ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Application of hybrid models for Advanced Process Control of a Twin Screw Wet Granulation Process

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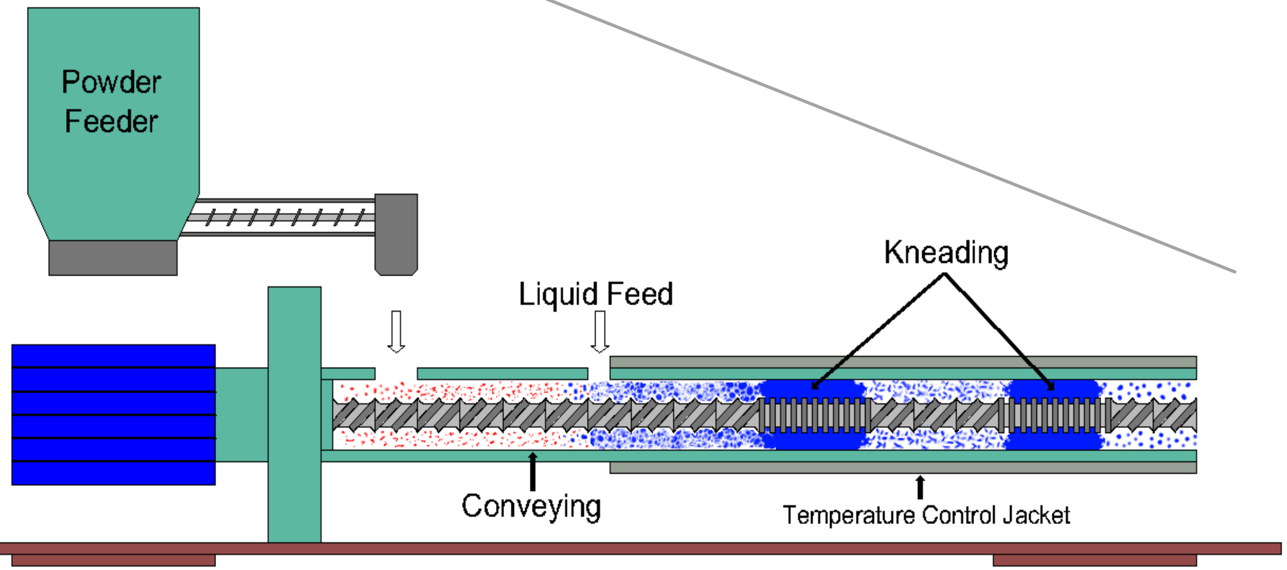
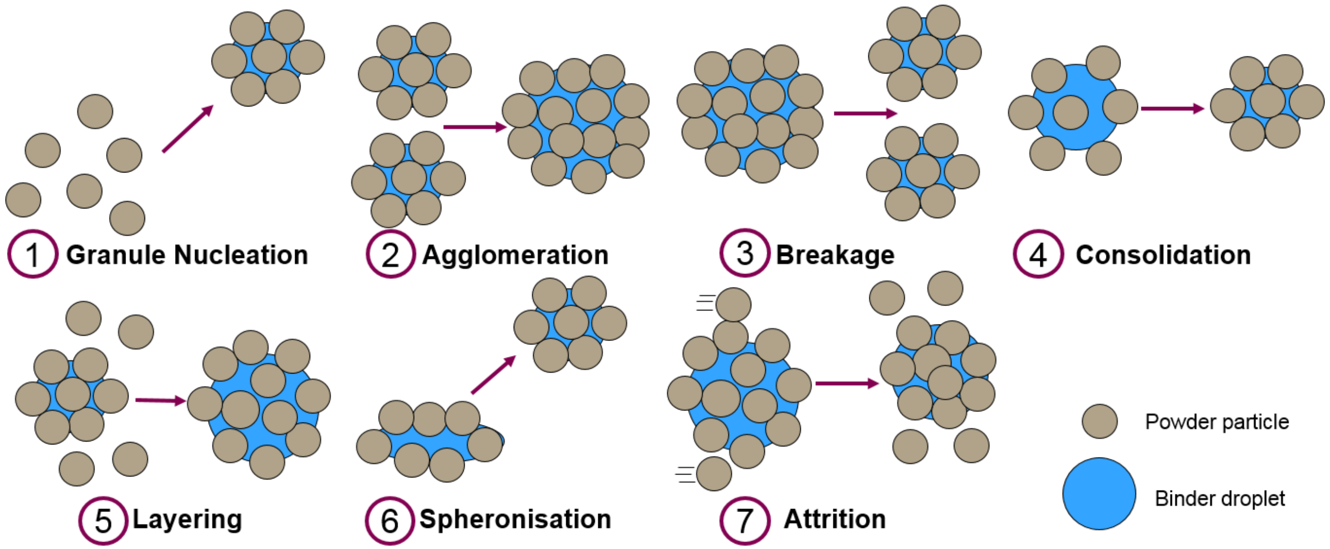
Overview of twin screw granulator (TSG)

Dispense → Wet Granulate → Dry → Mill → Lubricate → Tablet → Coat



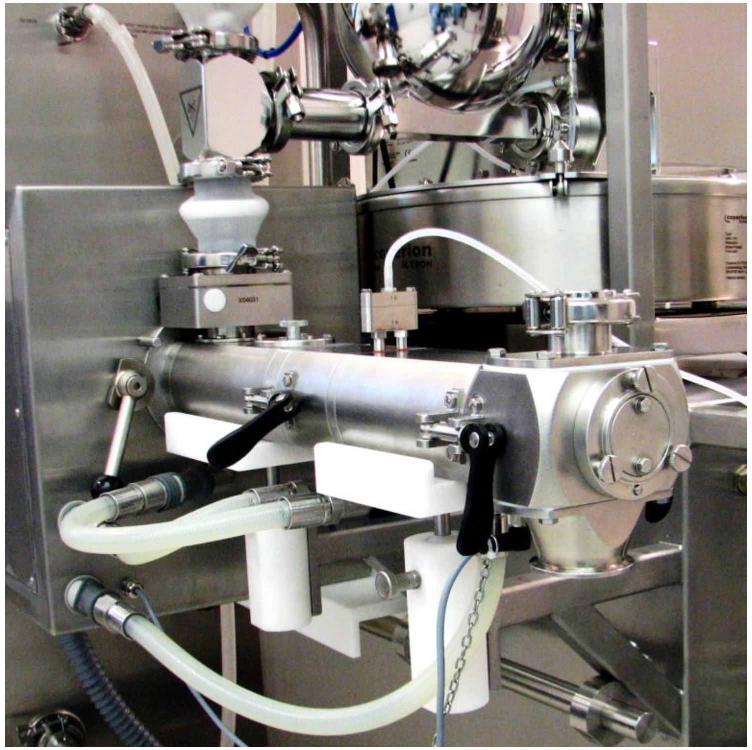
[Seem *et al*. 2015, *Pow Tech* 276]

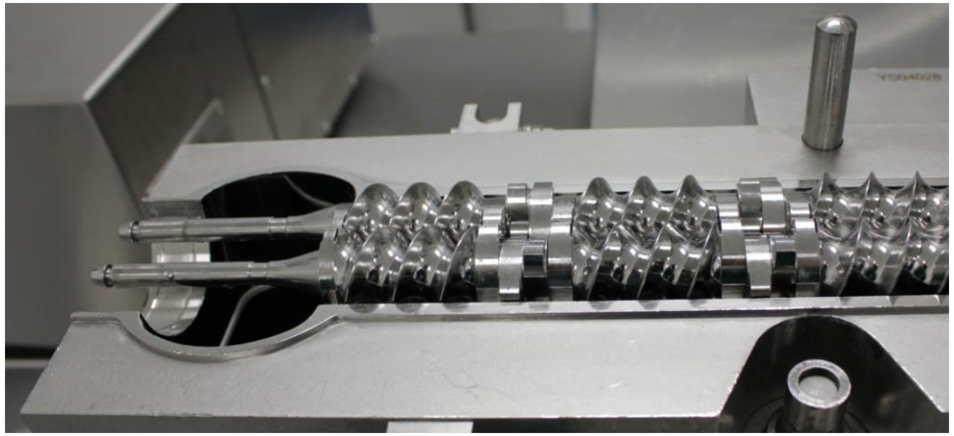
What happens within a TSG

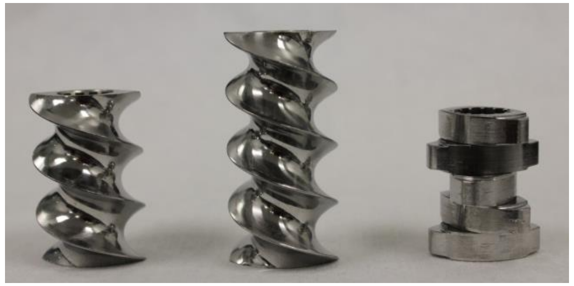


- Many rate processes occur simultaneously during the granulation process
- Population balance modelling can be used to model the changing properties of the granules as a result of these rate processes
- gFormulate has a model for a twin screw granulator

Overview of twin screw granulator







- Highly configurable screw layout
- Main process parameters
  - Powder feed rate
  - Liquid feed rate
  - Screw speed

- Finding an optimal design and operational space for a new formulation can consume significant time and material
- Routine monitoring and control of quality attributes is difficult (granule size, porosity,…)

User case

Can we develop a robust controller that will maintain quality attributes to set point:

- API concentration
- Granule size (D50)

… when the process is adjusted (e.g. a higher throughput)?

Ideally, with minimal wastage of API.

Setting the scene for “Statistical” and “Mechanistic” Models

Statistical, Empirical or Data Driven Models

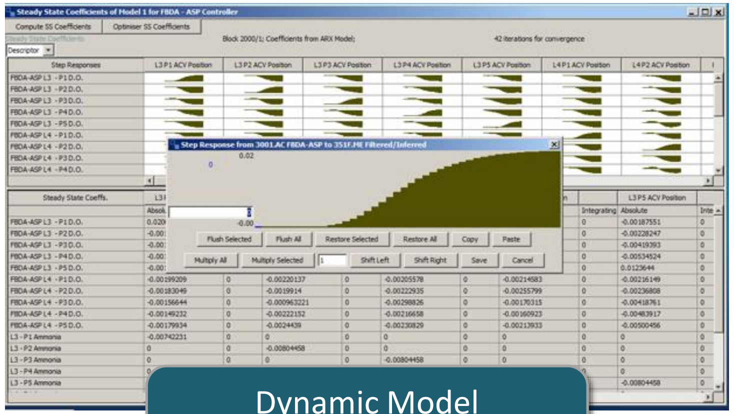
- Control: Dynamic Models
- Calibration: Static Models

Created from

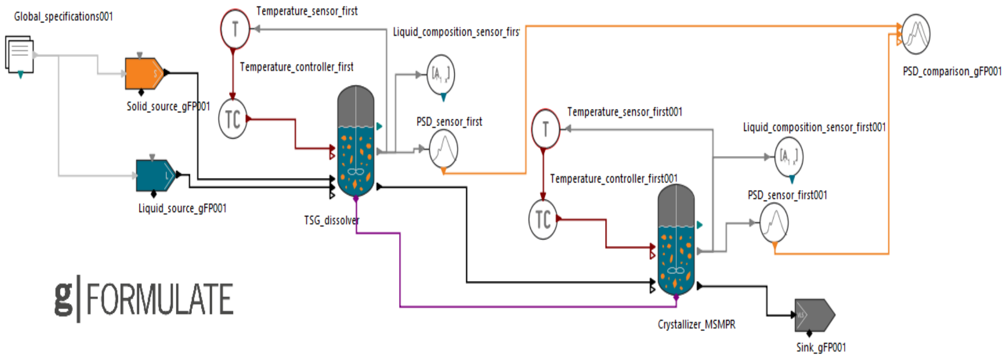
- Designed Plant Tests
- Historical Process Data

Mechanistic Models

- A model is one where the basic elements of the model have a direct correspondence to the underlying mechanisms in the system being modelled (1)
- Parameterised from experimental data



Dynamic Model for Control



Flowsheet model

(1) https://grey.colorado.edu/oreilly/index.php/Mechanistic_Model

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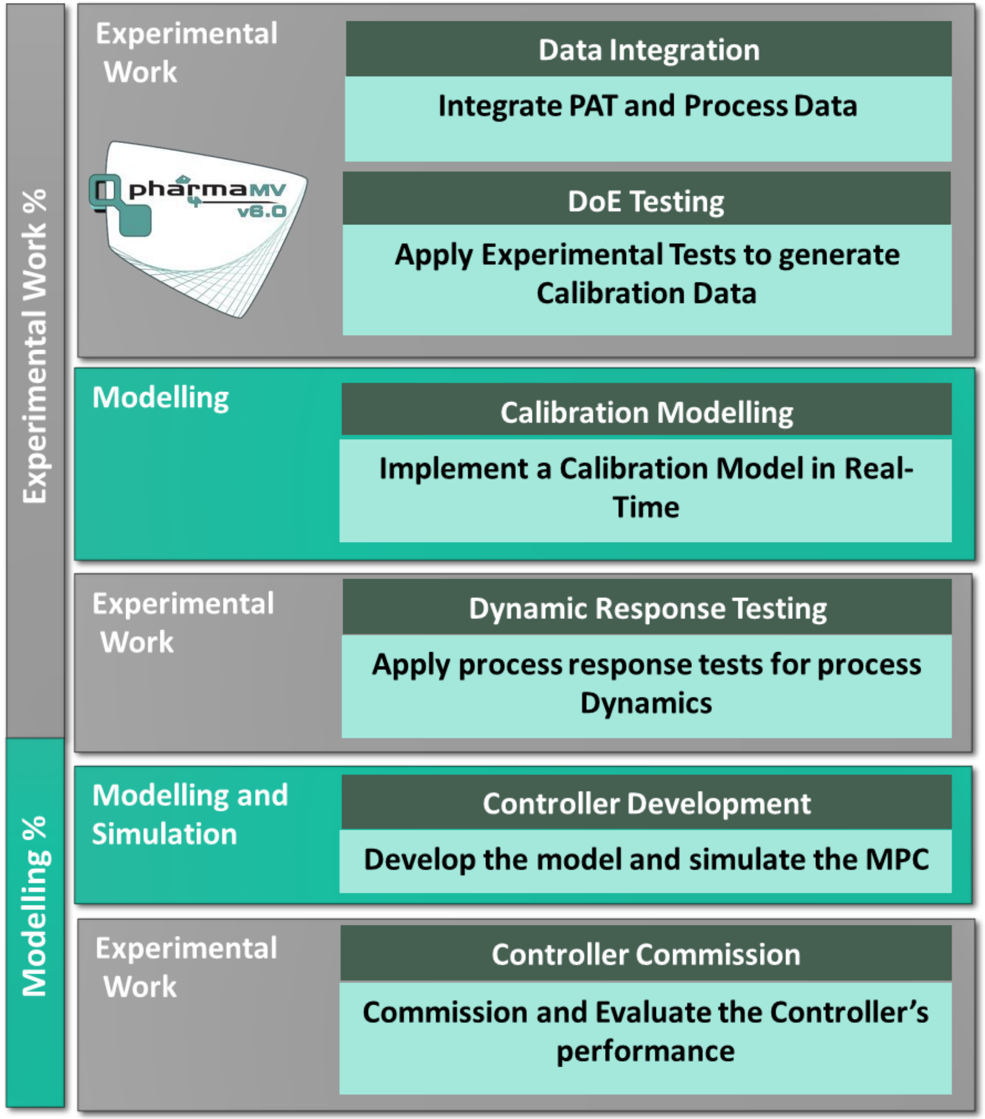
Data Driven Workflow:
Model predictive control development



PharmaMV is used to

- Execute experimental work consisting of DoE testing and dynamic process response testing.
- Develop calibration and dynamic models for process control.
- Tune the controller in simulation.
- Implement the controller on the process.

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Digital Design Based Workflow

Experimental Work %

Modelling %

Experimental Work

Data Collection
API concentration, Moisture, PSD, etc..

Data Integration
Integrate PAT and Process Data

Modelling

Model Development & Scale up
TWSG model development, scale up and validation (parameter estimation)

Calibration Modelling
Implement a Calibration Model in Real-Time

Virtual Dynamic Response Testing
Apply process response tests for granulation process modelling

Simulation

Controller Development
Develop the model and simulate the MPC

Experimental Work

Controller Commission
Commission and Evaluate the Controller's performance

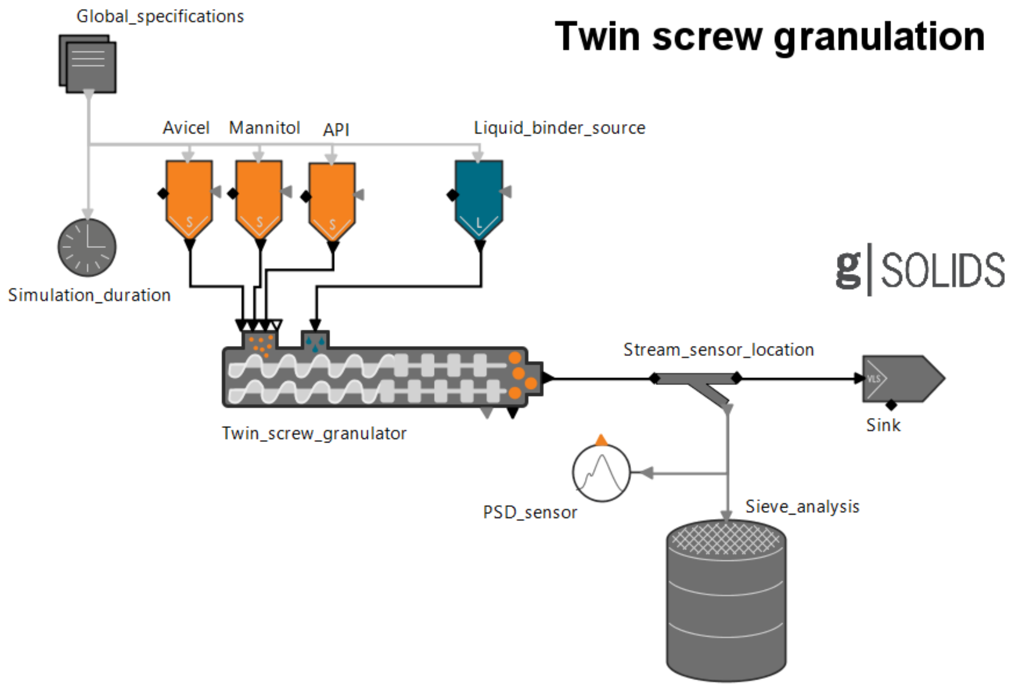
- Minimal experimental work to determine system's properties (feed rate operating range, liquid to solid ratio, API concentration, PSD) on different scales.
- PSE's gPROMS FormulatedProducts platform is used to develop a mechanistic Twin Screw Wet Granulator Model.
- Combining Perceptive's PharmaMV & PSE's gPROMS FormulatedProducts platforms, provides a fast and cost effective hybrid approach for developing a closed loop controller.

Twin-screw granulator model in gPROMS FormulatedProducts

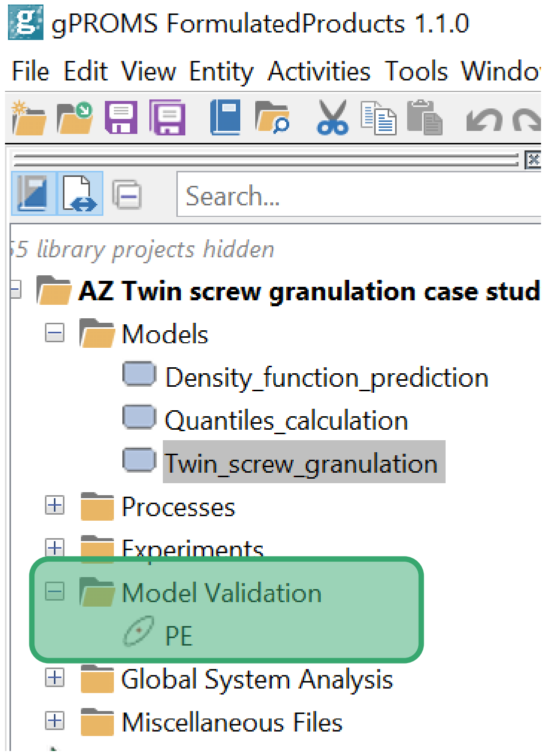
Creation of a wet granulate phase from fine powder particles by addition of liquid.

Specification of screw element types and configuration.

Evaluation of drop nucleation, breakage, layering, and consolidation mechanisms.



Model validation step



Model Inputs

- Blend PSD
- Bulk densities of the blend components
- Screw configuration and elements
- Flowrates of the powder and liquid binder

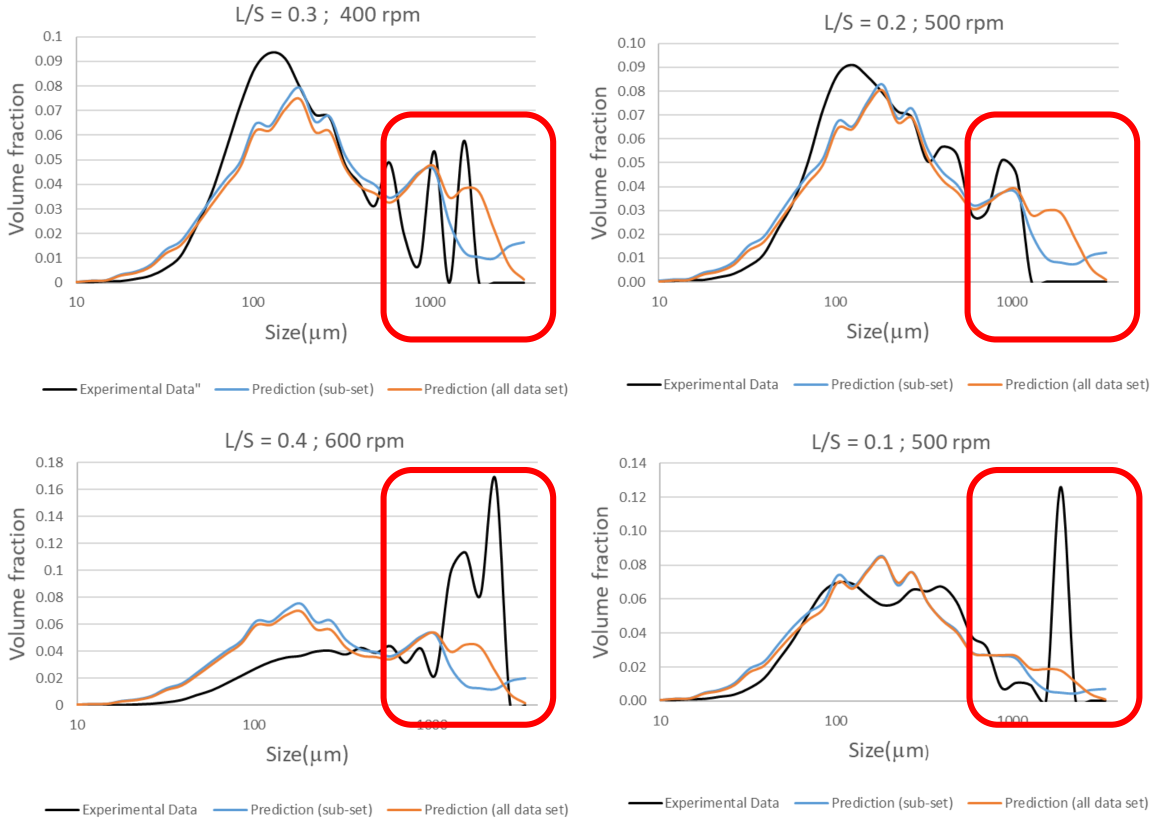
Mechanisms evaluated

- Drop nucleation
- Breakage
- Layering

Evaluations performed

- 24-experiments
- 5-experiments (500 rpm and L/S =0.1/0.2)

How many experiments are required to validate the model ?

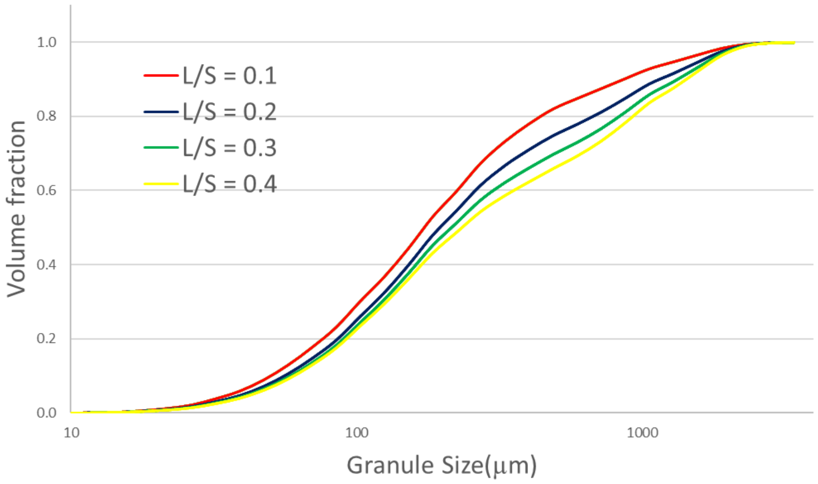


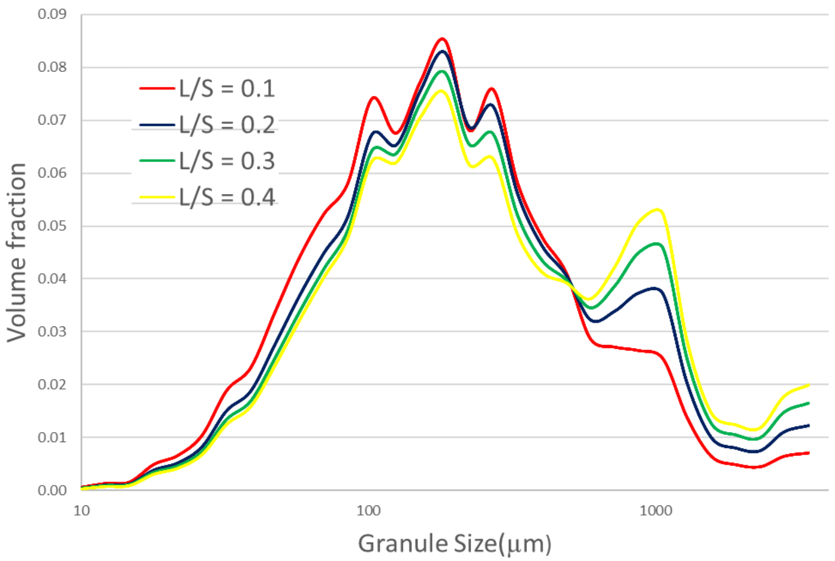
Model doesn't capture t   anule sizes

The 5-experiments data   e, however it shows different results for the l

Conclusion: Model can be calibrated with a smaller dataset

Model prediction : Effect of L/S on granule size distribution





ger granules and sr … t higher liquid-to-solid ratios.

- Model has a liquic … p nucleation is governed by the a …

Conclusion: Model can capture changes in the liquid-to-solid ratio

Dataset for analysis of different screw configurations

Table 3 Process parameters for TSG process scoping experiment Part 1.

TSG runs	L/S ratio	Liq addition nozzles	Screw speed (rpm)	Flow rate (kg/h)	Liquid addition rate (g/min)	Kneading element configuration
A1	0.06	0.8	500	15	15	6K
A2	0.08	0.8	500	15	20	6K
A3	0.16	0.8	500	15	40	6K
A4	0.08	0.8	500	15	20	3K
A5	0.08	0.8	500	15	20	6K6K

Experiments for Model Validation

Experiments for Parameter Estimation

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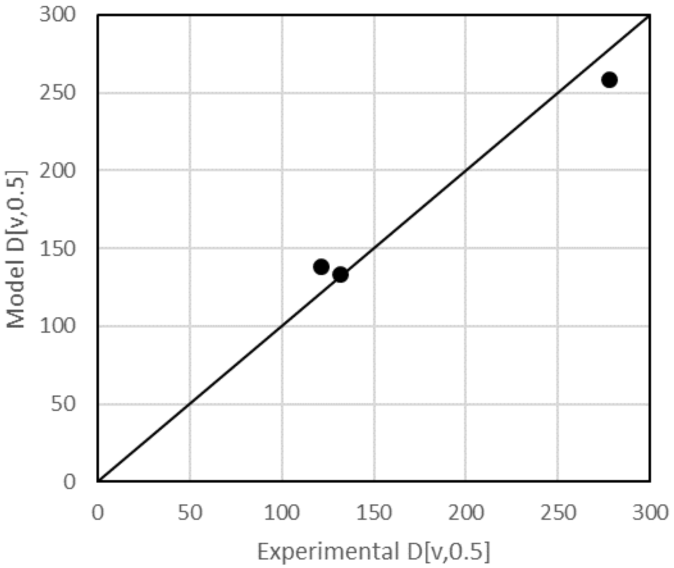
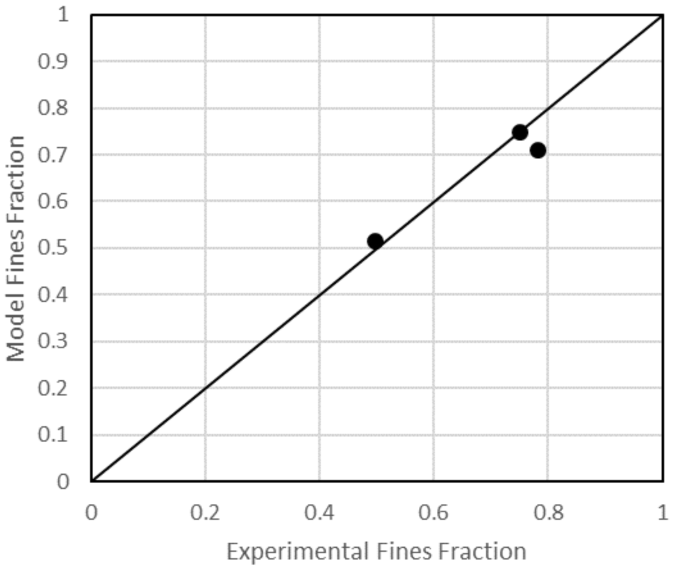
Model prediction vs. Experimental data

3. Experiments for Model Validation (A1, A2 & A3)





- Good prediction of the D[v0.5] and fines fraction variation with the liquid present in the process

Digital Design Workflow: gPROMS/PharmaMV Integration

The Virtual Process

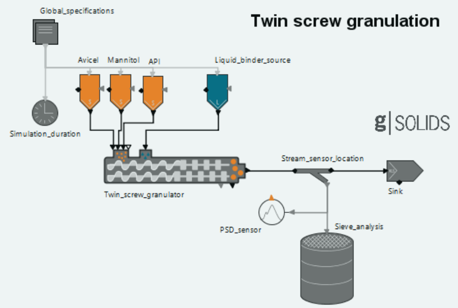
The Controller

Manipulated Signals

Measured Signals

gPROMS FORMULATED PRODUCTS

g|FORMULATE



pharmaMV v6.0

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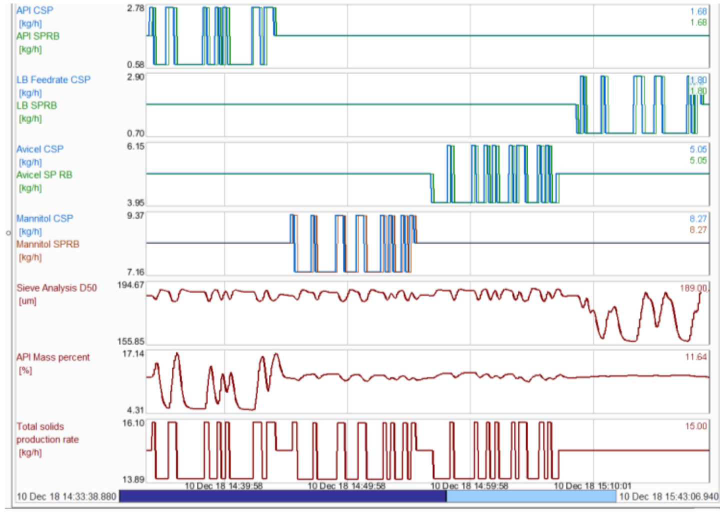
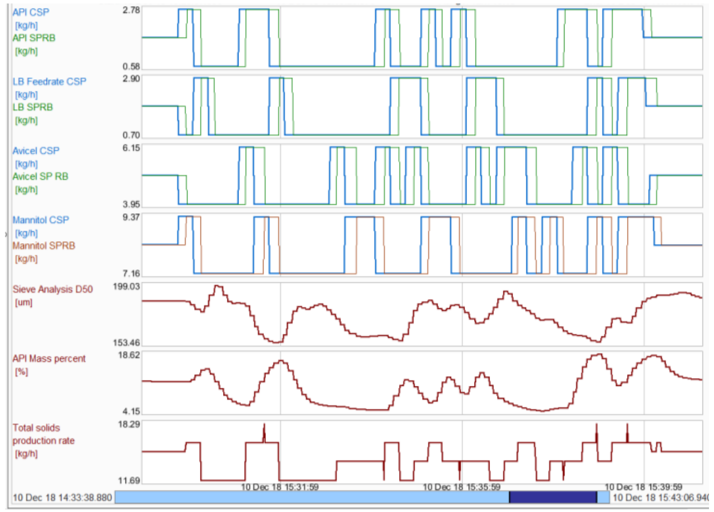
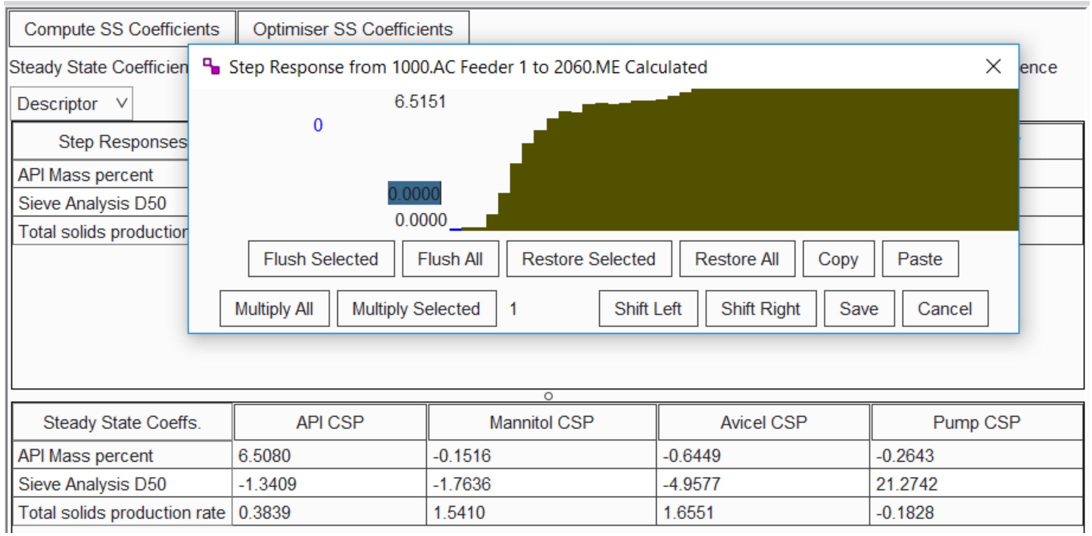
Statistical Model Development – PRBS step testing

- To identify a statistical model, Pseudo Random Binary Sequence (PRBS) step testing is applied to the gPROMS FormulatedProducts flowsheet model using PharmaMV.
- The screenshot below shows the step tests on the feeders and the corresponding response of API mass percent (%), d50 and total solids production rate.
- This data is statistically rich, allowing an accurate control model to be developed.

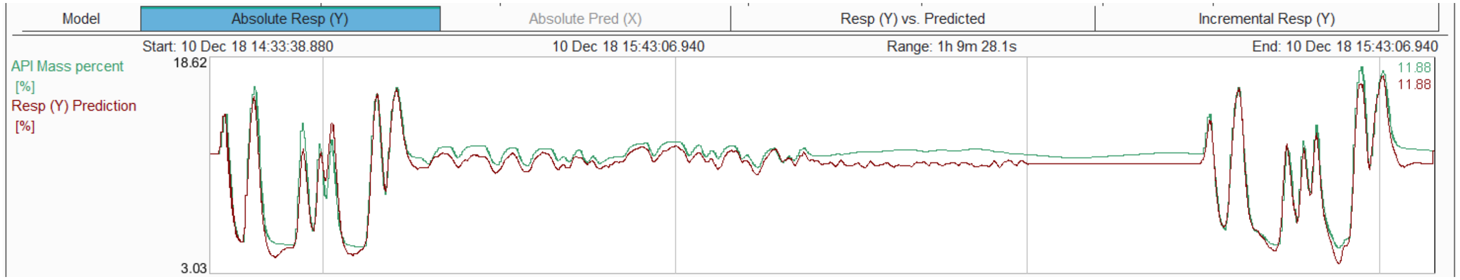




Statistical Model Development – Identification

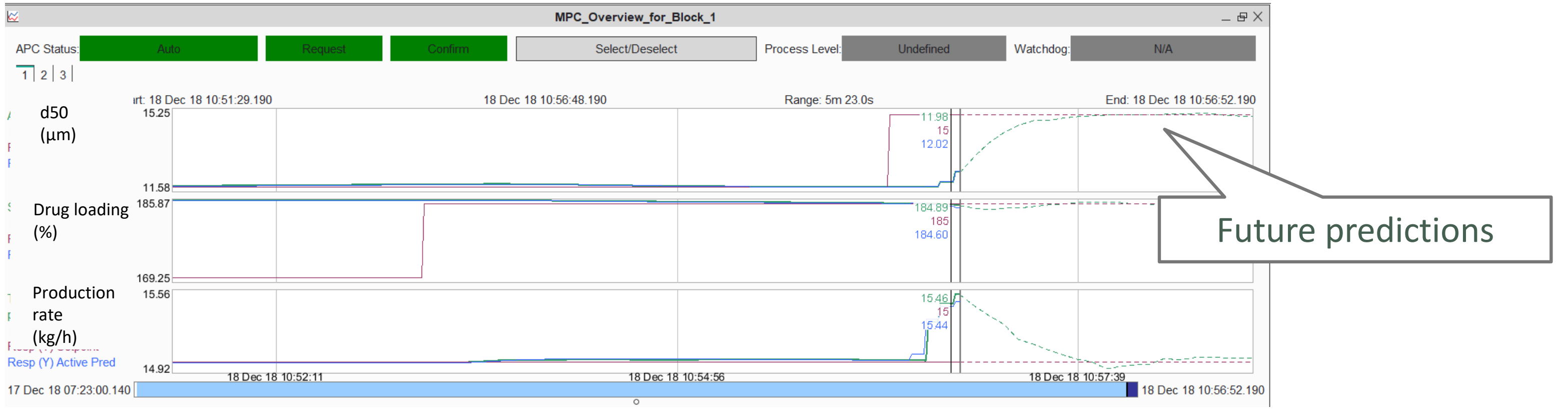


The statistical model is identified using the Recursive Least Squares (RLS) algorithm. The screenshot above shows the response of the API mass percent to a step change in the API feed rate.

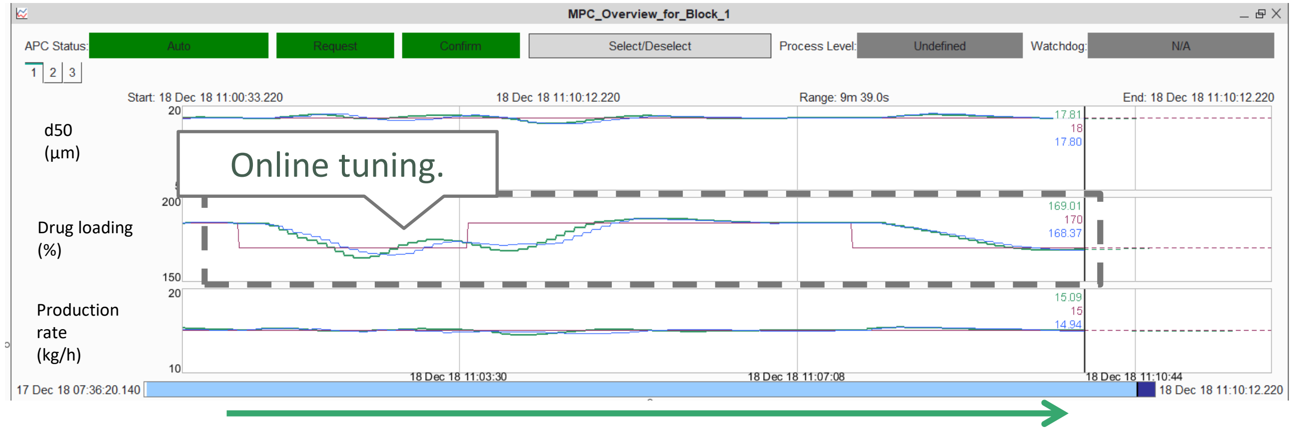


A comparison between the API mass percent and the model prediction shows good model performance

Twin Screw Wet Granulation Control – Overview

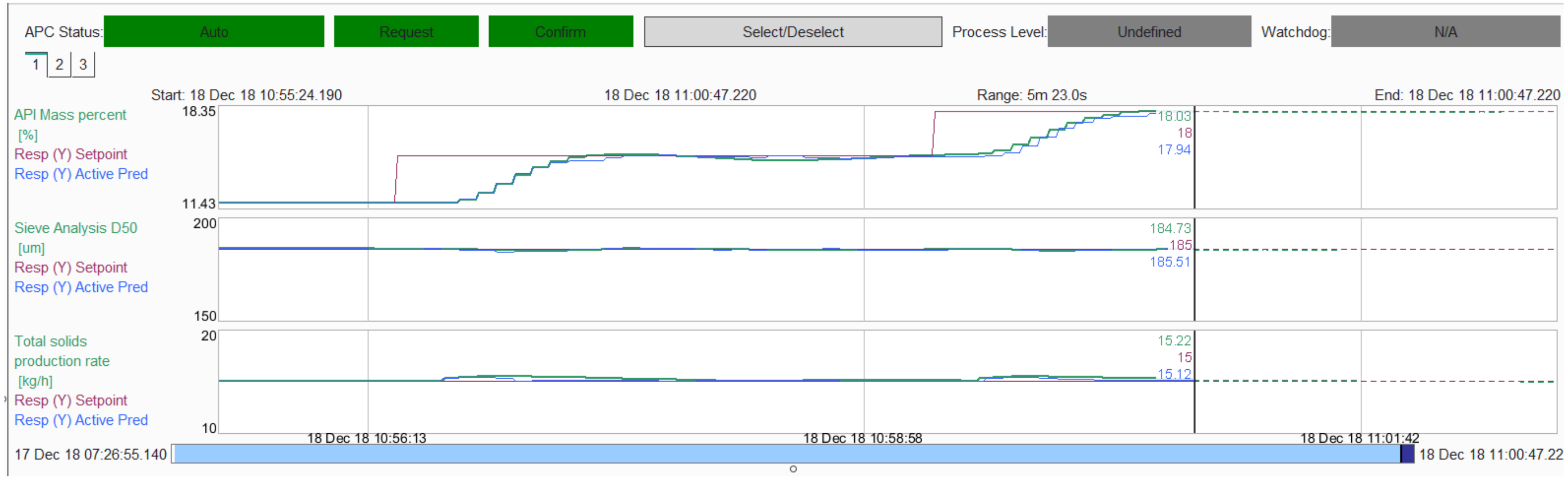


Post model development, the controller is commissioned and tuned using the flowsheet “Digital Twin”.

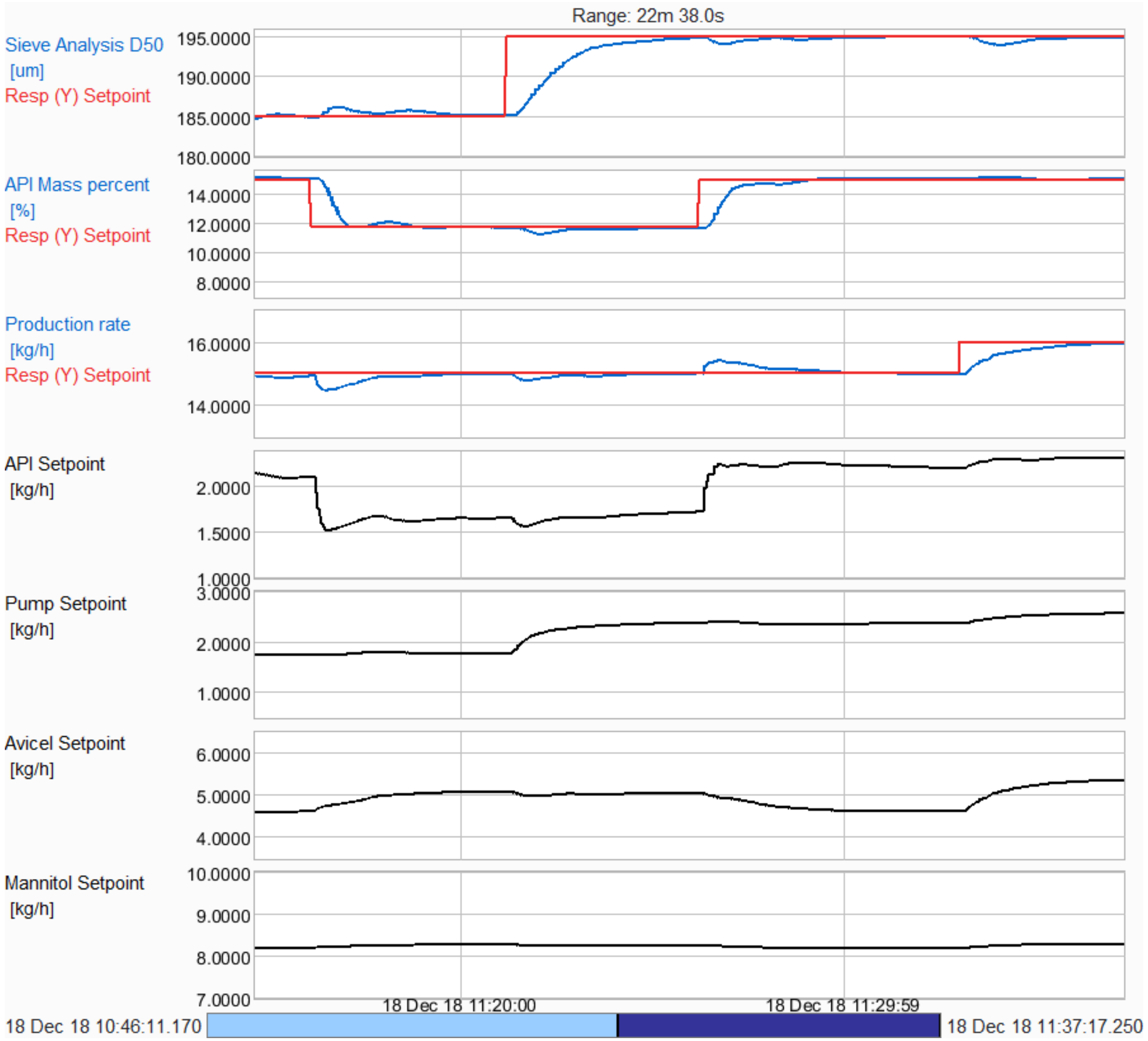


Twin Screw Wet Granulation Control – Results

- The MPC demonstrates well controlled response to a setpoint change in the API Mass percent from 11.75 to 15 to 18. The d50 closely tracks its set point while the API Mass percent is adjusted.
- The production rate is controlled at 15 kg/h through the run.



Twin Screw Wet Granulation Control – Results



- Through smooth manipulations of the feed rates and the pump set point, the API Mass percent, d50 and the production rate have been controlled for various set point changes.

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Conclusions

Benefits of digital design based workflow

- Cost-effective development of an advanced control solution for twin screw wet granulation control.
- Reduced experimental effort in developing process models and control strategies.
- Reduced wastage of the API material.
- Minimal interruption in the process production time for step-testing/model development.
- Accurate CQA control through APC that can lead to reduced variability in the process.

Future work

- Implement and demonstrate the digitally designed control strategy on the TWSG
- Introduce disturbances to show reduced variability in API concentration and d50.

Note that the same mechanistic model has been used for both **digital design** and development of the APC for **digital operation**, showing how development of a model can be used throughout a product and process lifecycle

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