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An experimental and simulation study of fluid bed granulation process using mechanistic modeling approach

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Content

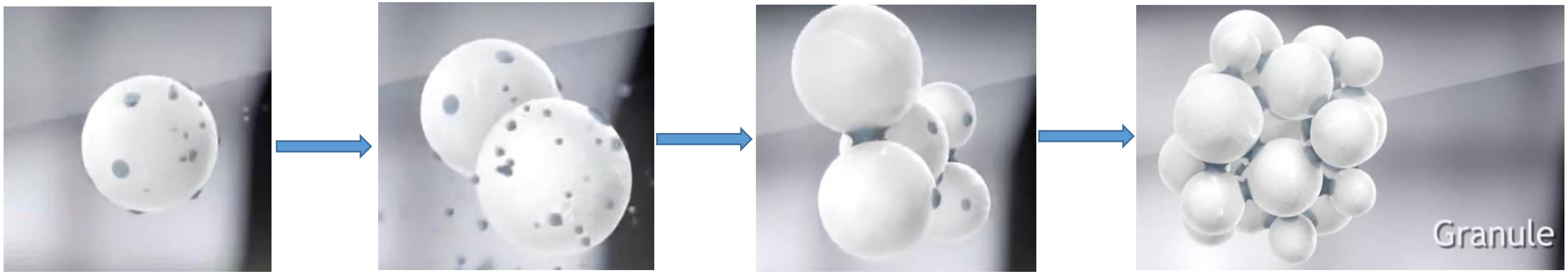
- Motivation
- Introduction of fluid bed granulation process
- Overview of experiment performed for pilot scale FBG process
- FBG simulation model
- Results and discussion
- Prediction of test experimental batch
- Summary
- Conclusions

Motivation

- Validation and development of mechanistic process models for fluid bed granulation (FBG) process via the flowsheet modelling in gSOLIDS framework
- Generalizing the developed FBG model through correlating the model parameters to the wide range of operating conditions, and various product formulations

What is granulation ?

Granulation is defined as a particle size enlargement process whereby small powder particles are gathered into larger, permanent structures in which the original particles can be distinguished



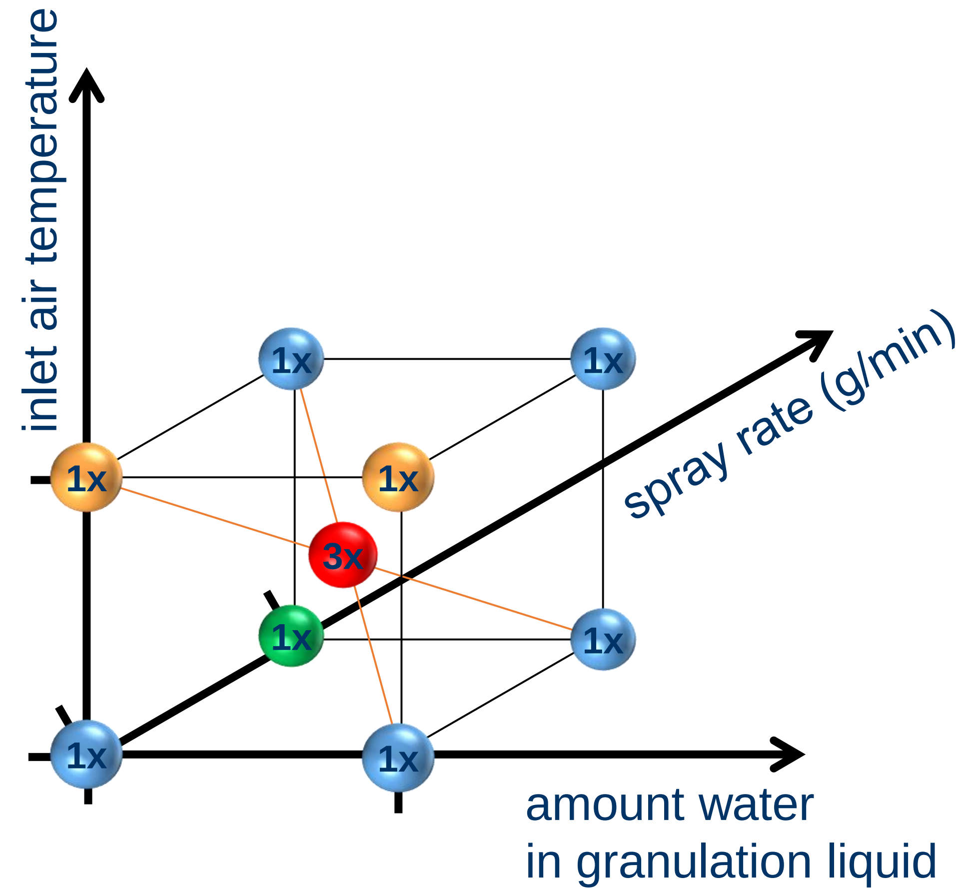
Why we prepare granules when we have powders ?

- To improve the flow characteristics of powders
- To densify the material
- To reduce dust
- To improve the compressibility of powders
- To increase the uniformity of drug distribution in the product
- To improve the appearance of the product

Fluid bed granulation process

Ref: Youtube

Design of experiments for FBG process



Number	batches
1	E140001 (center)
2	E140002 (wet)
3	E140003
4	E140004
5	E140005
6	E140006
7	E140007 (center)
8	E140008 (center)
9	E140009
10	E140010 (dry)
11	E140011 (dry)

VP02 formulation information

- Scale – Pilot scale
- Equipment – CPCG 30
- Batch size – 30 kg
- Materials used:
- Lactose
- MCC
- PVP (binder)

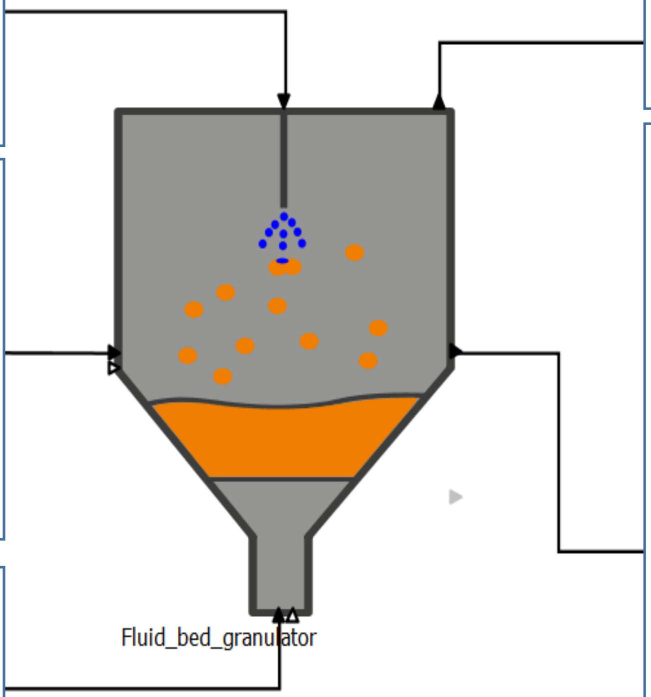
FBG simulation model in gSOLIDS

Input conditions for gSOLIDS simulation of FBG

- **<u>Initial spray Conditions</u> :**
  - Mass flow rate
  - Mass fraction water and binder
  - Temperature
  - Pressure

- **<u>Initial solid conditions:</u>**
  - Mass of material
  - Mass fraction of solid and water
  - Temperature
  - Bulk density
  - Particle size distribution

- **<u>Initial air conditions:</u>**
  - Mass flow rate
  - Mass fraction of air and water
  - Temperature
  - Pressure



- **<u>Equipment information</u>**
  - Volume of granulator
  - Heat transfer area
  - Ambient temperature

- **<u>FBG model :</u>**

Agglomeration model: Rajniak (2016)
- Parameter β_0 = PE
- Parameter s = PE
- Parameter x* = PE
- Parameter *d** = theoretically calculated

Drying model : Rhodes (1998)
- Parameter x_{cm} = PE
- Parameter h_w = PE

Spray model : Evaporation of spray
- Parameter K= PE

Simulation model

FBG model and its parameters :

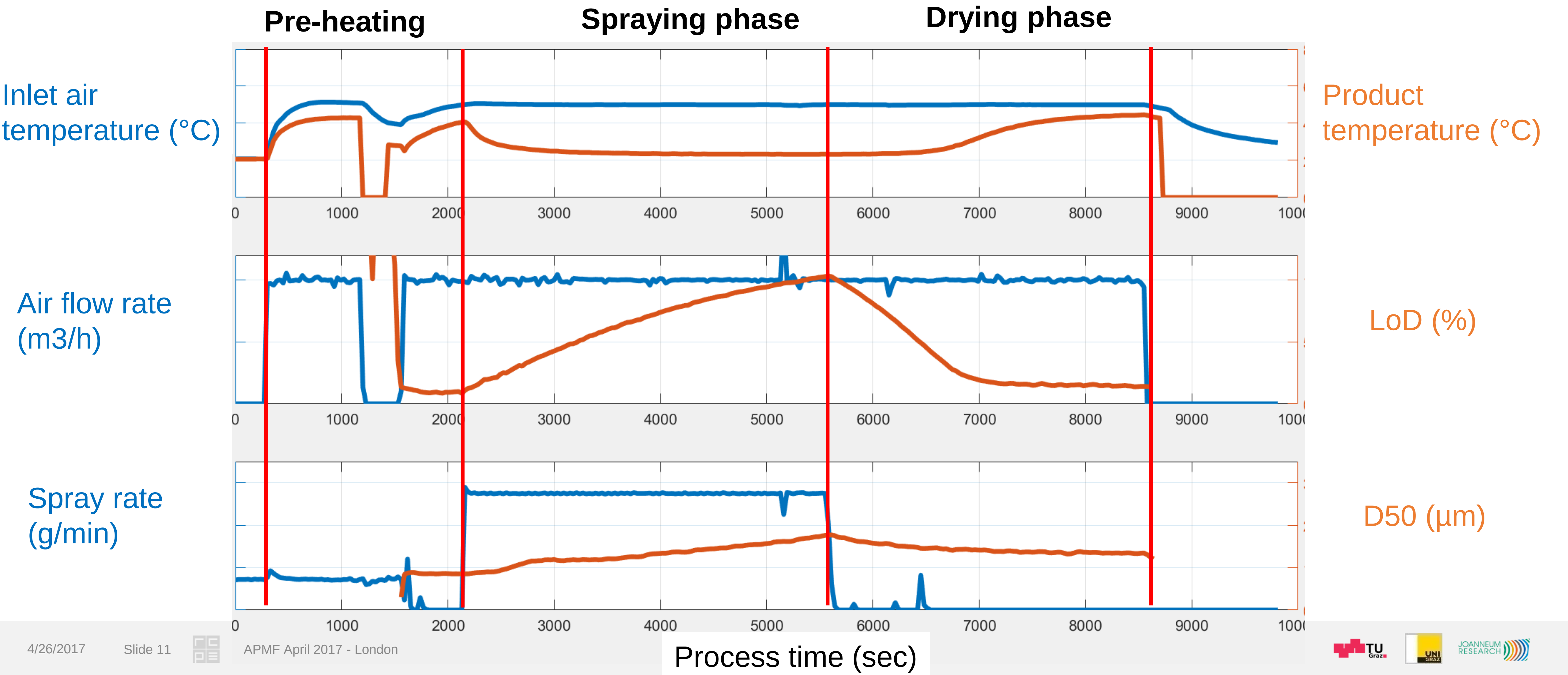
1. Agglomeration model: Rajniak (2016)
Parameters:
- Agglomeration constant β_0 (1/s)
- Critical reduced diameter *d** (µm)
- Scale factor s (µm)
- Critical binder to solid ratio x* (-)

2. Drying model : Rhodes (1998)
Parameters:
- Critical moisture content x_{cm} (kg/kg)
- Heat transfer coefficient h_w (W/m^2K)

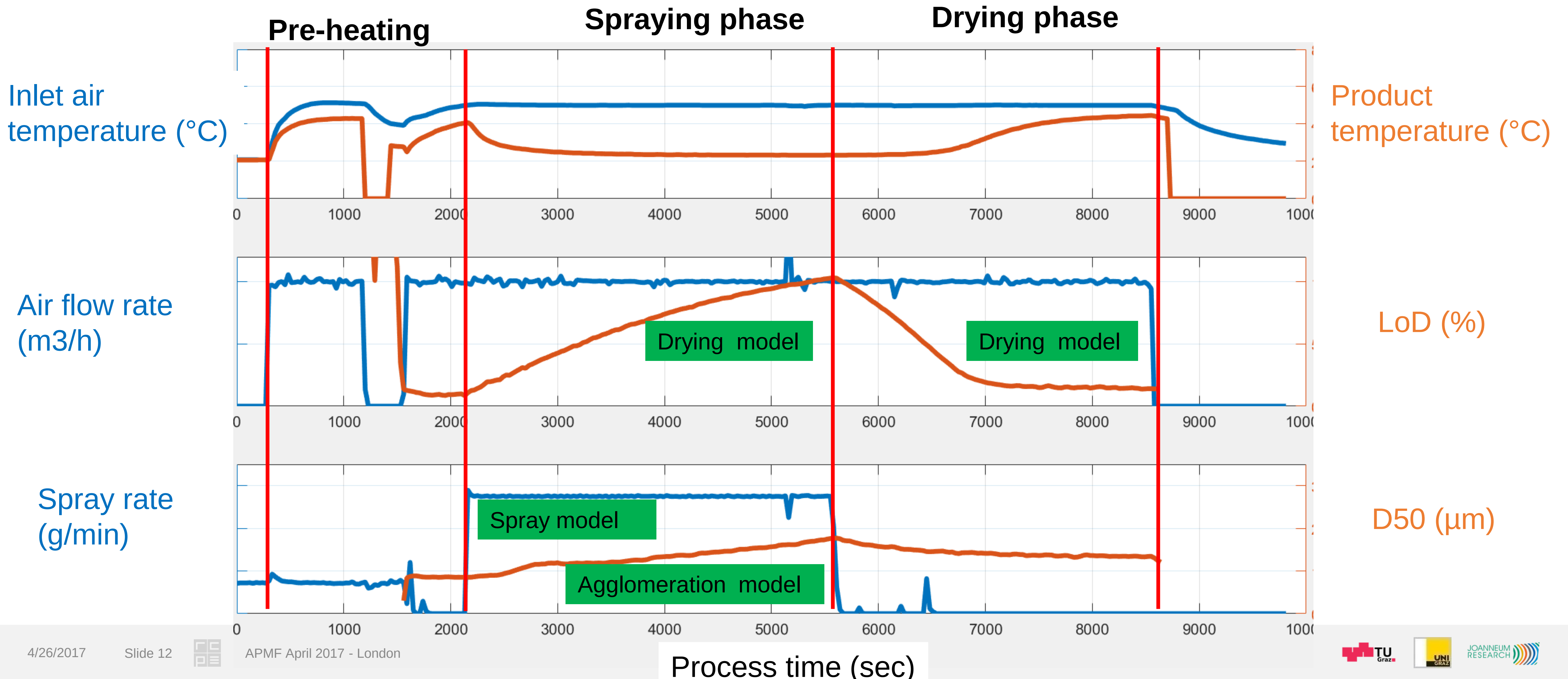
3. Spray model : Evaporation of spray
Parameter:
- Evaporation rate constant K (-)

- $\boldsymbol{\beta_0}$ = Agglomeration constant (higher = faster particle growth)
- ***d**** = Critical diameter (larger = larger final granule)
- **s** = Scaling factor (smaller = faster growth)
- **x*** = Critical binder/solid ratio (smaller = dryer the coating)
  - It is function of binder concentration.
  - It defines the stage when wetting regime transfers into agglomeration regime.
- $\mathbf{x_{cm}}$ = This is the moisture content at which the drying regime changes from constant rate to falling rate.
- $\mathbf{h_w}$ **=** It defines the heat loss from system to environment through geometry wall.
- **K =** It defines the rate at which spray droplet get evaporate from free falling droplet.

Different phases during granulation process and models applicable



Different phases during granulation process and models applicable

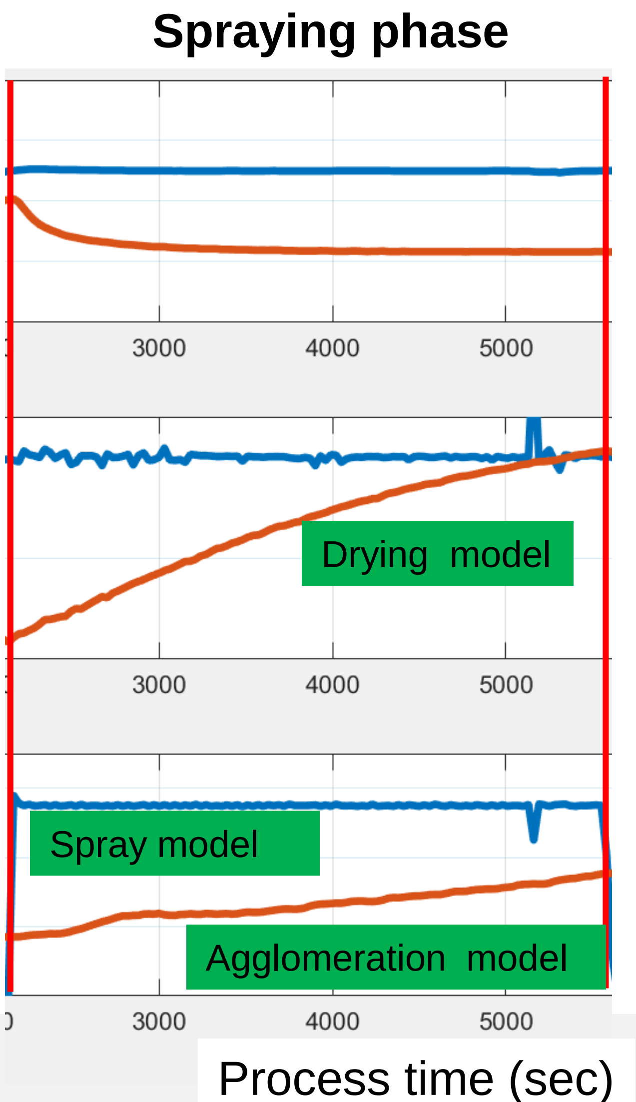


gSOLIDS simulation for spraying phase

Inlet air temperature (°C)

Air flow rate (m3/h)

Spray rate (g/min)



Product temperature (°C)

LoD (%)

D50 (µm)

Hypothesis

- Heat transfer coefficient h_w (from the wall to environment) can be set as constant due to limited range of temperature difference (inlet to ambience air temperature).
- Critical reduced diameter *d** can be calculated analytically.
- Agglomeration constant β_0 for all batches can be fixed due to constant volumetric flow rate of gas.

Methodology for simulation

Estimation of all model parameters for all batches within gSOLIDS

↓

gSOLIDS simulation

↓

Comparison of D50, LoD and Tp with the corresponding values in the experiments

↓

Obtaining the global value for parameters β_0, and h_w and calculation of d^*

↓

gSOLIDS simulation

↓

Comparison of D50, LoD and Tp with the corresponding values in the experiments

Parameter Estimation Results: VP02 formulation

- PE run individually for each batch (transient data of D50, LoD and product temp used for PE)
- all parameters are estimated

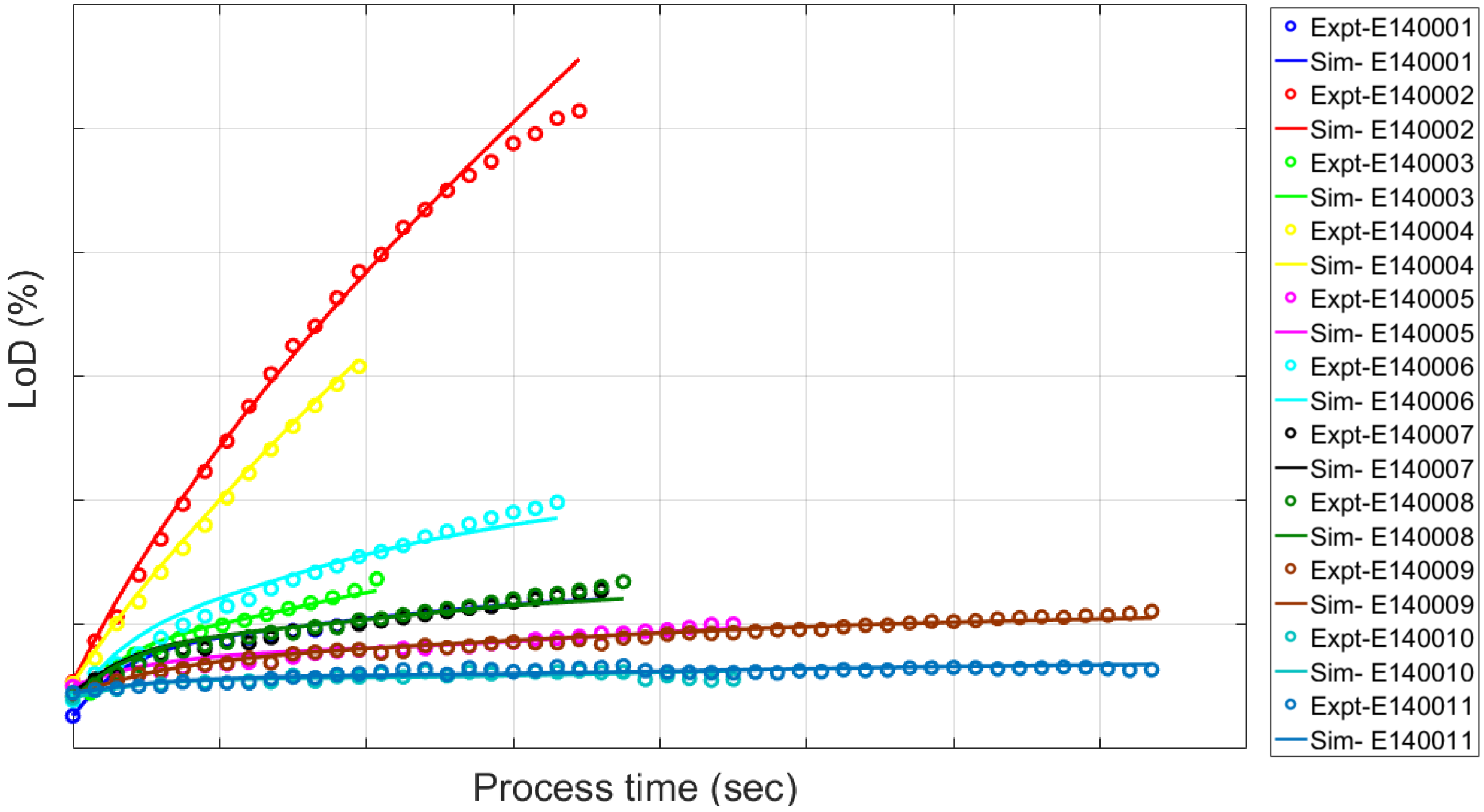
Batches	β_0 (1/s)	d^* [µm]	s [µm]	x* [-]	x_{cm} [kg/kg]	K [-]	h_w [W/m²K]
E140001 (center)	-9.79	200	39	0.065	0.109	0.7	14
E140002 (wet)	-11.36	180	30	0.018	0.211	0.6	7
E140003	-9.25	222	47	0.072	0.146	0.8	13
E140004	-9.3	206	37	0.052	0.144	0.57	2
E140005	-8.49	145	29	0.13	0.749	0.71	9
E140006	-9.58	180	57	0.065	0.175	0.85	19
E140007 (center)	-9.79	200	39	0.065	0.109	0.7	14
E140008 (center)	-9.79	200	39	0.065	0.109	0.7	14
E140009	-9.46	148	24	0.11	0.577	0.88	12
E140010 (dry)	-10.53	236	59	0.062	0.524	0.78	12
E140011 (dry)	-9.8	162	61	0.055	0.187	0.5	11

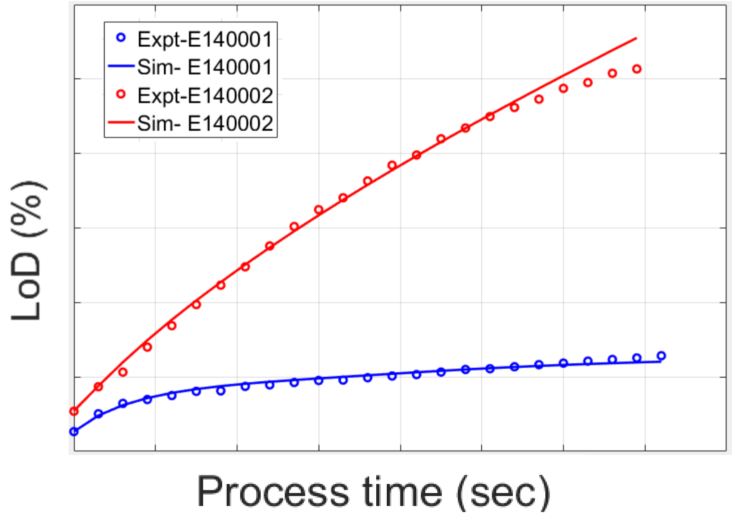
Parameter Estimation Results: VP02 formulation

- PE run individually for each batch (transient data of D50, LoD and product temp used for PE)
- Fixed value of β_0, h_w and calculated value of d^* are used

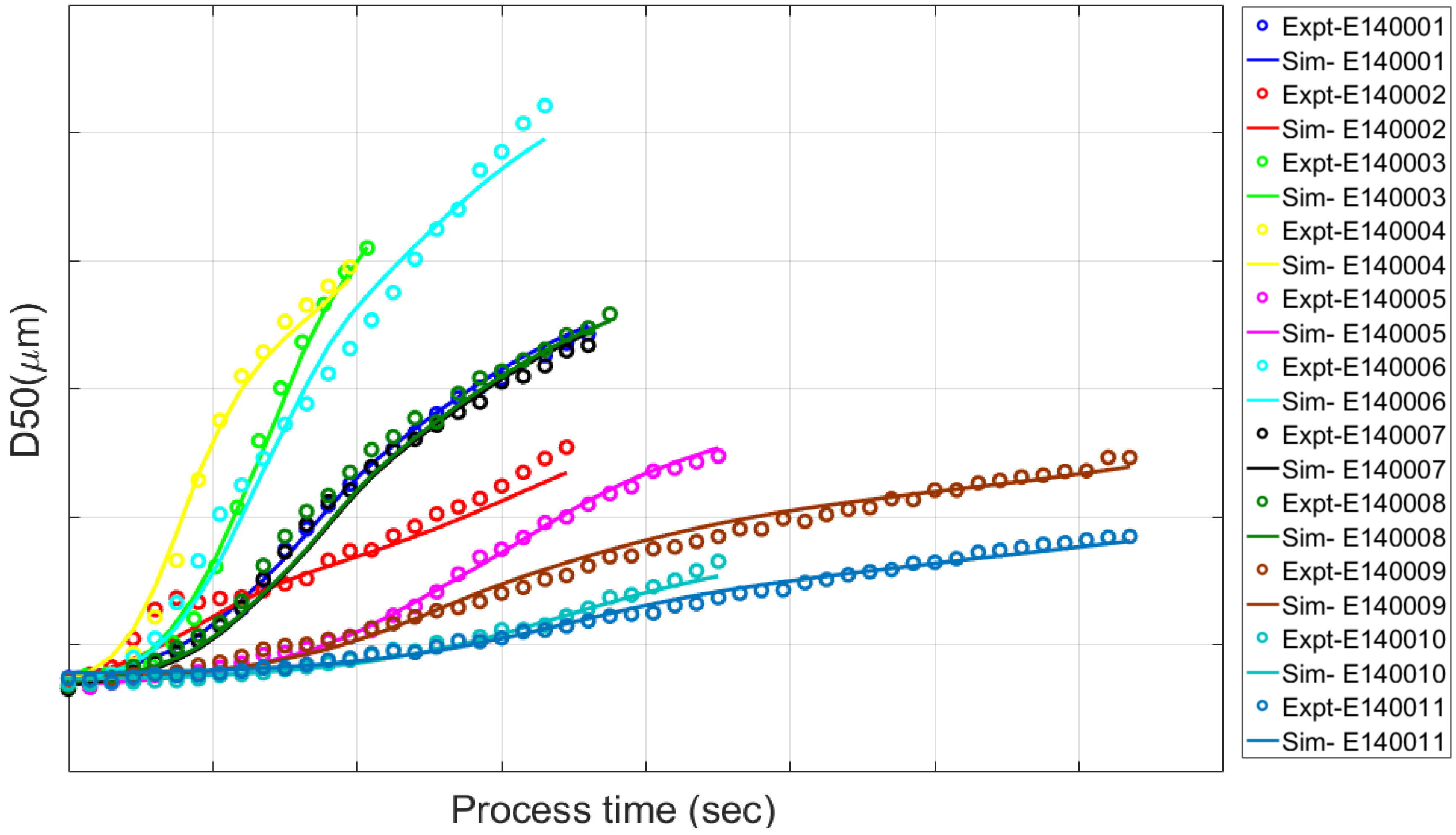
Batches	β_0 (1/s)	d^* [µm]	s [µm]	x* [-]	x_{cm} [kg/kg]	K [-]	h_w [W/m²K]
E140001 (center)	-9.5	166	46	0.067	0.1	0.67	12
E140002 (wet)	-9.5	113	22	0.01	0.297	0.67	12
E140003	-9.5	210	59	0.047	0.1	0.73	12
E140004	-9.5	210	35	0.025	0.39	0.71	12
E140005	-9.5	154	38	0.093	0.899	0.76	12
E140006	-9.5	180	57	0.057	0.1	0.77	12
E140007 (center)	-9.5	166	46	0.067	0.1	0.67	12
E140008 (center)	-9.5	166	46	0.067	0.1	0.67	12
E140009	-9.5	156	21	0.098	0.58	0.88	12
E140010 (dry)	-9.5	154	19	0.12	0.395	0.71	12
E140011 (dry)	-9.5	156	13	0.13	0.677	0.87	12

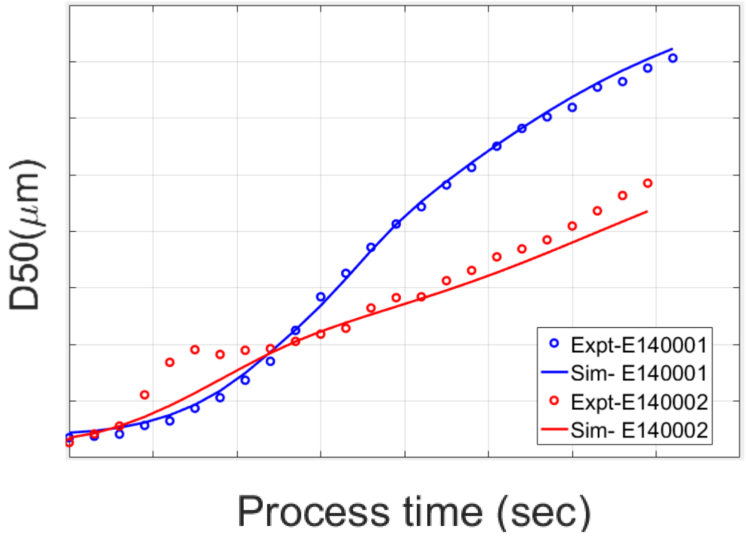
Validation results: LoD over process time



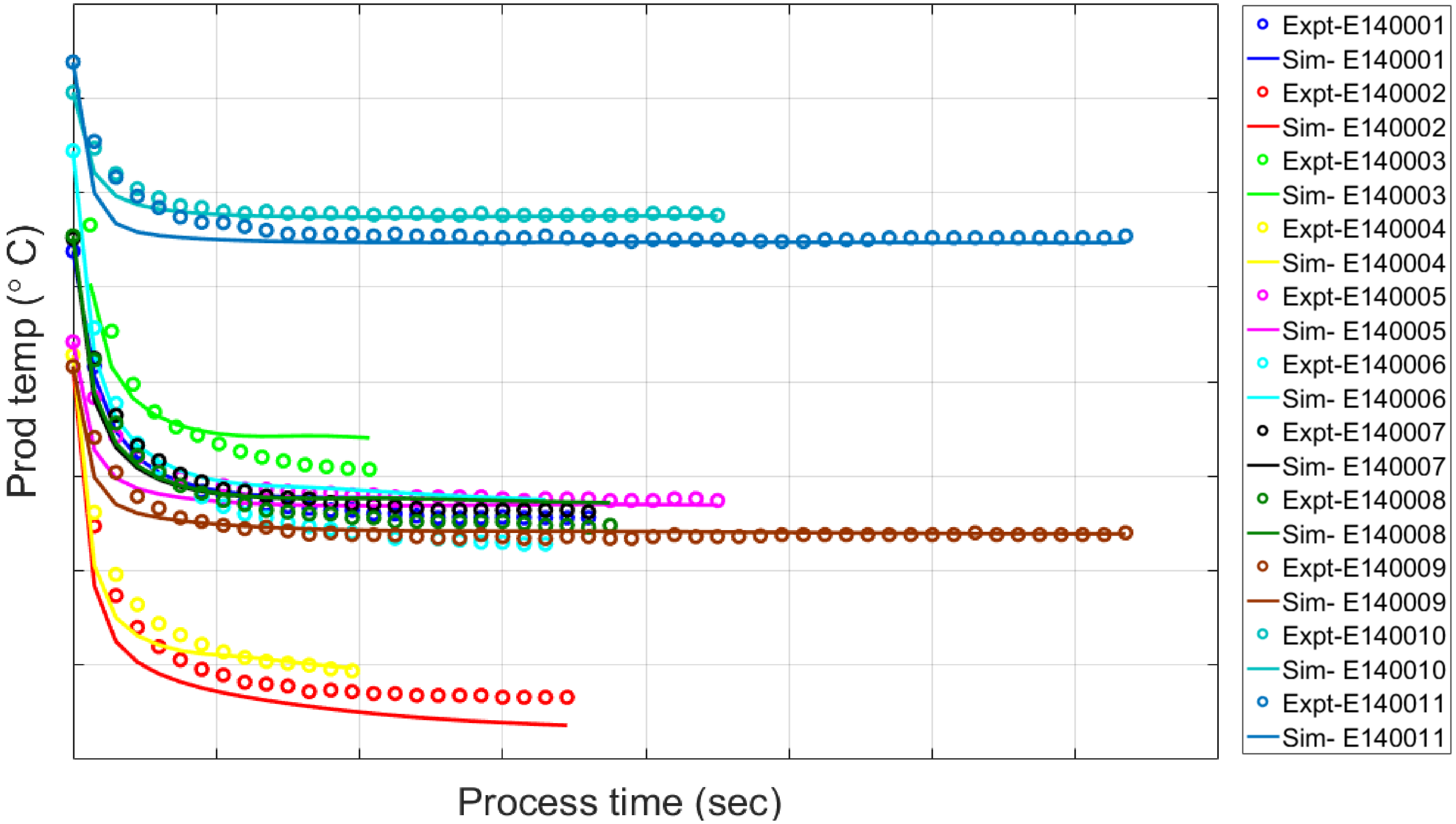


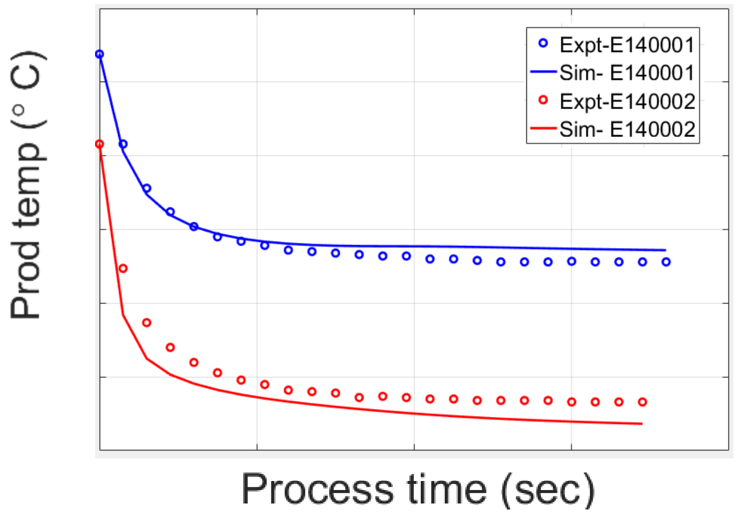
Validation results: D50 over process time





Validation results: Product temperature over process time

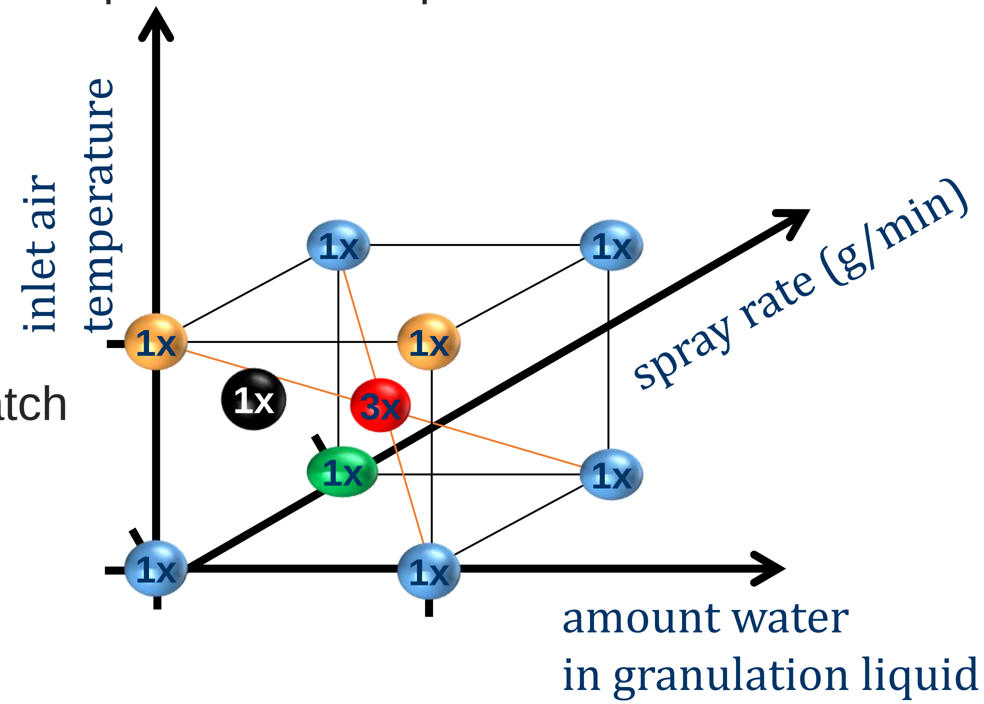




gSOLIDS simulation for test experimental batch

- Aim: examination of the validity of the developed model through gSOLIDS simulation of test experimental batch with new operating conditions and the same formulation.
- Criteria: comparison of granule size (D50), LoD and product temperature over process time and with corresponding values in the test experimental batch

1x test experimental batch



Methodology for simulation of test experiment batch

MODDE analysis is performed using estimated parameters including x^*, s, x_{cm}, K for set of batches

↓

Correlations for model parameters are obtained

↓

Model parameters for test batch are predicted

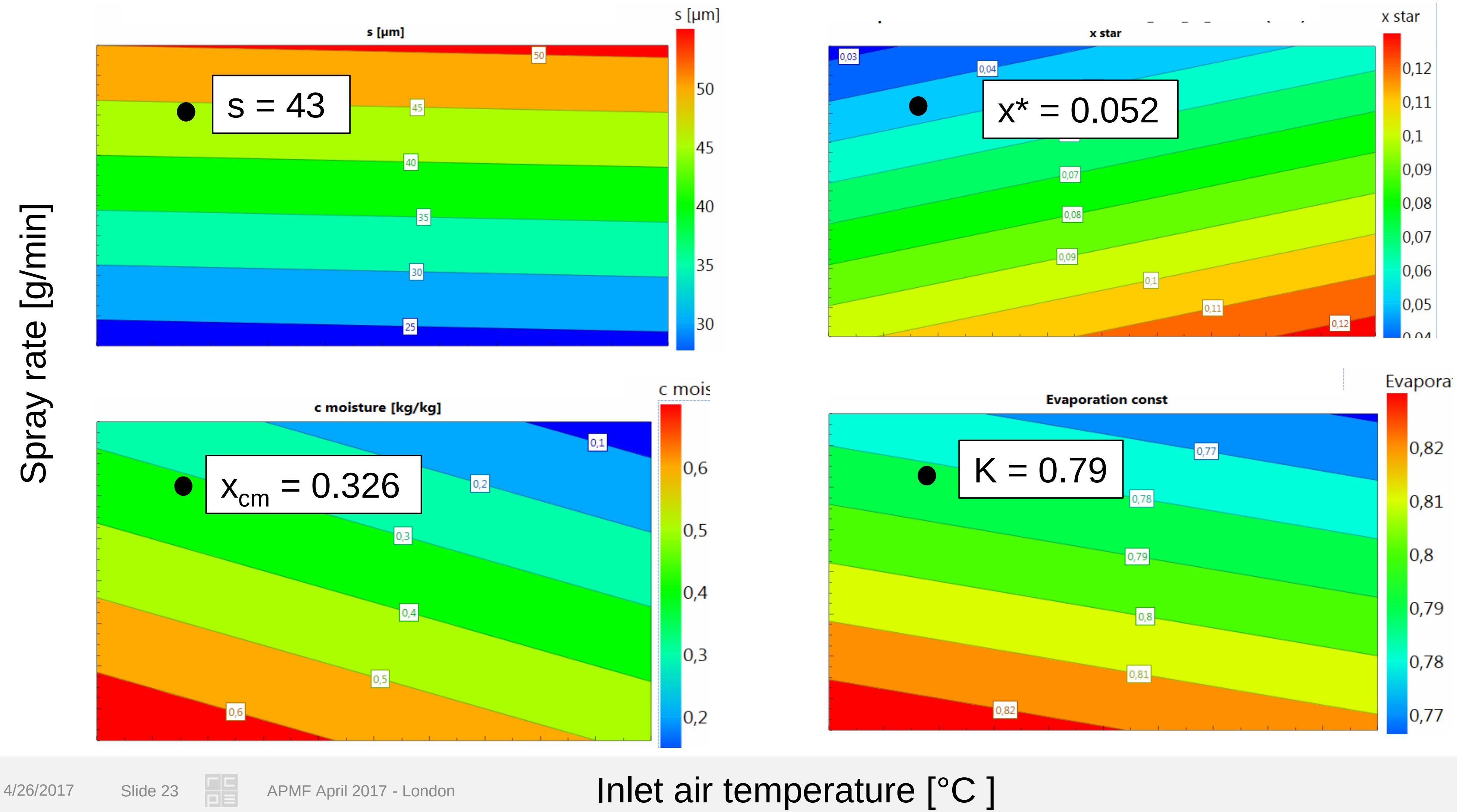
↓

gSOLIDS simulation for test batch

↓

Comparison of D50, LoD and Tp between simulation and experiment

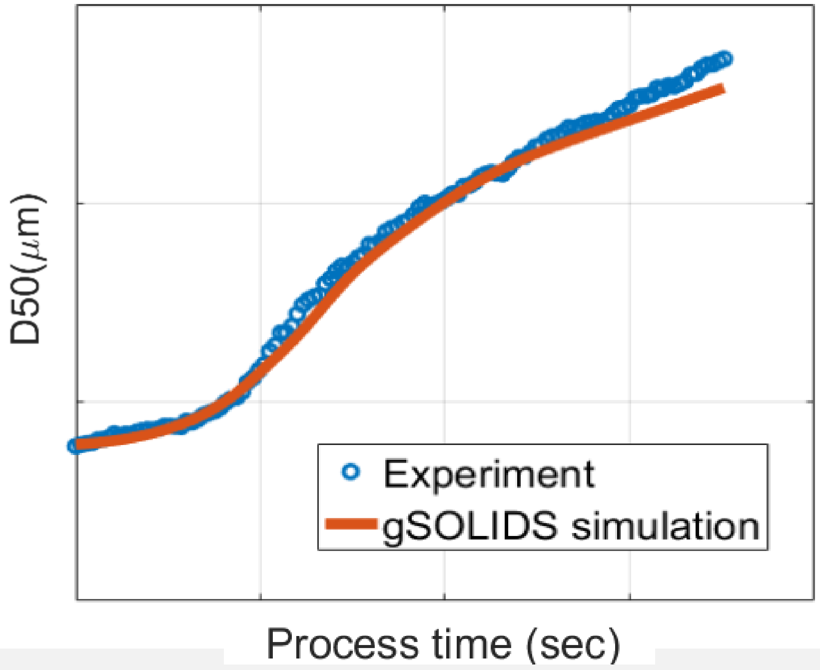
Modde analysis: predicted values of parameters s, x*, x_{cm}, and K

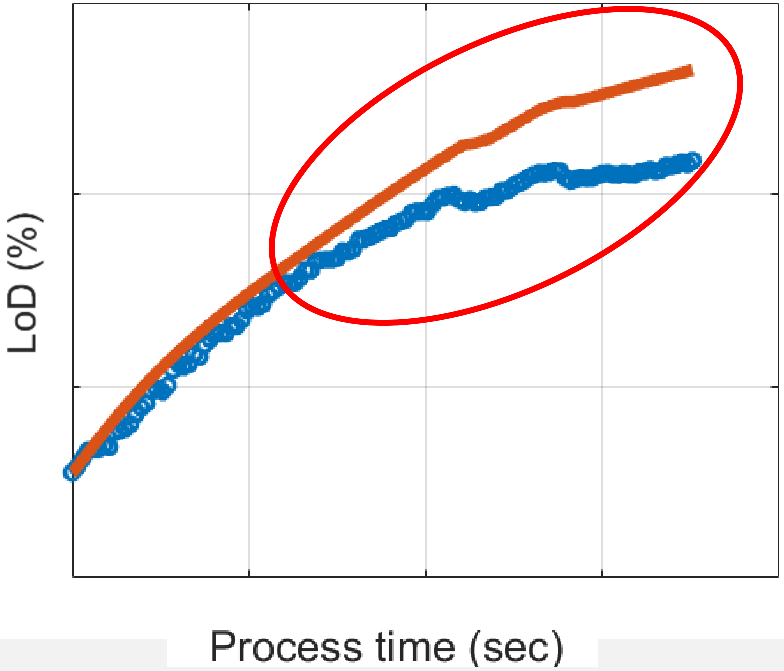


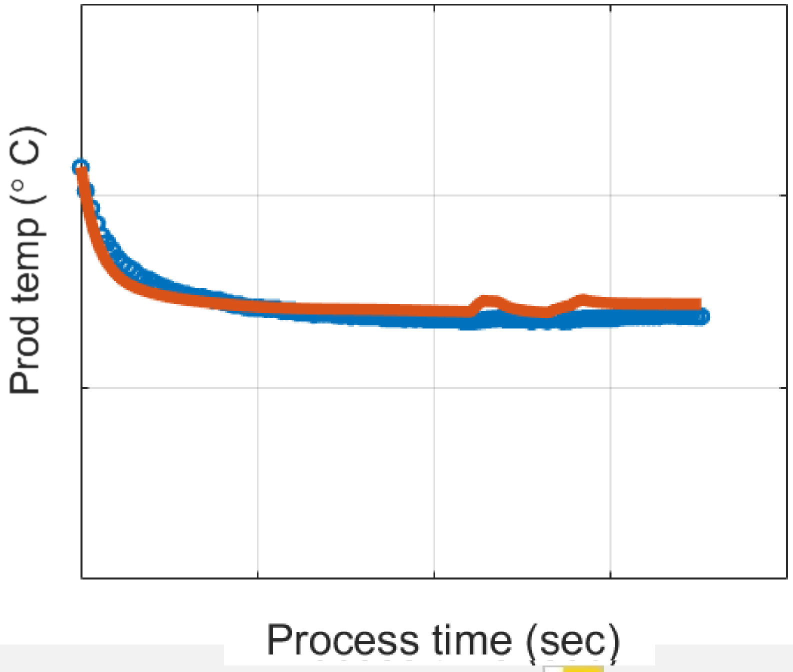
Results : comparison of simulation with test experimental batch

- Parameter **predicted from Modde analysis**

β_0 (1/s)	d^* [µm]	s [µm]	x* [-]	x_{cm} [kg/kg]	K [-]	h_w [W/m^{2}K]
-9.5	172	43	0.052	0.326	0.79	12



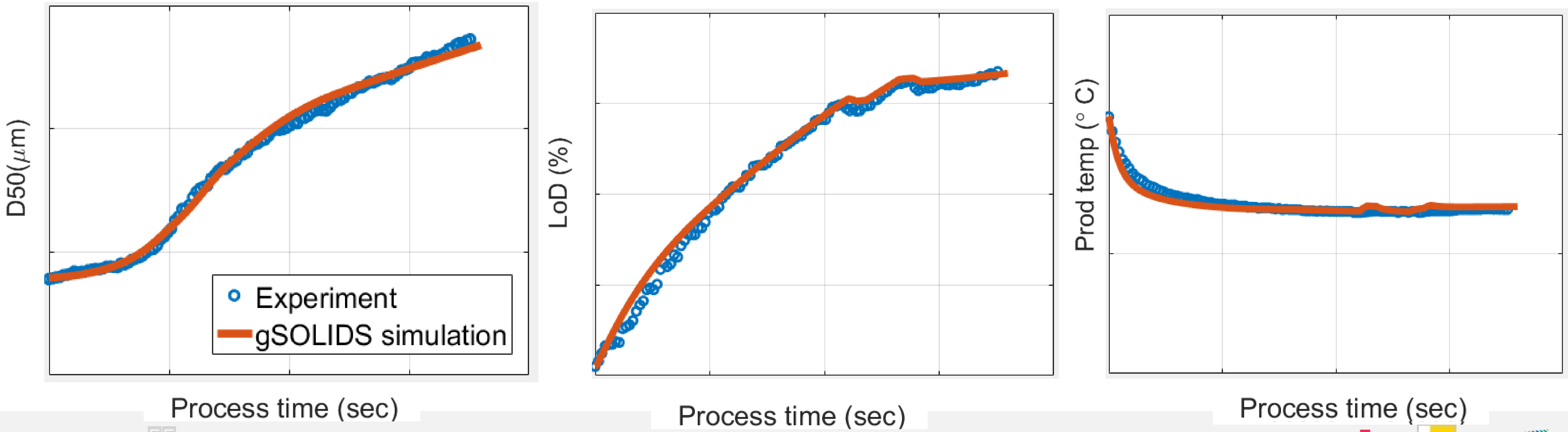




Results : comparison of simulation with test experimental batch

- Parameter **estimated**

β_0 (1/s)	d^* [µm]	s [µm]	x* [-]	x_{cm} [kg/kg]	K [-]	h_w [W/m²K]
-9.5	184	43	0.052	0.144	0.76	12



Summary

- Approach to simulate fluid bed granulation process using gSOLIDS
- Simulation strategy for the parameter estimation and approach to reduce the number of fitting model parameters
- We estimated parameter for 11 batches using experimental data
- Applying Modde analysis tool, we estimated the range of parameters for different operating points
- Proof of concept by prediction of test experimental batch

Conclusions

- The mechanistic model was improved in terms of model parameters
  - Transient D50, LoD and Product temperature were in good agreement with experimental data almost for all studied batches
  - The biggest deviation regarding D50 was observed by high spray rate and low inlet air temperature, i.e. the wet batch
- Examination of the model validity for test experimental batch
  - Simulation prediction of D50 and product temperature is quite good
  - Prediction shows some deviation in LoD which may be caused by critical moisture content. This can be a point for improvement of the model in the future study.

Thank you for your attention