Crysta'Days | November 2023

Upscaling with the SCT-PILOT unit

Secoya
FLUIDIFY PHARMA

1

The new SCT-P□LOT

Secoya Crystallization Technology

SCT-pilot instrument

SCT-P□LOT uses:

- **□dentical parameter settings** as the SCT-LAB environment
- **Single use fluidics** for easy and complete cleaning
- **All inserts and reactors are interchangeable between SCT-LAB and SCT-P□LOT**
- **□n-depth testing** continuous operation and **erroneous operation control**
- **Recipe determination**
- **GLP** version available
- Government funding for independent cGMP development

Enhanced study delivers:

- □deal coupling with maturing and isolation strategy
- Full recipe for operations with industrial equipment

W□TH L□M□TED USE of T□ME and material

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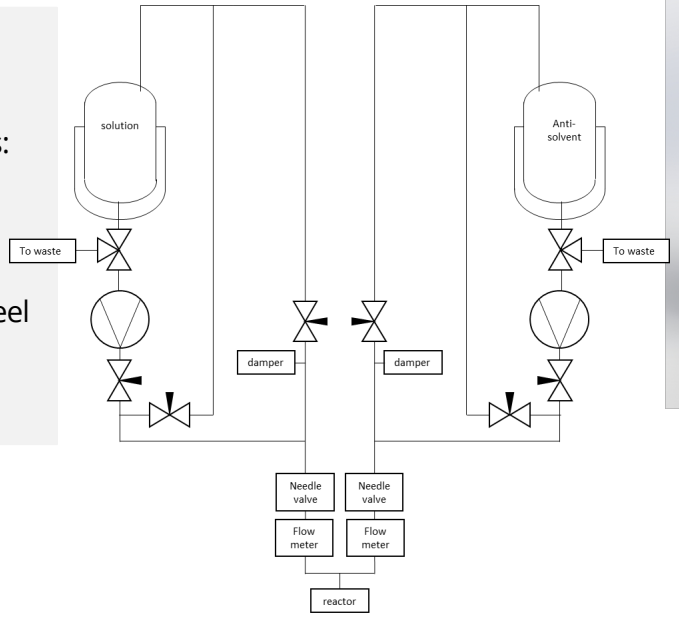
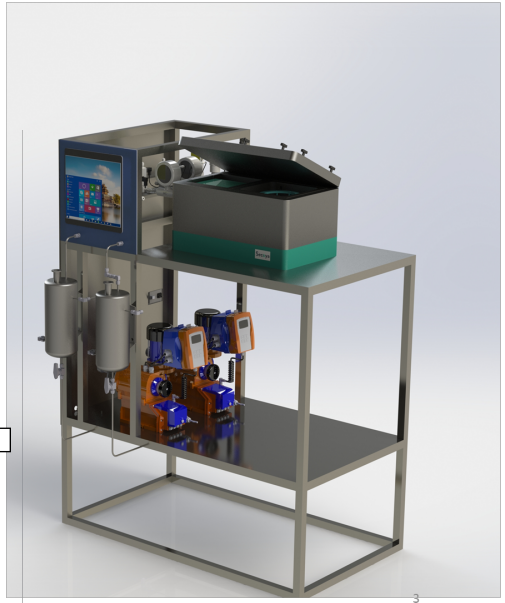
SCT-pilot instrument

SCT-P□LOT changes in bewteen versions:

- Selection of new pump type to increase cleaning capacity and reduce material losses: 150 mL dead volume reduced to 5 mL
- Complete emptying of the vessels
- Materials in contact with chemicals:
  - Glass and PTFE
  - □nterior part of pumps in stainless steel metal, other materials on request
- □dentical and validated flow rate stability





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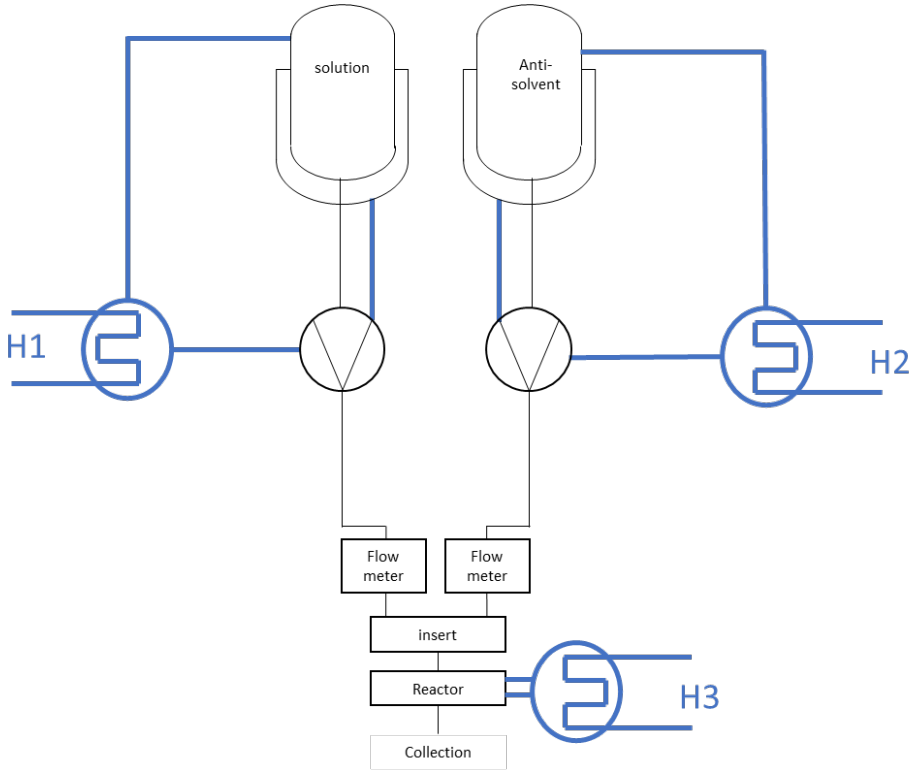

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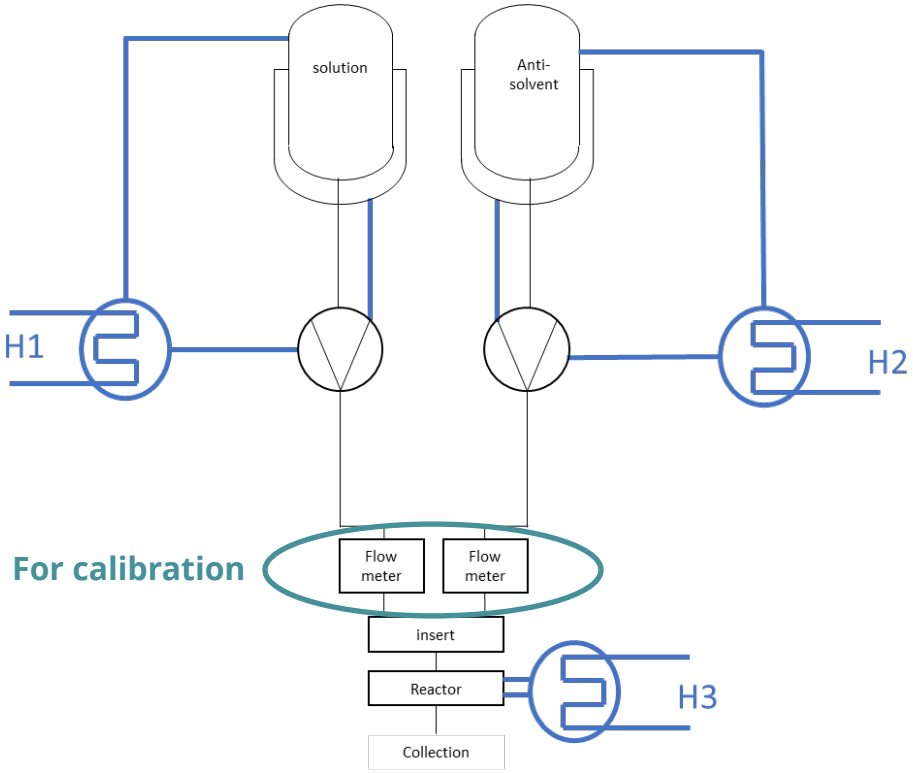

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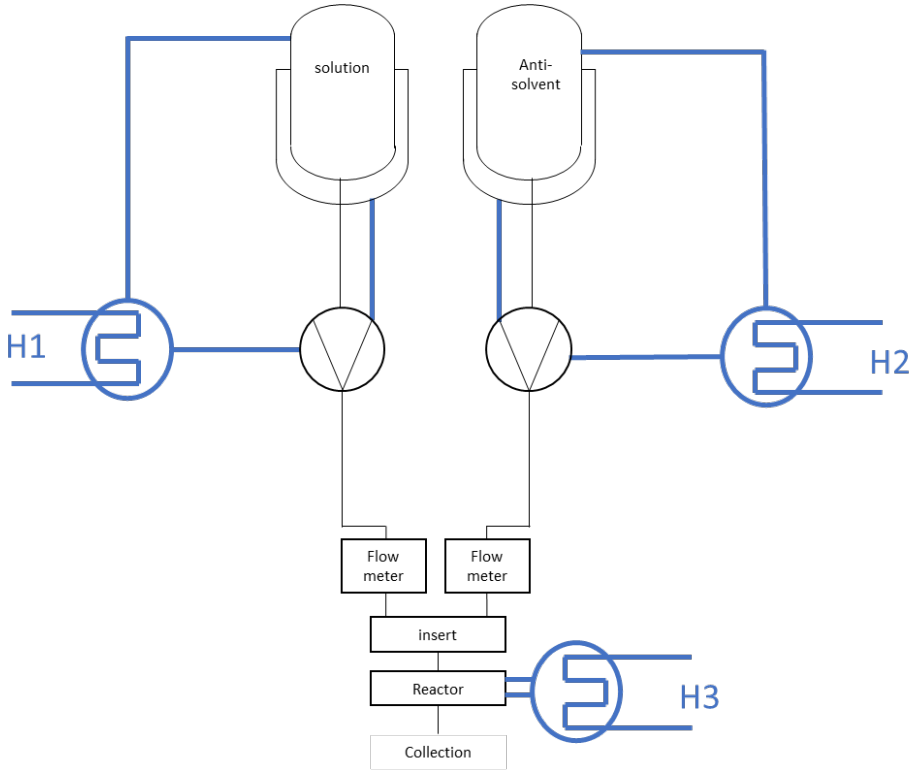
SCT-pilot instrument

SCT-P□LOT technical specifications:

- Three different temperature zones from 5 to 85°C
- Flow rates between 1 and 100 mL/min, different pump heads may lead to better stability in different ranges
- Pressure drop possible up to 40 bar – very important for highly viscous materials
- Single use consumables
- □dentical set of inserts and reactors
- Standard equiped with 2L glass lined vessels, agitated – may be exchanged with other vessels if required

- Pressure control for blockages
- Known OEM suppliers: Hubert thermostats and Knauer pumps.



2
Case studies

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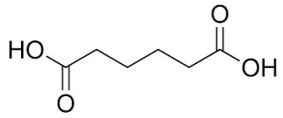
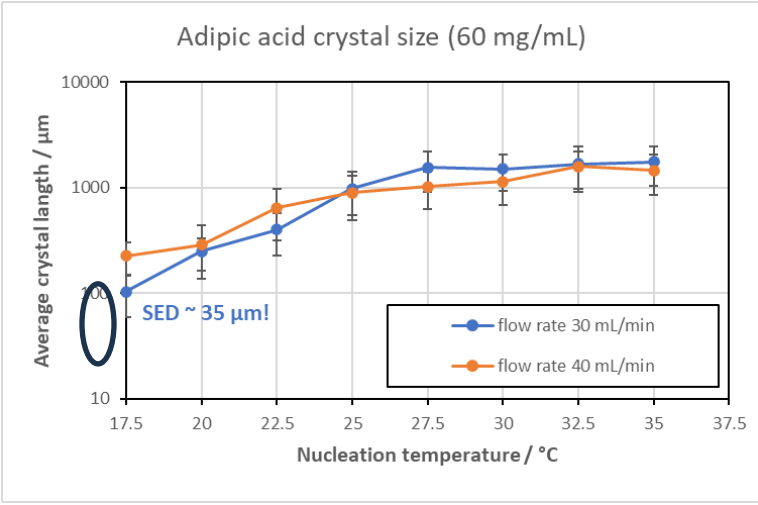
SCT-pilot instrument long-term operation

Adipic acid



Laboratory conditions: searching for different crystal attributes

Parameter	Adipic acid
Insert	Cooling – 0
Reactor	3 mL
Solution temperature (°C)	60
Solution concentration (mg/mL)	60
Flow rate (mL/min)	30 and 40
Nucleation temperature °C	various
Crystal growth conditions	Gathering at RT, 15 minutes maturing



remark: lower nucleation temperatures resulted in fast blockages during cleaning

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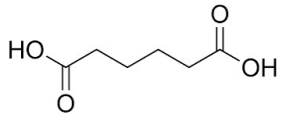
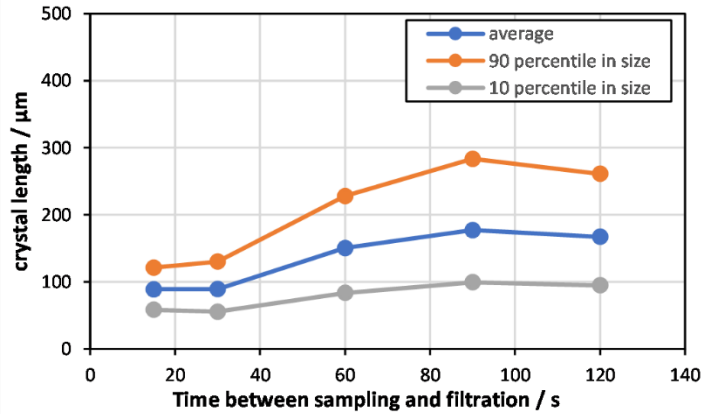
SCT-pilot instrument long-term operation

Adipic acid



Laboratory conditions: looking at crystal growth rate

Parameter	Adipic acid
nsert	Cooling – 0
Reactor	3 mL
Solution temperature (°C)	60
Solution concentration (mg/mL)	60
Flow rate (mL/min)	30
Nucleation temperature °C	20
Crystal growth conditions	Filtration at different collection times



remark: product gathered and filtered after one night at RT results in identical size

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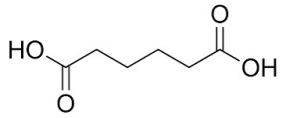
SCT-pilot instrument long-term operation

Adipic acid



Laboratory conditions duplicated on pilot unit:
Preparation of 8 L solution

Parameter	**Adipic acid**
nsert	Cooling – 0
Reactor	3 mL
Solution temperature (°C)	60
Solution concentration (mg/mL)	60
Flow rate (mL/min)	30
Nucleation temperature °C	17.5
Crystal growth conditions	Filtration 2 minutes after gathering

- Sampling was done every 30 minutes during 10 minutes to collect 300 mL of slurry,
- Slurry was gathered in bottle and filtered after 120 sec

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SCT-pilot instrument long-term operation

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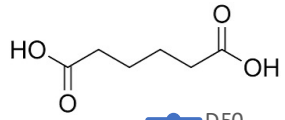

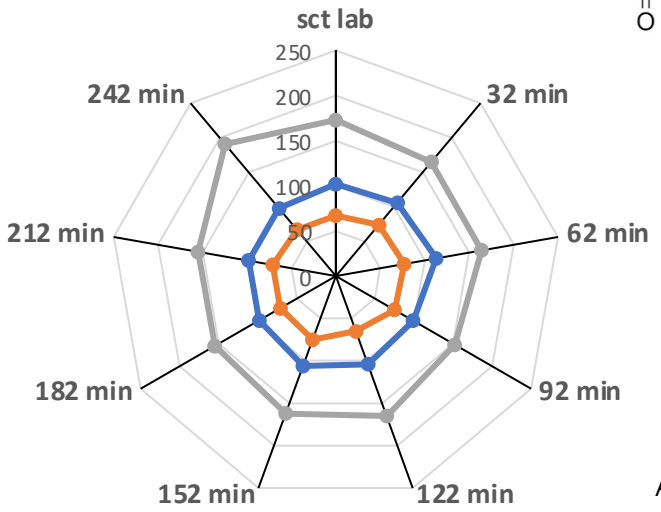

Axis = size in µm

4 hour run without disruptions
Symetry in graph indicates stability of product over time
Lab parameters fully extrapolated

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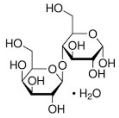
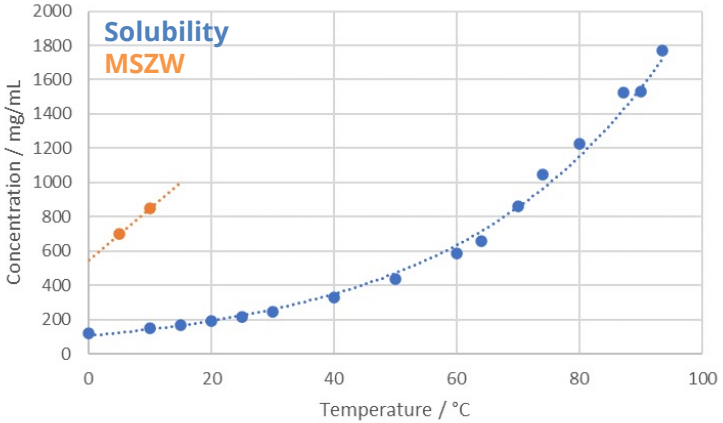
SCT-pilot instrument long-term operation

Lactose



Laboratory conditions set for **lactose**

Parameter	Lactose
Insert	Specific execution for highly viscous materials
Reactor	7 mL
Solution temperature (°C)	85
Solution concentration (mg/mL)	**850**
Flow rate (mL/min)	20
Nucleation temperature °C	5
Crystal growth conditions	Gathering in waiting tank for 18 hrs



remark: The insert and reactor are heavily modified to counter the viscosity effect

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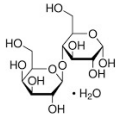
SCT-pilot instrument long-term operation

Lactose



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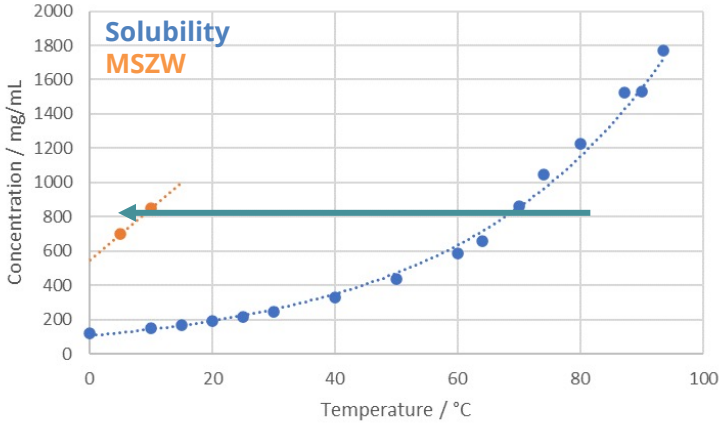

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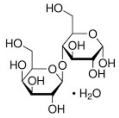

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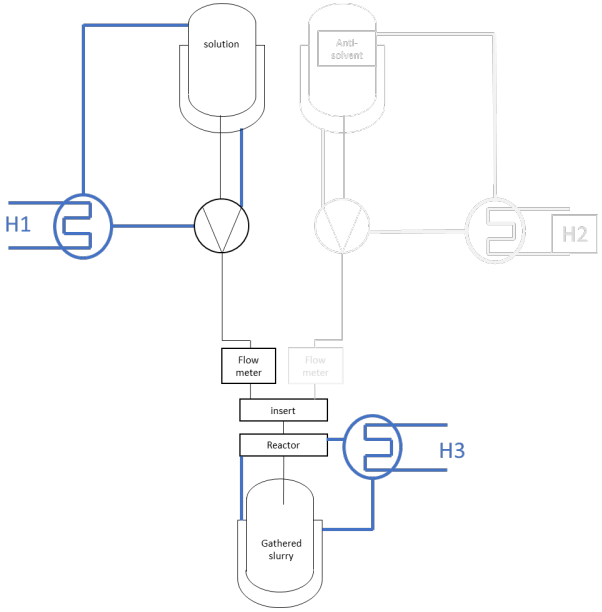

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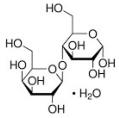

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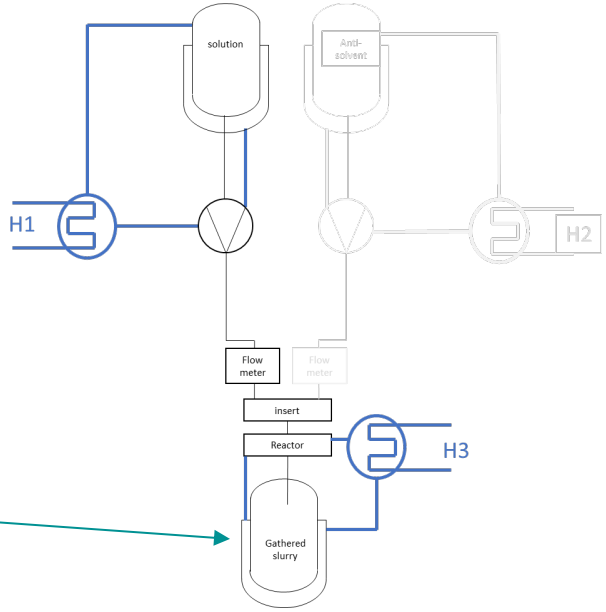

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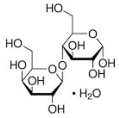
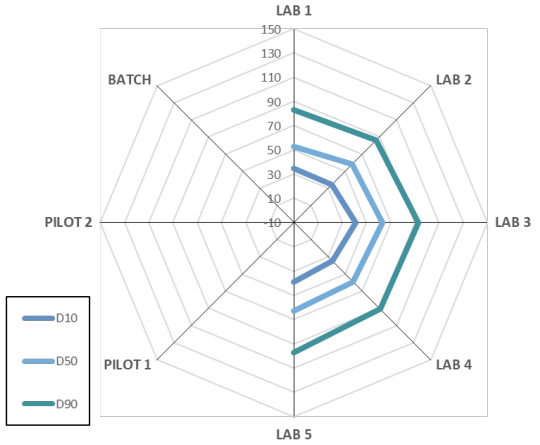
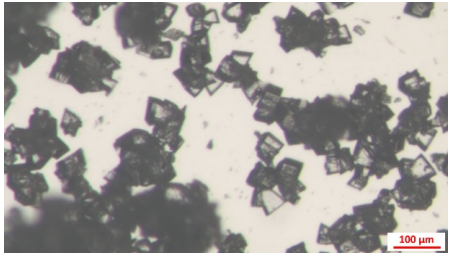




Axis = size in µm

Lab repetition 1



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Lab parameters fully extrapolated

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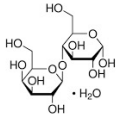

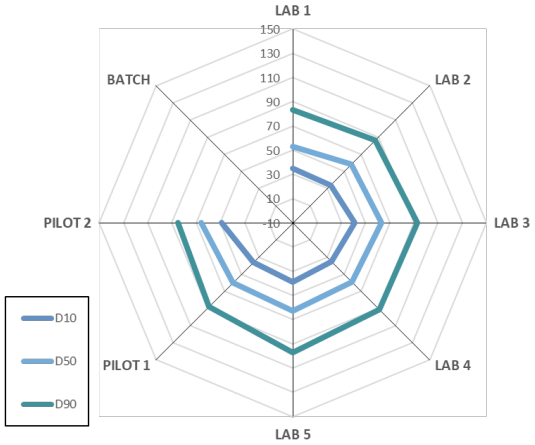

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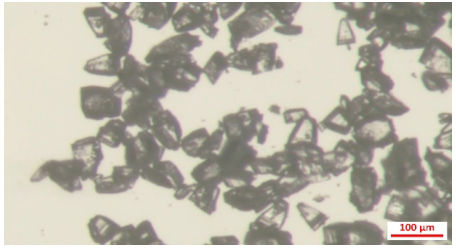

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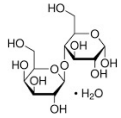
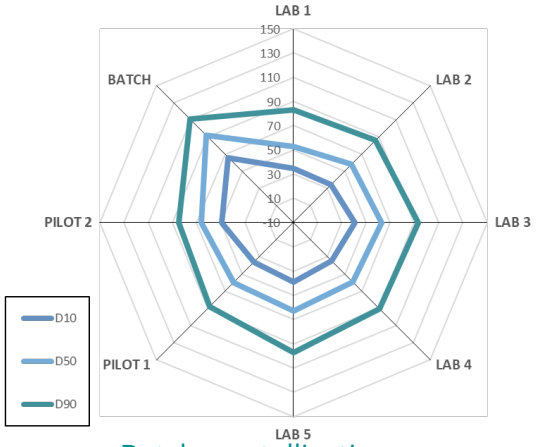
Batch cross-test without passage through reactor results in 50% larger crystals with huge lumps of crystals

Lactose

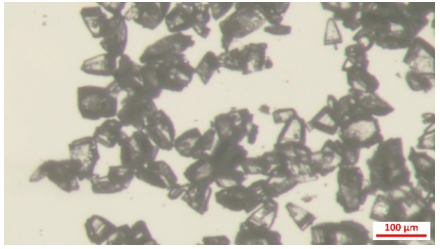




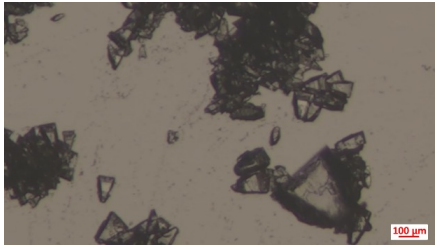
Batch crystallization

Axis = size in µm

Pilot repetition 1



Batch test



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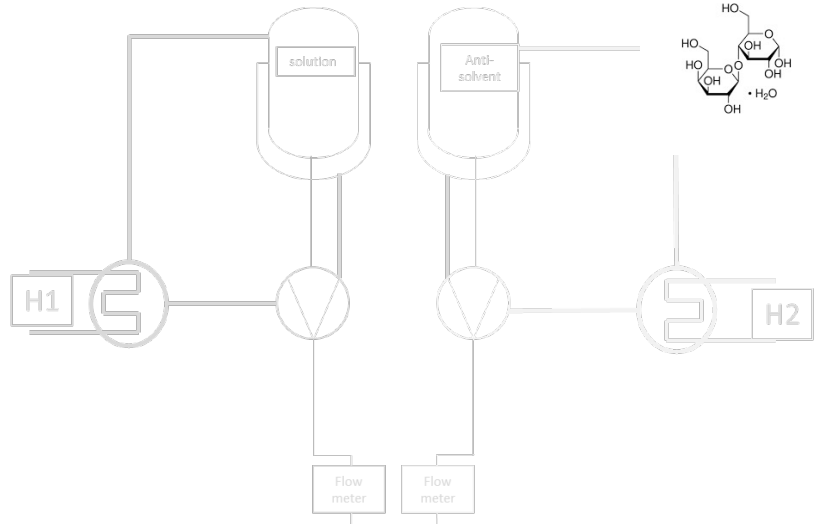

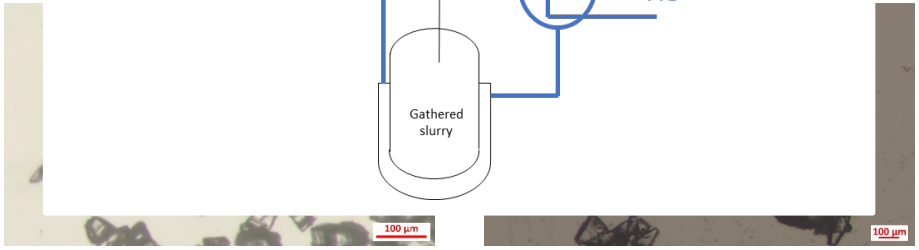

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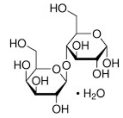
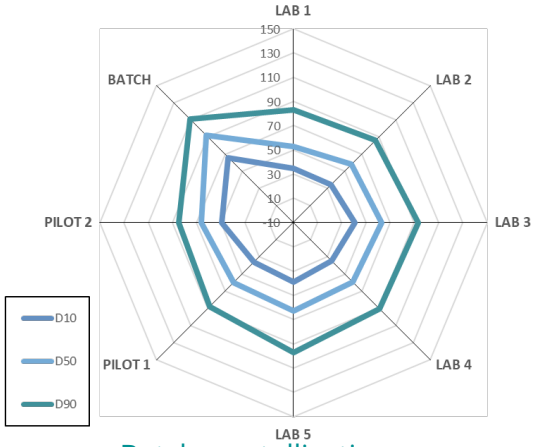
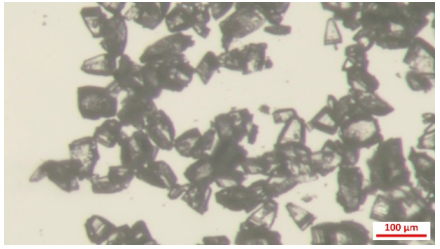




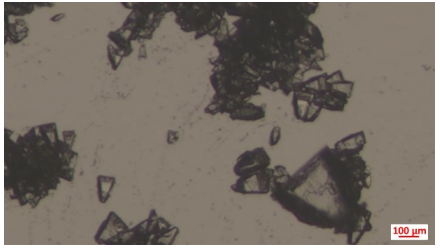
Batch crystallization

Axis = size in µm

Pilot repetition 1



Batch test



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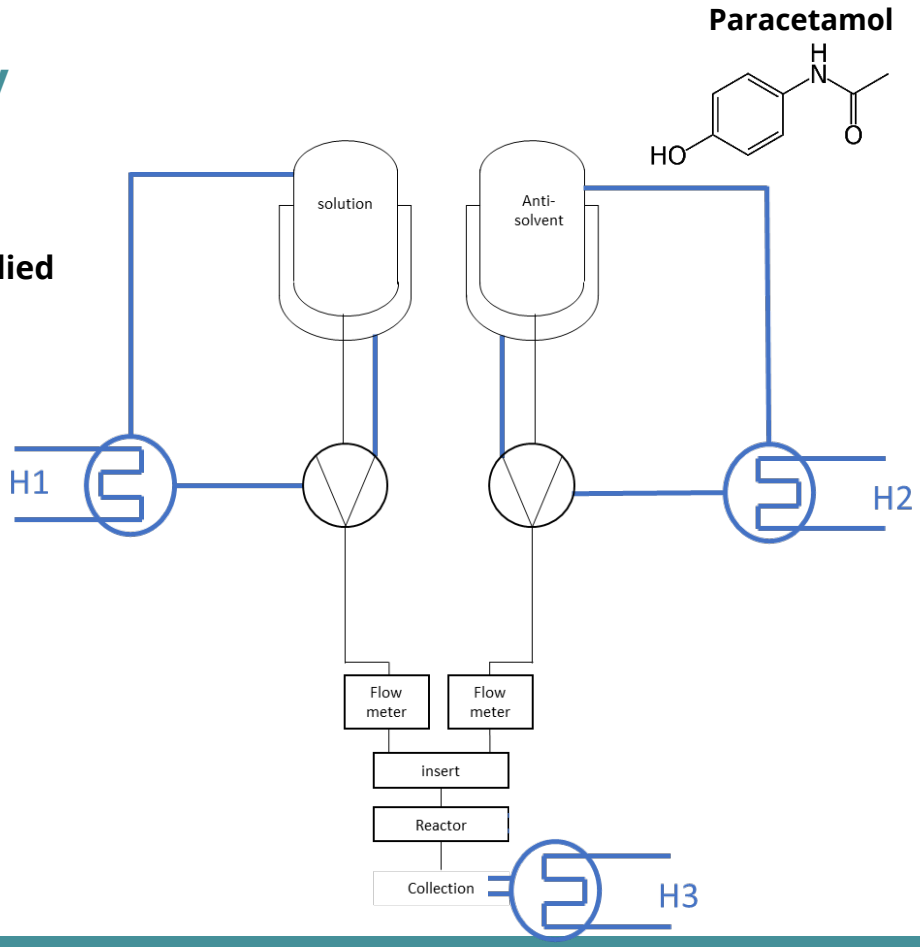
SCT-pilot instrument long-term operation

Laboratory conditions set for **Paracetamol, directly applied to pilot**

Parameter	Paracetamol
Insert	T cross
Reactor	1m
Solution temperature (°C)	50
Solution concentration (mg/mL)	75
Flow rate (mL/min)	40/40
Nucleation temperature °C	RT
Crystal growth conditions	Collection in tank at 5°C for 30 min



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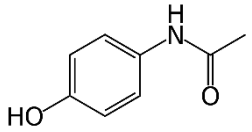
SCT-pilot instrument long-term operation

Paracetamol



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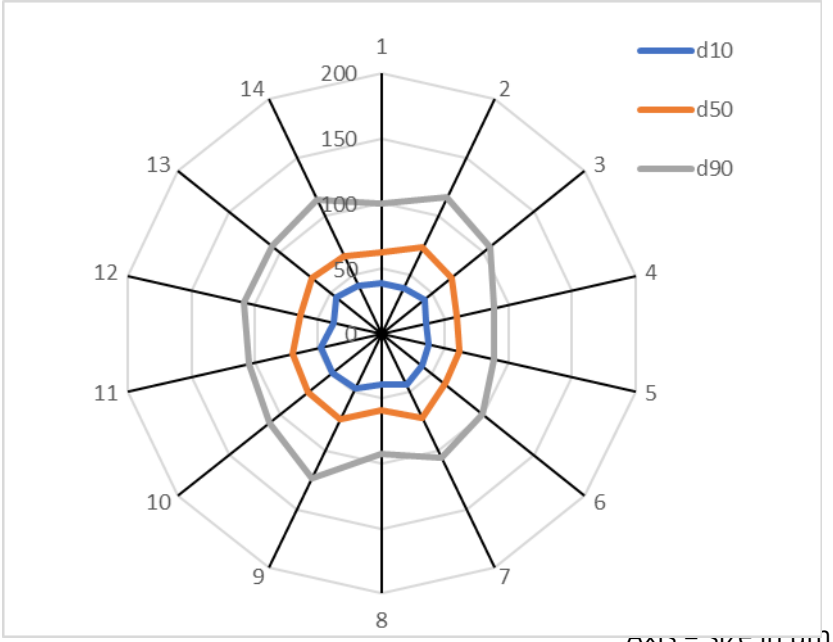

Axis = size in µm

3

Production strategy

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SCT-ICE instrument

INDUSTRIAL CRYSTALLIZATION UNIT – ICE is based on:

- **Identical Reactor setup** of laboratory equipment
- **cGMP design and execution**
- **Molecule specific or multiproduct aproach**
- Reactors in parallel in standard equipment up to 10 modules
- **Cleaning in place**
- **Automated software, open for communication to its surroundings**
- Depending on solubilities and applied rates: 1.5 to 3 ton of solid product per module per year

SCT-ICE with 5 modules

Reactor module

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SCT-ICE instrument

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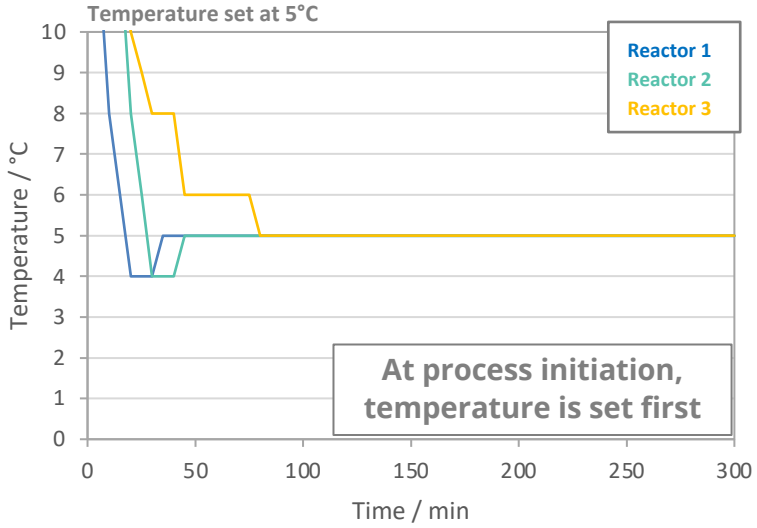
Reliable Upscaling with identical set of parameters

Quality by Design approach (QbD):

Upscaling means placing **identical** reactors in **parallel**

Product overall quality is defined by temperature and flow stability



Secoya Crystallization Technology

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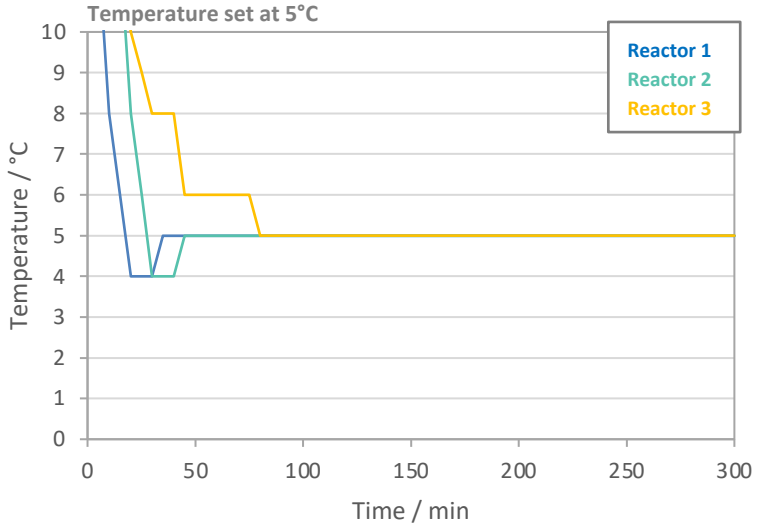
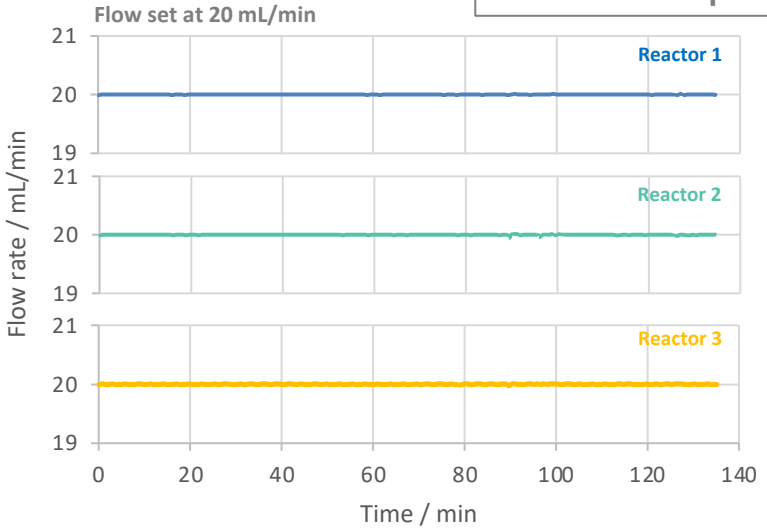


Secondly, the reactors are opened



Secoya Crystallization Technology

Reliable Upscaling with identical set of parameters

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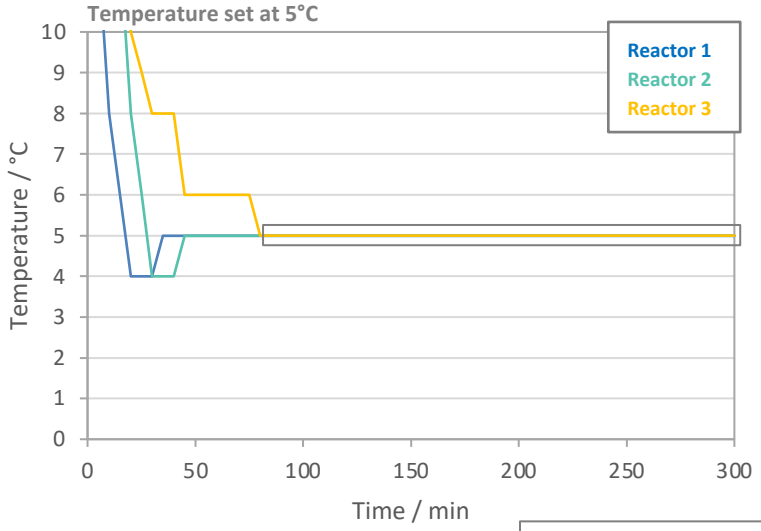
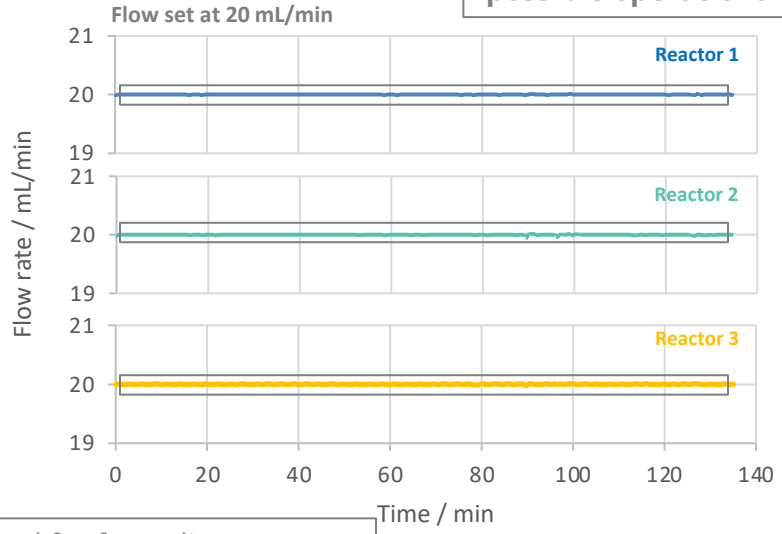
Aim for the smallest possible operational zone





Real-time parameter control for fast adjustments and closing of reactors to maintain product quality

Secoya Crystallization Technology

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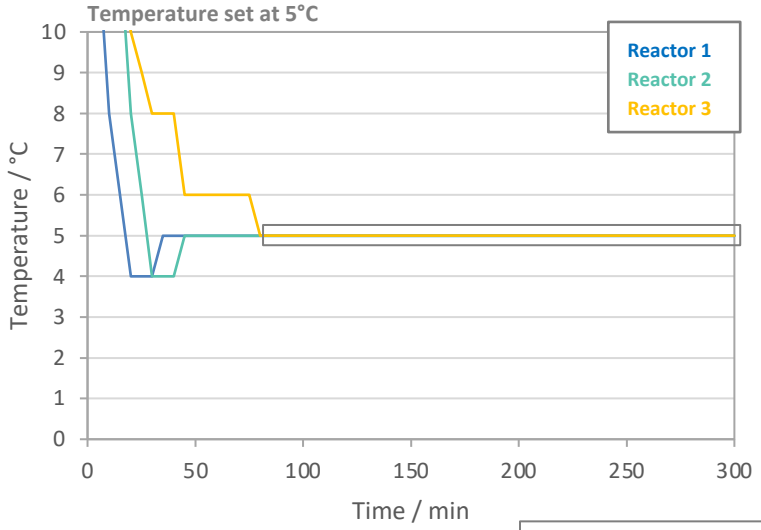
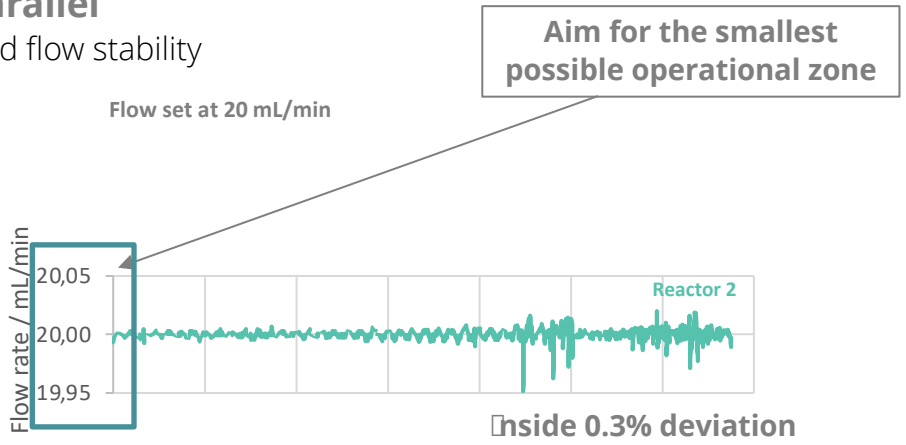




Real-time parameter control for fast adjustments and closing of reactors to maintain product quality

Secoya Crystallization Technology

Importance of operational zonewidth

Aim:

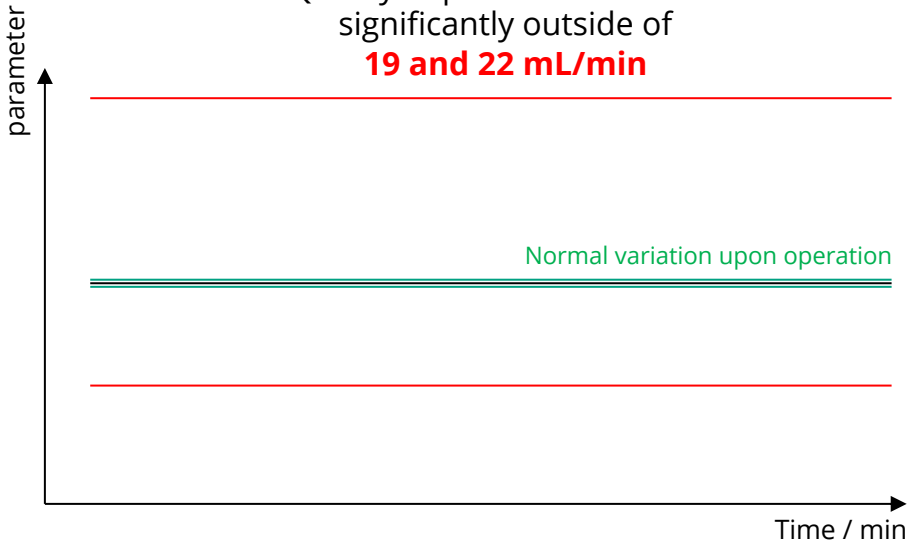
Create identical residence time at **identical temperatures**

Benefit:

- **More uniform conditions** of continuous operations means more **quality control by the design** of the instrument and operation
- Determination of **small operational zonewidths**, **extra space for adjustment of tests before running out of hand**

Test Flow Rate variation between
19.95 and 20.05 mL/min

Boundary conditions:
Quality of product is affected significantly outside of
19 and 22 mL/min



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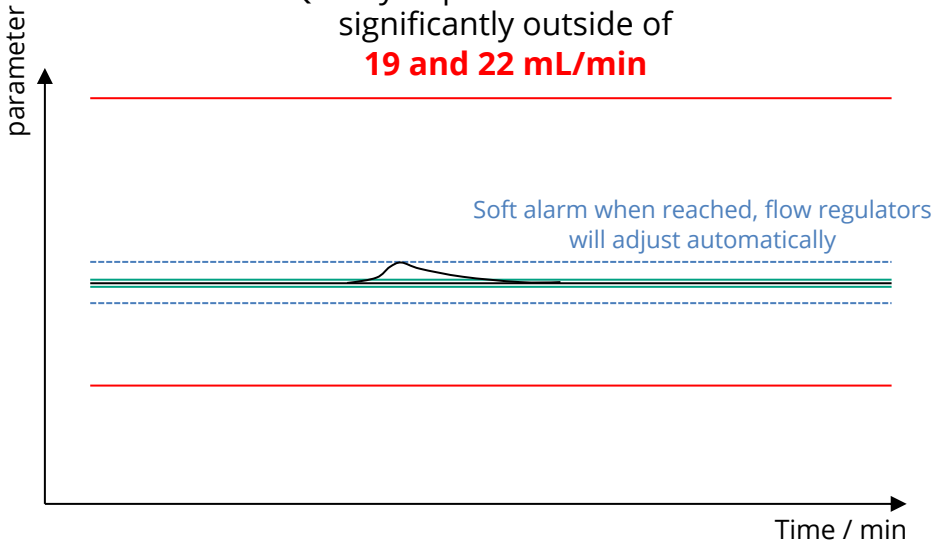

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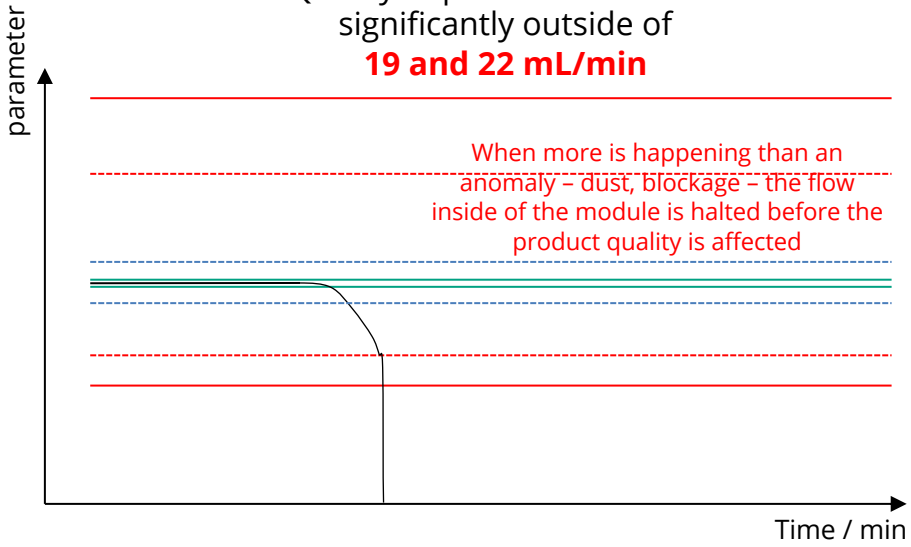


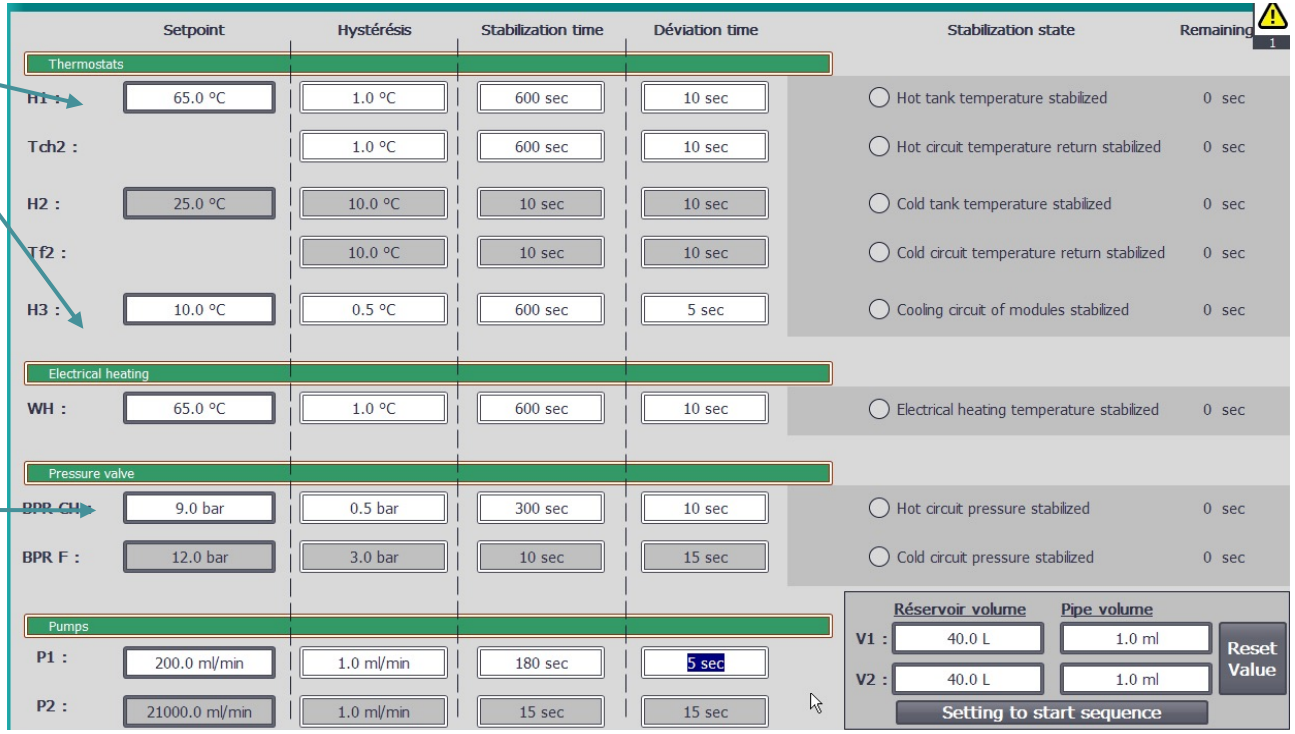
Secoya Crystallization Technology

Introduced into the parameter set on the CE equipment

Solution temperature

Peripheral system

Total pump flow rate



Secoya Crystallization Technology

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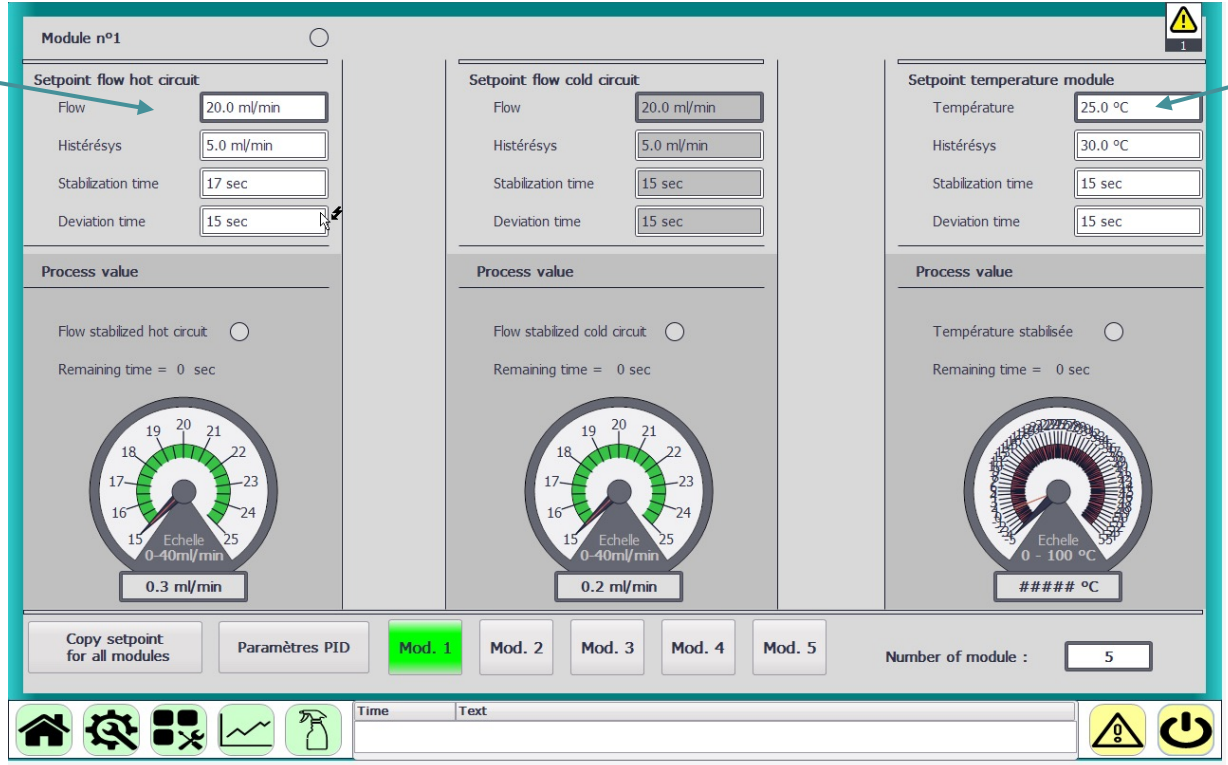
Flow rate in reactor

Nucleation temperature



nside modules

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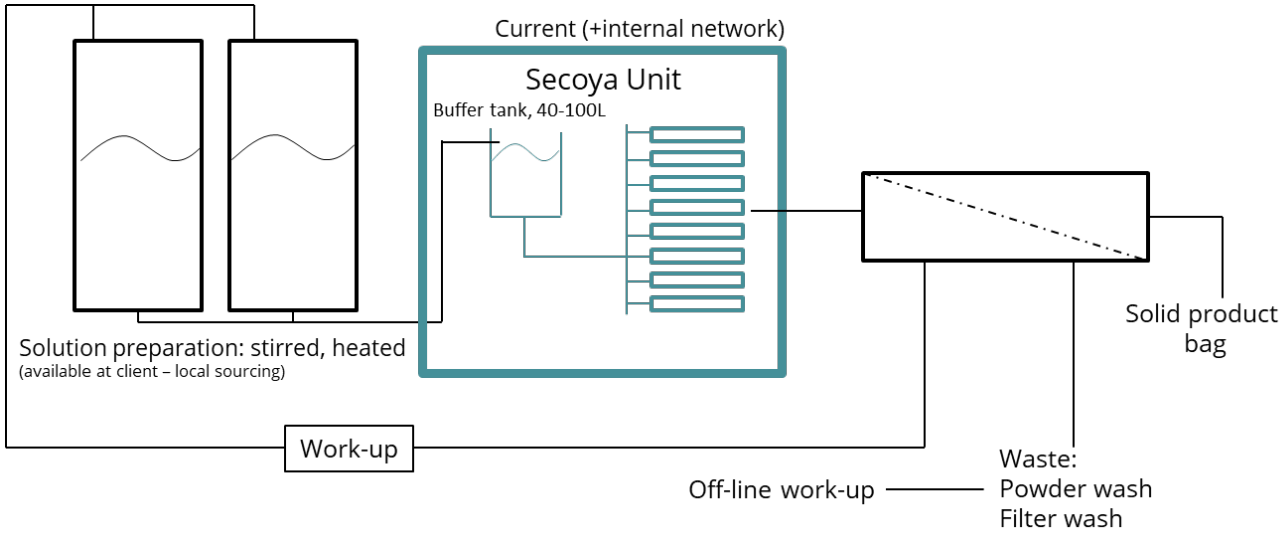
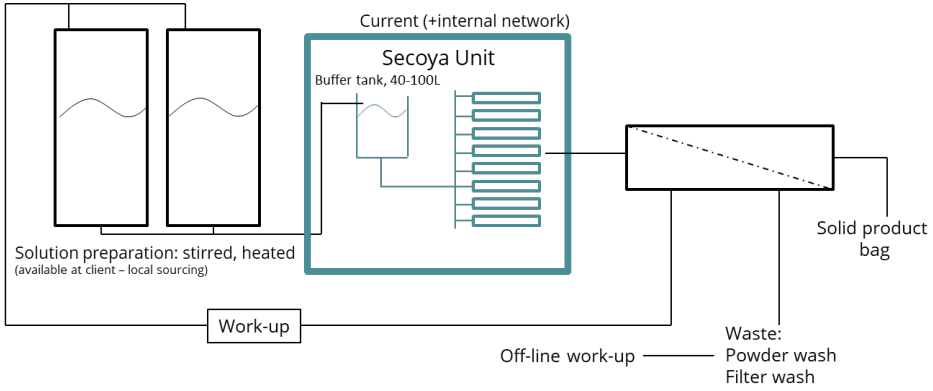


Secoya Crystallization Technology

Upscaling strategy – based on actual examples

- Production request: **25 kg/day** for a production of 100 kg/week
- Only working hours, operations possible during 12 hrs: 1 hr setup, 9 hrs to run, rest for cleaning (2 shift basis with overlap)
- Solubility in solvent: 250 mg/mL
- Solubility at equilibrium (5°C): 50 mg/mL
- Possible yield: 200 mg/mL solvent
- Obtained: 94 % yield = 196 mg per mL solution injected
- Flow rate: 30 mL solution/min/reactor
- Production rate per hour ~ **350 g/hr/reactor**
- 8 reactors produce per 9 hours 25.2 kg
- Use bonus of two modules to shorten production times

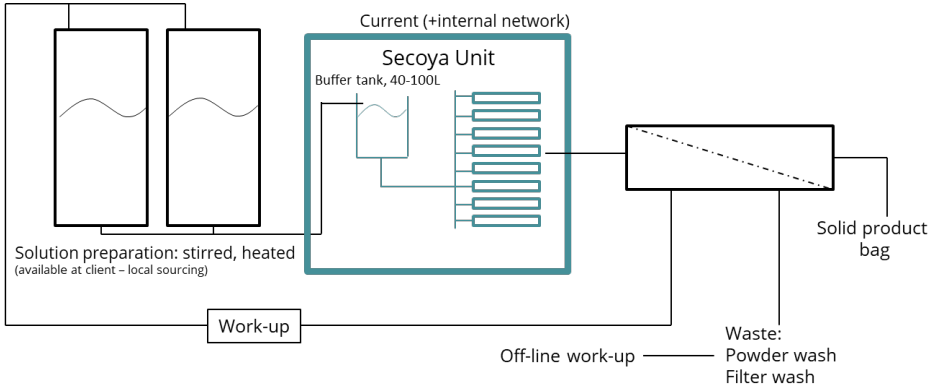


1 Growth tank to collect material at temperature, agitated
Filtration with dimensionalized candle filter to shorten filtration time and to allow washing and during inside the tank with DrMueller

Secoya Crystallization Technology

Upscaling strategy – based on actual examples

- Production request: **50 ton per yea**r, split in weekly productions
- 5 days' work week, cleaning procedure included, nucleation reactor may run overnight
- Solubility in solvent: 850 mg/mL
- Solubility at equilibrium (5°C): 150 mg/mL
- Possible yield: 700 mg/mL solvent
- Obtained: 95 % yield = 665 mg per mL solution injected
- Flow rate: 20 mL solution/min/reactor
- Production rate per hour ~ **798 g/hr/reactor**
- 50 reactors produce per 3 days 2.87 ton
- Ideal scenario: 17 batches per year which leaves space for events + increased production



3 growth tanks are filled consequently to cope with 18 hr growth time
Filtration and CIP + module cleaning on Thursday and Friday

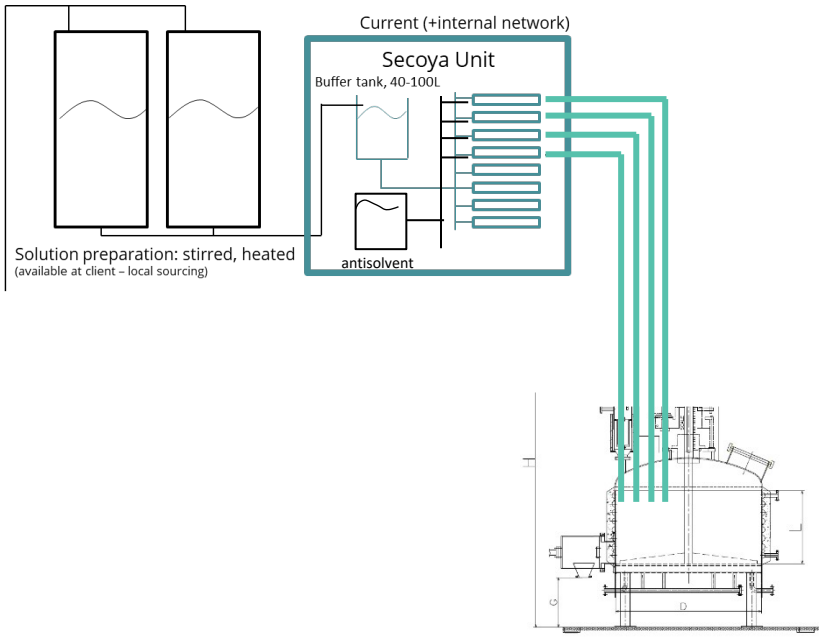
Secoya Crystallization Technology

Upscaling strategy – based on actual examples

- Production request: reactive crystallization of inorganic salt
- 5 days' work week, 2 shift basis for a 12 hr production + cleaning possibility
- **5 kg solids/hour** = 200 kg/week = 9 ton/45 weeks operation
- Possible yield: 100 mg/mL solution with 1/5 mixing ratio with antisolvent

  !!!!! This reactive crystallization does not require a reactor, only turbulent mixing and a larger execution of the insert is applied, running at 200 mL/min for the solution side and 1000 mL/min for the antisolvent side

- 4 nozzles applied, directly implemented onto a Nutsche filtration unit. Production rate attained **1.2 kg/hr/reactor**



4

Other production strategies
PIPELINE – client input

How to implement Secoya at industrial level - Discussion

We see levels of entry that are more feasible to introduce the technology into industry:

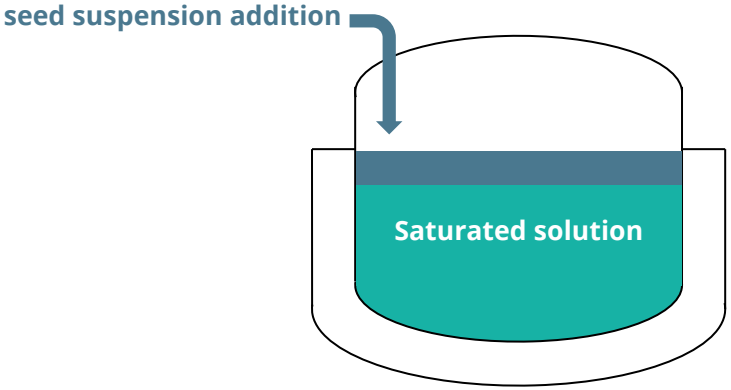
- HPAPI as we control the size of product and maniplations are ower
- Specific formulations: Drug product level, skipping one or more steps in DP development
- Benefit to couple to continuous tablettling machines - Fette – at DP level

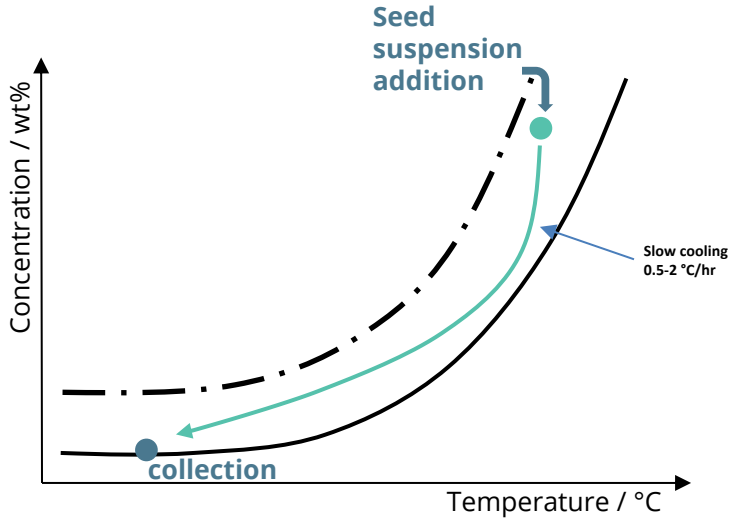
More classic API substance production, splitted from Drug product manufacturing, we see interest, but difficulties in entering into these sites as the **change** necessary to implement our units is drastic/ 'adventorous'

Preparation of high quality seeds – both dried or in suspension

Seeding Strategy

- Generate seeds of desired size and PSD, at equilibrium condition
- Add seed suspension to solution – might be dried (storage) or in suspension
- Perform a ‘classic’ batch crystallization





Produced slurry used as starting point for MSMPR setup

Use as continuous feeder of nuclei into MSMPR setup

- Generate seeds
- Continuously added to first CSTR tank
- Product is removed from first and sent to a second at lower temperature