Development of a continuous in-line monitored lab plant for nanoparticle production based on the Microfluidizer® technology

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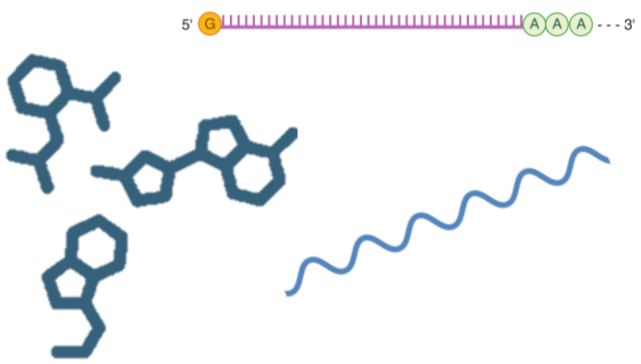
Federal Ministry Republic of Austria Climate Action, Environment, Energy, Mobility, Innovation and Technology
Federal Ministry Republic of Austria Labour and Economy
FFG Promoting Innovation.
Das Land Steiermark Wirtschaft, Tourismus, Regionen, Wissenschaft und Forschung
SFG NEUES DENKEN. NEUES FÖRDERN.

Nano Drug Delivery

Active pharmaceutical ingredient

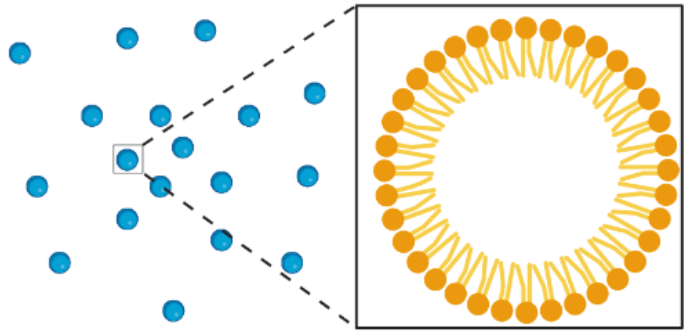


Poor solubility

Low permeability

Enzymatic degradation

Encapsulation of drugs in nanoparticles



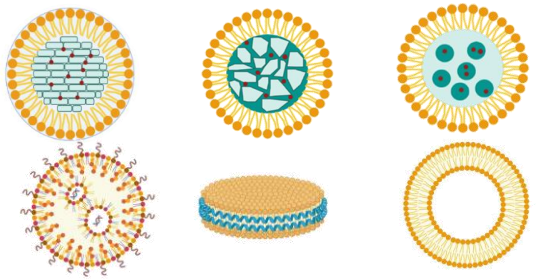
Size: 10 – 500 nm

Different physical and chemical properties

Types of nanoparticles

Polymer-based

Lipid-based



Inorganic

Nanocrystals

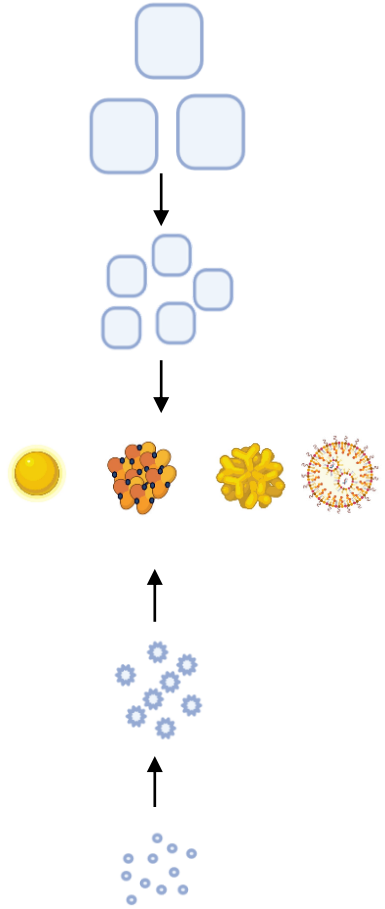
Nano Drug Delivery Production

Manufacturing strategies

Top-down

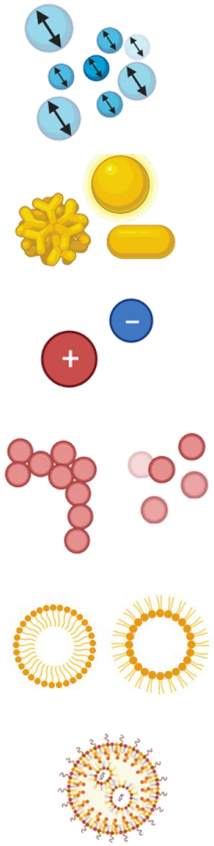
Nanoparticles

Bottom-up

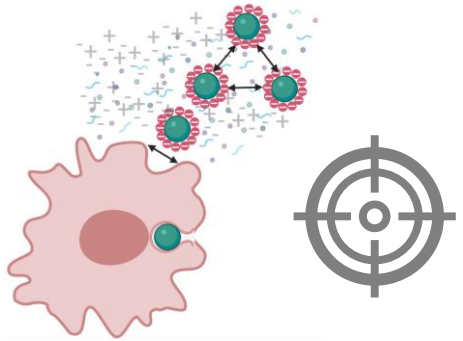


Critical quality attributes (CQAs)

- Size
- Shape
- Surface charge
- Stability
- Morphology
- Loading capacity



Direct impact on biopharmaceutical performance



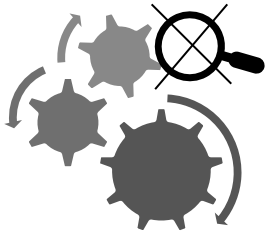
Smallest quality changes during manufacturing might lead to massive changes that impair efficacy and safety

Current Production of Nano Drug Delivery

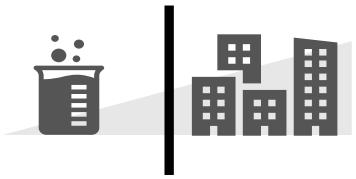
Batch-based, discontinuous

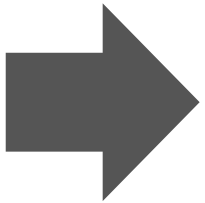
Step 1 → Step 2 → Step 3

Not adequately monitored

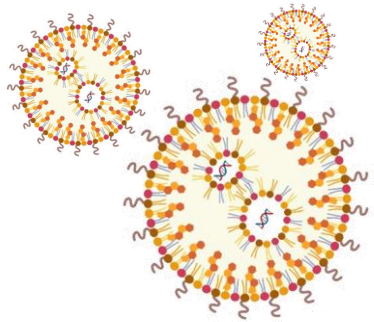


Difficult to scale





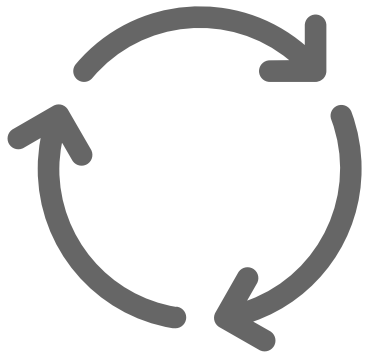
Low quality products



Time

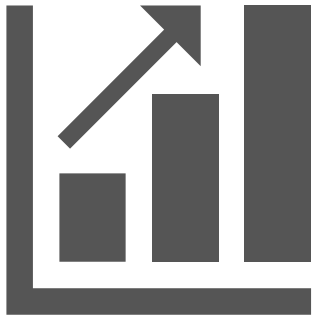
Money

NanoFacT-Project



Continuous, robust, flexible

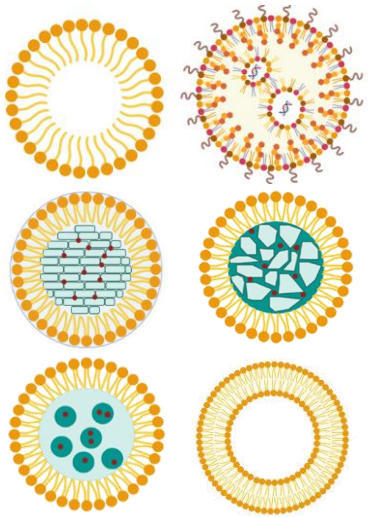
Real time monitored

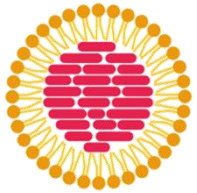


Scalable

Lipid-based Nano Drug Delivery Systems

Lipid-based nanoparticles





Solid lipid nanoparticles (SLN)

Nanostructured lipid carriers (NLC)

- Consist of a solid lipid
- Perfect crystalline structure

- Consist of a solid and a liquid lipid
- Imperfections in the crystal lattice

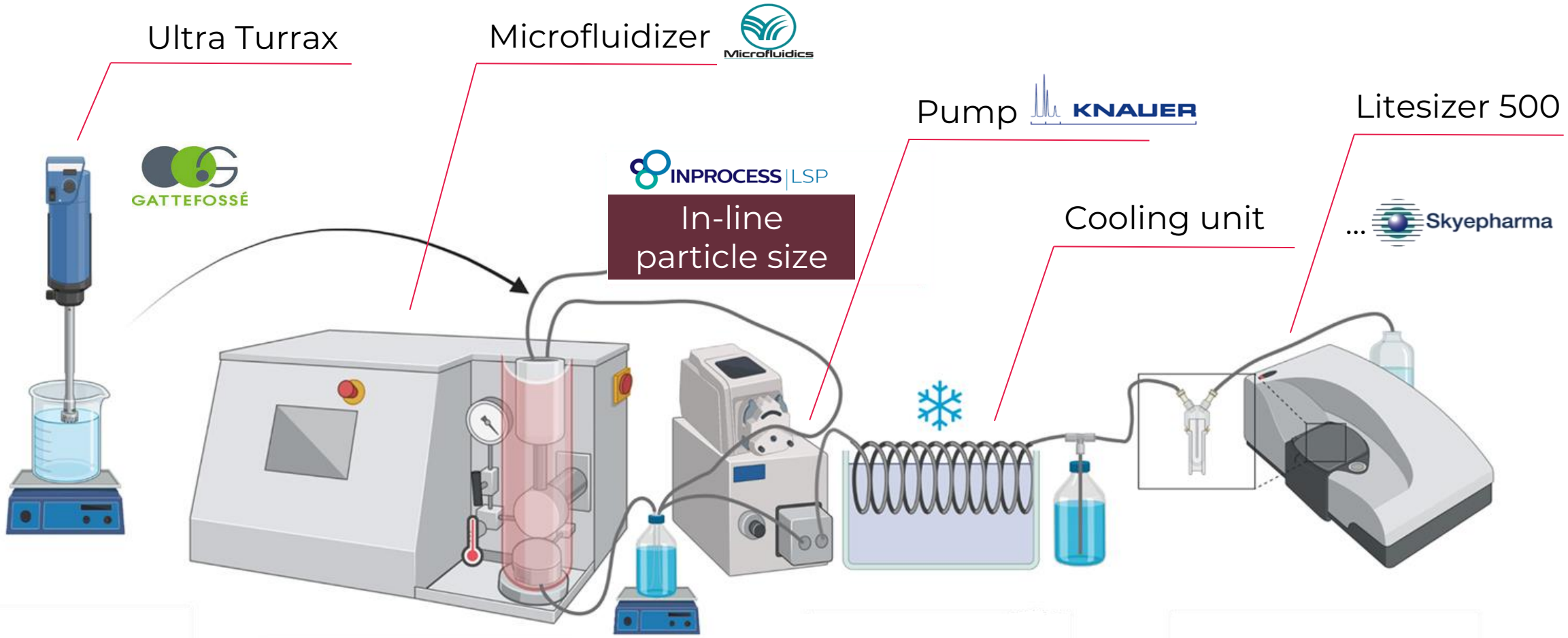
Solid lipid
Precirol ATO 5
Gelucire 43/01

Liquid lipid
Labrafac lipophile WL1349 (L)

Stabilizer
Tween 80

GATTEFOSSÉ

Top-down Production Line



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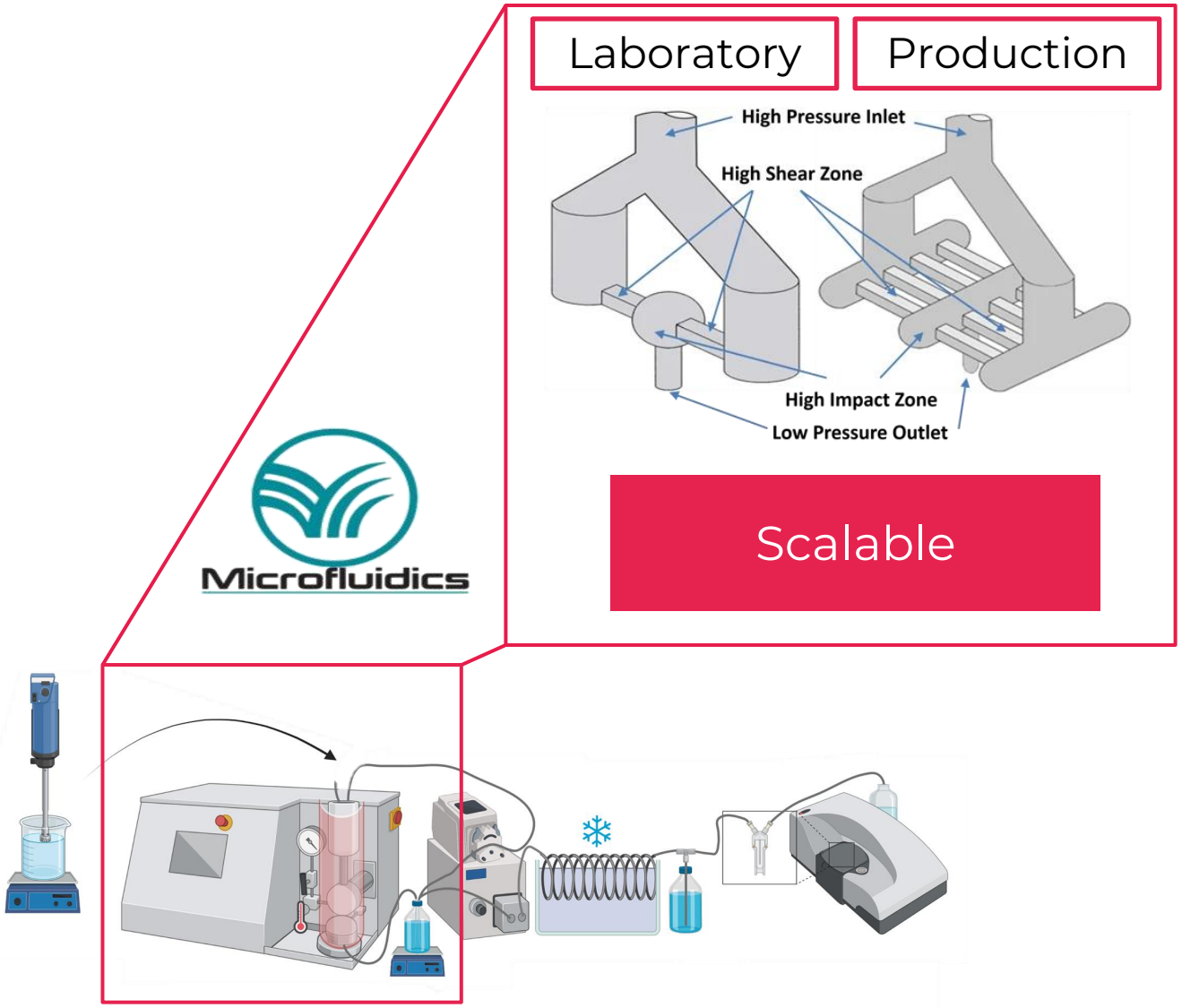
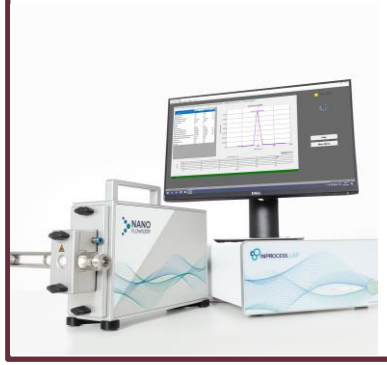
Microfluidizer® Interaction Chambers™



- Fixed-geometry Interaction Chamber™
- Fluids are forced at constant pressures
- Alignment of microchannels in parallel with a single output reservoir
- Entire product stream experiences identical shear, resulting in consistent quality regardless of volume

Particle Size Measurements

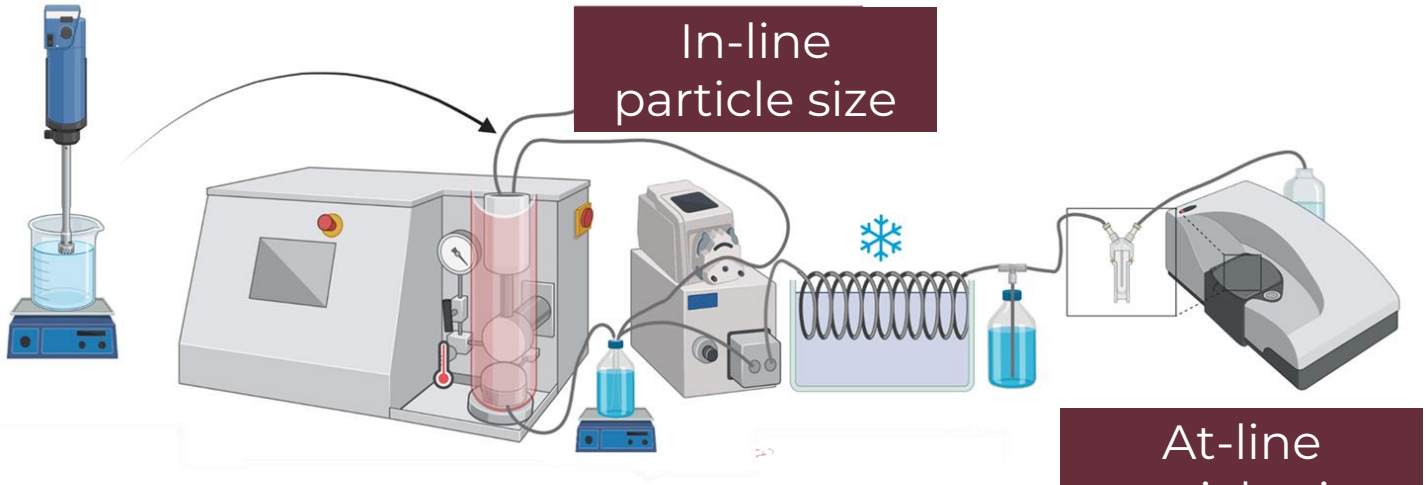
In-line particle size



- Spatially Resolved Dynamic Light Scattering (SR-DLS)
- Measurements of turbid samples
- Measurement in flow conditions
- Real-time monitoring

At-line particle size

- Conventional Dynamic Light Scattering (DLS)
- Sample preparation (e.g. dilution) required
- Possibility to combine with zeta potential measurements



CMAs and CPPs Influencing CQAs

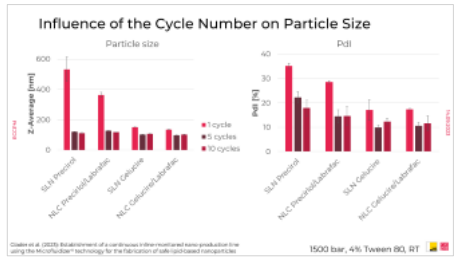
Matrix composition

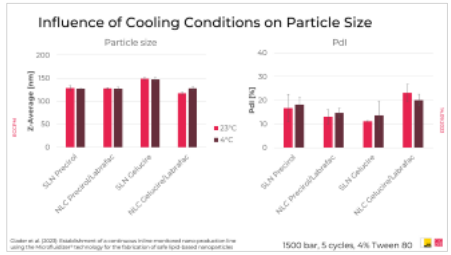
Lipid concentration

Stabilizer concentration*

Speed*

Time*





Pressure

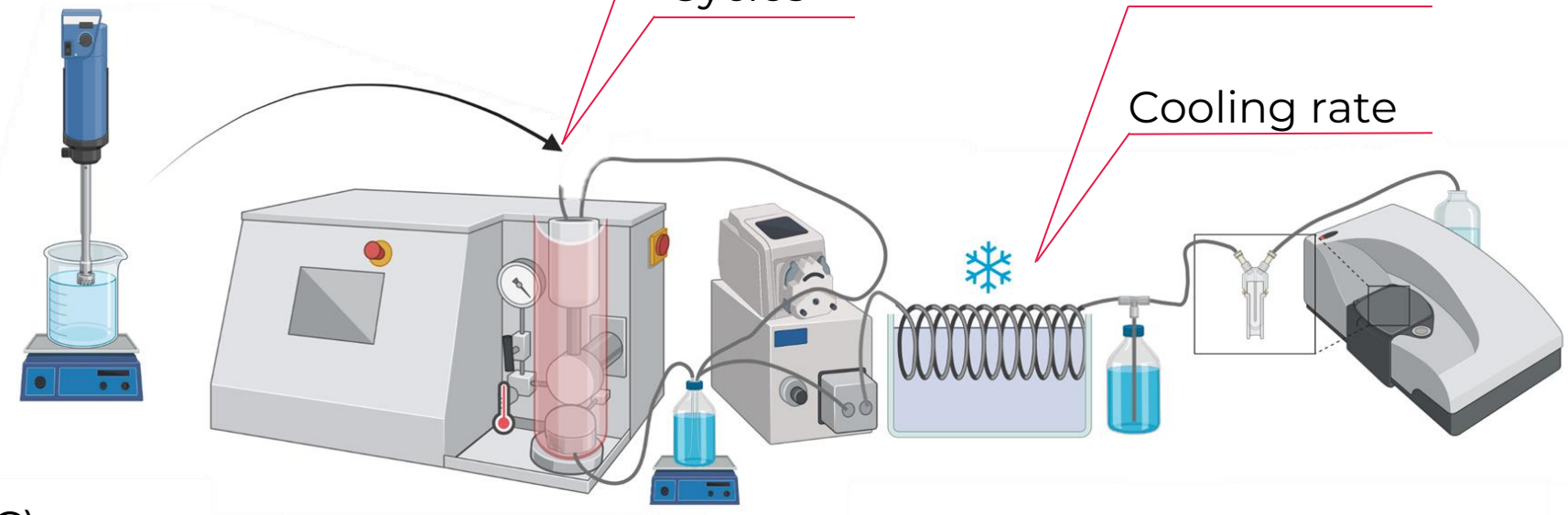
Cycles

Final product temperature

Cooling rate

Solid lipid nanoparticles (SLN)

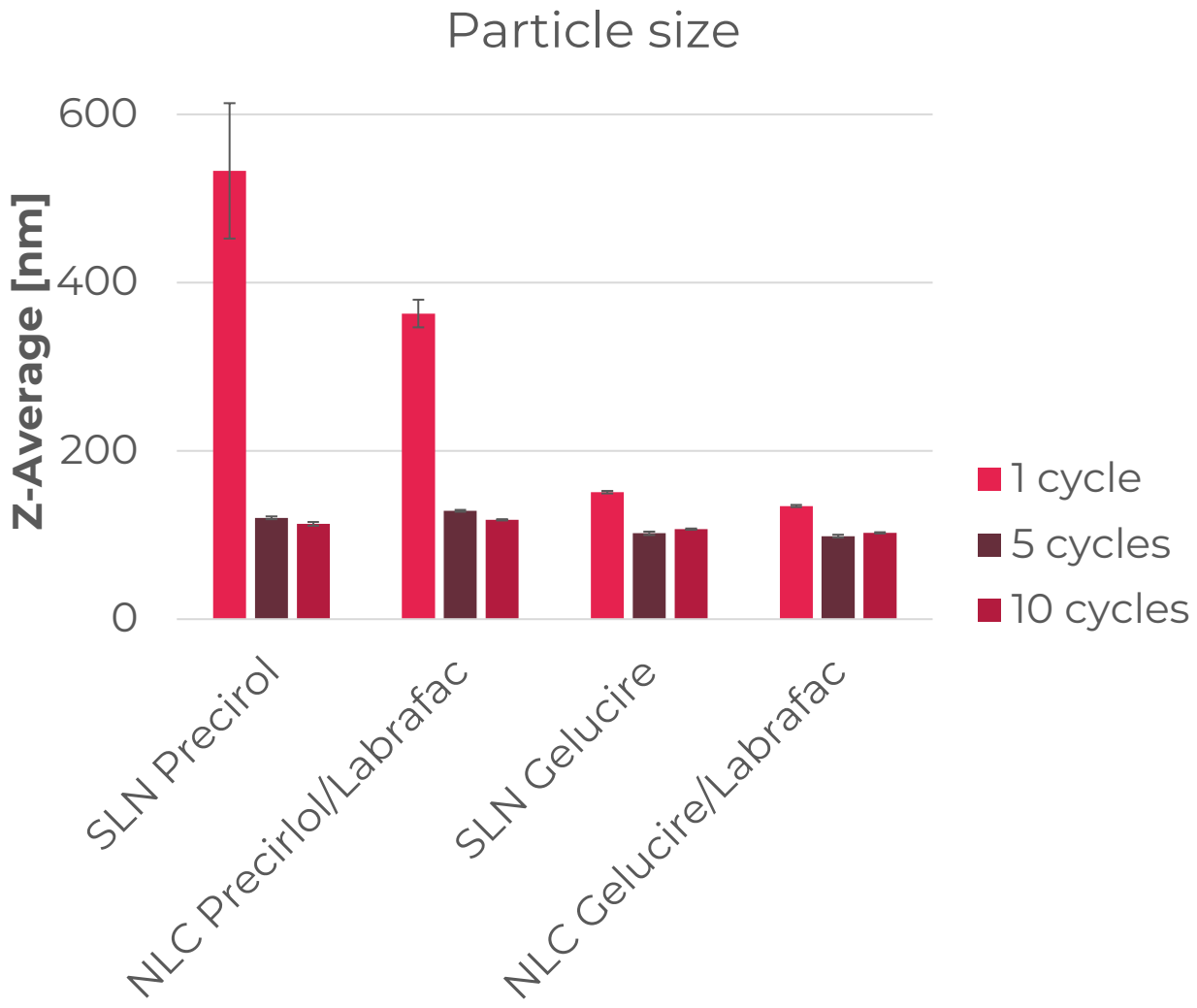
Nanostructured lipid carriers (NLC)

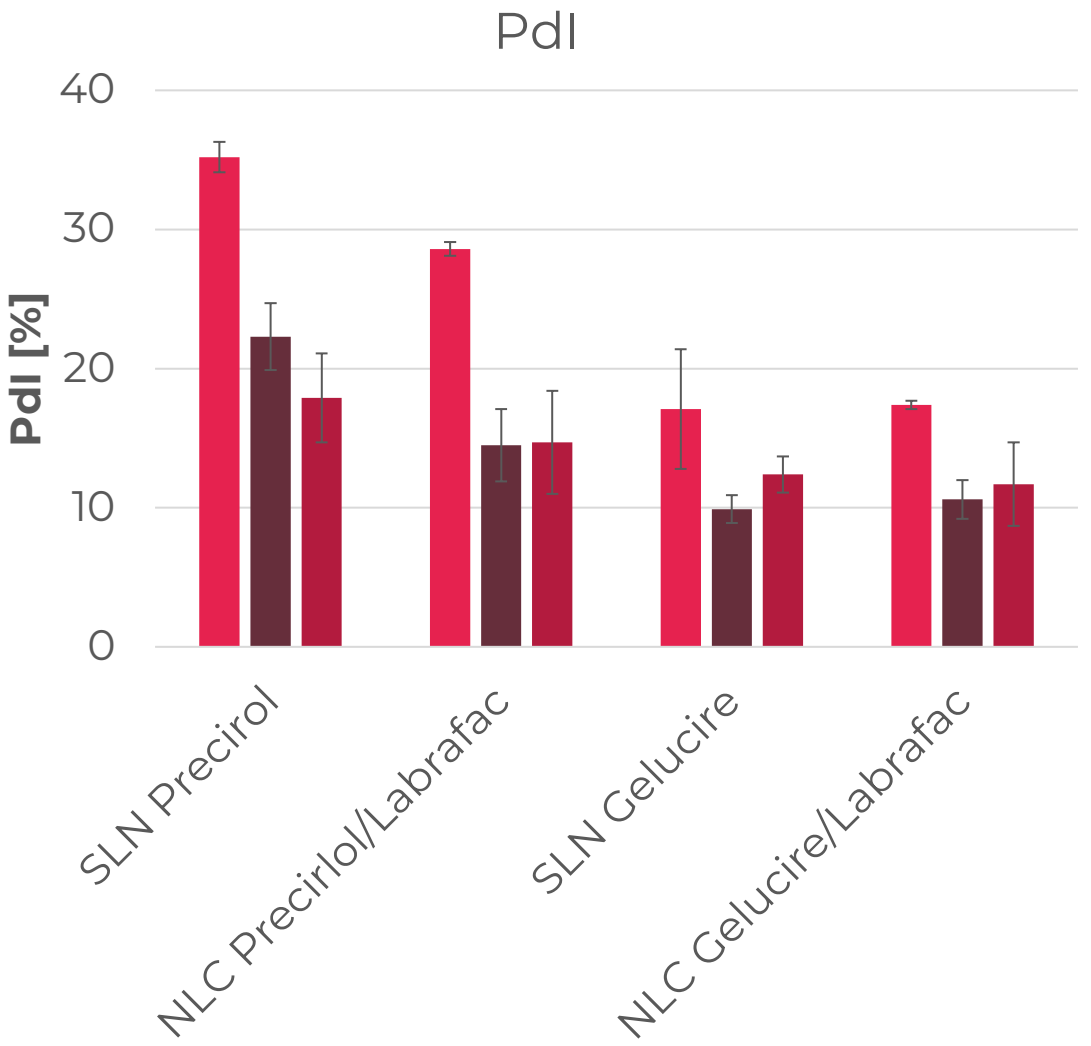


* Not considered in the following DoE studies

Glader et al. (2023): Establishment of a continuous inline-monitored nano-production line using the Microfluidizer® technology for the fabrication of safe lipid-based nanoparticles

Influence of the Cycle Number on Particle Size





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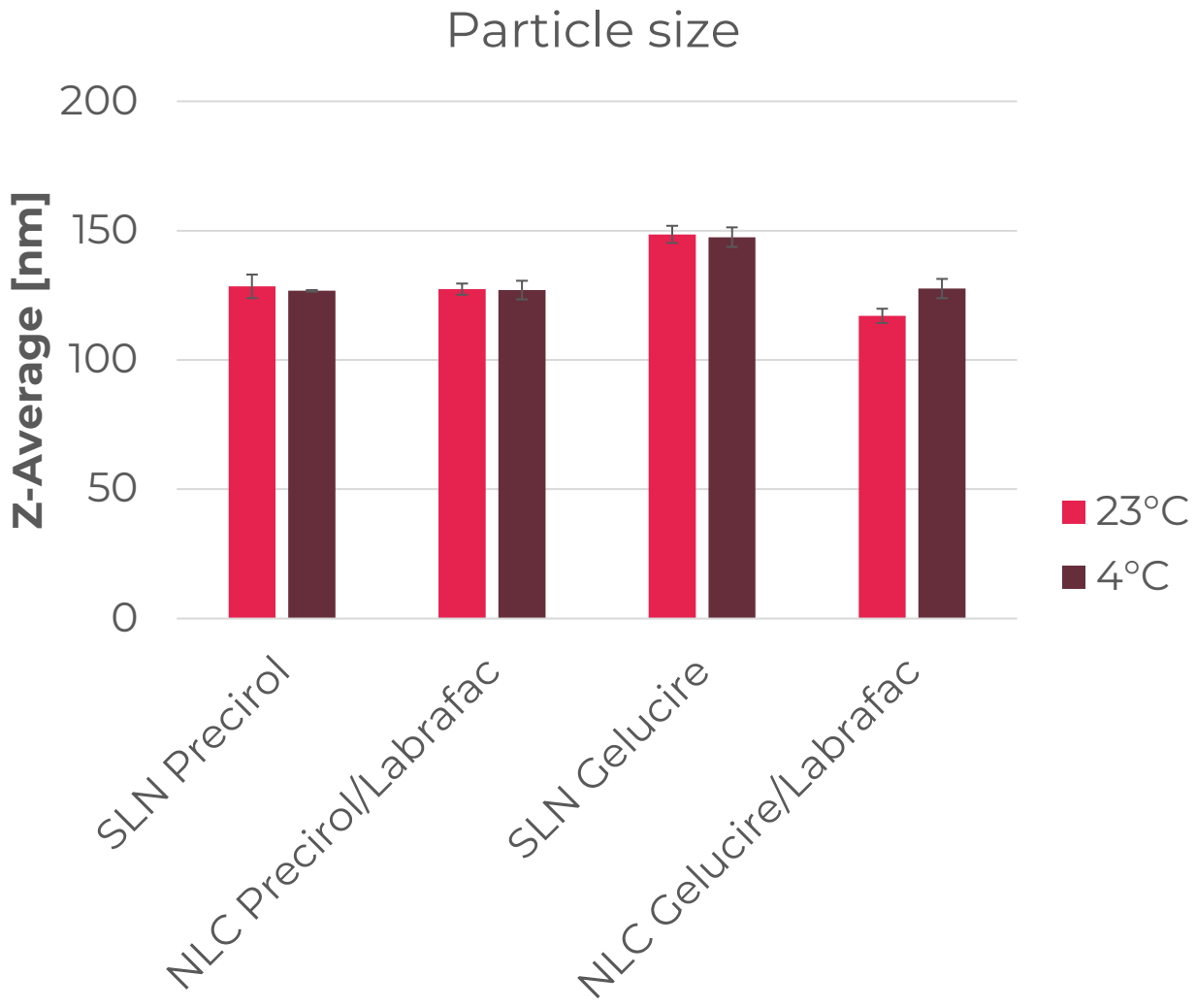
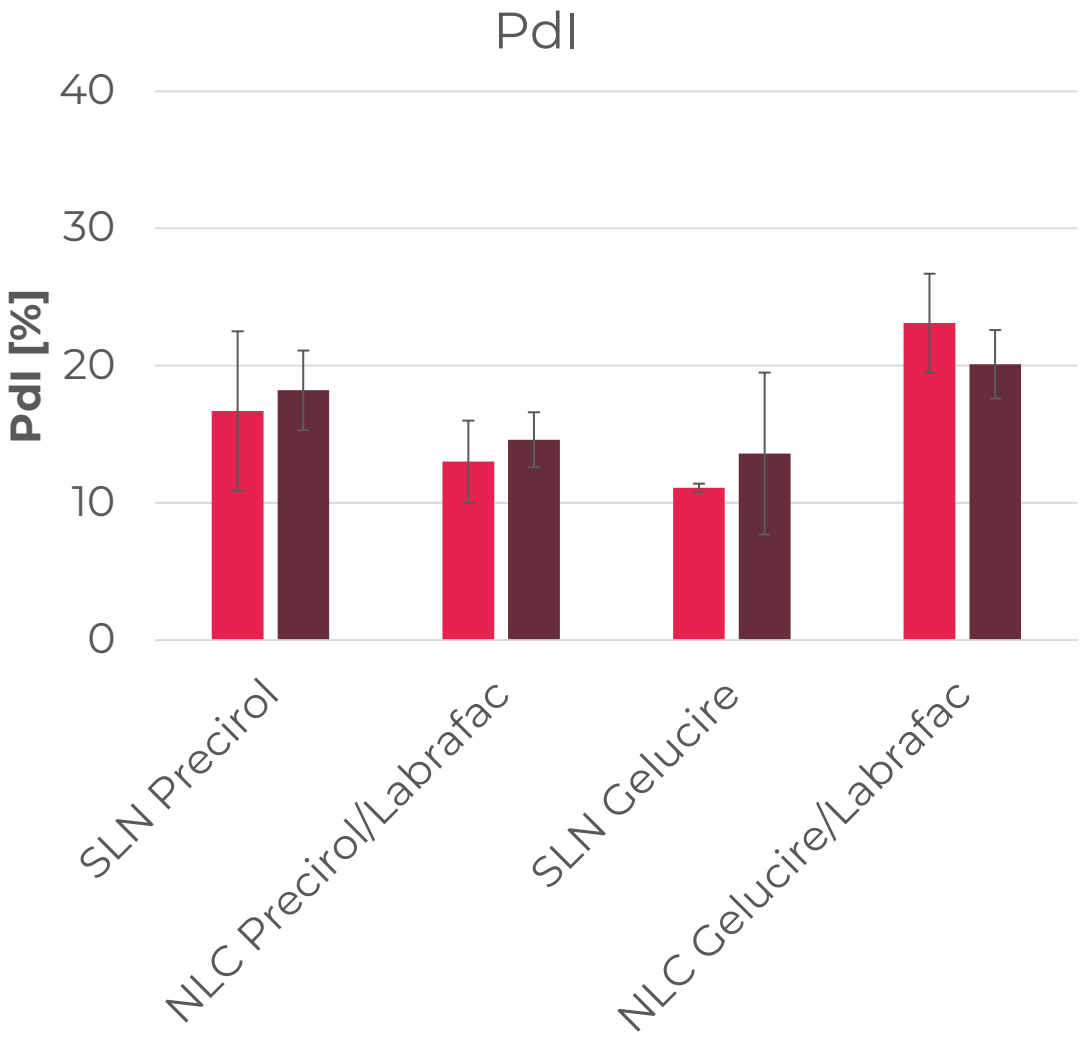
1500 bar, 4% Tween 80, RT

Influence of Cooling Conditions on Particle Size





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Glader et al. (2023): Establishment of a continuous inline-monitored nano-production line using the Microfluidizer® technology for the fabrication of safe lipid-based nanoparticles

1500 bar, 5 cycles, 4% Tween 80

CMAs and CPPs influencing CQAs

Matrix composition

Lipid concentration

Stabilizer concentration*

Speed*

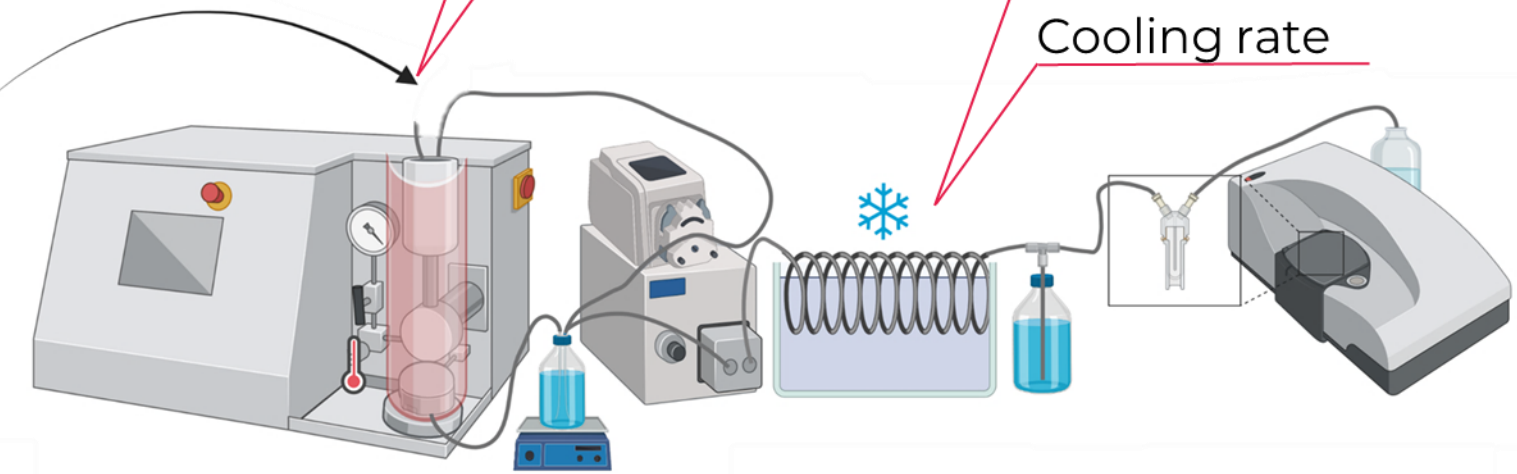
Time*

Pressure

Cycles

Final product temperature

Cooling rate



Solid lipid nanoparticles (SLN)

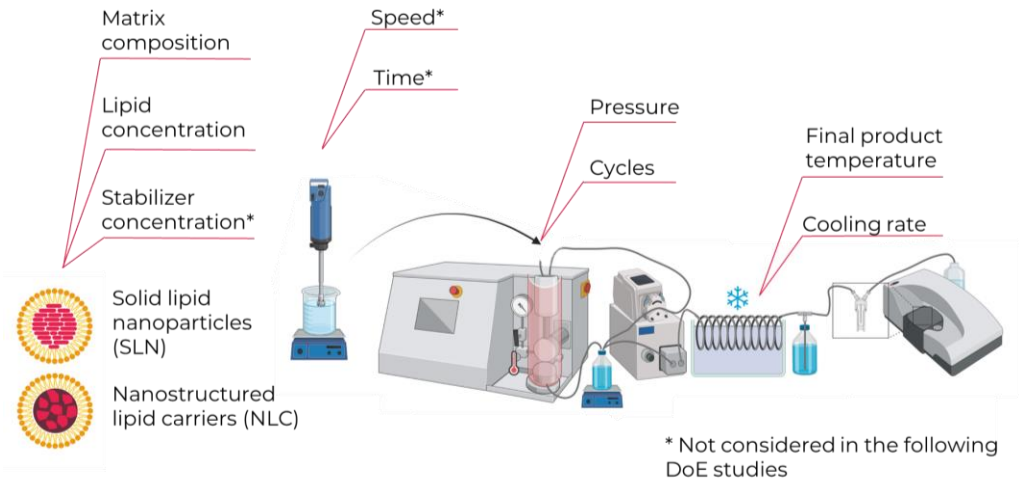
Nanostructured lipid carriers (NLC)

* Not considered in the following DoE studies

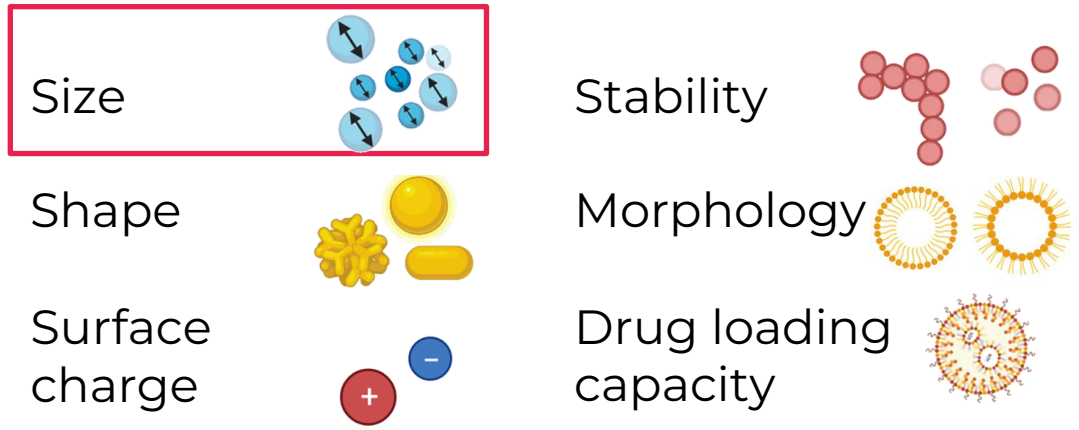
Design of Experiment Studies (DoE)

- Based on the MODDE® software
- To study the effect of multiple input parameters on the CQAs
- To improve process understanding
- To optimize the process to target specific CQAs

Input parameters (Factors)



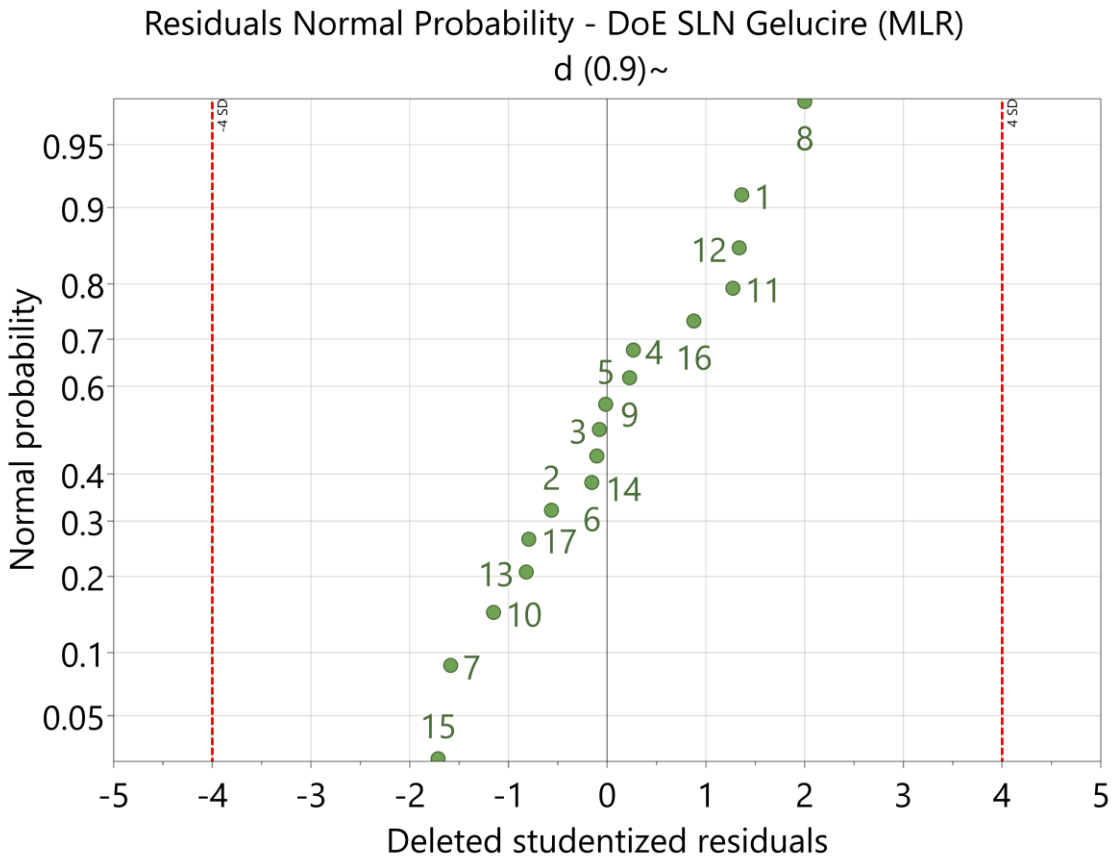
Output parameters (Responses)

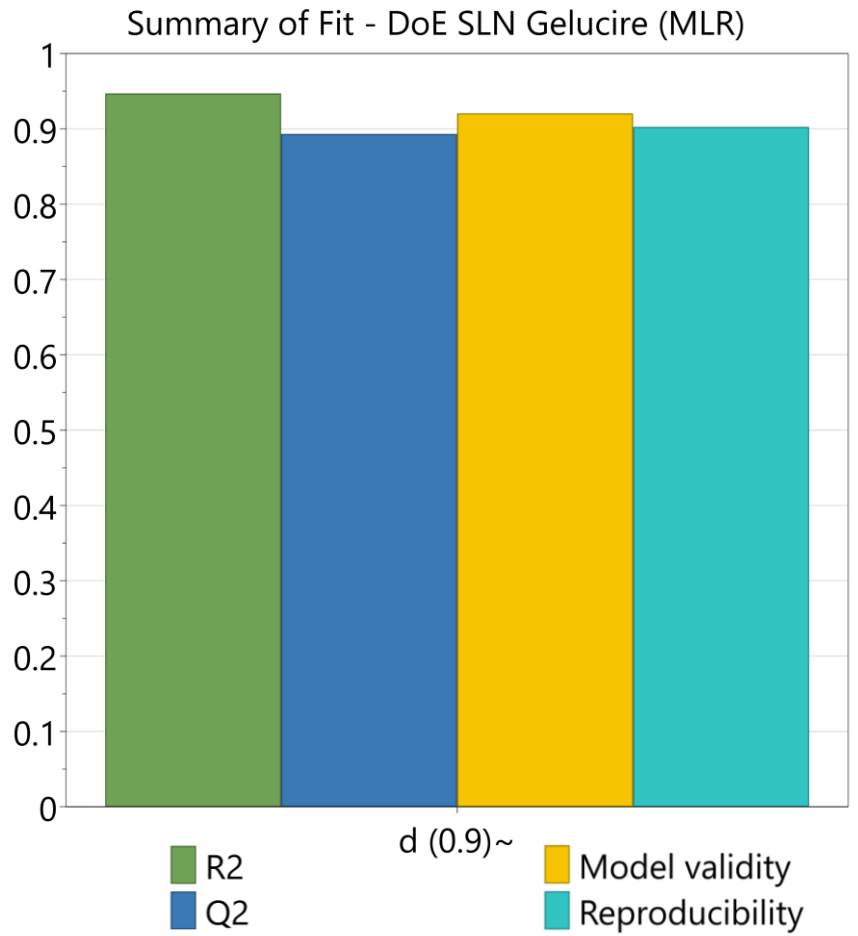


Critical quality attributes (CQAs)

Glader et al. (2023): Establishment of a continuous inline-monitored nano-production line using the Microfluidizer® technology for the fabrication of safe lipid-based nanoparticles

DoE Studies - Evaluation of the Model





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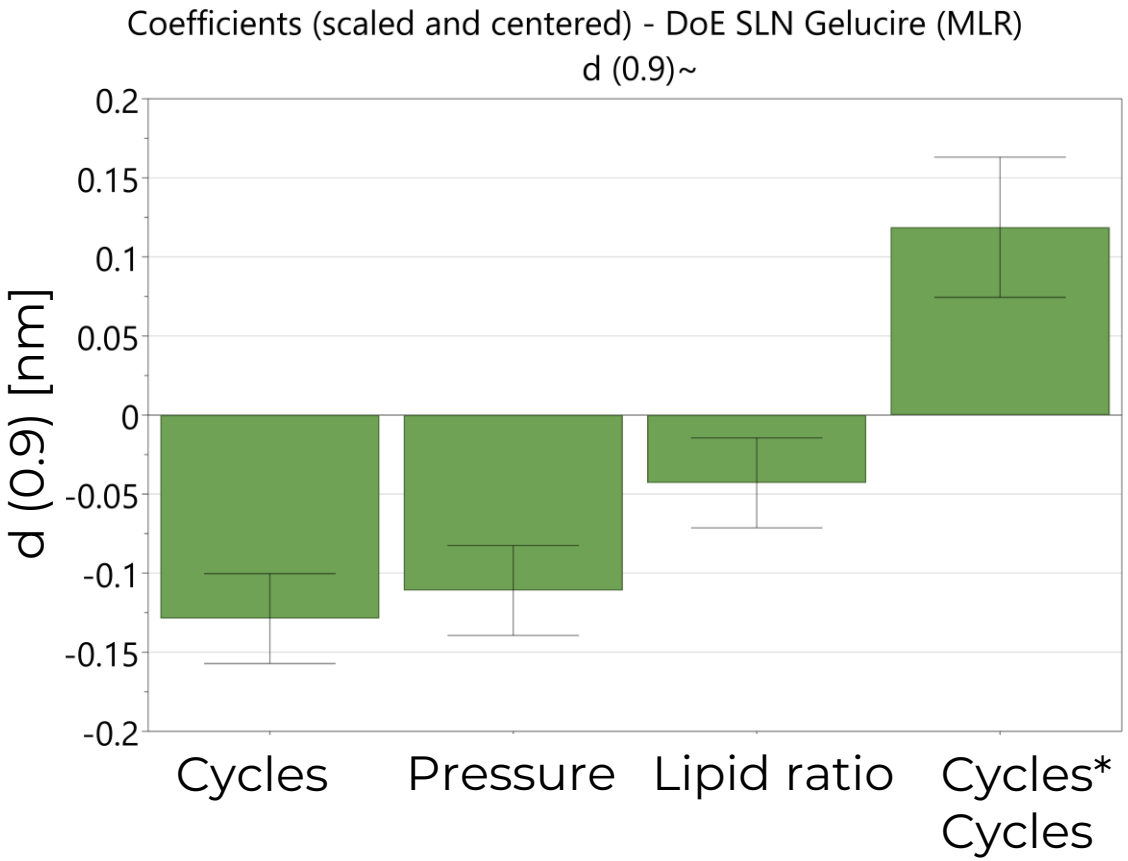
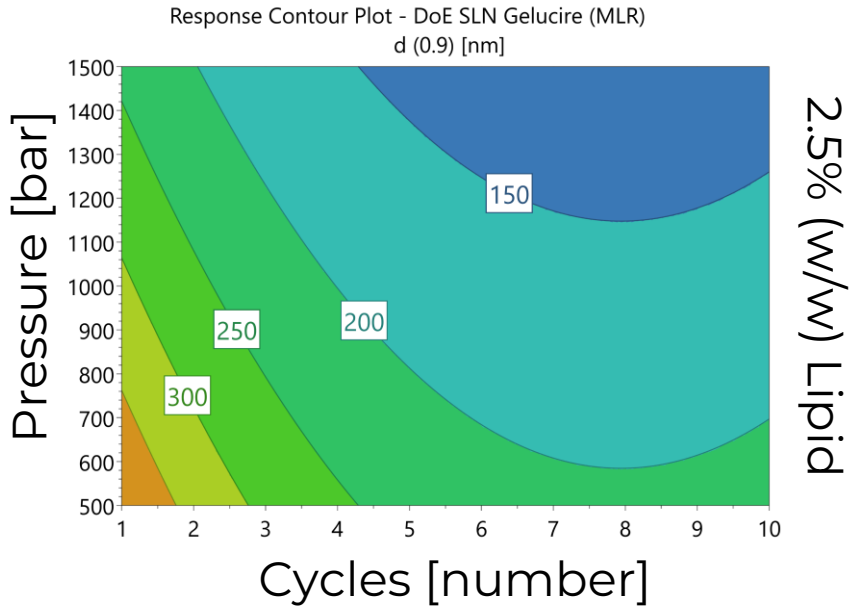
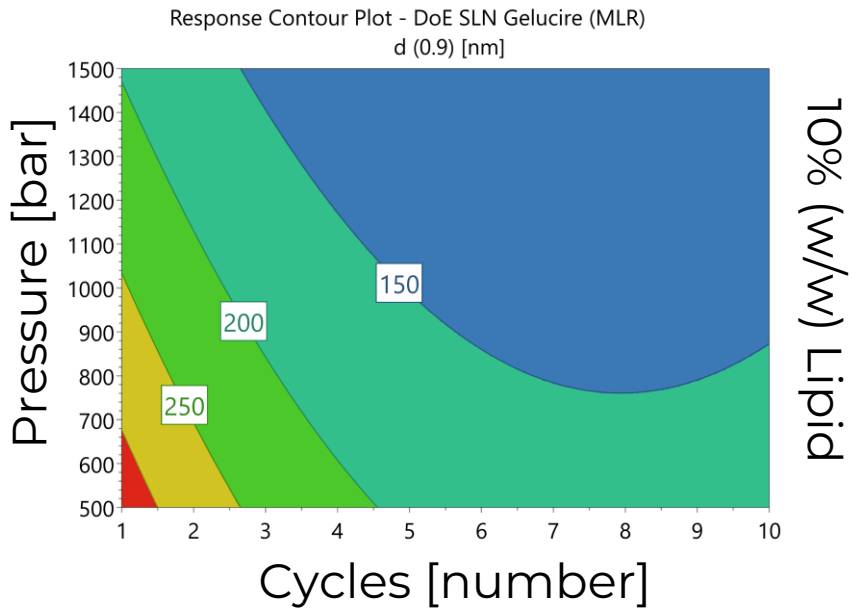
DoE Studies - Visualization of the Model







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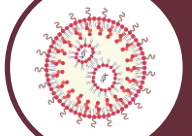
Conclusion and Outlook

- Continuous preparation of nanoparticles using scalable processes
-  Establishment of thorough process understanding through DoEs
-  Process optimization enables particle production with defined characteristics
-  Testing of applicability for more complex matrix compositions
- Verification of scalability to an industry relevant scale

Let‘s continue the conversation.

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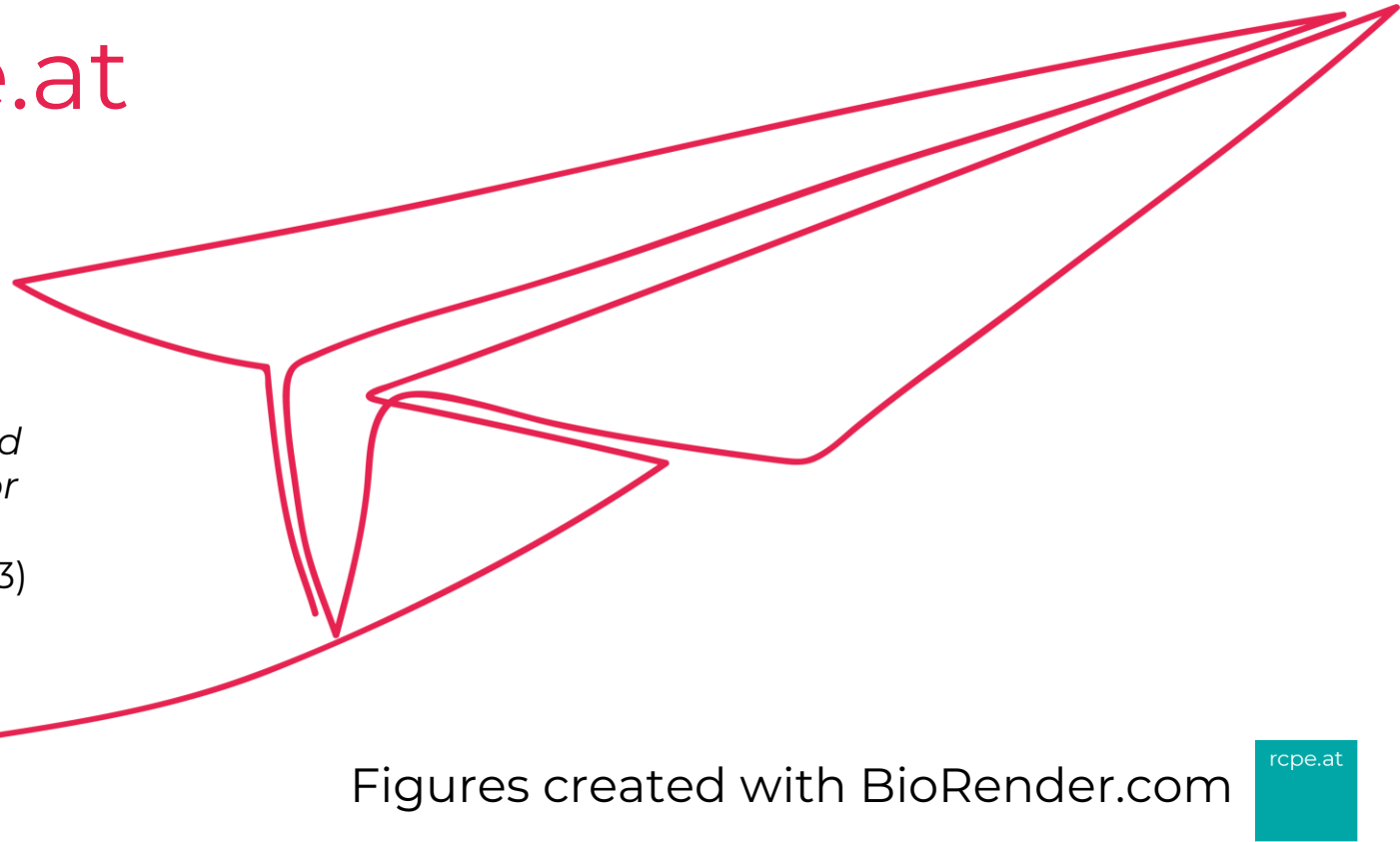

Literature:

Short communication
Glader et al.: “*Establishment of a continuous inline-monitored nano-production line using the Microfluidizer® technology for the fabrication of safe lipid-based nanoparticles*”
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