DIGITAL TOOLS FOR EXTRUSION PROCESS DESIGN

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Scientific Area Leader, Modeling and Prediction

Pharmaceutical Hot Melt Extrusion

- Hot Melt Extrusion is a one-step, continuous manufacturing step used to produce a variety of pharmaceutical dosage forms, from oral to implantable dosage forms, and filaments for Filament-Based 3D Printing
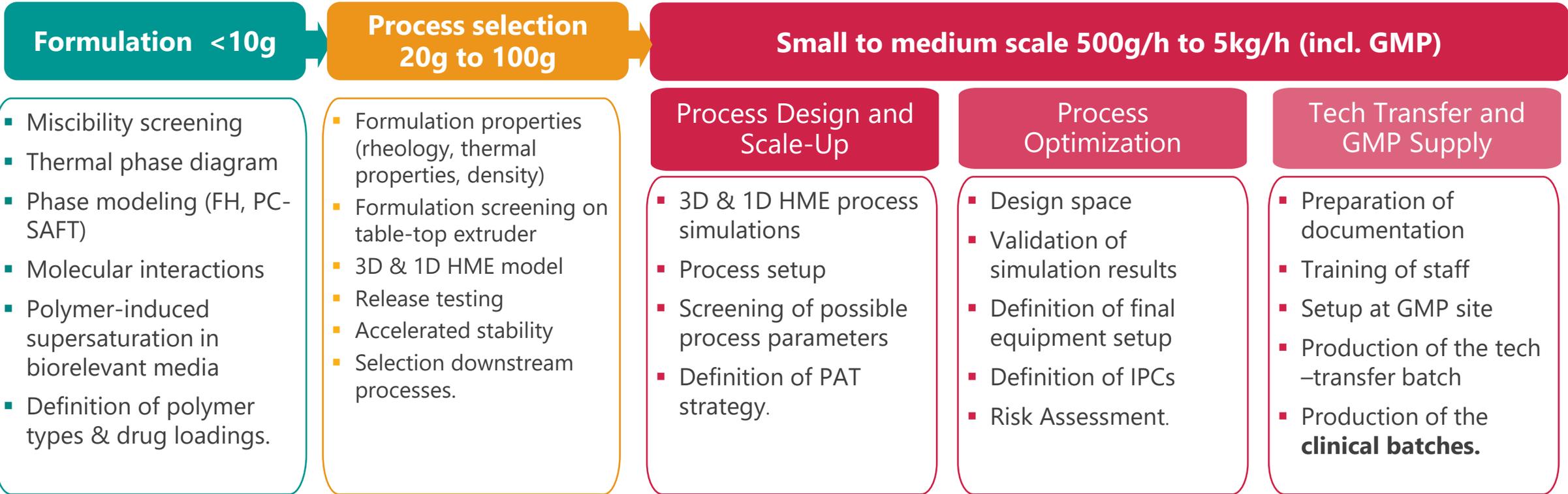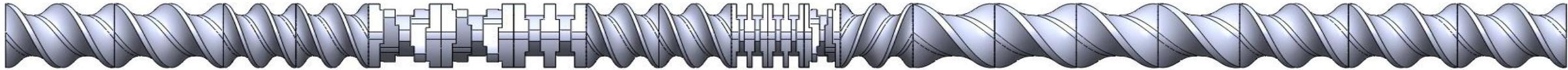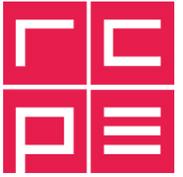
Formulation perspective

- How to formulate my ASD, extended-release implant, co-extrudate, filament...
- Can my API survive the process?
- Which excipients could be suitable for the extruder and my API?
- How stable will my ASD be?

Process development perspective

- How do I setup the process efficiently for my formulation?
- What quantities of formulation do I need at the early stage?
- How much does my process impact the product quality versus my formulation?
- How to choose the proper process window?
- How to perform scale-up?
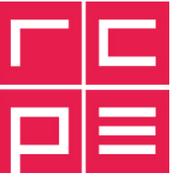
HME: Pre-clinical process development

Formulation <10g → **Process selection 20g to 100g** → **Small to medium scale 500g/h to 5kg/h (incl. GMP)**

Formulation <10g	Process selection 20g to 100g	Process Design and Scale-Up	Process Optimization	Tech Transfer and GMP Supply
• Miscibility screening • Thermal phase diagram • Phase modeling (FH, PC-SAFT) • Molecular interactions • Polymer-induced supersaturation in biorelevant media • Definition of polymer types & drug loadings.	• Formulation properties (rheology, thermal properties, density) • Formulation screening on table-top extruder • 3D & 1D HME model • Release testing • Accelerated stability • Selection downstream processes.	• 3D & 1D HME process simulations • Process setup • Screening of possible process parameters • Definition of PAT strategy.	• Design space • Validation of simulation results • Definition of final equipment setup • Definition of IPCs • Risk Assessment.	• Preparation of documentation • Training of staff • Setup at GMP site • Production of the tech –transfer batch • Production of the **clinical batches.**

J. Matić, A. Paudel, H. Bauer, R. A. L. Garcia, K. Biedrzycka, and J. G. Khinast, "Developing HME-Based Drug Products Using Emerging Science: a Fast-Track Roadmap from Concept to Clinical Batch," AAPS PharmSciTech, vol. 21, no. 5, p. 176, Jul. 2020.

1D HME XPS

Pharmaceutical Hot Melt Extrusion

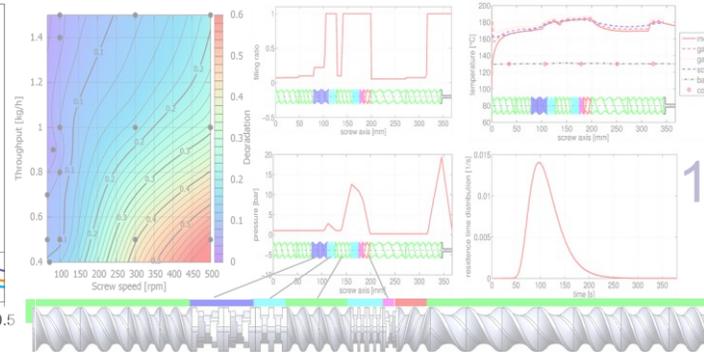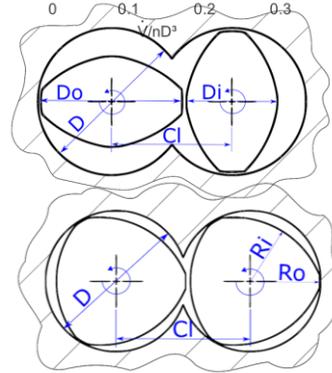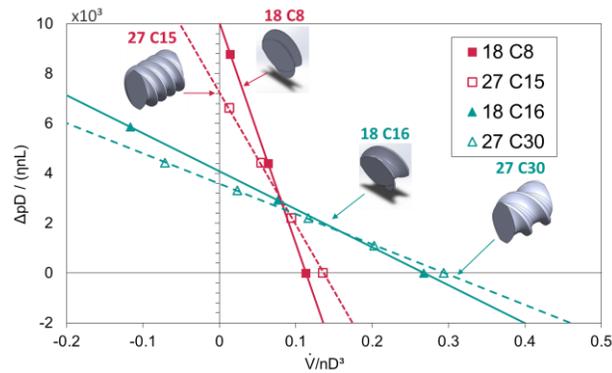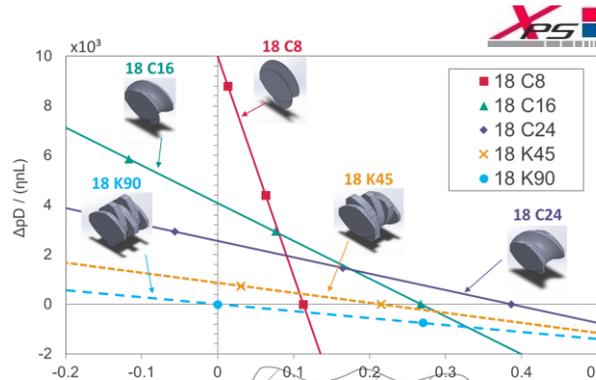Hot Melt Extrusion (HME) is a **continuous**, **one-step** drug production process.
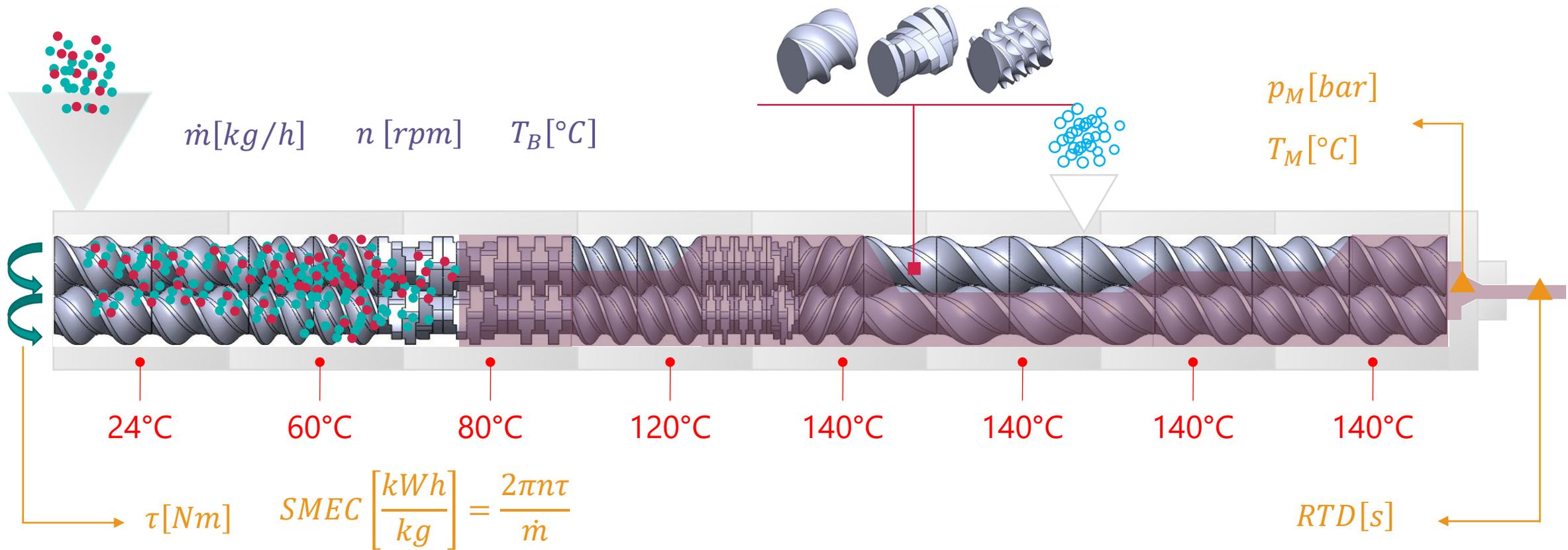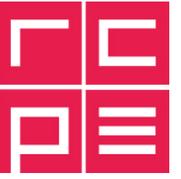
$\dot{m}[kg/h]$ $n\,[rpm]$ $T_B[°C]$

$p_M[bar]$

$T_M[°C]$

24°C   60°C   80°C   120°C   140°C   140°C   140°C   140°C

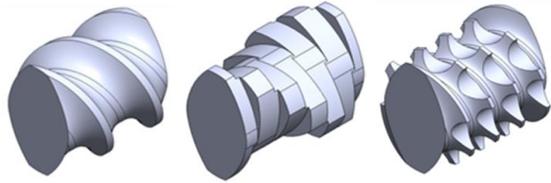$\tau[Nm]$ $SMEC\left[\dfrac{kWh}{kg}\right] = \dfrac{2\pi n\tau}{\dot{m}}$
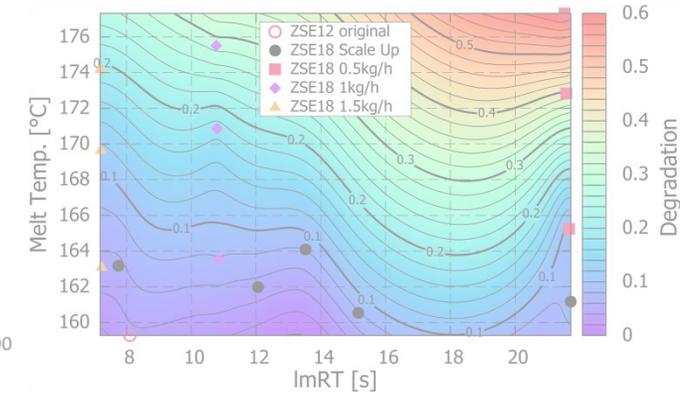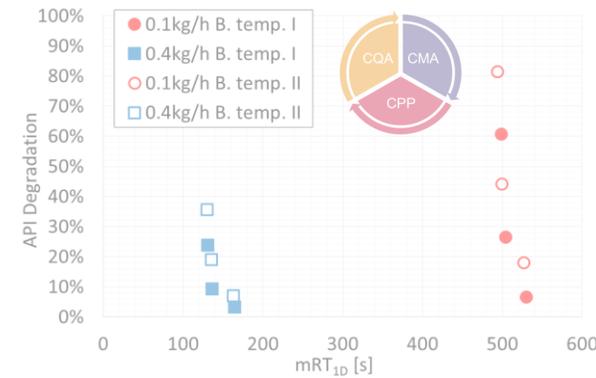
$RTD[s]$

Pharmaceutical Hot Melt Extrusion

Investigate individual screw elements

Investigate the process and product quality connection

1D HME

18mm ➡ 27mm

Numerous tools for virtual process design
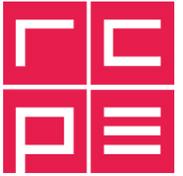
High fidelity simulations

- Simulations of complex fluids, geometries, and free surface flow

- Characterization of the screw elements:
  - What is the conveying capacity and pressure build-up of the screw?
  - How much energy input can be expected?
  - What is the mixing performance of the screw? What kneading or mixing elements should be used?
  - How high is the heat generation?
  - How do elements compare from different vendors and different extruder scales?

- Design and analysis of novel screw elements, tailored to
  the processing task and formulation

Eitzlmayr, J. Matić, and J. G. Khinast, "Analysis of flow and mixing in screw elements of corotating twin-screw extruders via SPH," AIChE J., vol. 63, no. 6, pp. 2451–2463, Jun. 2017.
H. Bauer, J. Matić, and J. Khinast, "Characteristic parameters and process maps for fully-filled twin-screw extruder elements," Chem. Eng. Sci., p. 116202, Oct. 2020.
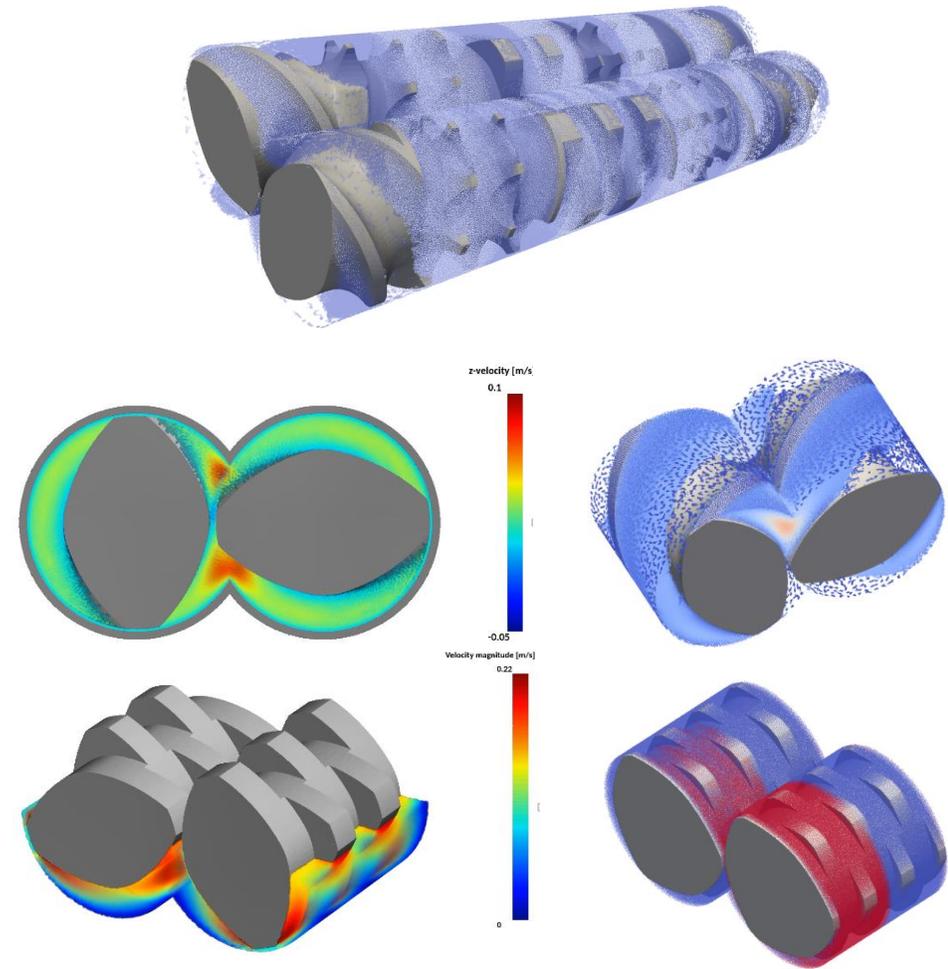
Screw element analysis for HME

SPH screw analysis

**Investigate distributive mixing
with back-pressure**
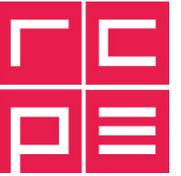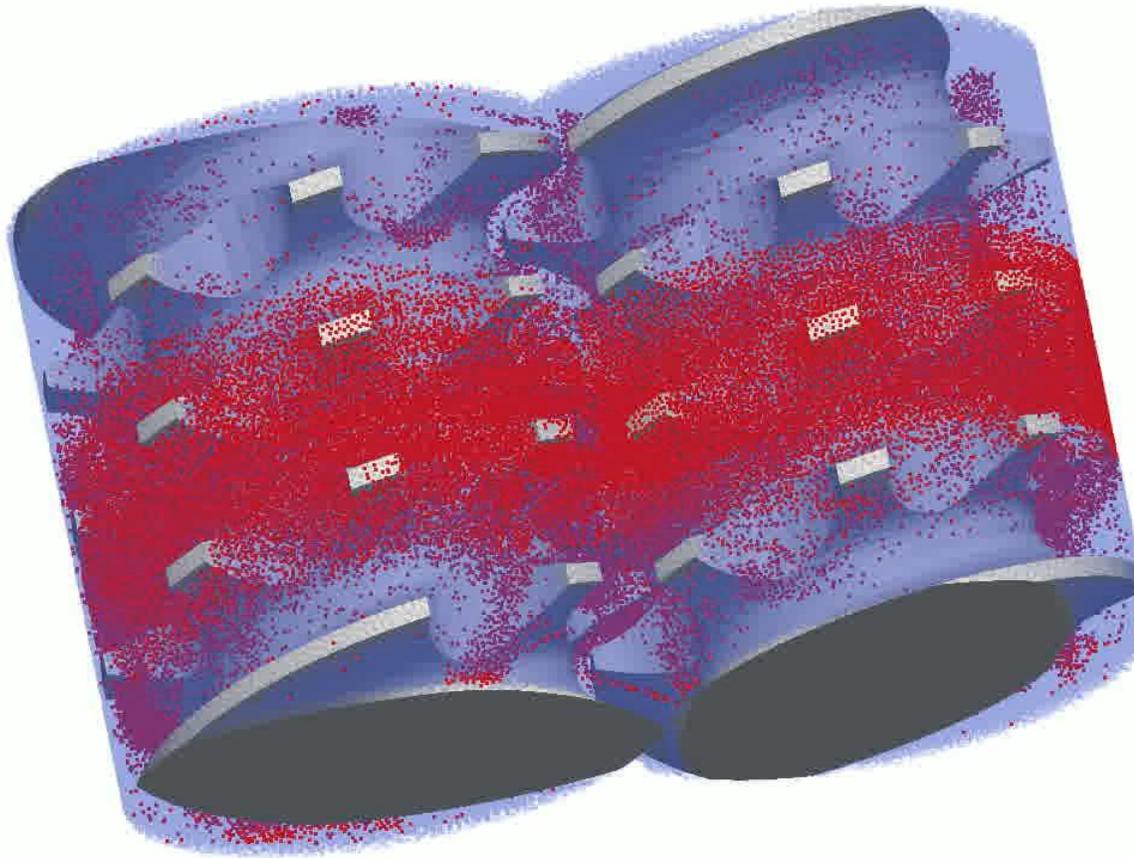
Types of screw elements

SPH screw analysis
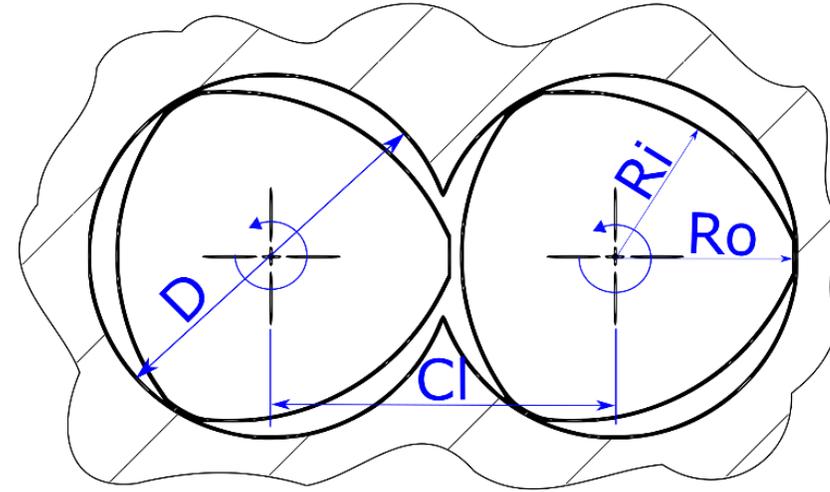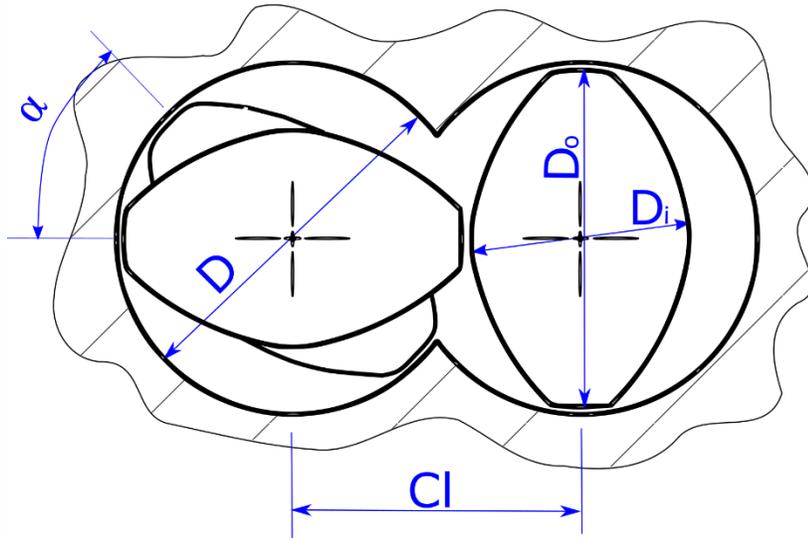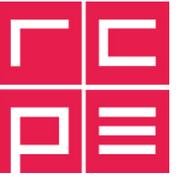
Conveying Elements
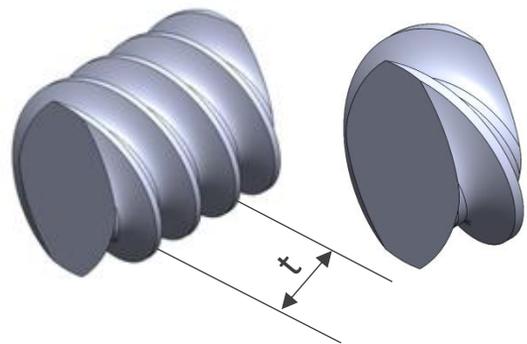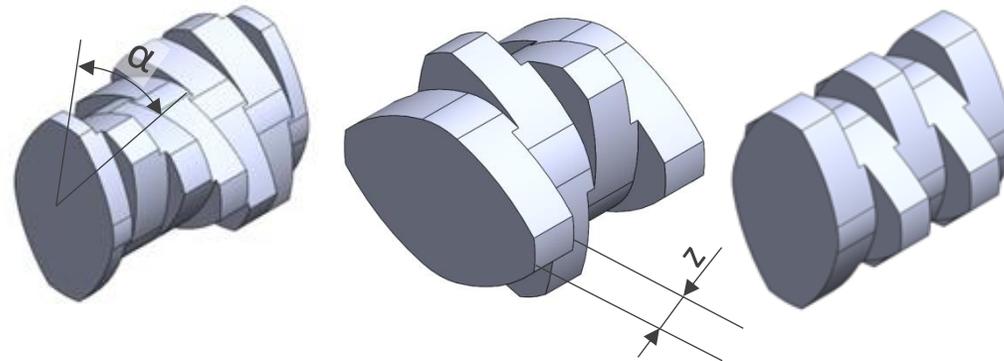
Kneading Elements

Mixing Elements
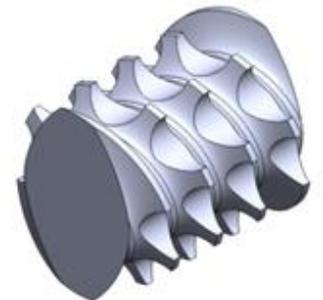
Dimensionless theory

Dimensional Analysis for Extruder Screws (Pawlowski*)

*Pawlowski, J., *Die Ähnlichkeitstheorie in der physikalisch-technischen Forschung*, Berlin/Heidelberg, Springer Publishers, 1971.
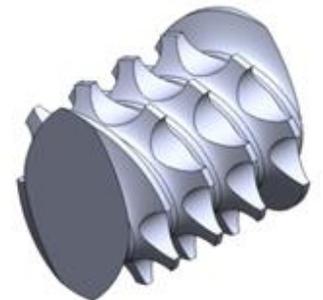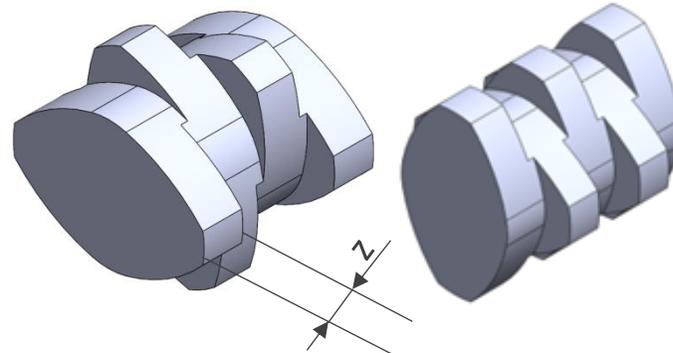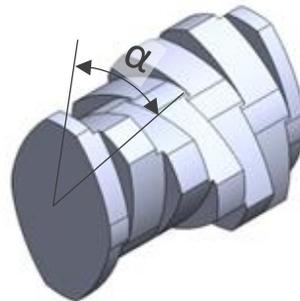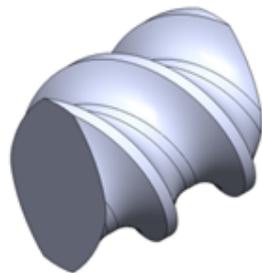
dim-less pressure drop $\dfrac{\Delta p D}{\eta n L}$

Inherent conveying capacity

A2

"backward pumping" "active conveying" "overdriven"

$\Lambda < 0$ $0 < \Lambda < 1$ $\Lambda > 1$

$\dfrac{\dot{V}}{nD^3}$ dim-less flow rate

A1

$\Lambda = 0$ $\Lambda = 1$
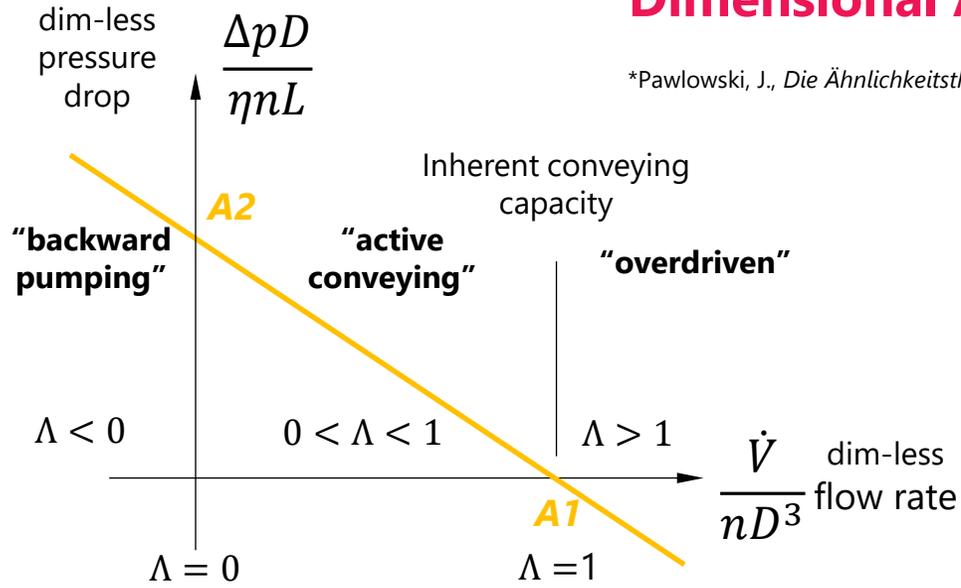
$$\frac{\Delta p D}{\eta n L} = A_2 \cdot \left(1 - \frac{1}{A_1}\frac{\dot{V}}{nD^3} \right)$$

For creeping flow (Re → 0):
linear and
independent of *n, D, L, η, ρ*
(geometrical similarity, Newtonian, creeping flow)

Conveying Elements

Kneading Elements

Mixing Elements
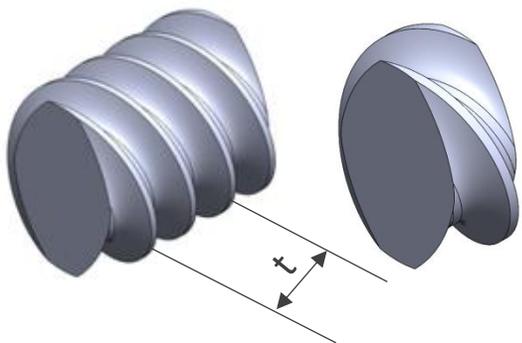
Screw pair performance

Pressure characteristics
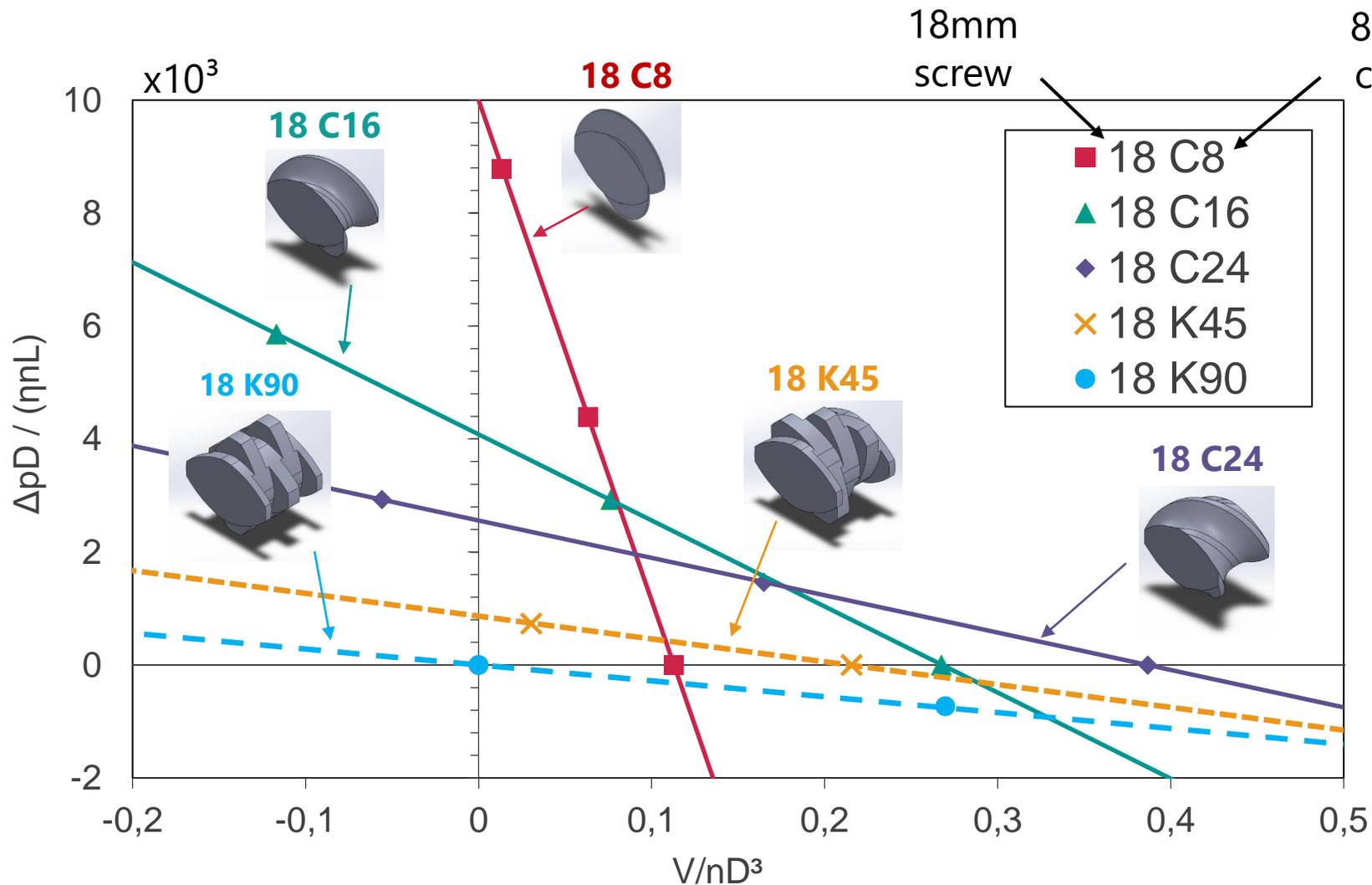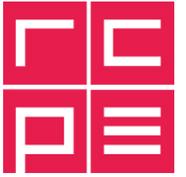
How is this useful?

1. Screw configuration assembly and definition of CPPs;
2. Screw transfer during scale-up;

J. Matić, A. Witschnigg, M. Zagler, S. Eder, and J. Khinast, "A novel in silico scale-up approach for hot melt extrusion processes," Chem. Eng. Sci., vol. 204, pp. 257–269, Aug. 2019.

Screw transfer

Screw transfer during scale up
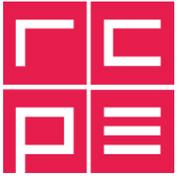
- Define the functional processing section;
- Make sure to transfer those functional processing sections so as to retain their dimensionless length and functionality (conveying capacity, power input, mixing performance…)

18mm ➡ 27mm

Screw pair performance

Pressure characteristics

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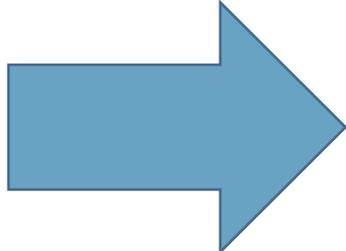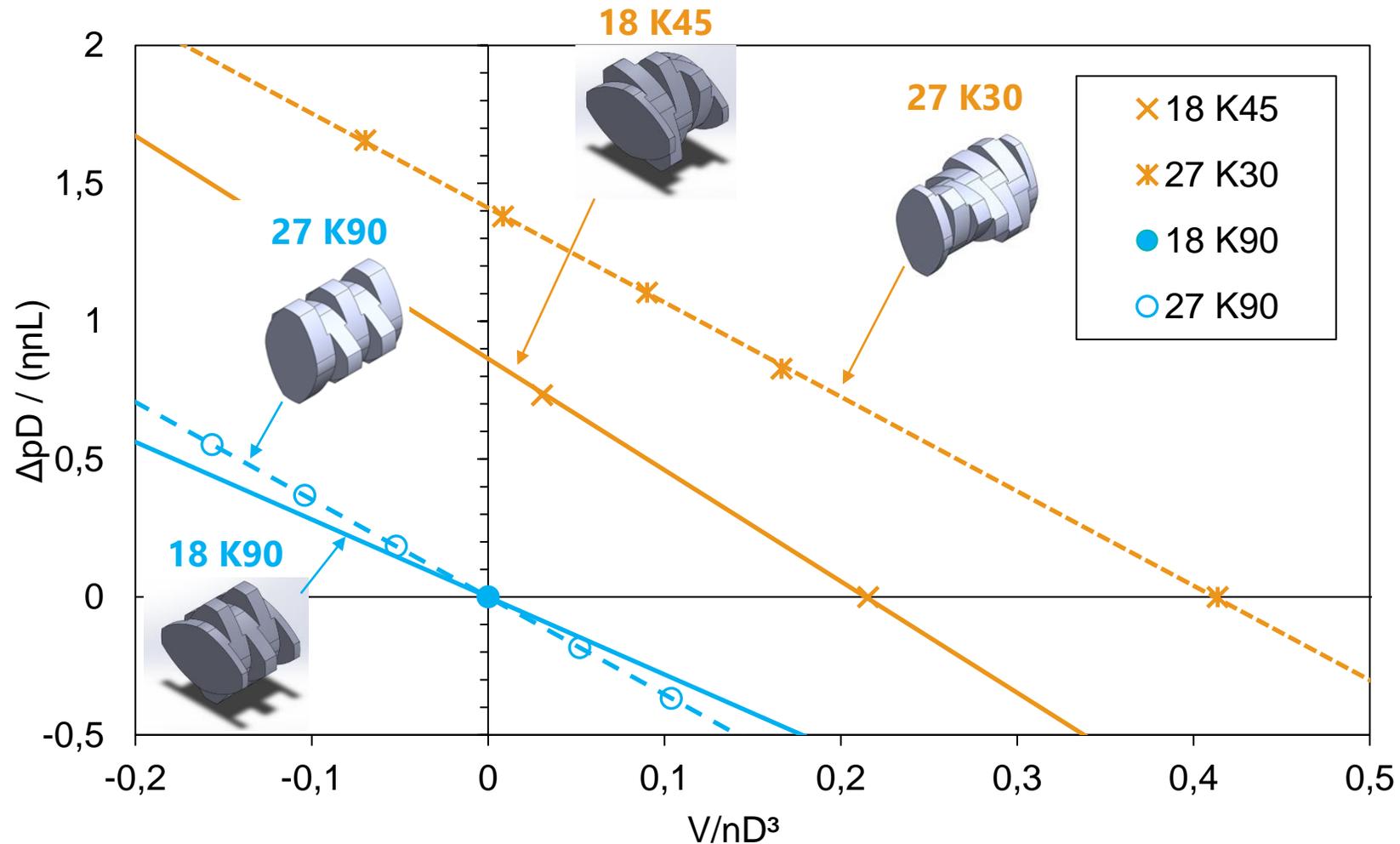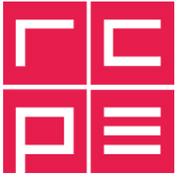
Ongoing Research with Coperion

Behavior of non-Newtonian fluids
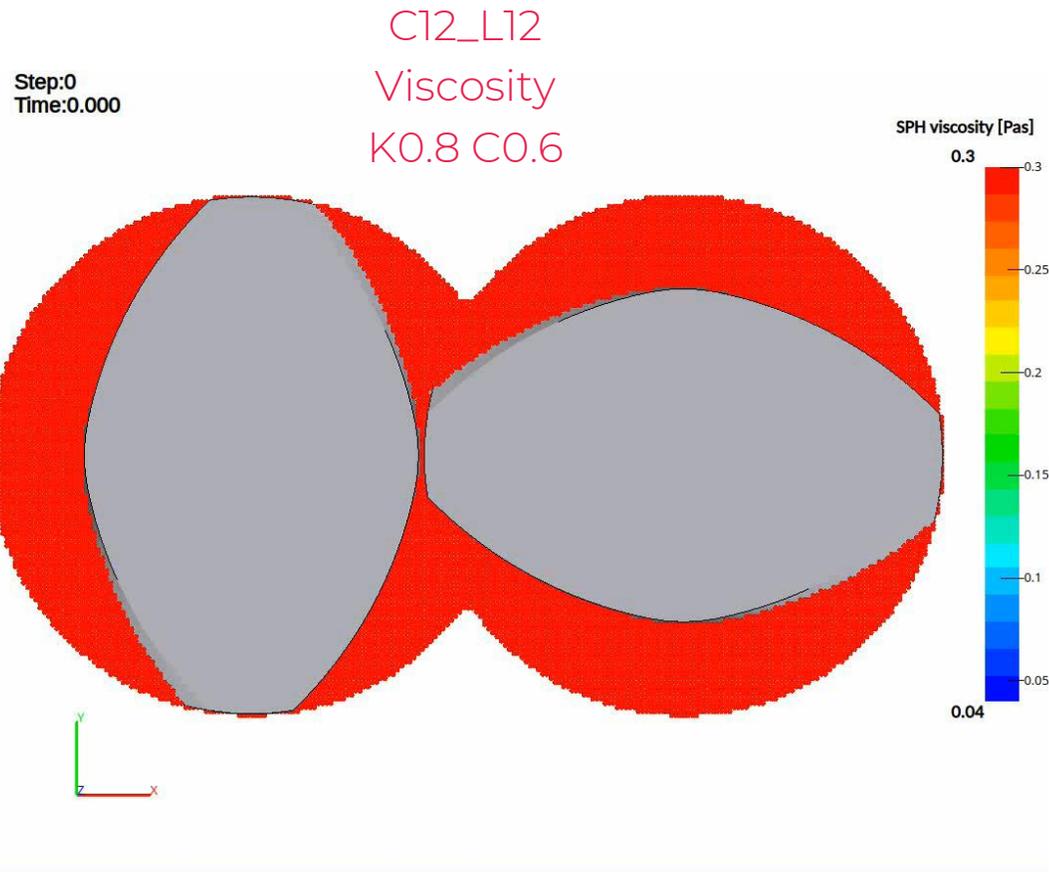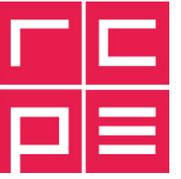
C12_L12
Viscosity
K0.8 C0.6

Pharmaceutical Hot Melt Extrusion

Investigate individual screw elements

Investigate the process and product quality connection
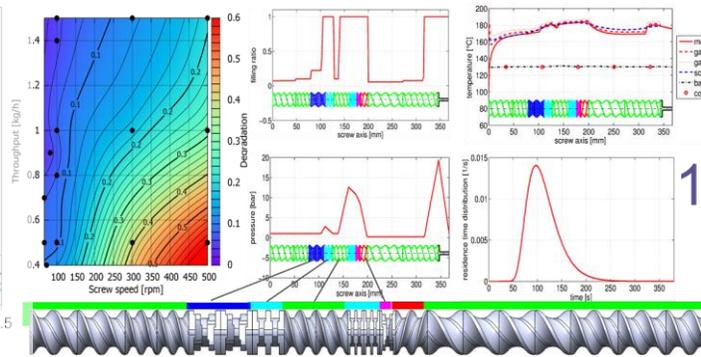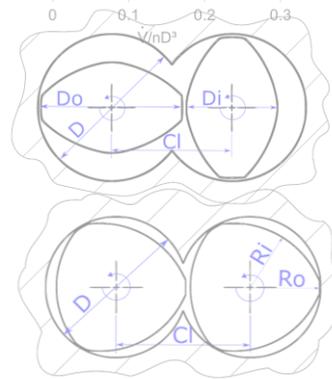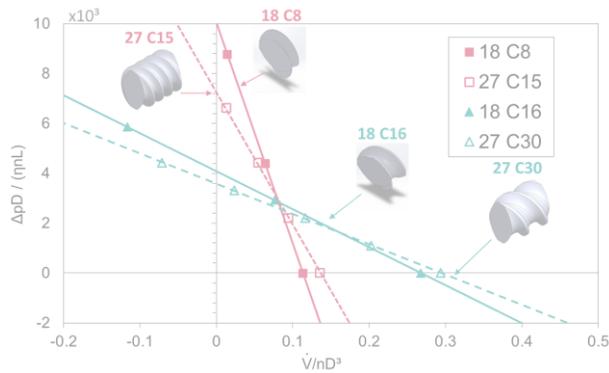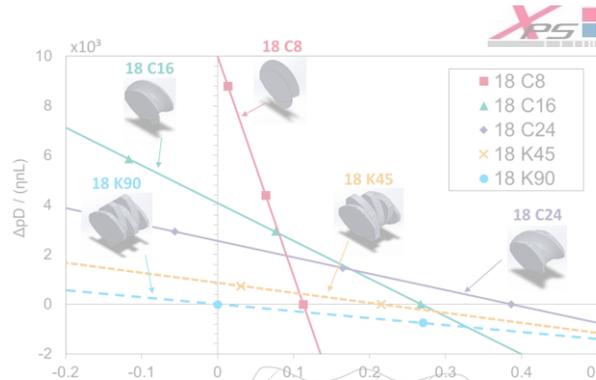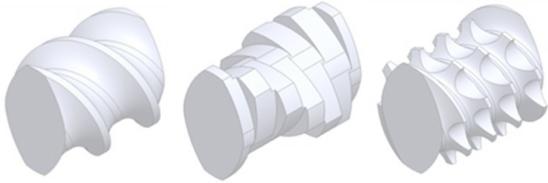
1D HME

18mm ➔ 27mm

HME processing zones

Powder feeding

Secondary feeding

Degassing zone

Melting zone

Mixing zone(s)

Downstream

$\tau[Nm]$ $SMEC[kWh/kg]$

$\dot{m}[kg/h]$ $n\,[rpm]$ $T_B[°C]$
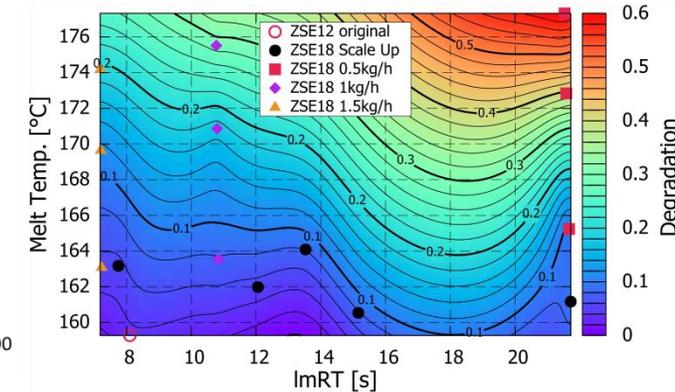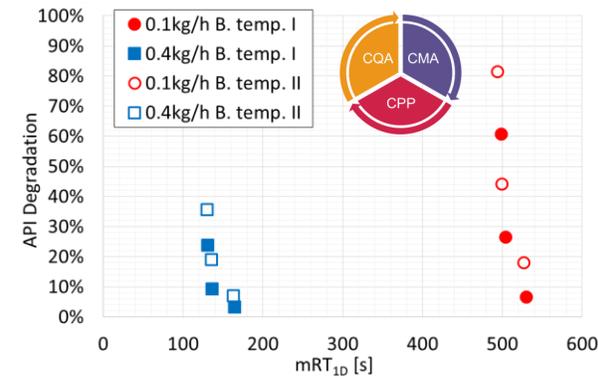
$T_M[°C]$ $p[bar]$ $RTD\,[s]$
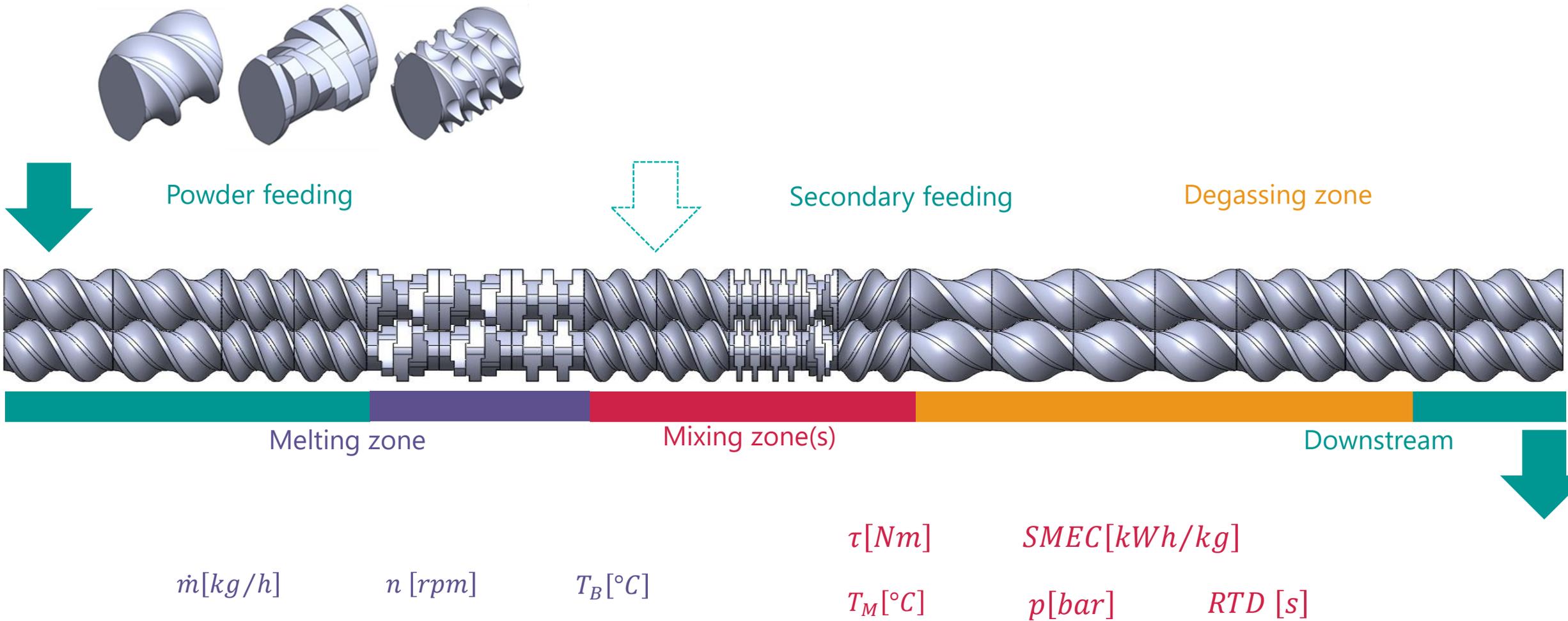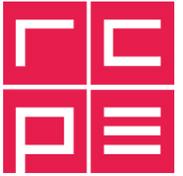
Numerous tools for virtual process design
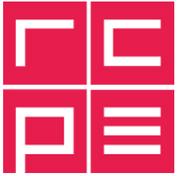
1D HME simulations

- Quick and easy-to-use full process simulations
- *In silico* test bench for process development:
  - Test different screw configurations
  - Test different screw speed, throughput, and barrel temperature settings
  - Test different formulations
- Detailed process analysis, e.g. filling degree, melt temperature, residence time distribution…
- *In silico* process setup on different extruders, process transfer, and scale-up

Input
- High fidelity simulations;
- Material data
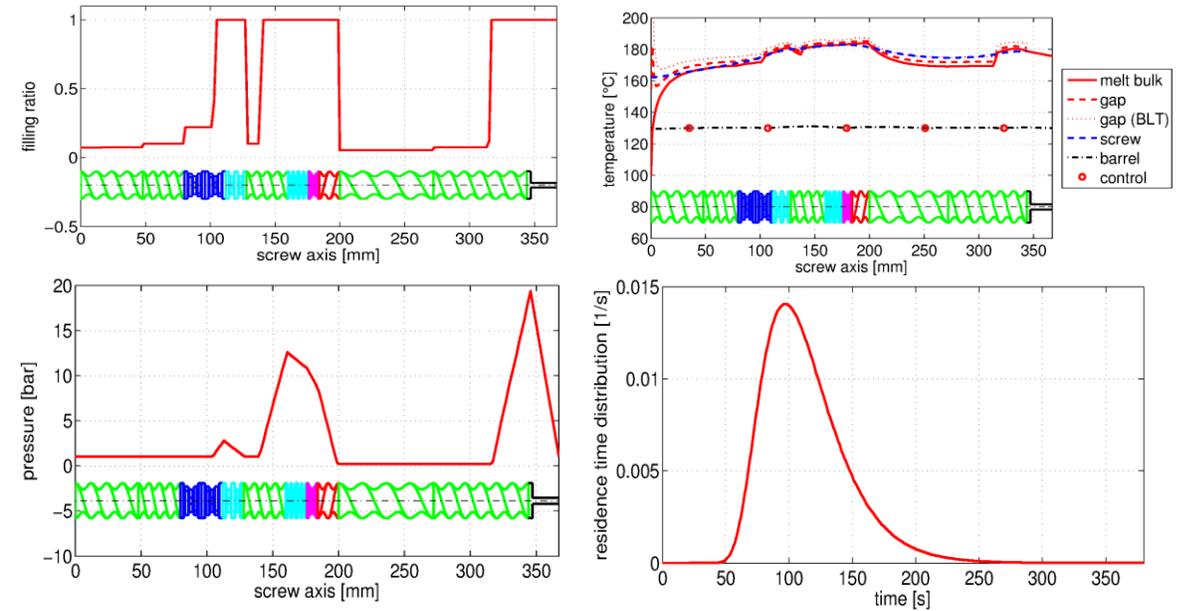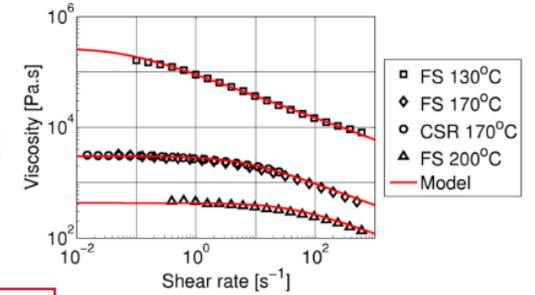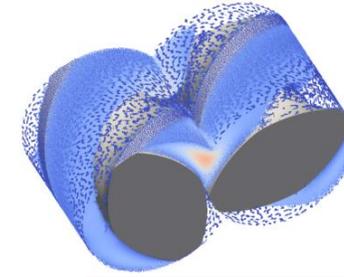
J. Matić, A. Witschnigg, M. Zagler, S. Eder, and J. Khinast, "A novel in silico scale-up approach for hot melt extrusion processes," Chem. Eng. Sci., vol. 204, pp. 257–269, Aug. 2019.

A. Eitzlmayr et al., "Mechanistic modeling of modular co-rotating twin-screw extruders," Int. J. Pharm., vol. 474, no. 1–2, pp. 157–176, Oct. 2014.

17

Formulation Properties for Process Setup

Viscosity
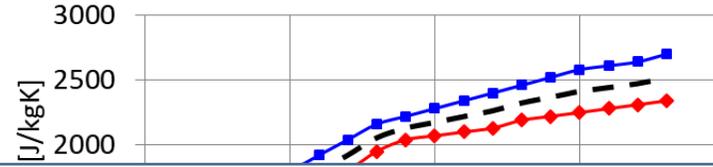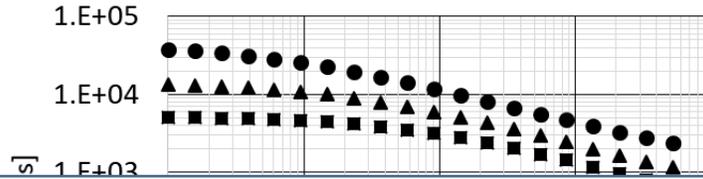
Heat Capacity

Guide the Formulation Development to ensure that the Physical Formulation Properties are in line with the Production Technology.

Thermal Conductivity
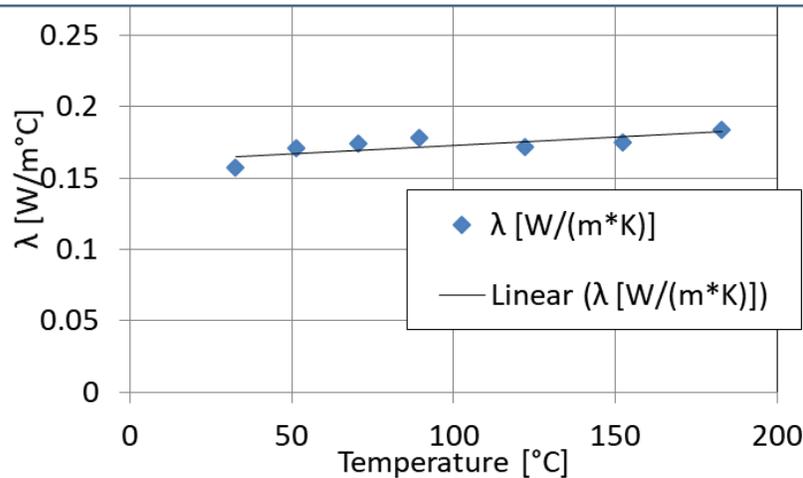
Spec. Volume
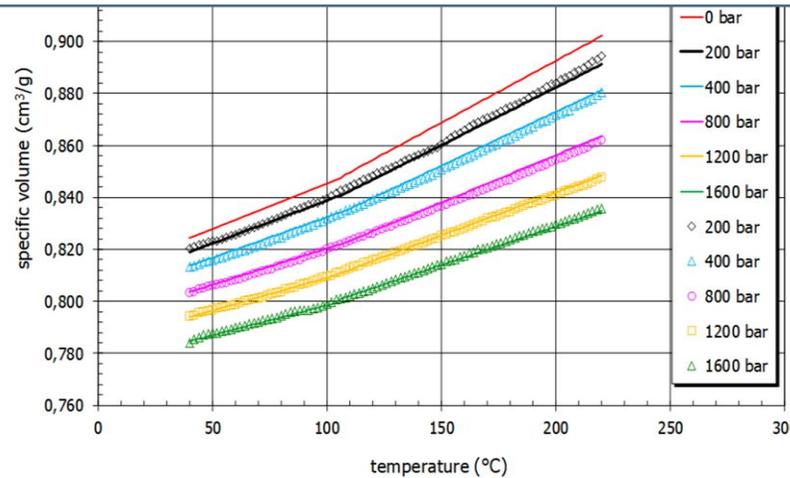
1D HME process design
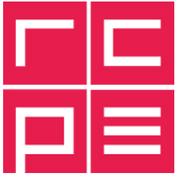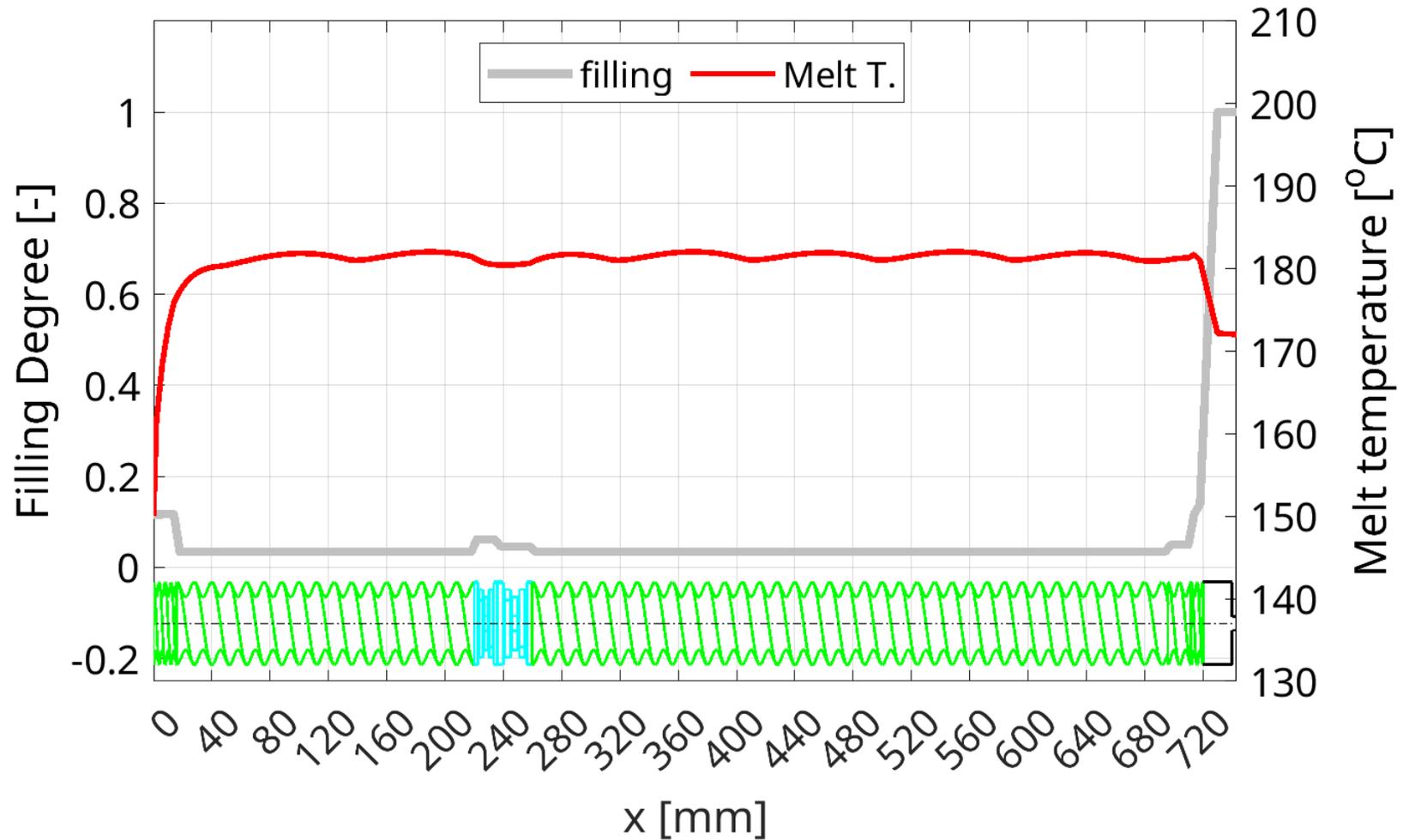
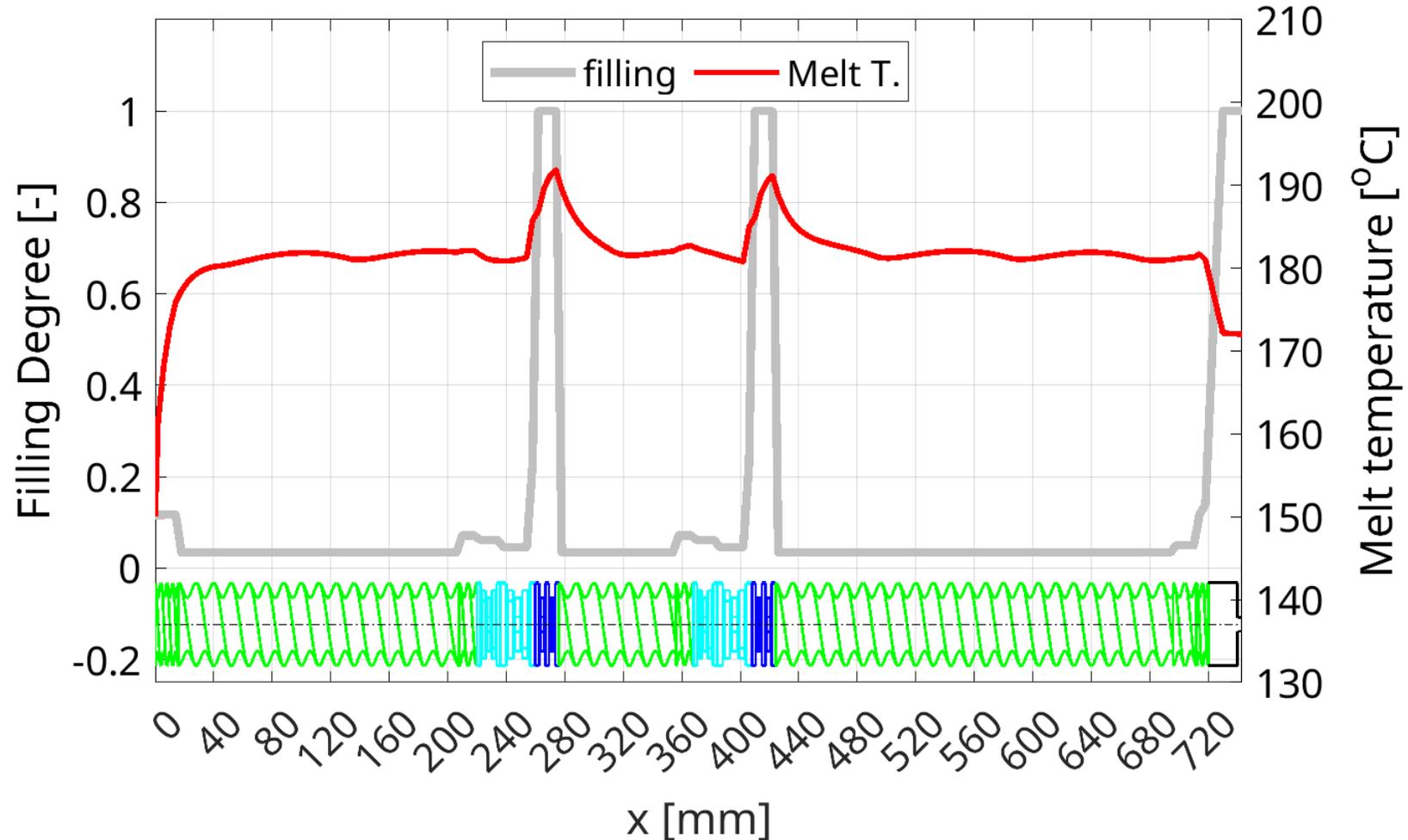eXtended Particle Simulations
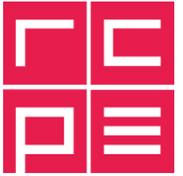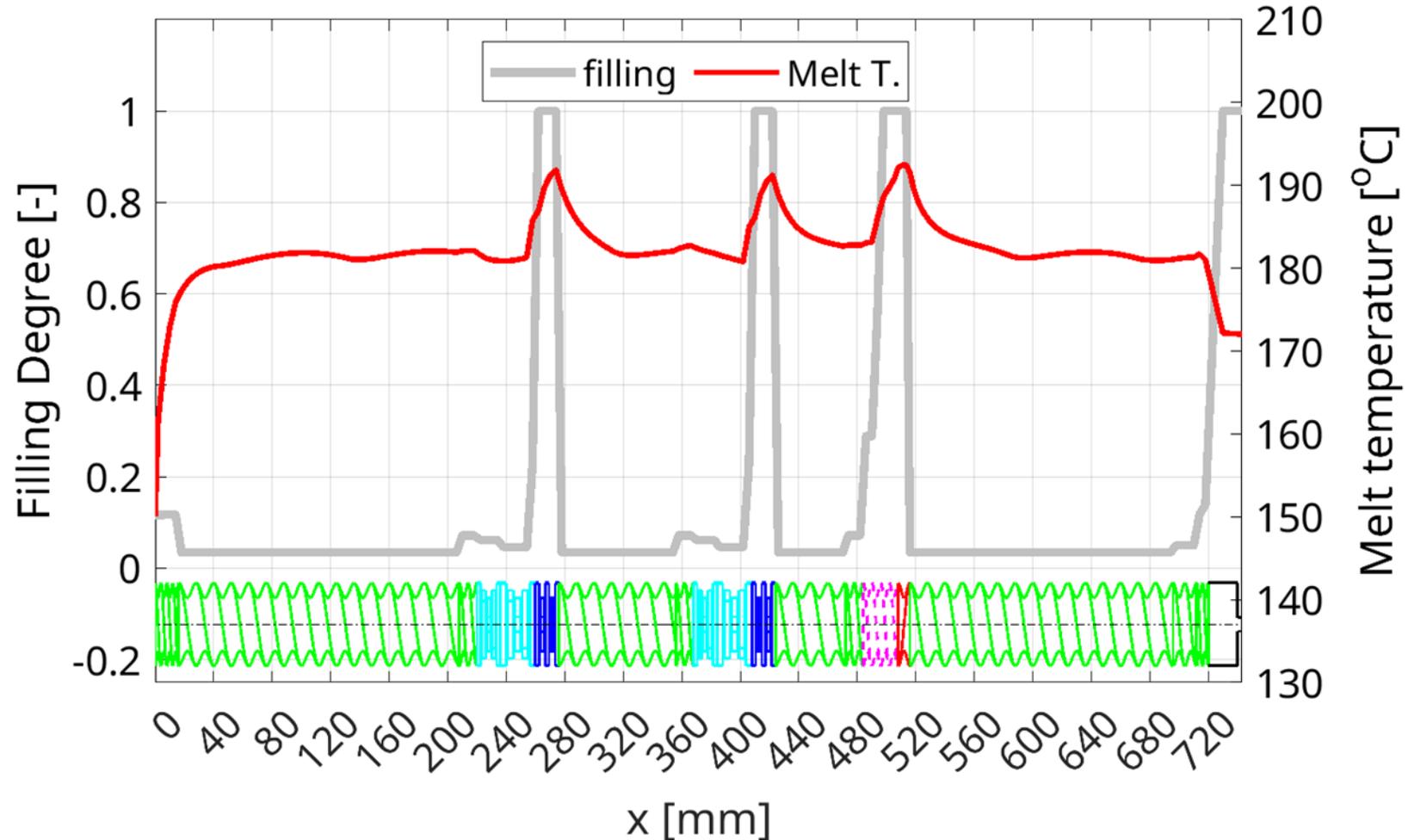**eXPS** **1D HME**
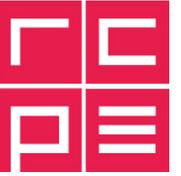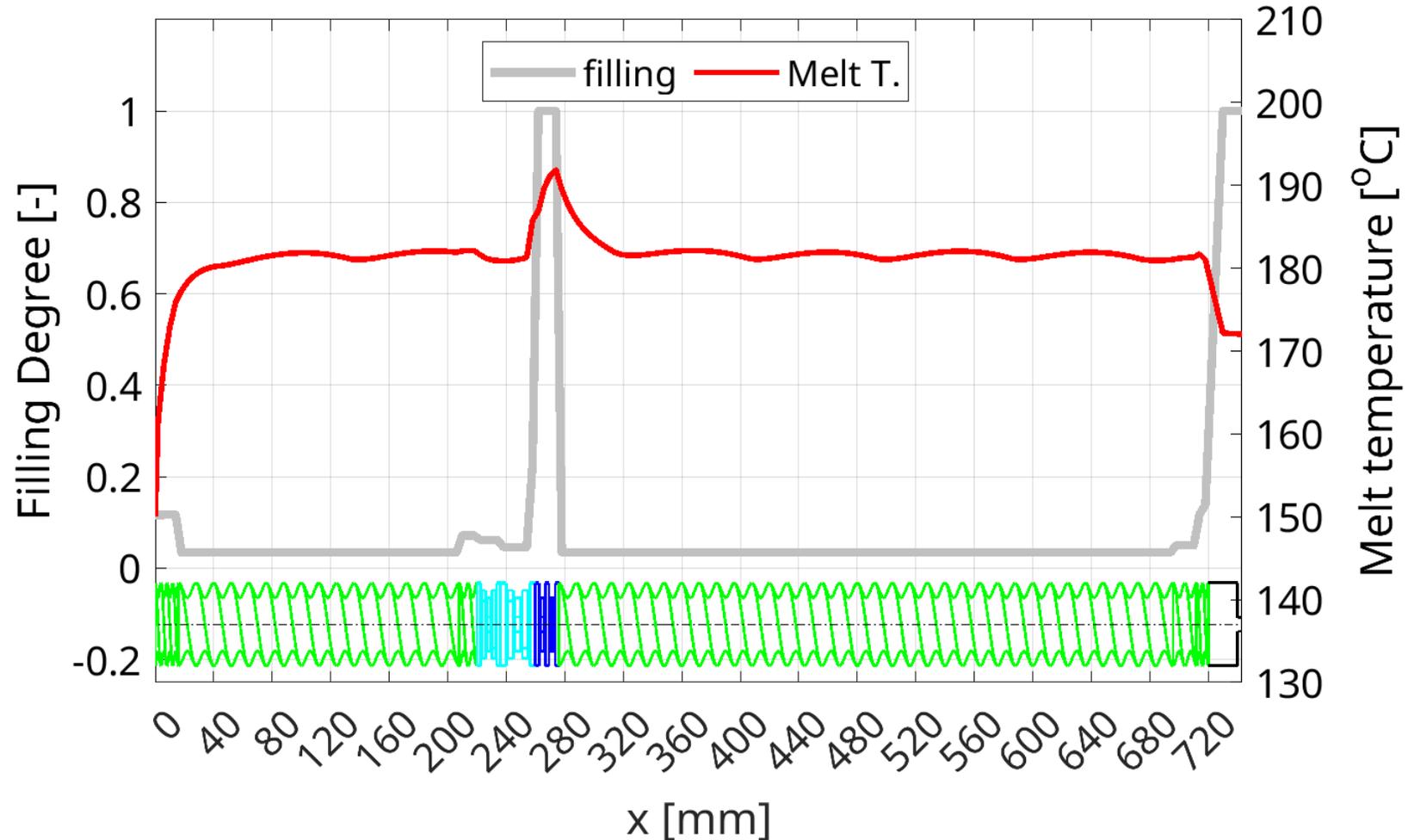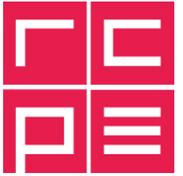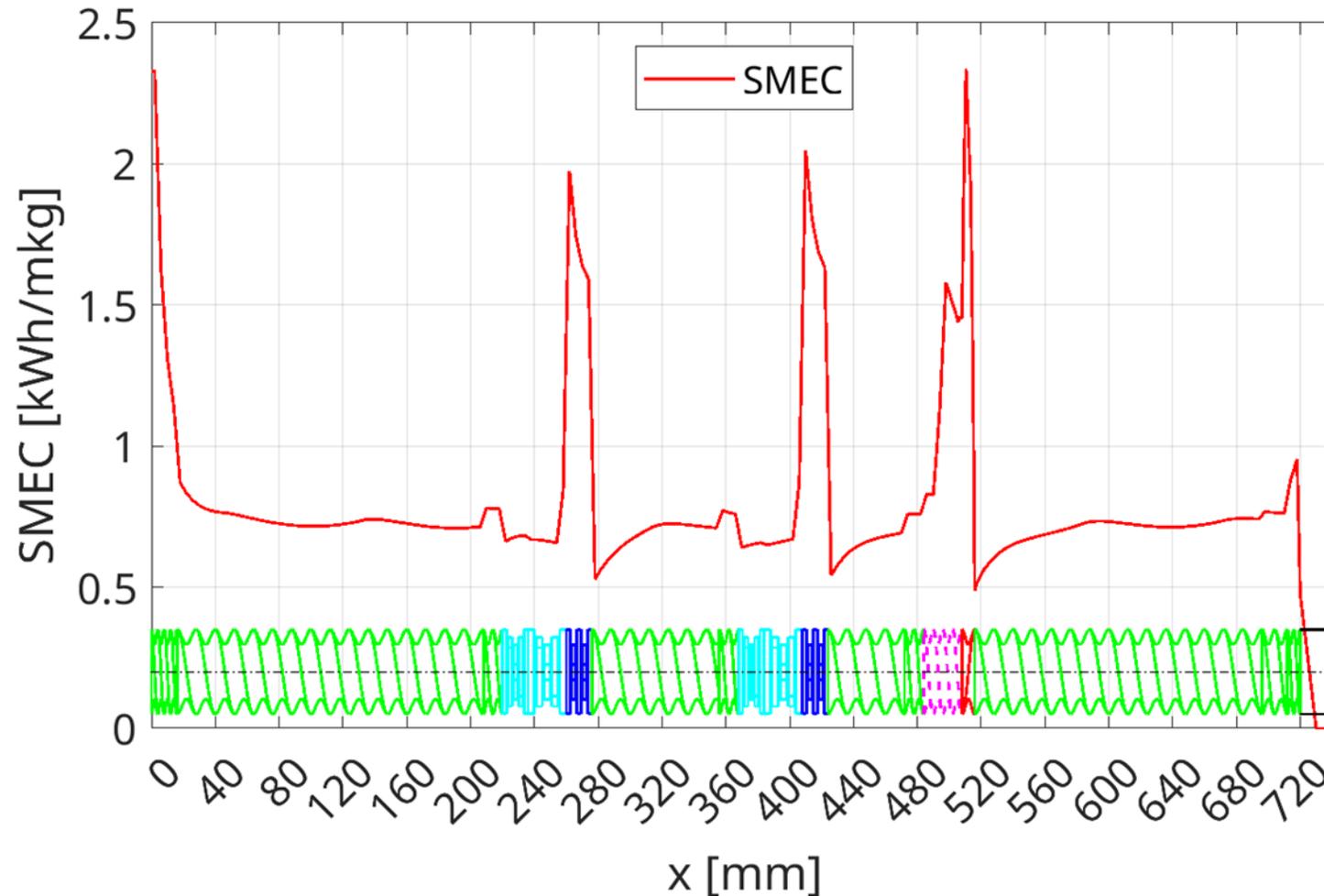
$\dot{m}\,[kg/h]$

$n\,[rpm]$

1D HME process design

Coperion ZSK18 process design study
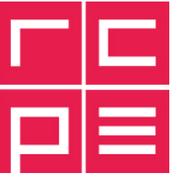
$\dot{m}[kg/h]$

$n\ [rpm]$

1D HME process design

Coperion ZSK18 process design study

1D HME process design

$\dot{m}\,[kg/h]$

$n\,[rpm]$

1D HME process design

Coperion ZSK18 Process Design Study

$\dot{m}[kg/h]$

$n \ [rpm]$

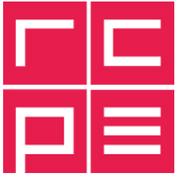# 1D HME process design

Coperion ZSK18 Process Design Study
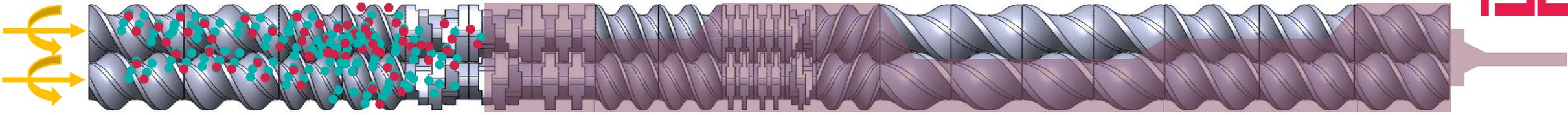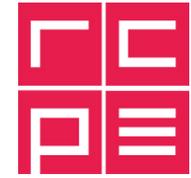
$\dot{m}\,[kg/h]$
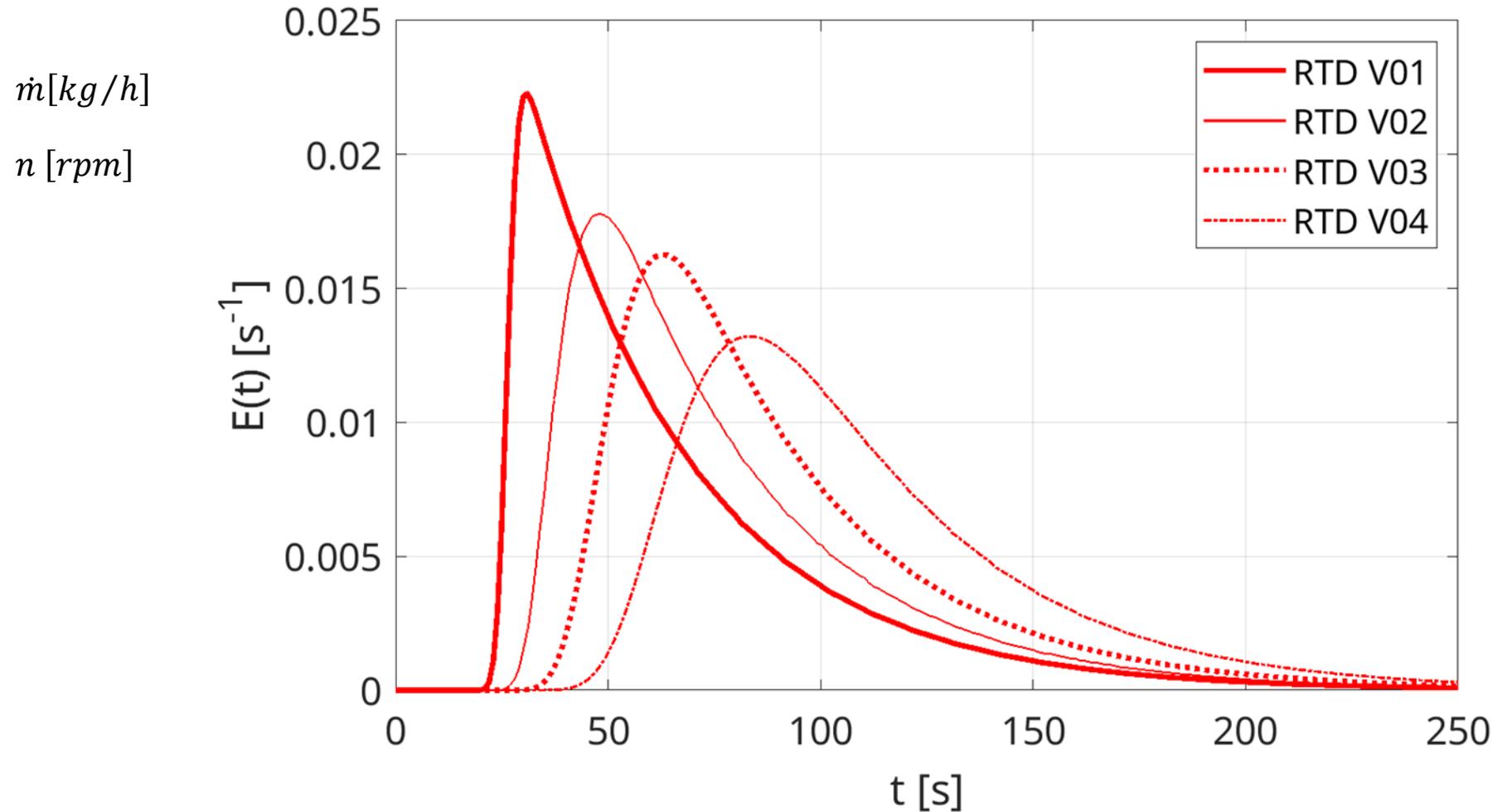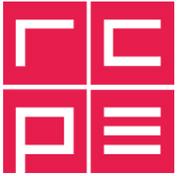
$n\,[rpm]$

Validation

1D HME process design

Validation
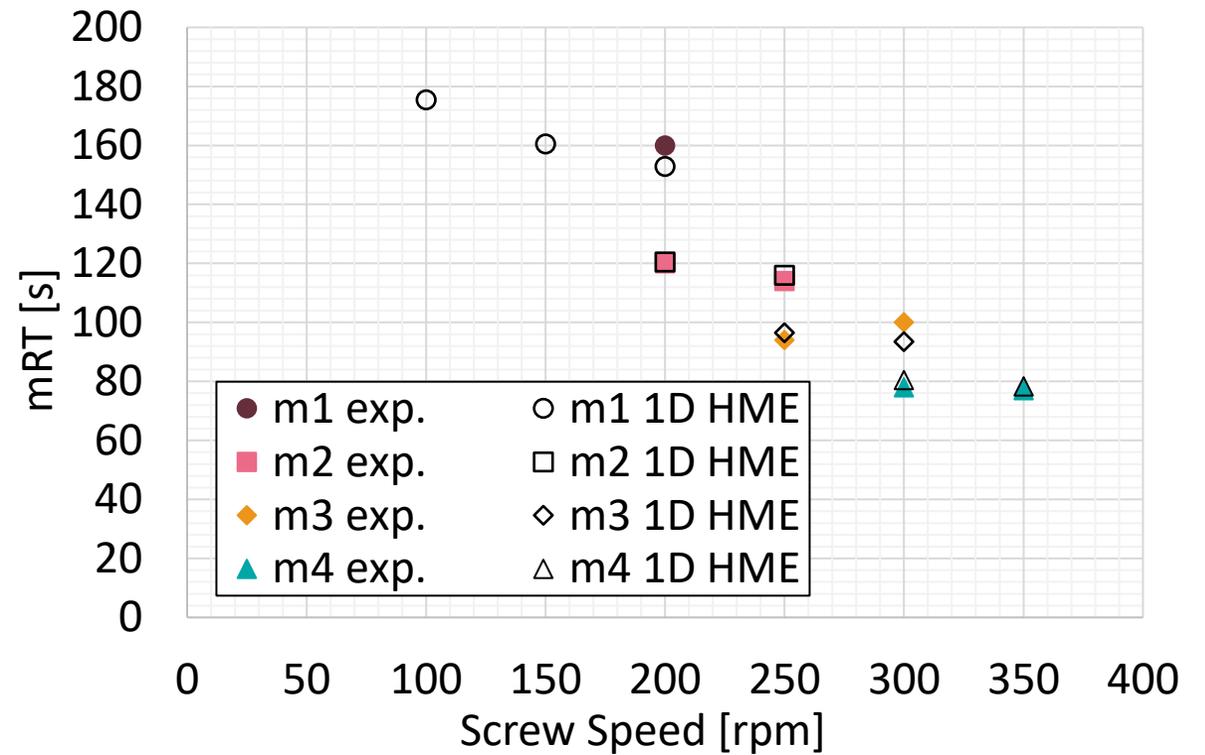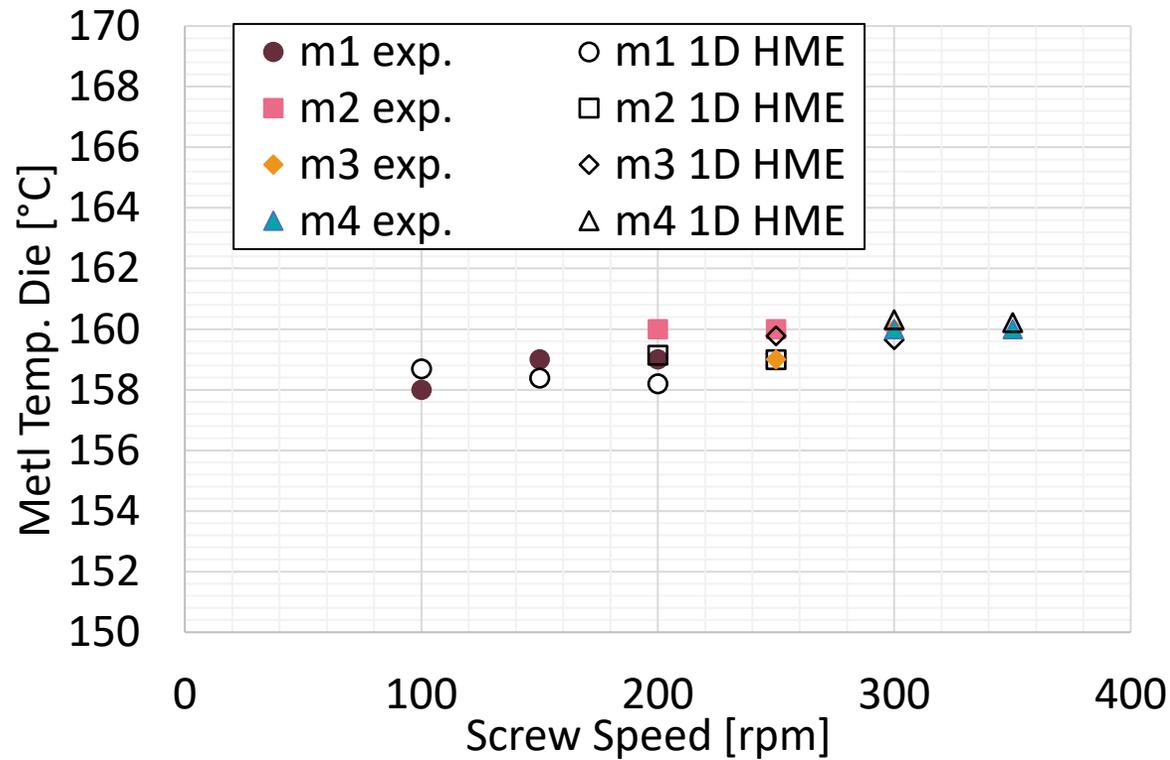
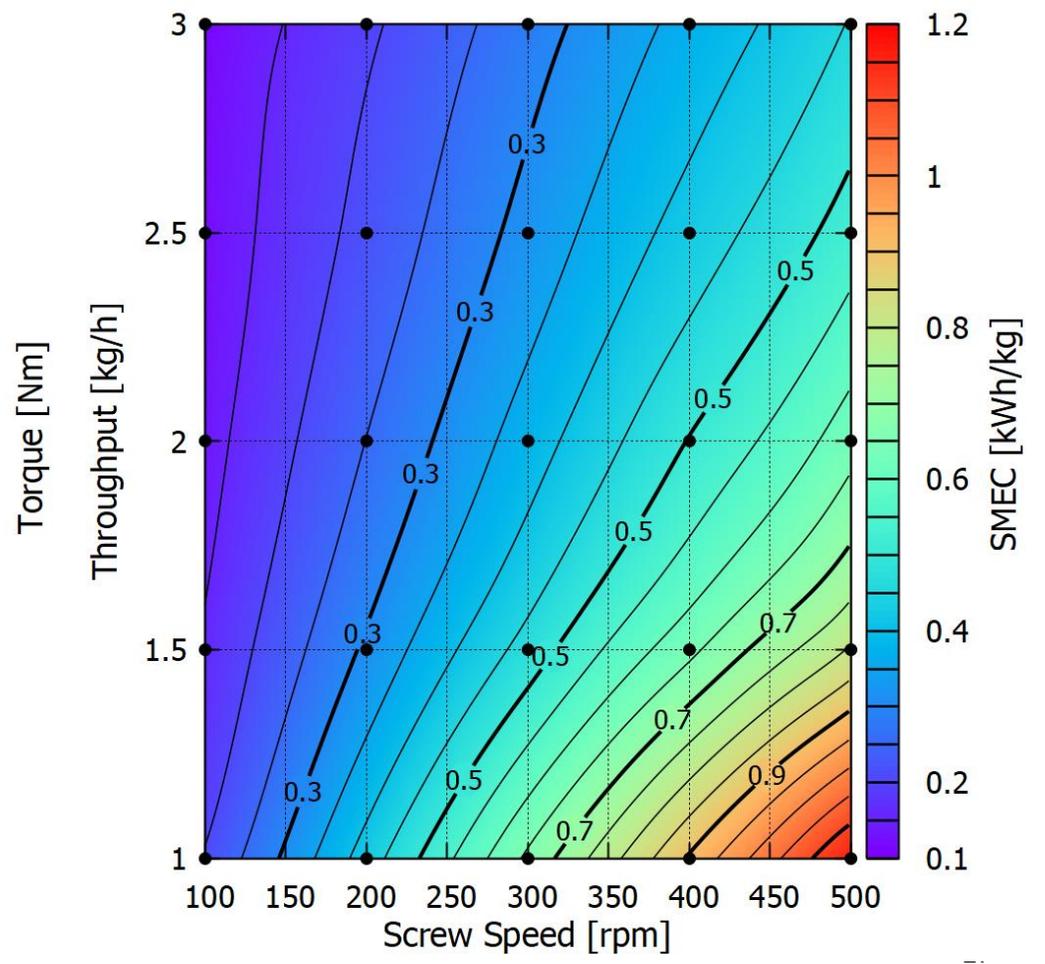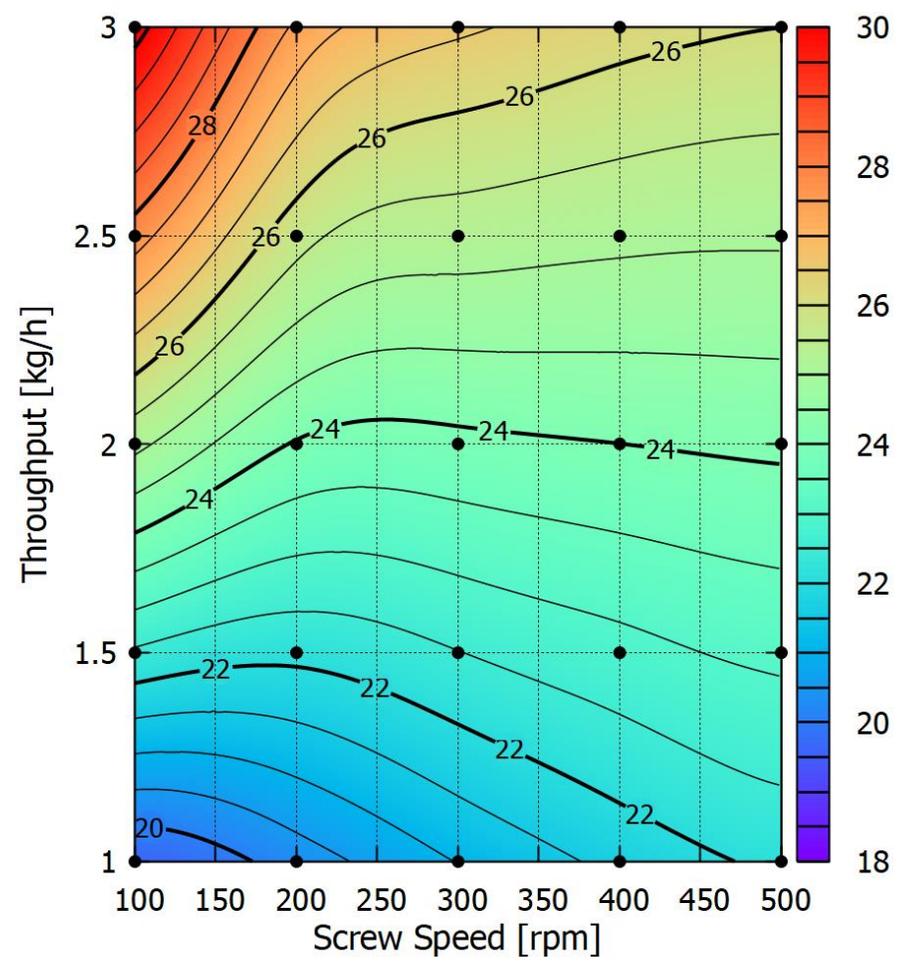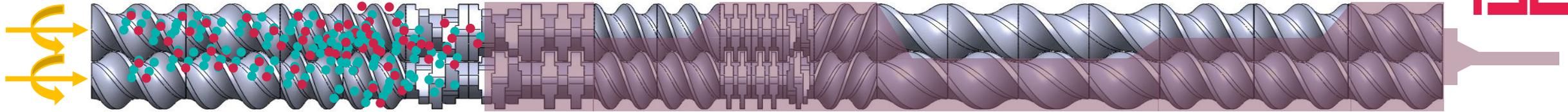# Choosing the right process space

18mm

$\dot{m}[kg/h]$

$n\ [rpm]$

$T_B[°C] = const.$

$\tau[Nm]$

$$SMEC = \frac{2 \cdot \pi \cdot n \cdot \tau}{\dot{m}}$$
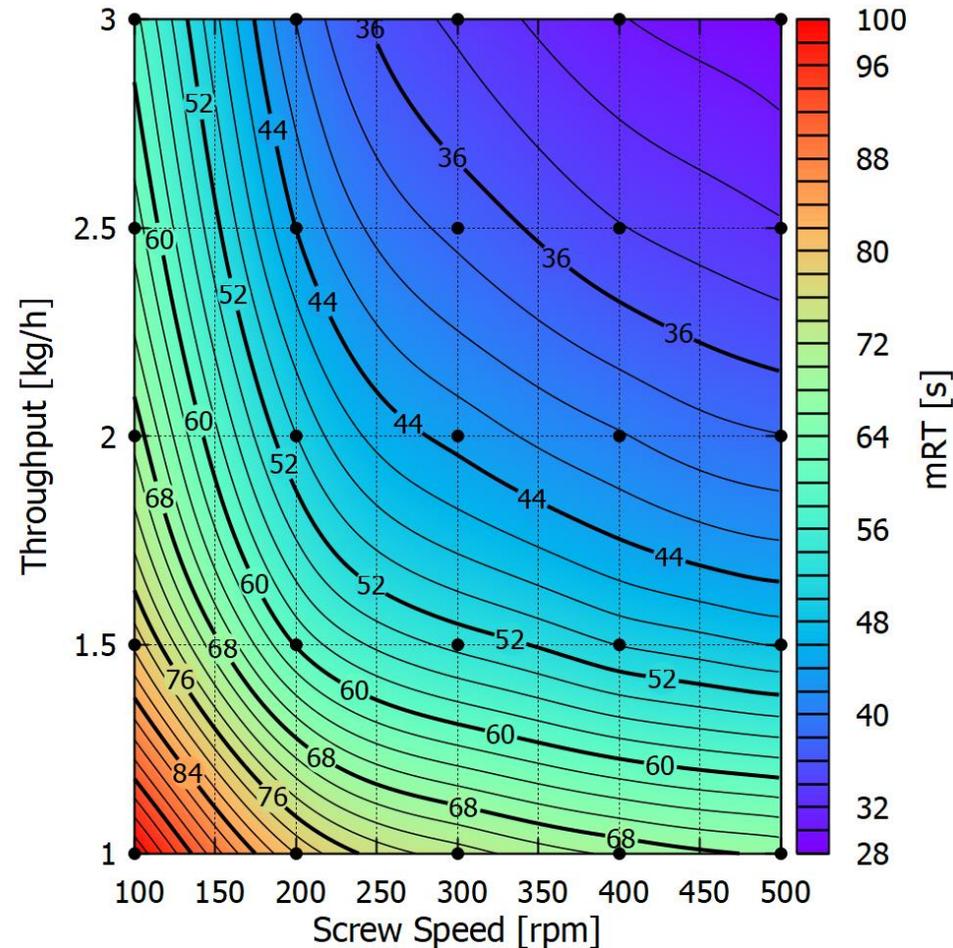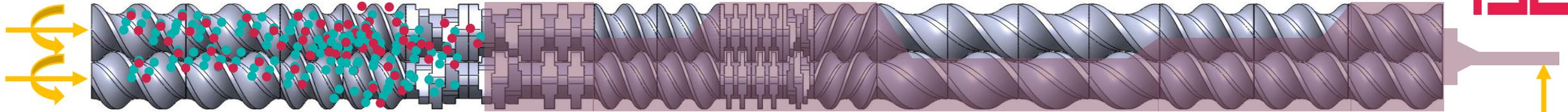
Choosing the right process space

18mm

$\dot{m}\,[kg/h]$ ↓ ↑

$n\,[rpm]$ ↓ ↑

$T_B\,[°C] = const.$

$mRT\,[s]$

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Choosing the right process space

18mm

$\dot{m}\,[kg/h]$ ↓ ↑

$n\,[rpm]$ ↑

$T_B[°C] = const.$

$T_{Die}\,[°C]$

$T_{Barrel} = 150°C$

eXtended Particle Simulations

eXPS 1D **HME**
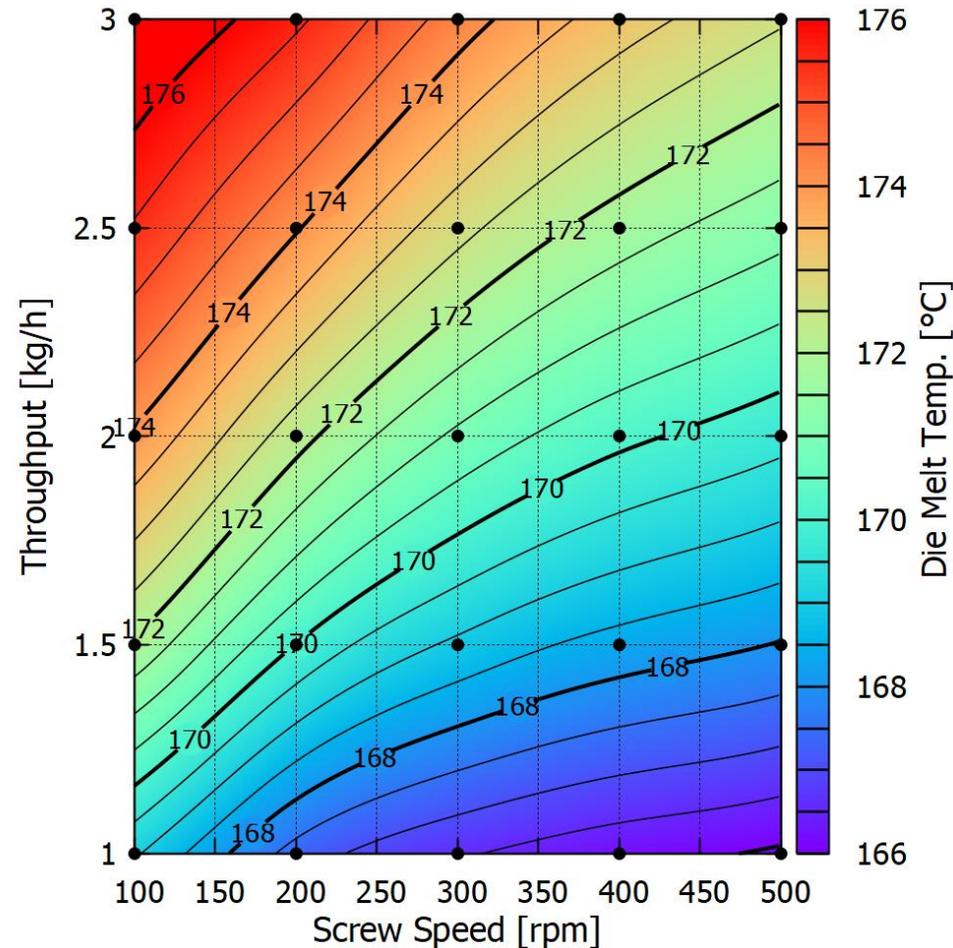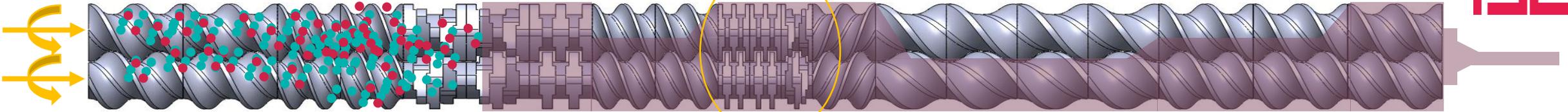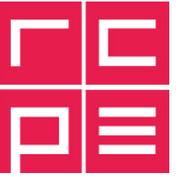
18mm

$\dot{m}\,[kg/h]$ ↓ ↑

$n\,[rpm]$ ↓ ↑

$T_B\,[°C] = const.$

$T_{loc}\,[°C]$

$lmRT\,[s]$

$T_{Barrel} = 150°C$

Left plot:
- X-axis: Screw Speed [rpm] (100–500)
- Y-axis: Throughput [kg/h] (1–3)
- Color bar: AvMelt [°C] (174–188)
- Contour labels: 176, 178, 180, 182, 184, 186

Right plot:
- X-axis: Screw Speed [rpm] (100–500)
- Y-axis: Throughput [kg/h] (1–3)
- Color bar: lmRT [s] (5–30)
- Contour labels: 10, 15, 20, 25
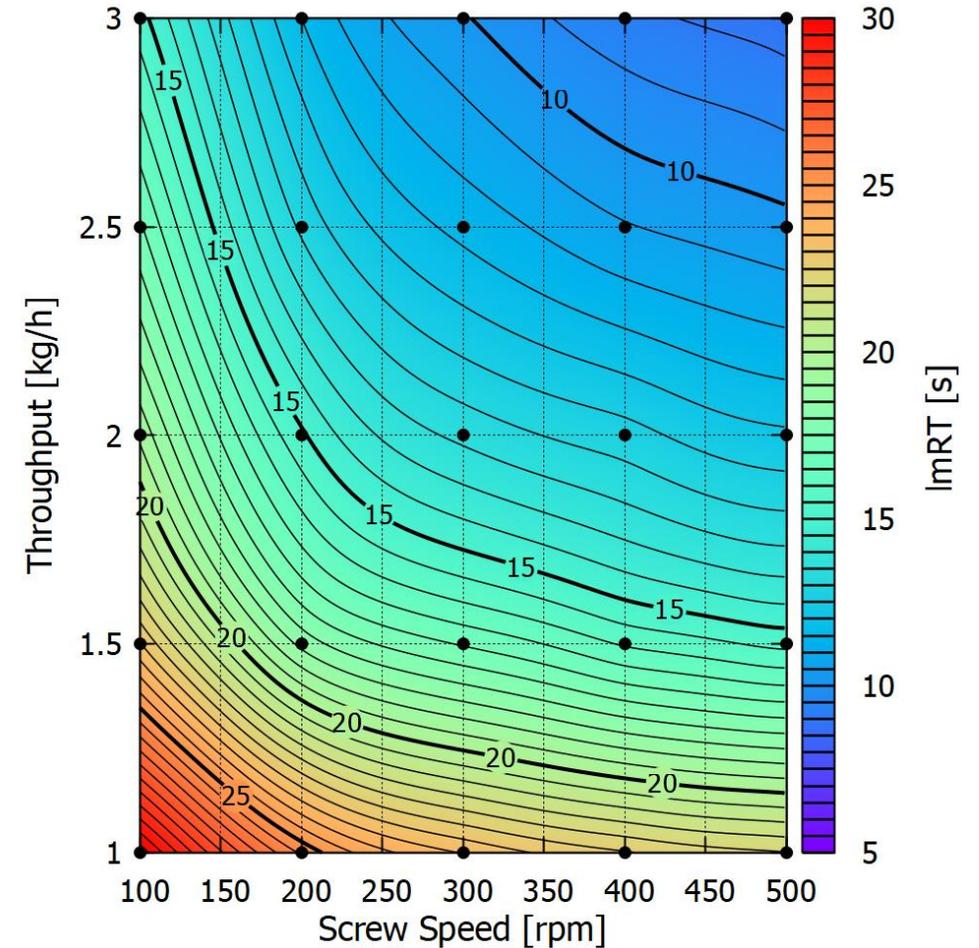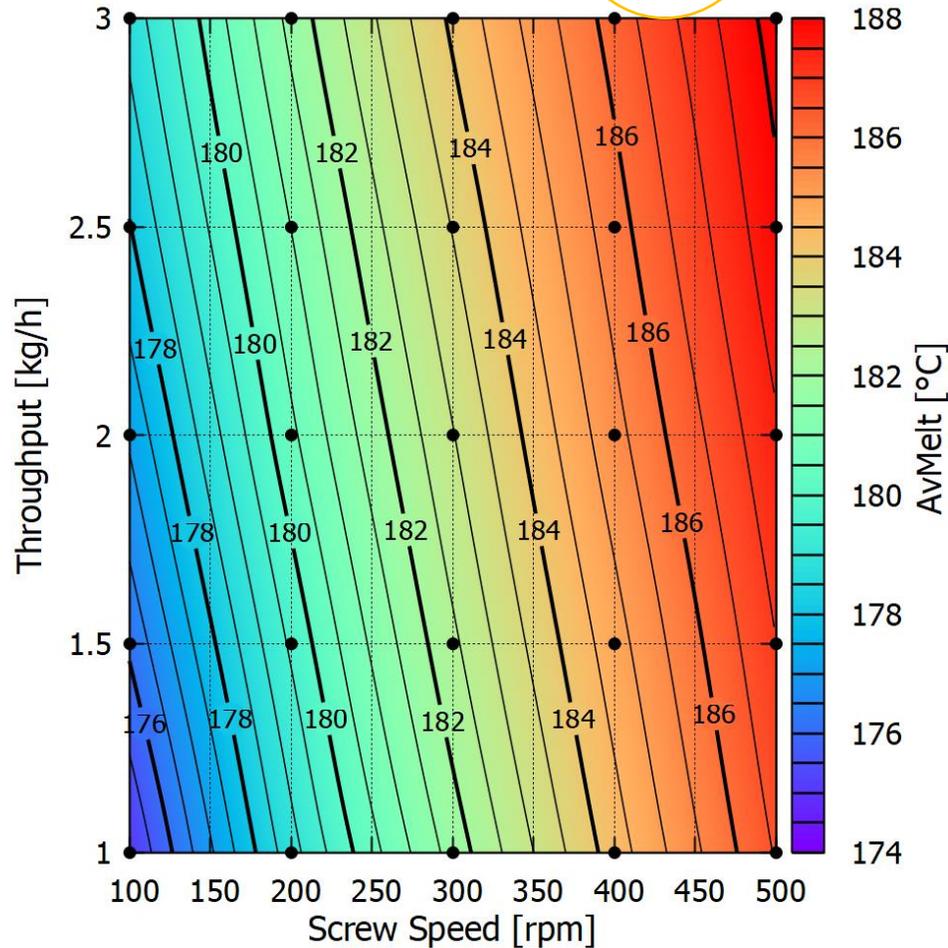
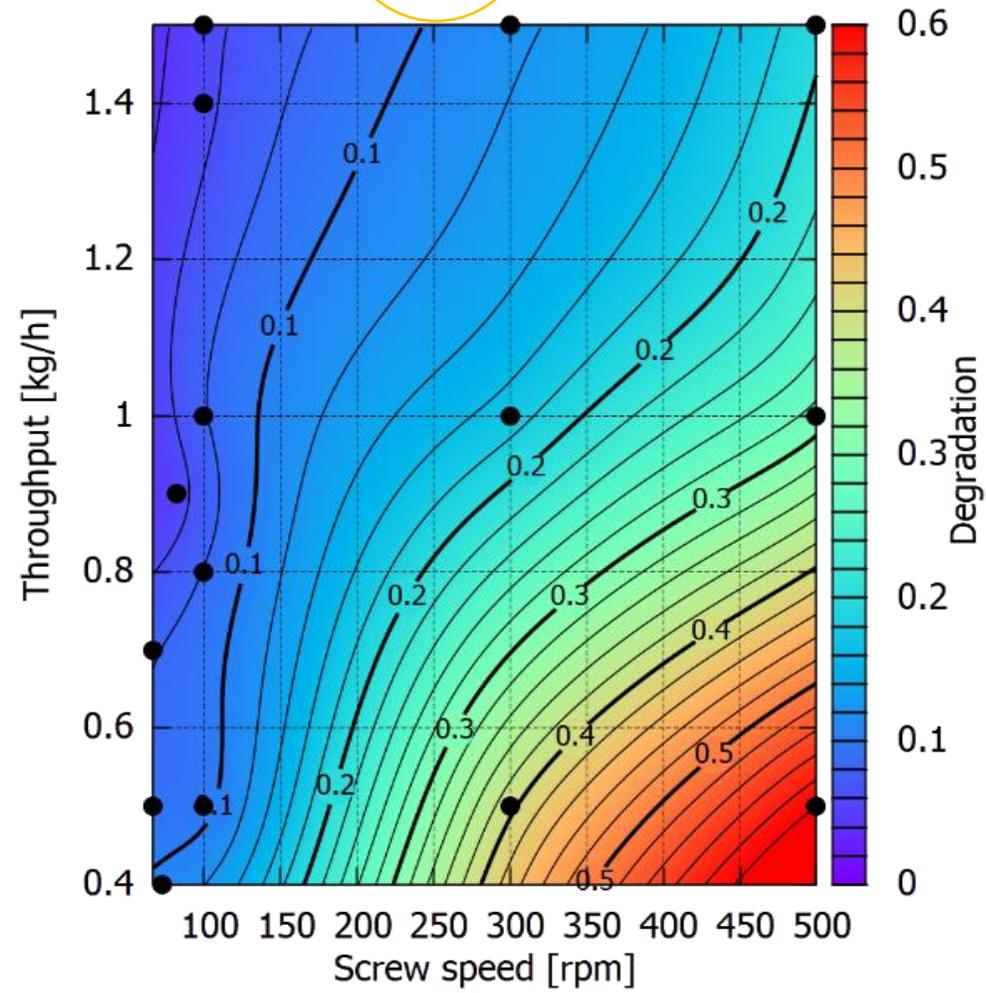# Choosing the right process space
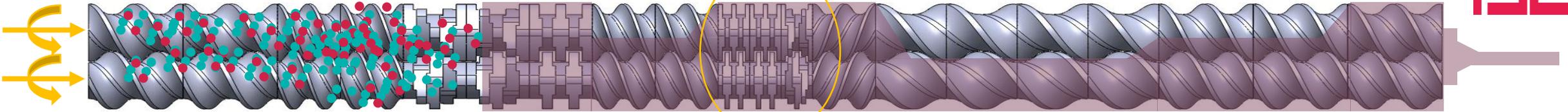
18mm

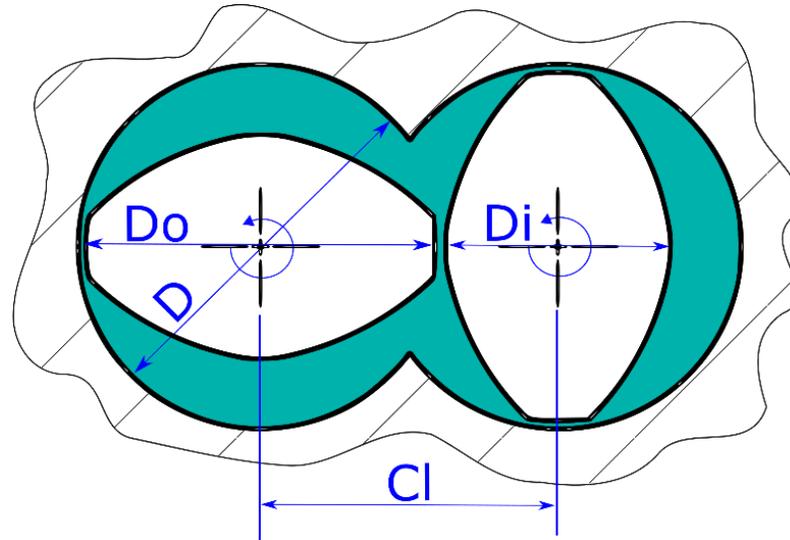$\dot{m}[kg/h]$ ↓↑

$n\ [rpm]$ ↑

$T_B[°C] = const.$

CQA

J. Matić et al., "Towards predicting the product quality in hot-melt extrusion: Small scale extrusion," Int. J. Pharm. X, vol. 2, p. 100062, Dec. 2020, doi: 10.1016/j.ijpx.2020.100062.

J. Matić et al., "Towards predicting the product quality in hot-melt extrusion: Pilot plant scale extrusion," Int. J. Pharm. X, vol. 3, p. 100084, Dec. 2021, doi: 10.1016/j.ijpx.2021.100084.
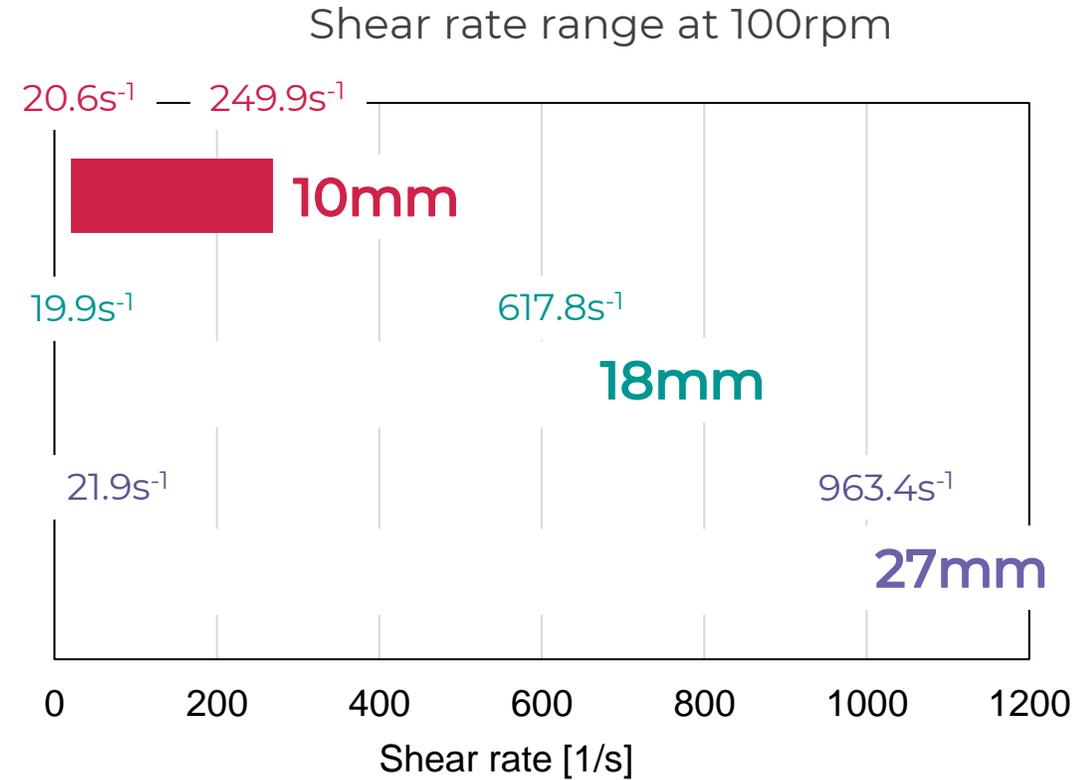
31

Process Scale-up and Transfer

Scale-up Considerations

	10mm	18mm
D [mm]	9.3	18
D_o [mm]	9	17.8
D_i [mm]	5.6	11.8
D_o/D_i [-]	1.6	1.51
Cl [mm]	7.5	15

	27mm
D [mm]	27.2
D_o [mm]	27
D_i [mm]	18.4
D_o/D_i [-]	1.47
Cl [mm]	23

	10mm	18mm	27mm
D_o [mm]	10.5	17.8	27
A_{cr} [mm²]	65.25	175.32	376.64

Shear rate range at 100rpm

- 10mm: $20.6\,s^{-1}$ — $249.9\,s^{-1}$
- 18mm: $19.9\,s^{-1}$ — $617.8\,s^{-1}$
- 27mm: $21.9\,s^{-1}$ — $963.4\,s^{-1}$

Shear rate [1/s]

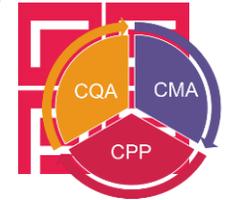# Choosing the Right Process Space
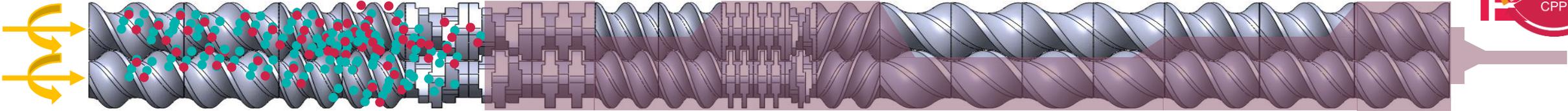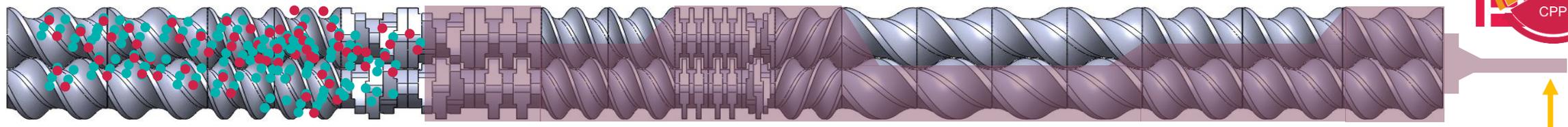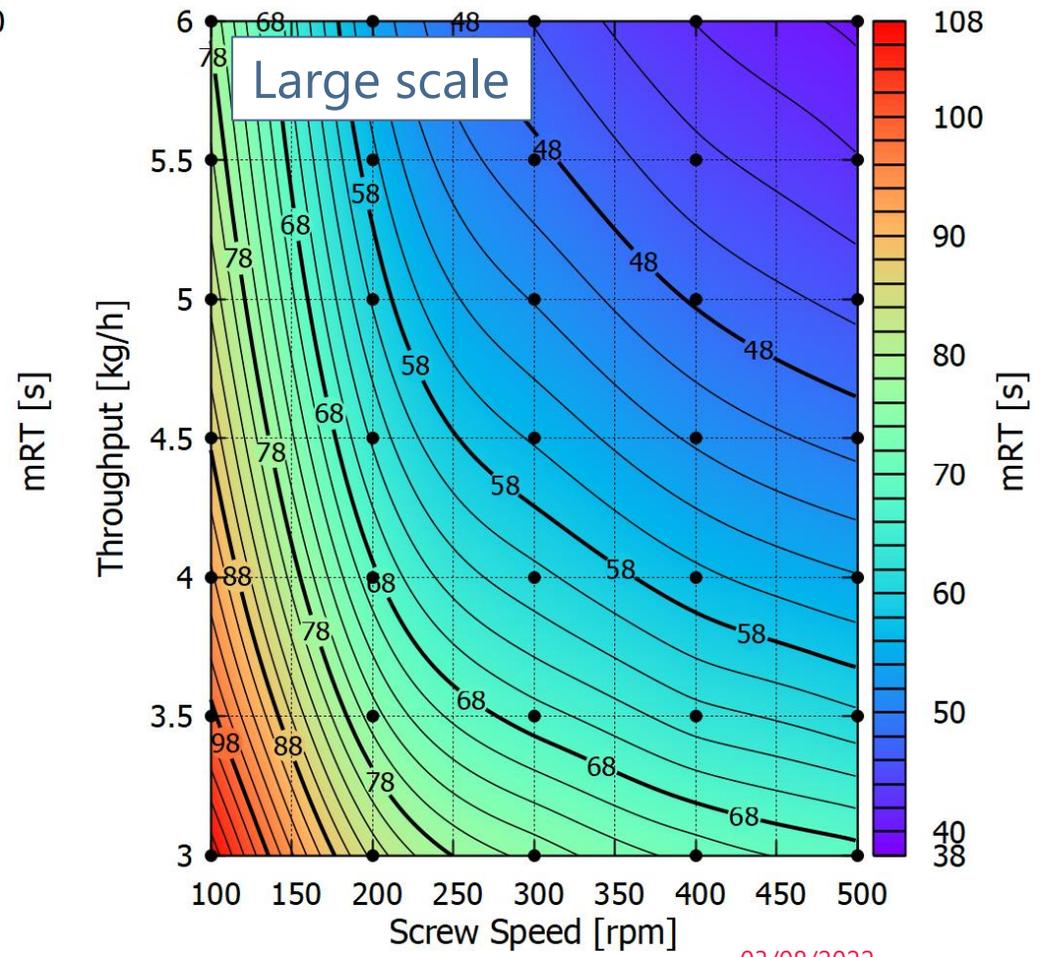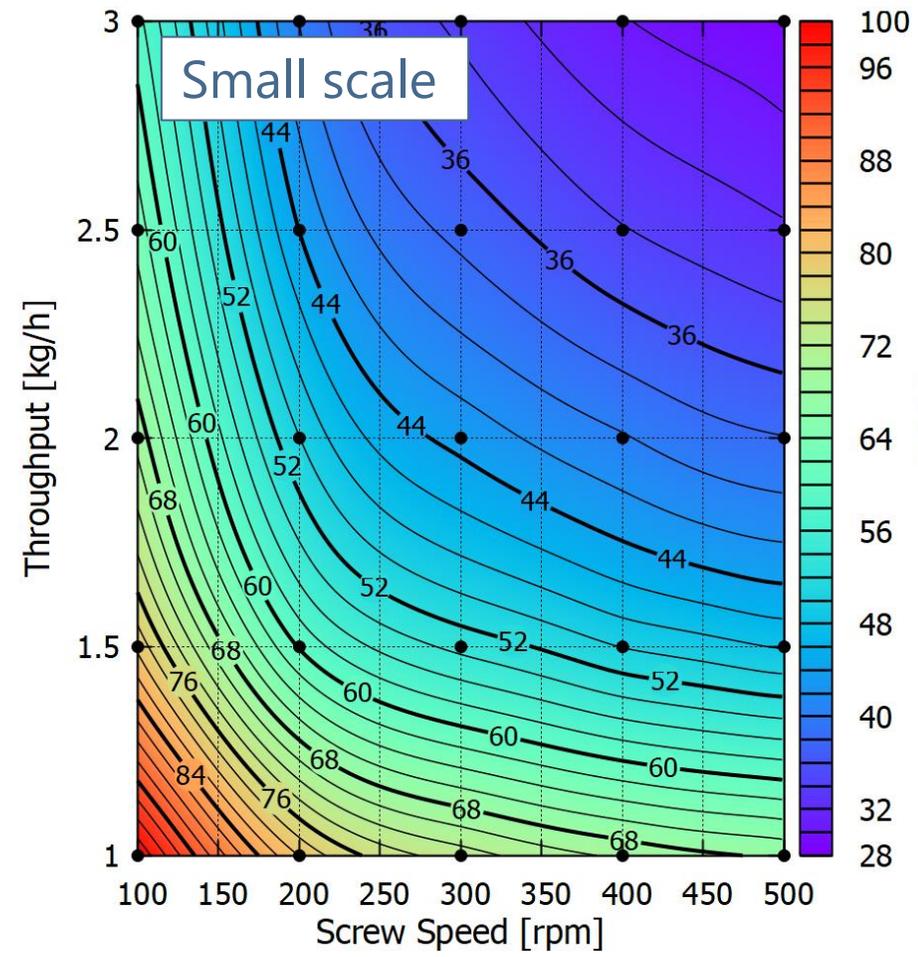

$\dot{m}[kg/h]$ ↓ ↑

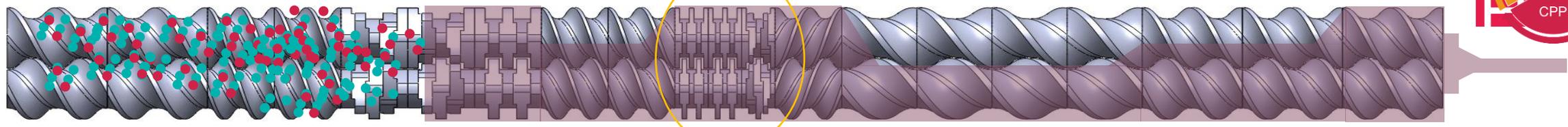$n\ [rpm]$ ↓ ↑

$T_B[°C] = const.$

$\tau[Nm]$
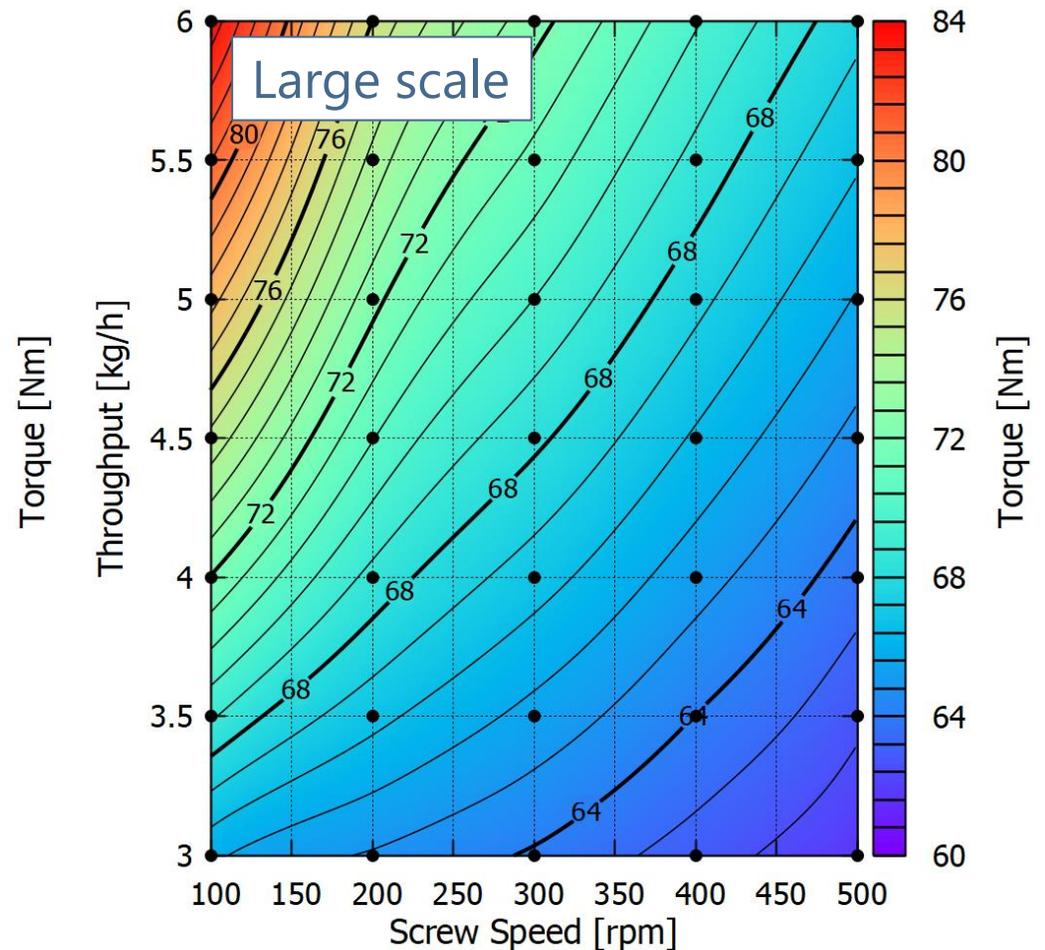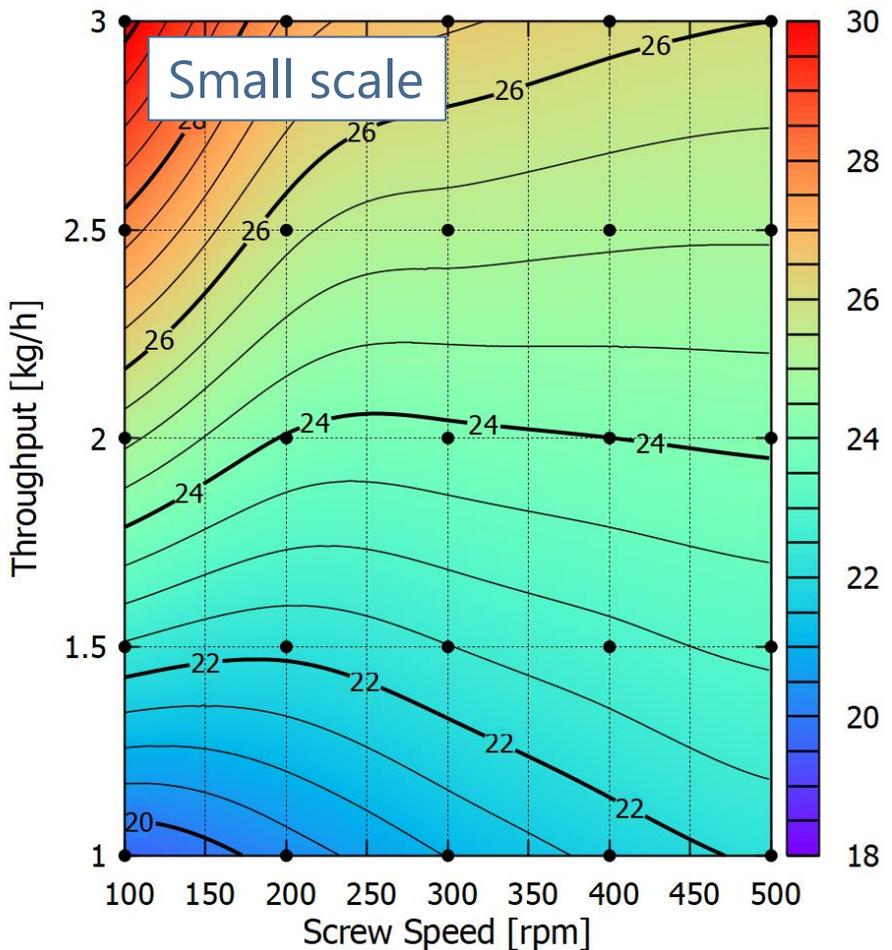
Choosing the Right Process Space

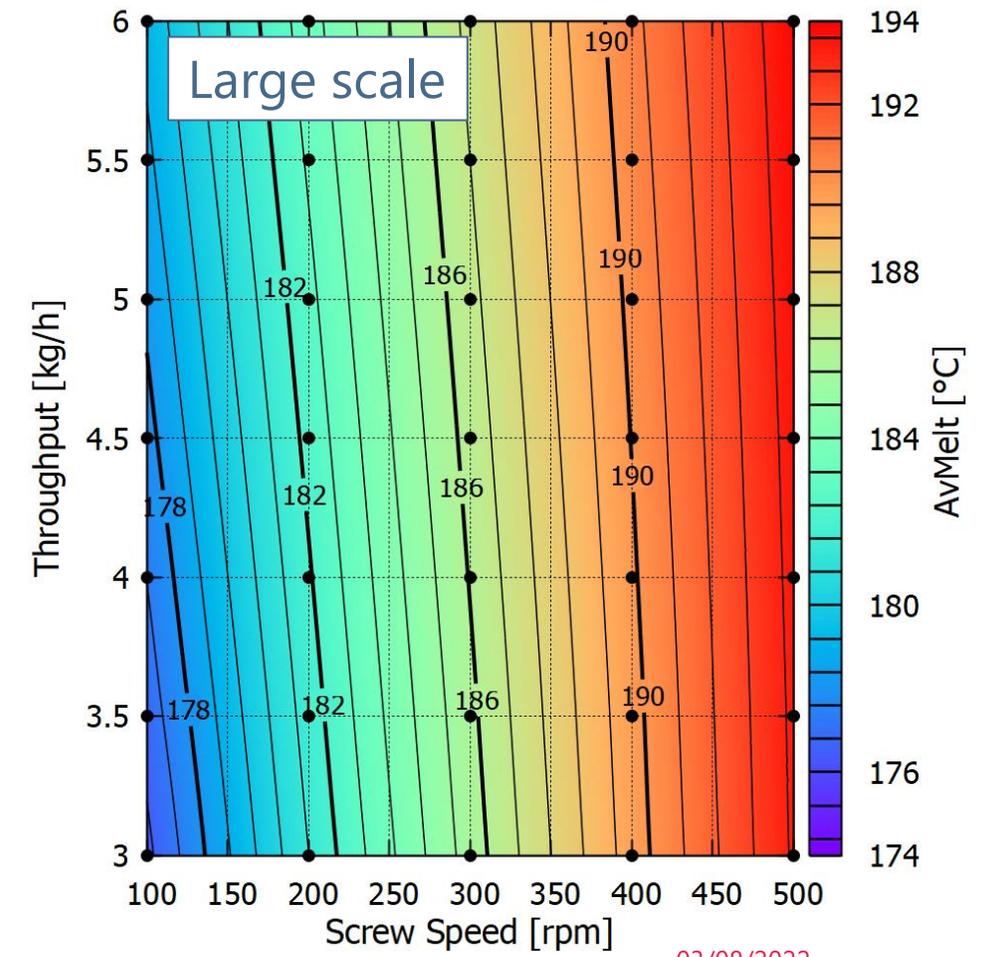$\dot{m}\,[kg/h]$ ↓ ↑

$n\,[rpm]$ ↓ ↑

$T_B\,[°C] = const.$

$mRT\,[s]$

Choosing the Right Process Space

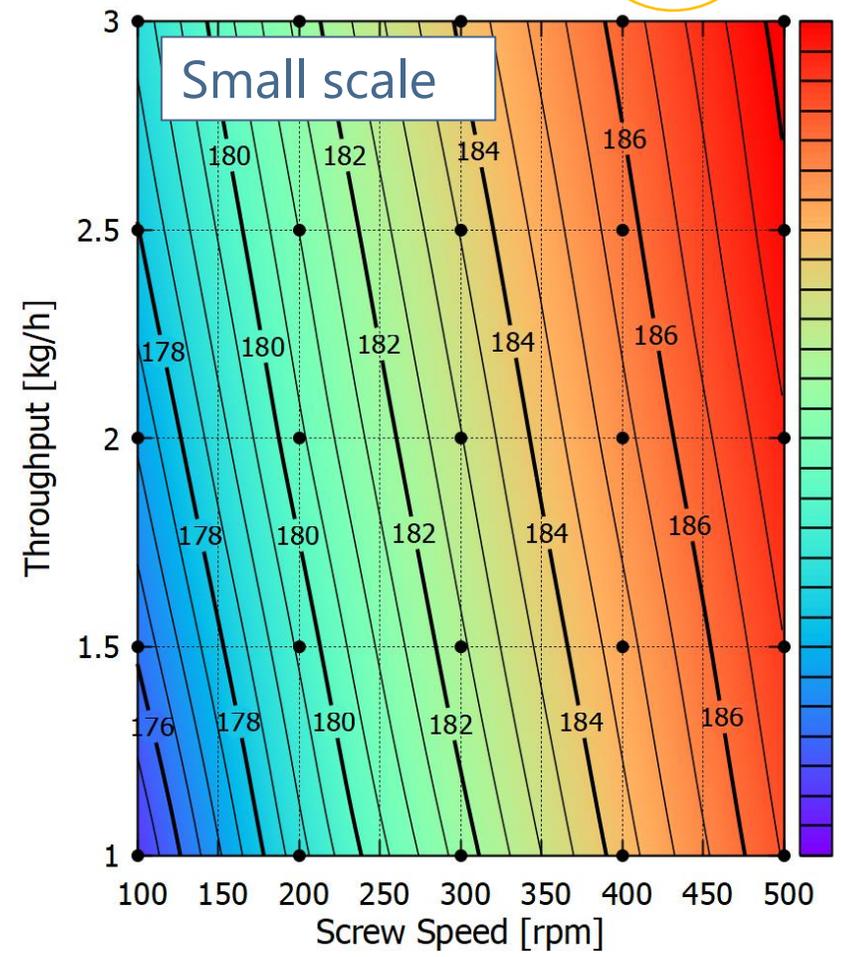$\dot{m}\,[kg/h]$ ↓ ↑

$n\,[rpm]$ ↓ ↑

$T_B[°C] = const.$

$T_{loc}[°C]$

$T_{Barrel} = 150°C$

Small scale

Large scale

Process and material characterization

J. Matić et al., "A novel in silico scale-up approach for hot melt extrusion processes," Chem. Eng. Sci., vol. 204, pp. 257–269, Aug. 2019.
J. Matić, A. Paudel, H. Bauer, R. A. L. Garcia, K. Biedrzycka, and J. G. Khinast, "Developing HME-Based Drug Products Using Emerging Science: a Fast-Track Roadmap from Concept to Clinical Batch," AAPS PharmSciTech, vol. 21, no. 5, p. 176, Jul. 2020, doi: 10.1208/s12249-020-01713-0.
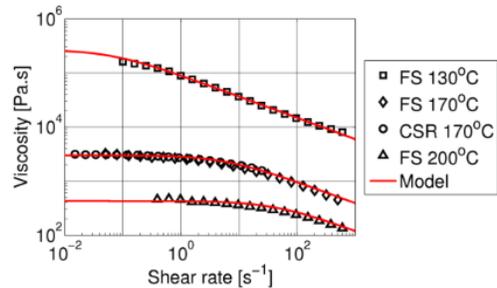
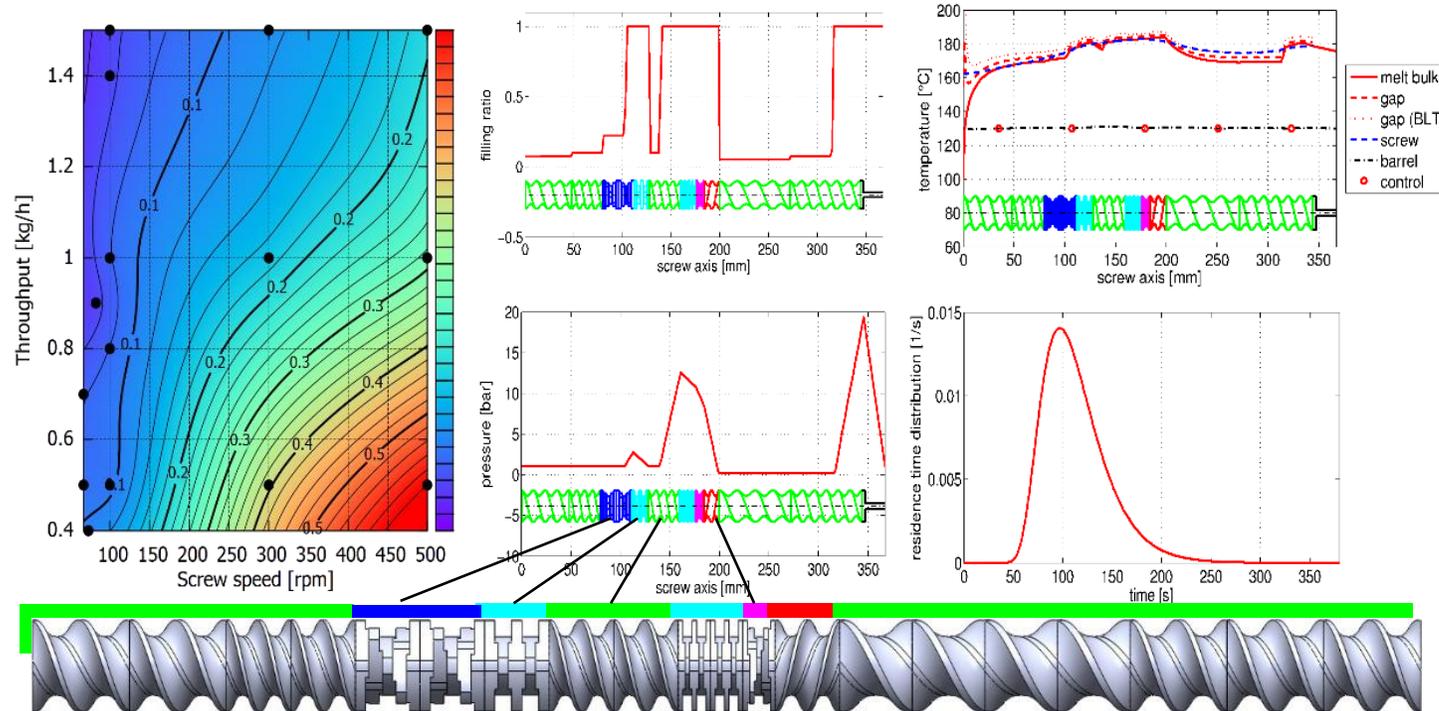**Transfer and experimental verification**

Screw Characterization
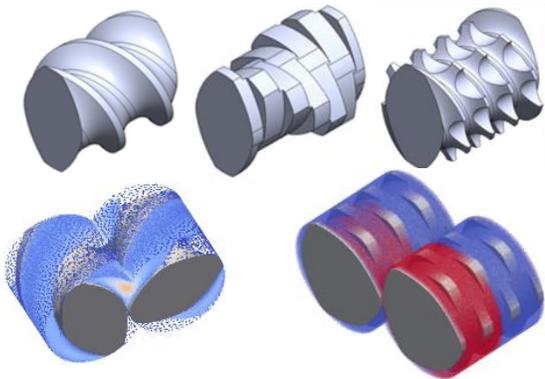
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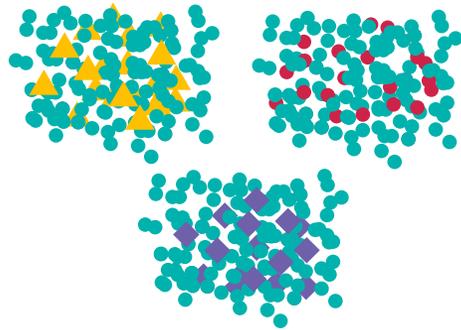
Virtual process development and scale-up
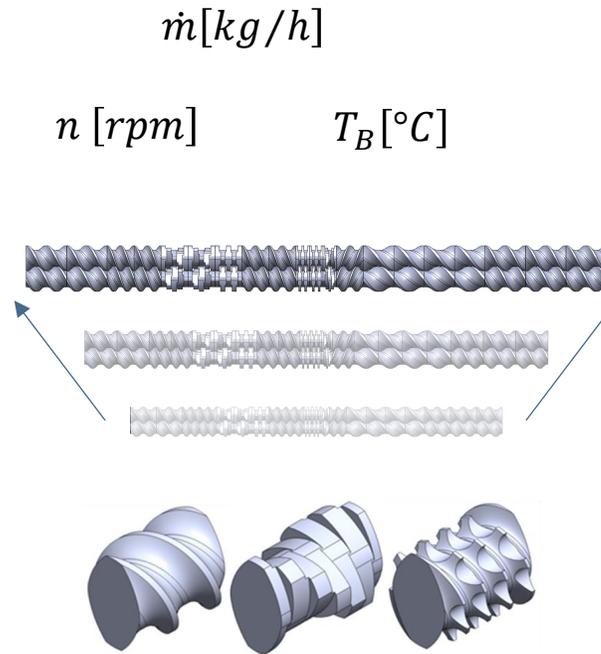
Pharmaceutical HME at RCPE
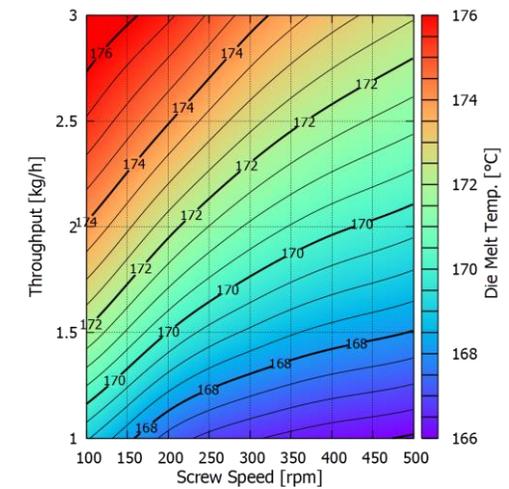
Holistic product design using ObD

Formulation Design and Product Testing

Process Design & Transfer

In Silico **Development Testbed**

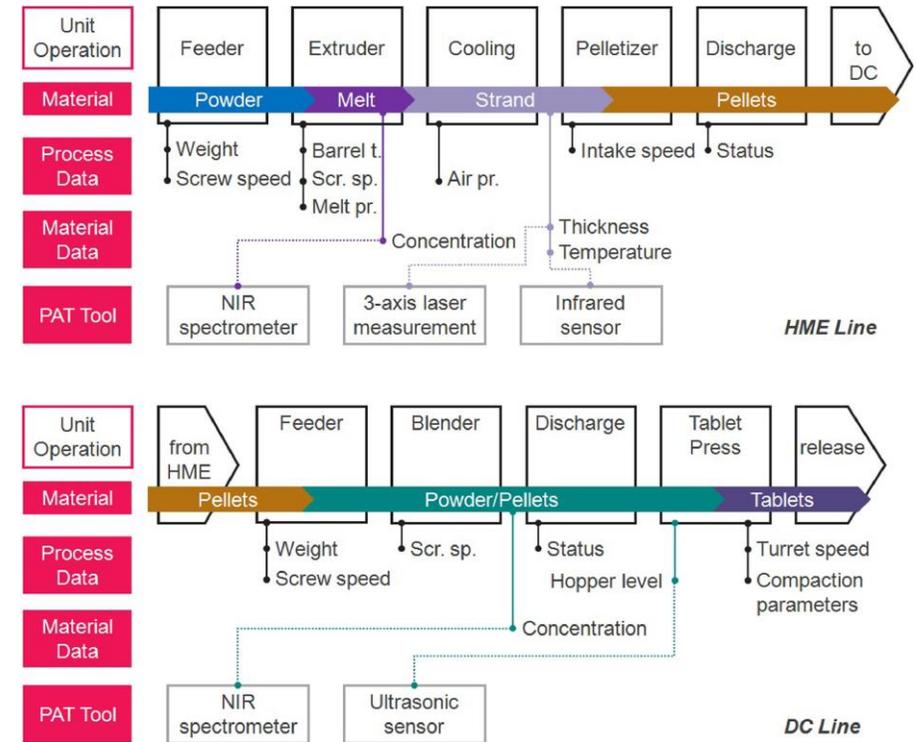$$\dot{m}\,[kg/h]$$

$$n\,[rpm] \qquad T_B\,[°C]$$
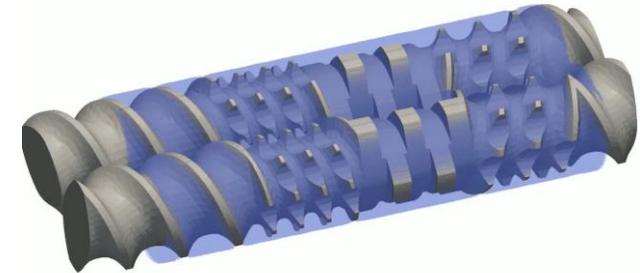
Pharmaceutical HME at RCPE

Holistic product design using ObD

State-of-the-Art Facilities

- Increasing size
- Large 27mm
- Single Screw19
- Coperion ZSK18
- Table top 9mm

Novel Downstream Technologies


Advanced Process Control
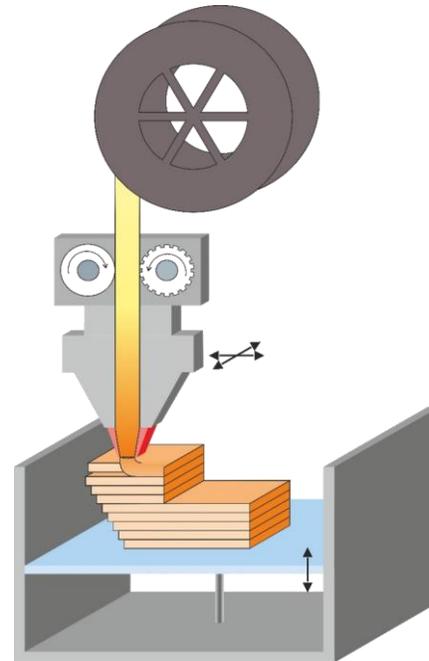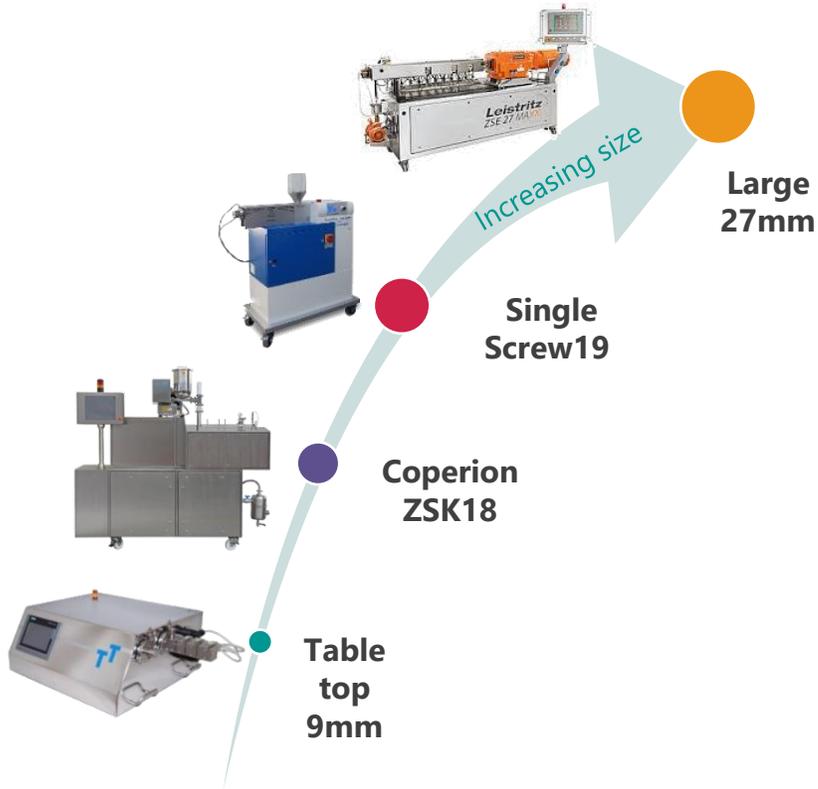
Conclusion

J. Matić, A. Paudel, H. Bauer, R. A. L. Garcia, K. Biedrzycka, and J. G. Khinast, "Developing HME-Based Drug Products Using Emerging Science: a Fast-Track Roadmap from Concept to Clinical Batch," AAPS PharmSciTech, vol. 21, no. 5, p. 176, Jul. 2020.

Goal: Ensure high quality medicines developed rapidly, waste free and under the QbD guidelines using *in silico* tools.
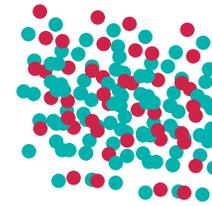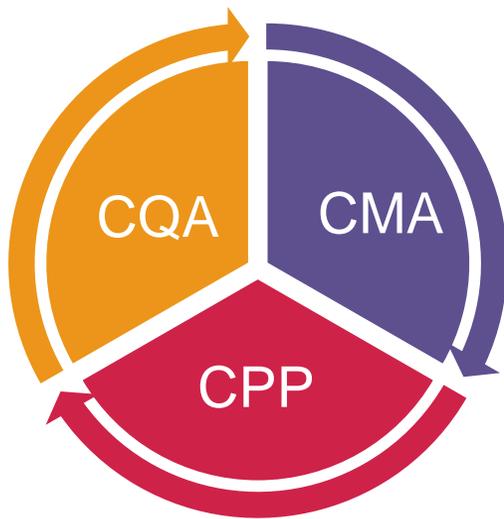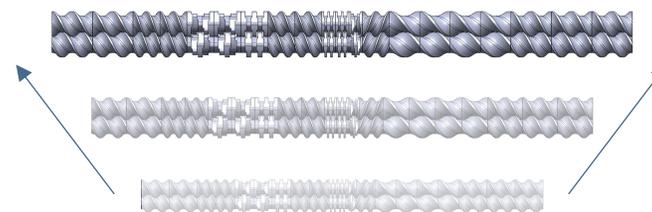
Formulation Design
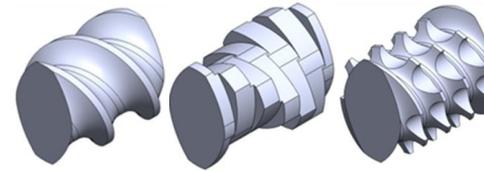
Screw Element Selection

$$\dot{m}[kg/h]$$
$$n\,[rpm]\,T_B[°C]$$

Processing Design and Transfer

CQA

CMA

CPP

THANK YOU FOR YOUR ATTENTION!

Dr. Josip Matić
Scientific Area Leader, Modeling and Prediction