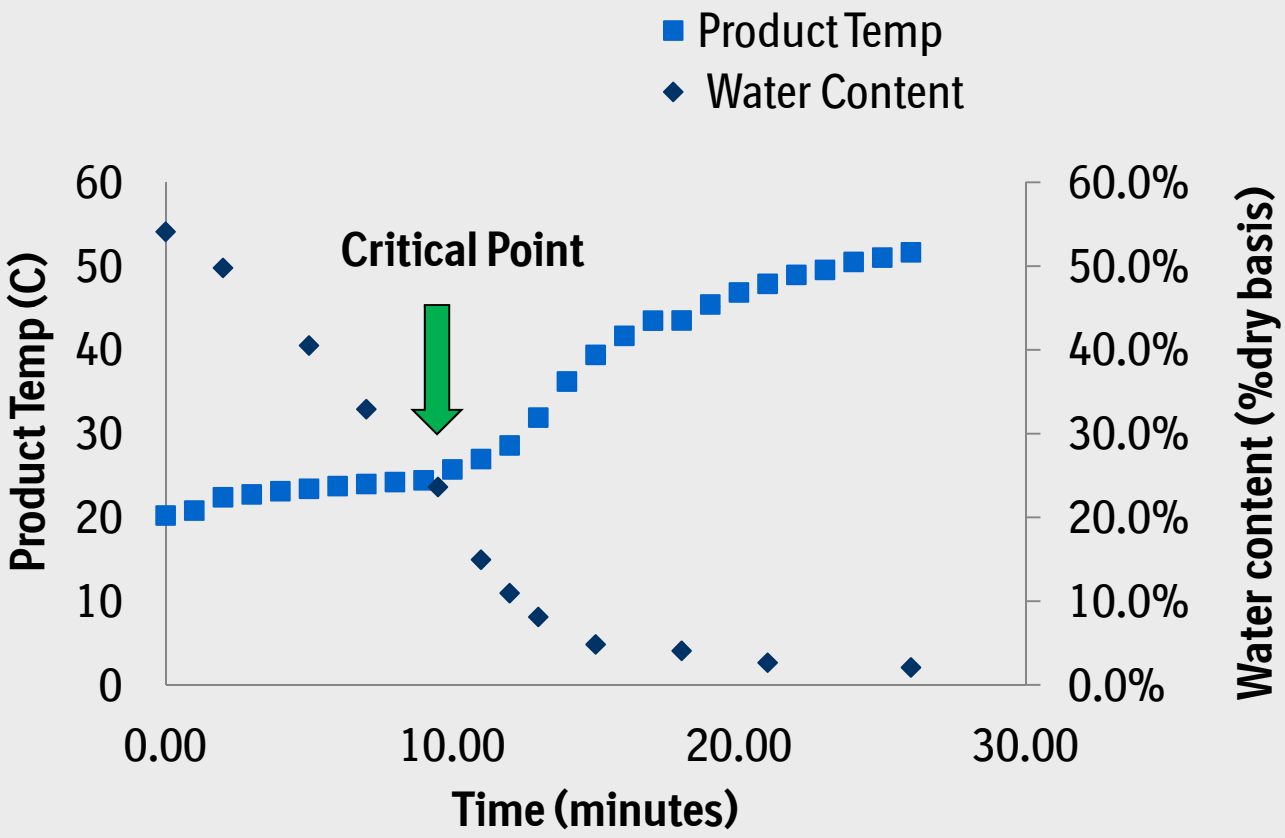
Case Study 1 – Lab Scale Fluid Bed Drying

- Standard formulation for high shear wet granulation (HSWG) (microcrystalline cellulose, lactose, PVP K30)
- HSWG, followed by fluid bed drying (GPCG 5 fluid bed dryer 3 kg batch size)

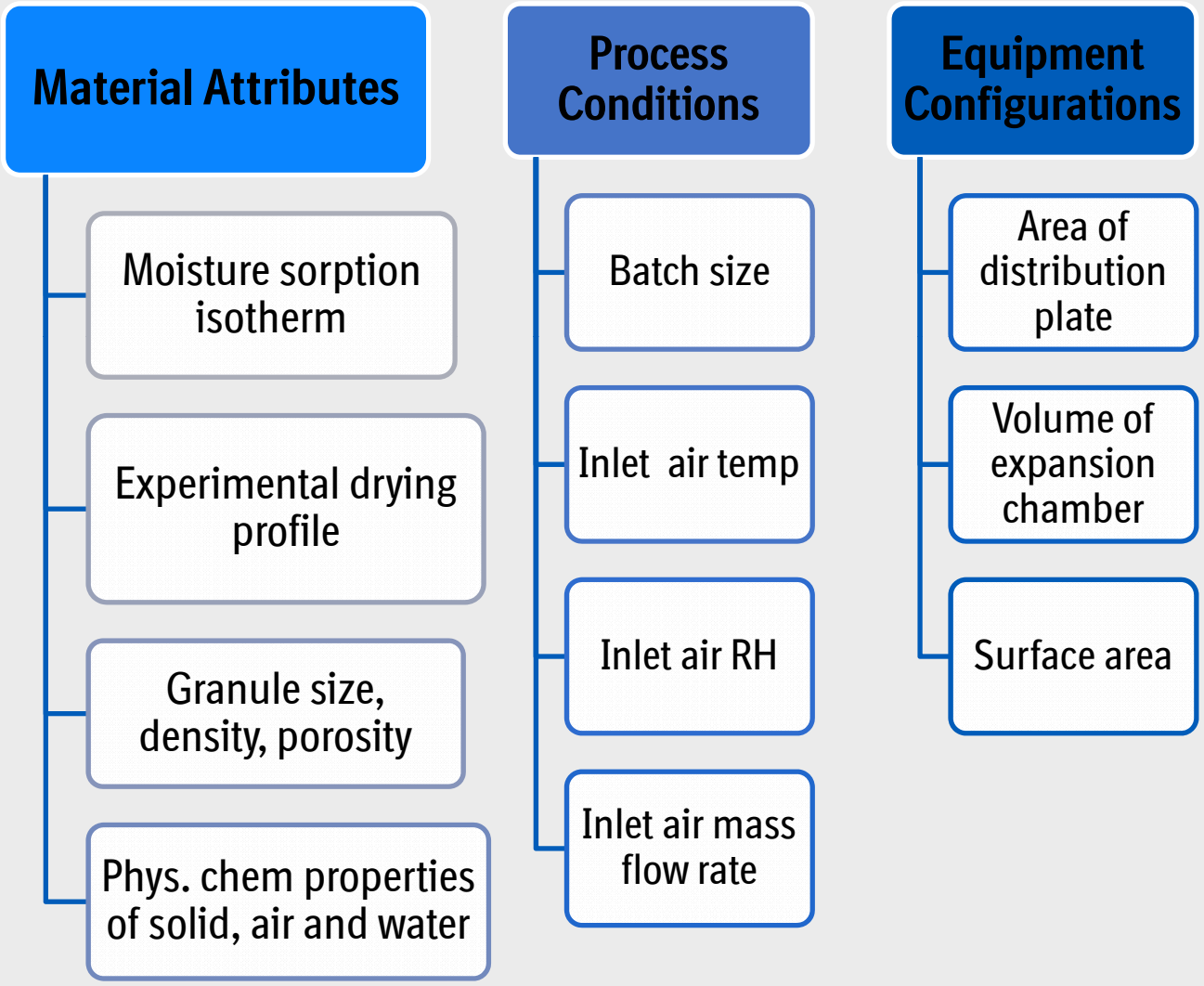


	10% water	50% water	100% water
Appearance	Fluffy powder	Granules	Large Snow balls
D50 (um)	~80	~600	~4000

Typical Drying Profile of the Placebo Formulation

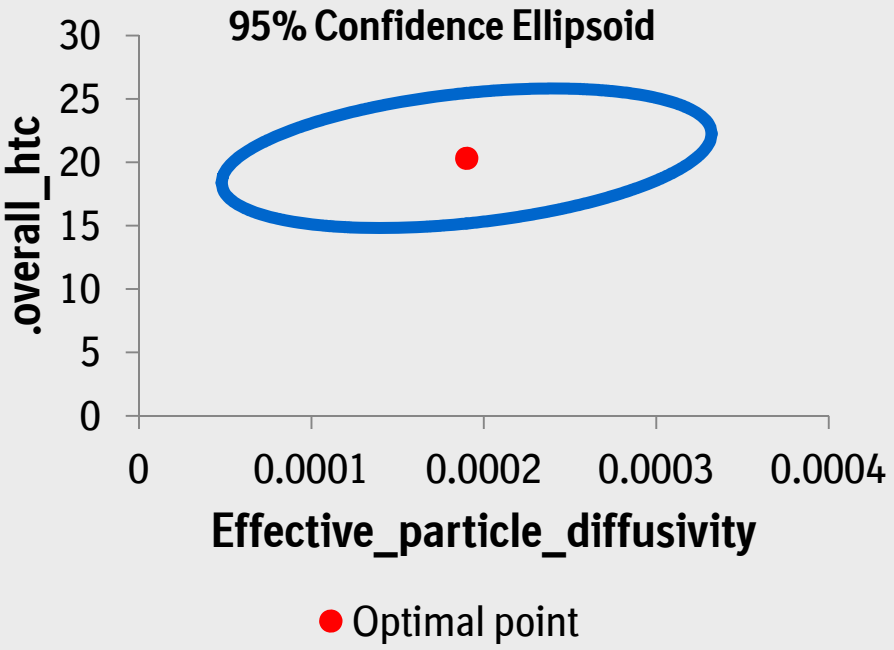


Experimental Input for Simulation

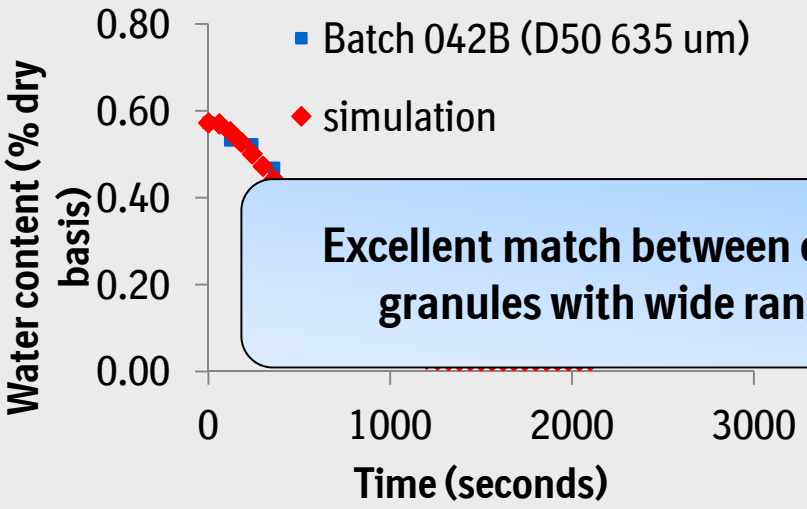


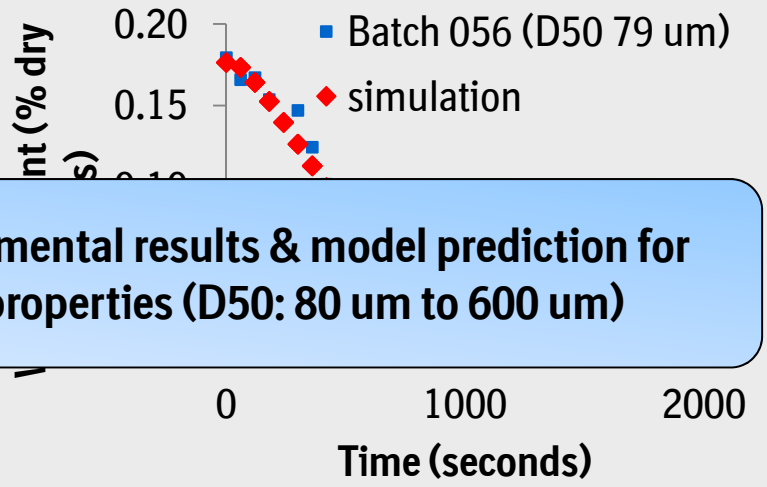
Parameter Estimation

- Parameter estimation based on drying profile of one experimental batch (Batch 052, D50 of 500 um):
  - Combined resistance: particle diffusivity
  - Overall heat transfer coefficient
- Used the model to predict drying profiles for 4 batches

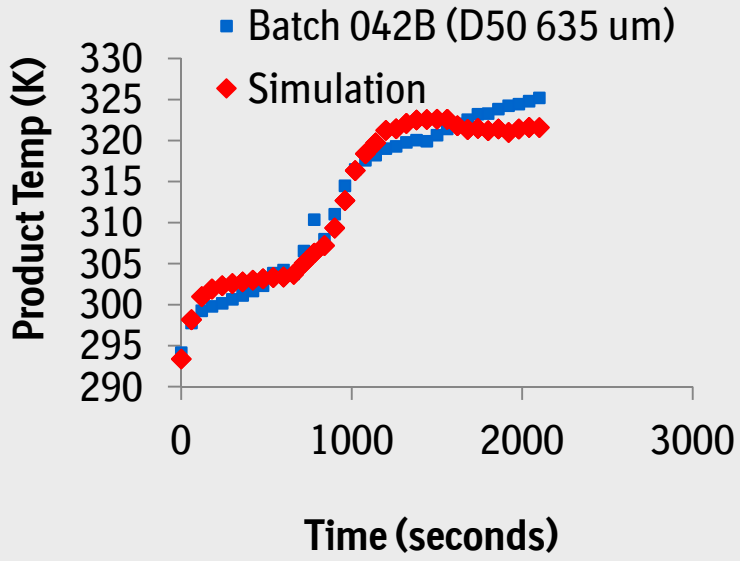


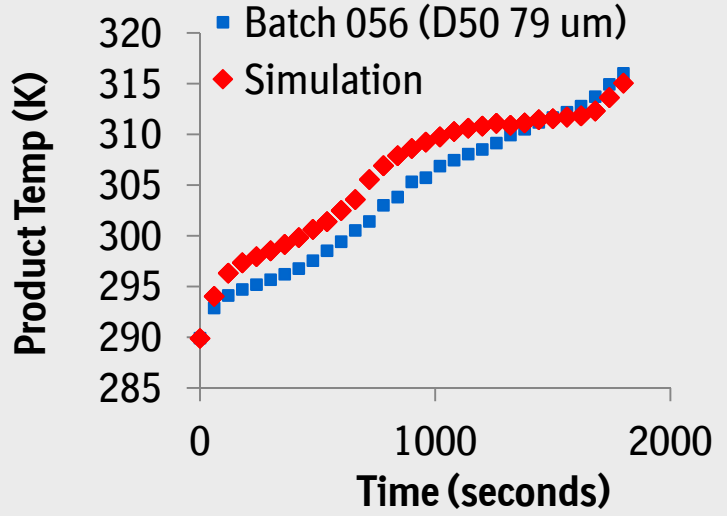
Comparison of Simulation vs Experimental Results
(Placebo granules with D 50 ranging from D50 80 um to 635um)



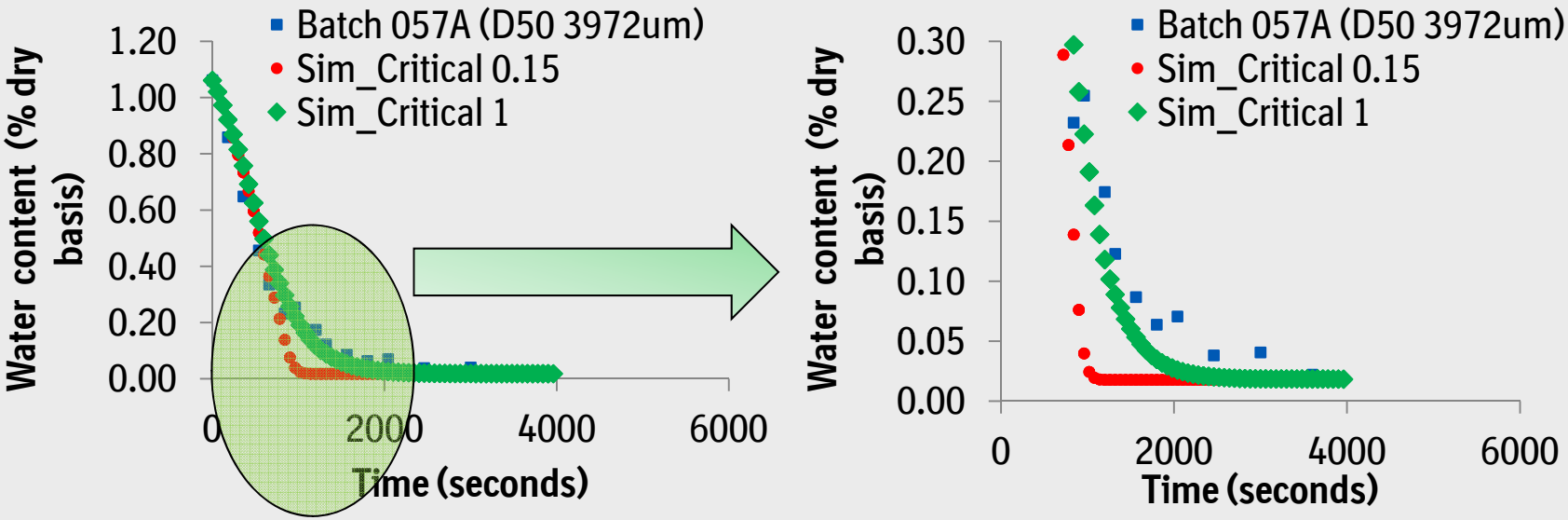


Excellent match between experimental results & model prediction for granules with wide range of properties (D50: 80 um to 600 um)





Validation of Fluid Bed Drying Model – Lab Scale (Placebo granules with D50 of 4000 um)



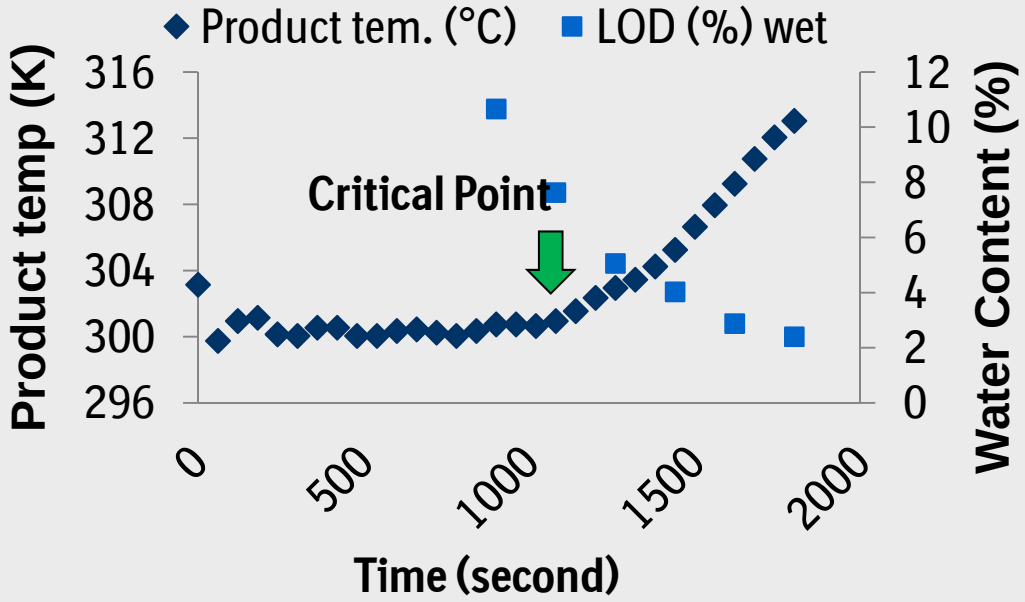
- Model over predict the drying rate of snow ball granules which is saturated with 100% of water.
- Prediction accuracy significantly improved after increasing the critical moisture content from 15% to 100%

Case Study 2 – Pilot & Full Scale Fluid Bed Drying of Product A

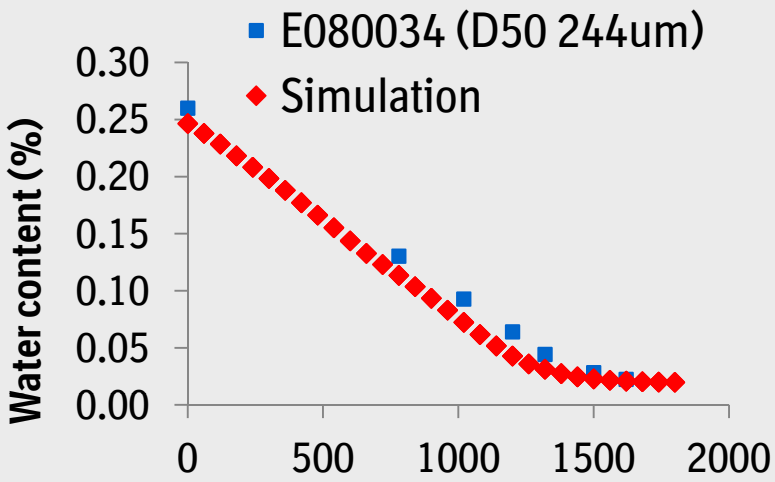
- **Product A**
  - 2 strengths: 2.5 mg & 50 mg granulation
  - High shear wet granulation followed by fluid bed drying
  - Equipment for fluid bed drying:
    - Glatt GPCG 30 (pilot scale)
    - Glatt GPCG 60 (full scale)

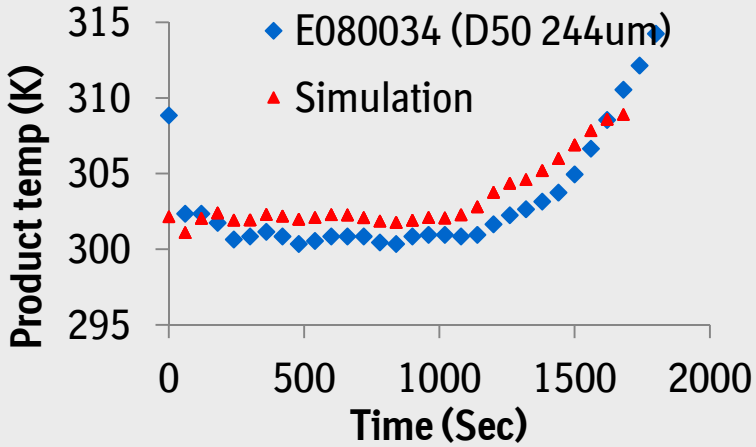
- **Parameter estimation**
  - Particle diffusivity
  - Overall heat transfer coeff.
  - Experimental input
    - 50 mg: 2 batches
    - 2.5 mg: 1 batch

- **Model Validation**
  - Use the model to predict process outcome of 3 batches

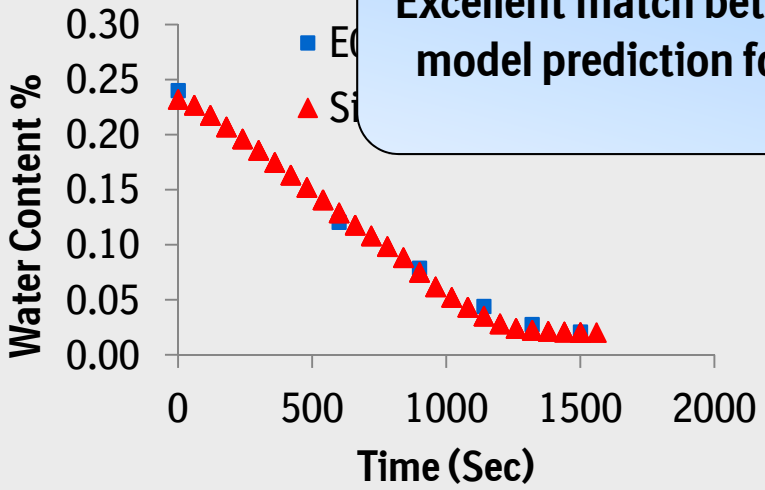


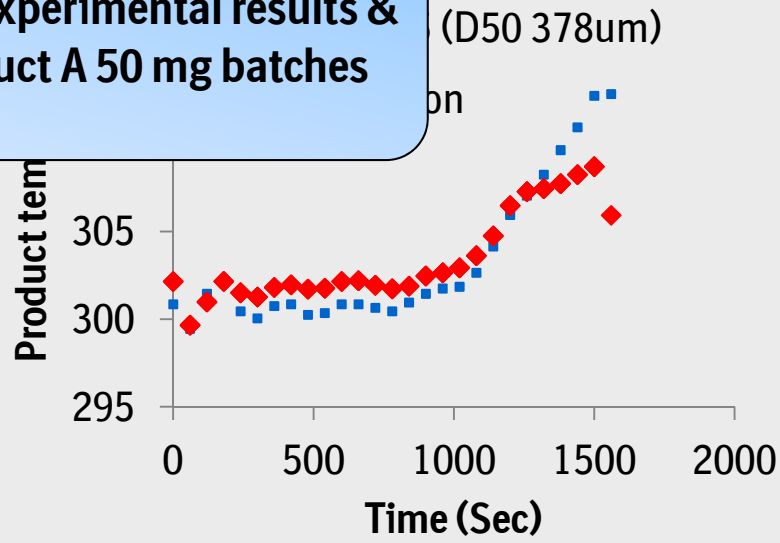
Model validation – Granule Water Content & Product Temp (50 mg Granulation Pilot Scale Glatt GPCG 30)



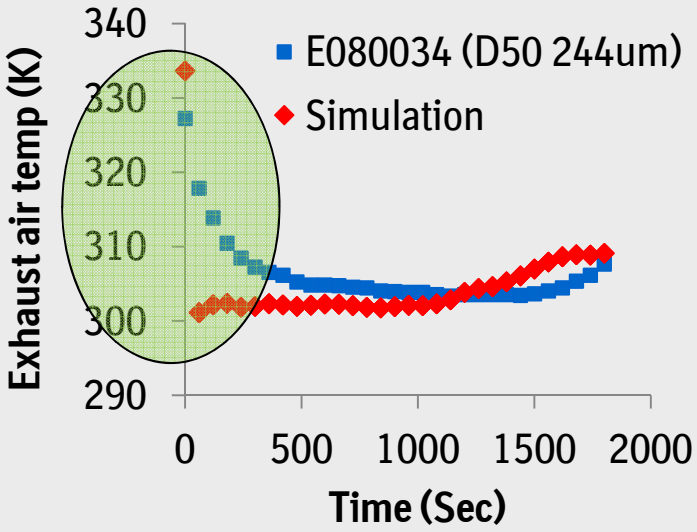


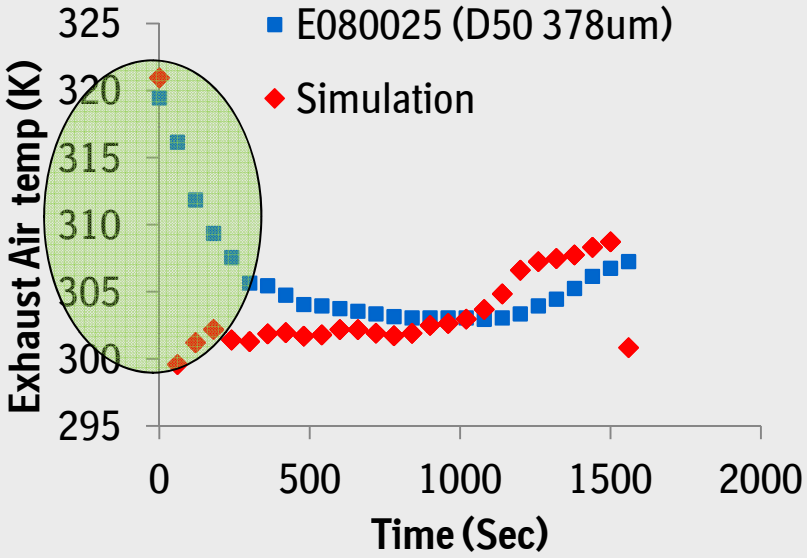
Excellent match between experimental results & model prediction for product A 50 mg batches





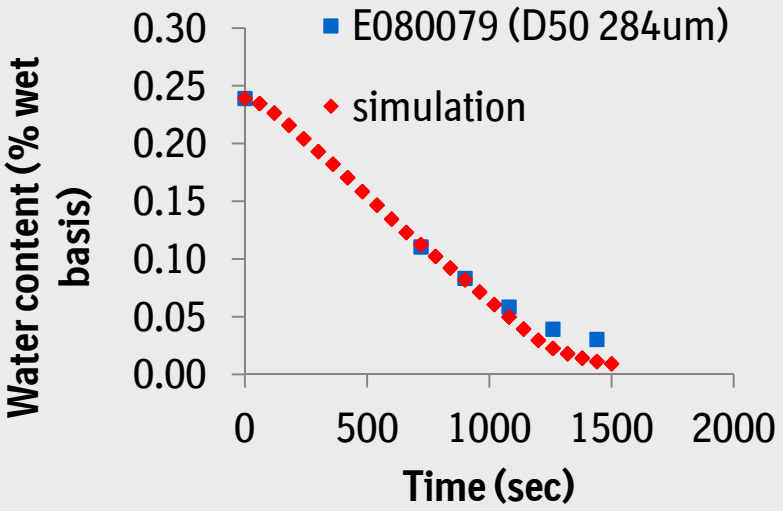
Model Validation - Exhaust Air Temperature (50 mg Granulation Pilot Scale Glatt GPCG 30)

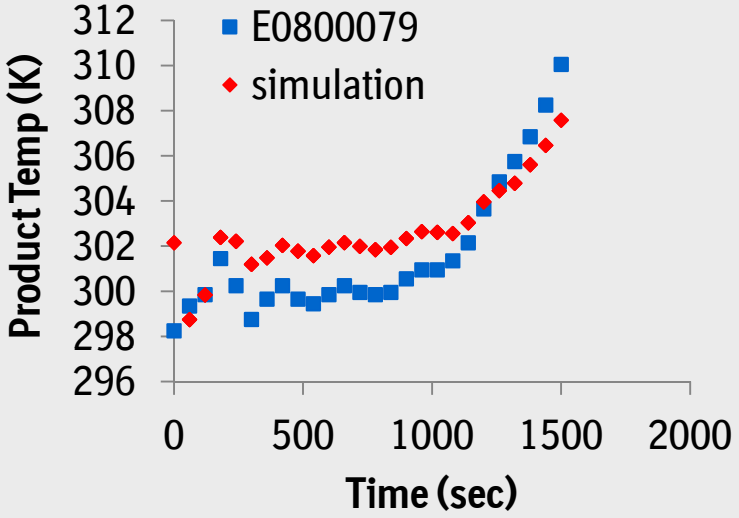


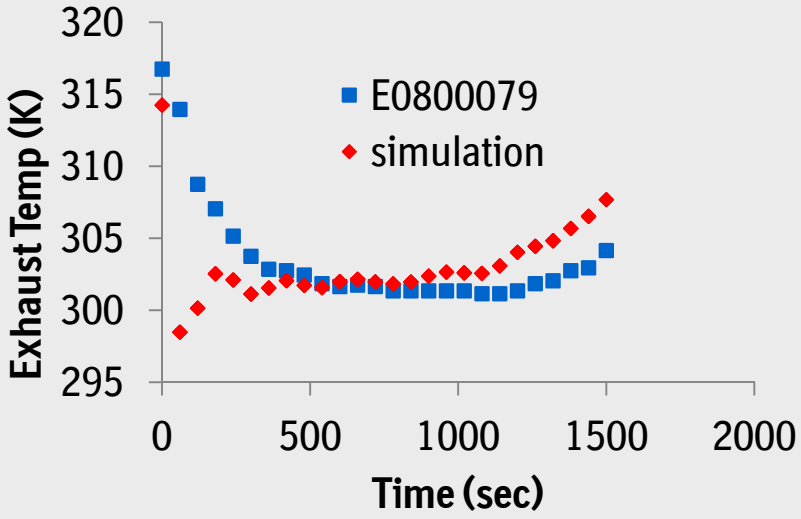


- Initial discrepancy in exhaust air temperature between experimental values and model prediction may indicate that the assumption of "well mixed system" may not be accurate for the beginning of batch manufacturing.
- But exhaust air temperature is less of a concern for pharmaceutical manufacturing

Comparison of Simulation vs Experimental Outcome (2.5 mg Granulation Pilot Scale GPCG 30)

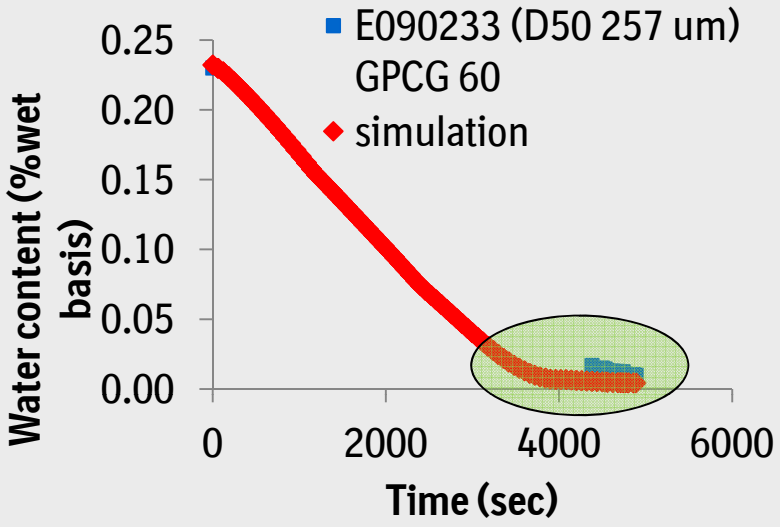


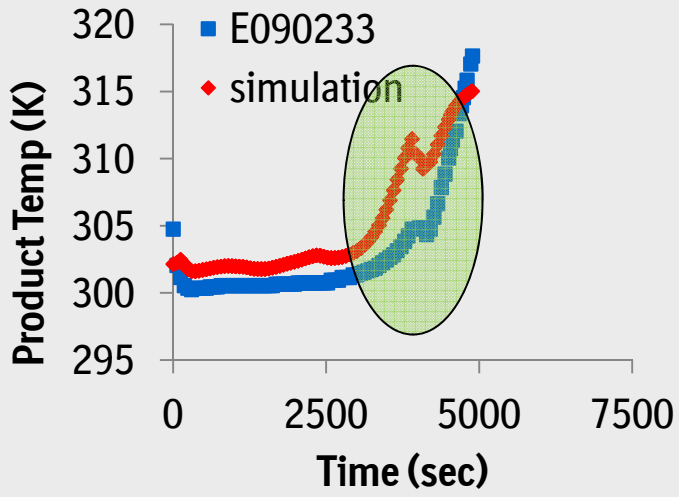


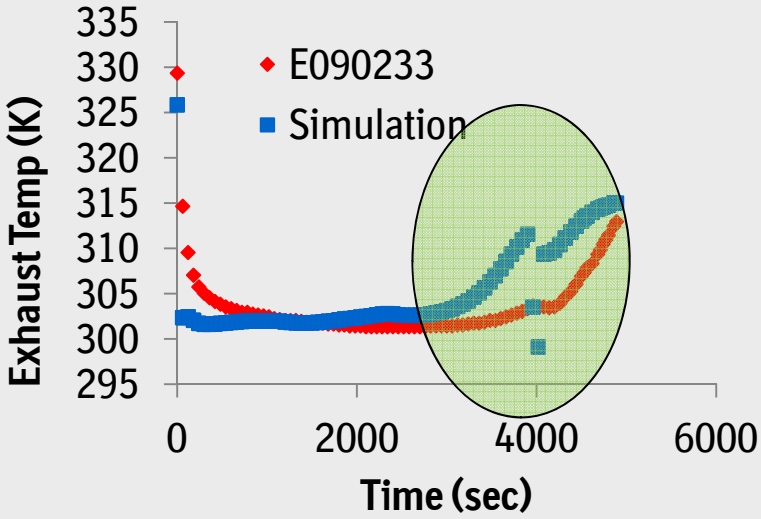


Excellent match between experimental results & model prediction for product A 2.5 mg batch

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

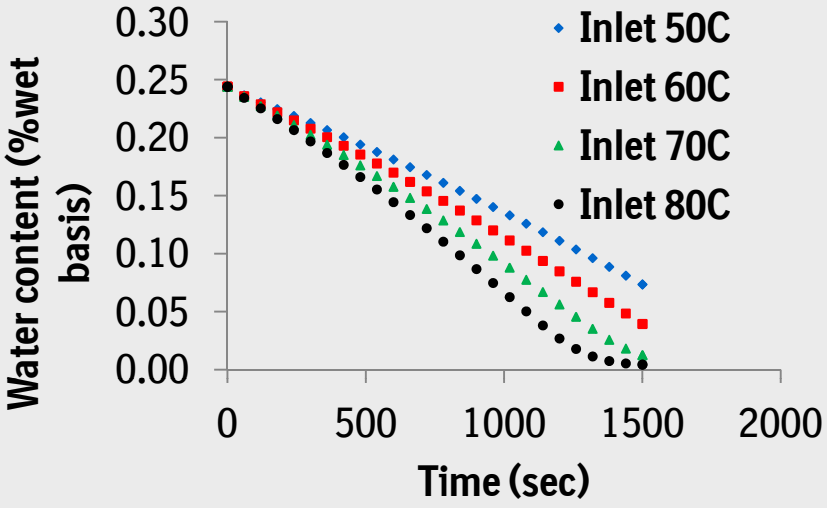


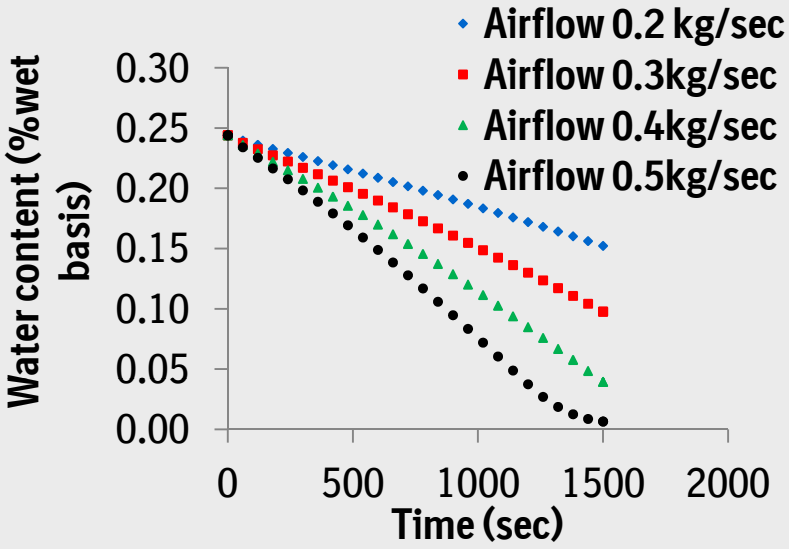


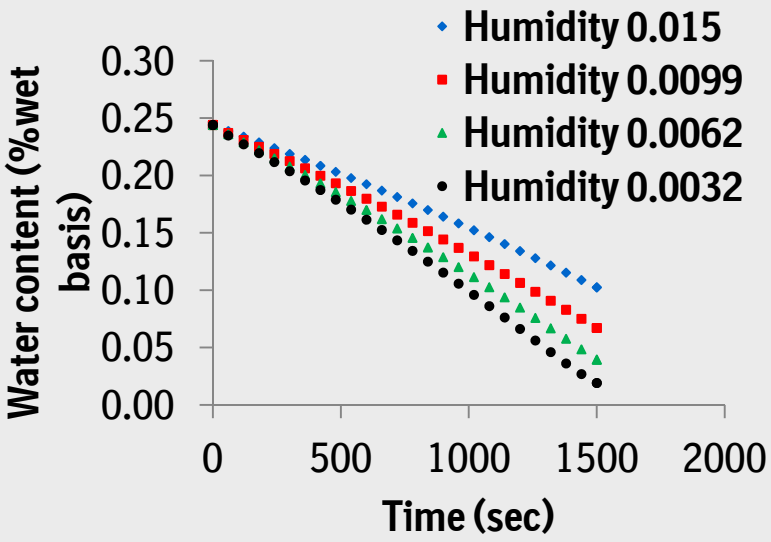


- More discrepancy between model prediction & experimental values for full scale than the lab and pilot scale
- The assumption of "well mixed system" needs to be re-evaluated for large scale fluid bed dryer

Process Parameter Sensitivity Analysis (Product A 2.5 mg granulation GPCG 30)







- Sensitivity analysis reveled the importance of process parameter on drying profile.
- Process modeling is a valuable tool to provide process understanding with much reduced experimental efforts

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