

Crysta'days | November 8 2023

Introduction to Secoya Crystallization  
Technology

**Secoya**  
FLUIDIFY PHARMA



# Secoya Crystallization Technology

Where we are now

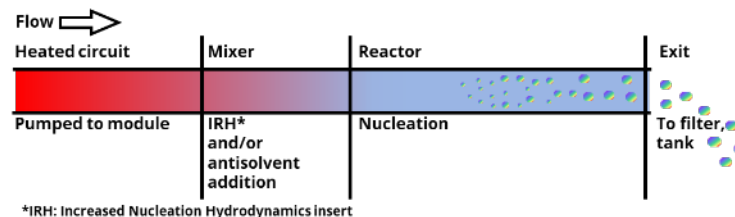
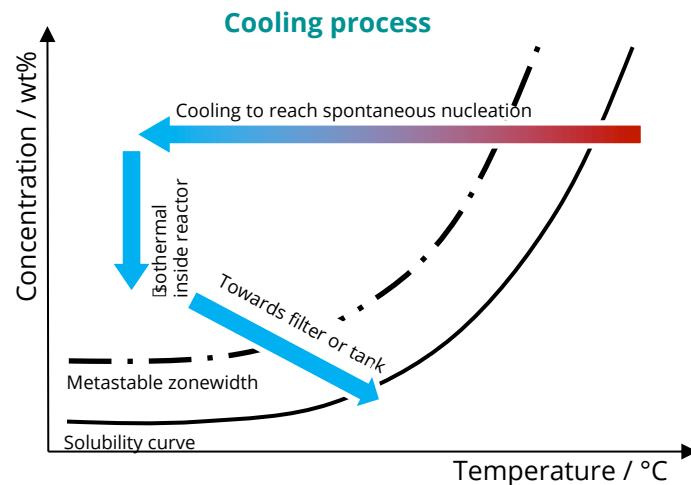


## Several crystallization modes

- Cooling crystallization
- Antisolvent co-flow mode
- Antisolvent frontal mode

## High control on size and dispersity

- From nm to 400  $\mu\text{m}$  size
- Low polydispersity (span < 2)
- Excellent flowability (non charged particles)



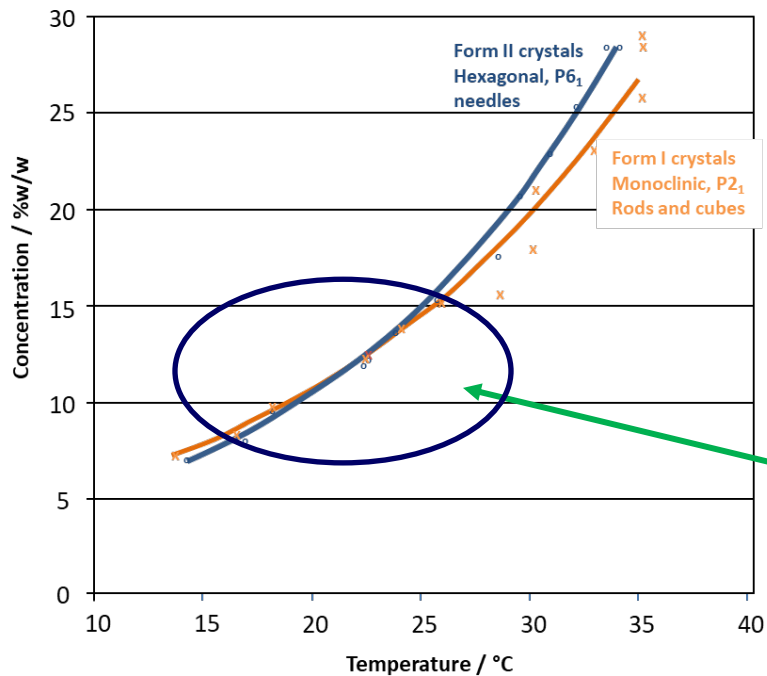
Rimez et al., Crystal Growth & Design (2018)

*Any parameter influencing the nucleation can be optimized and control to allow a final crystal size selection adapted to the application, in one step and with a low size distribution.*

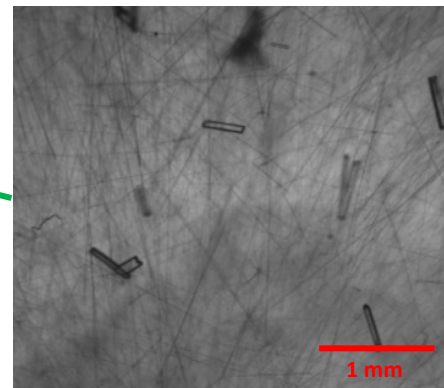
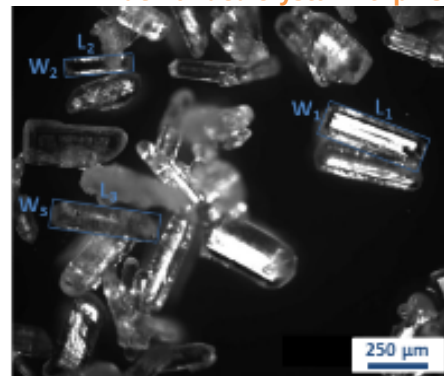


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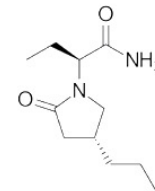
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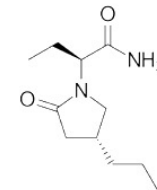


demanded crystal morphism



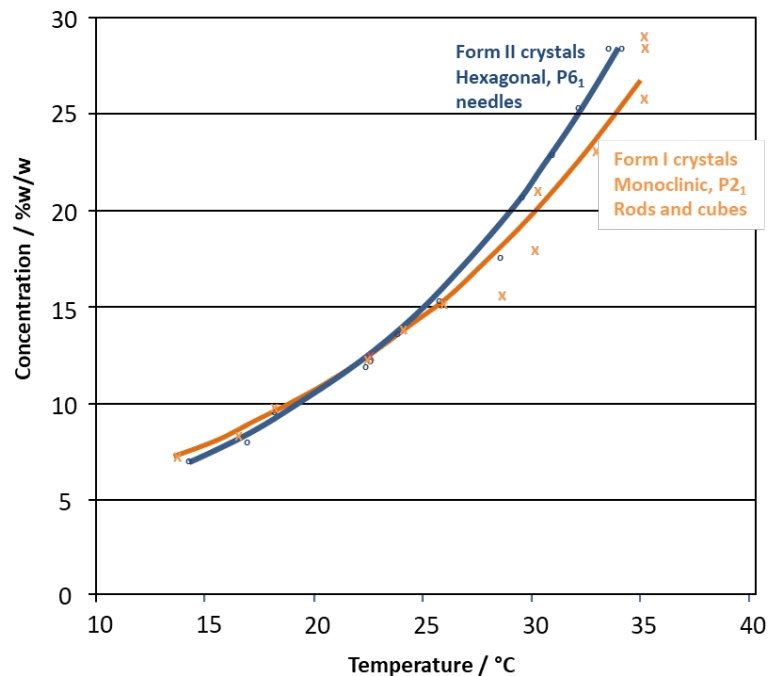
## Brivaracetam





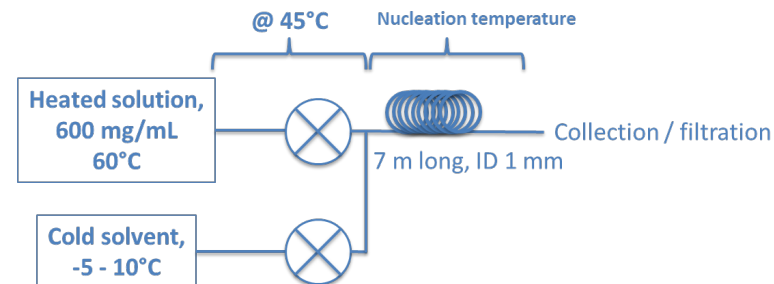
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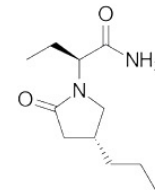
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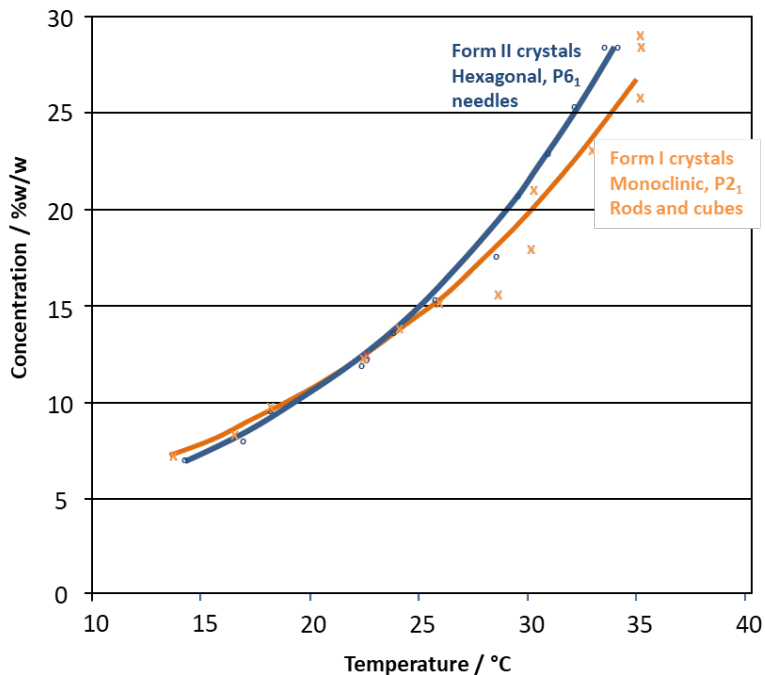
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- Any interaction with foreign bodies
- Droplet crystallization in microfluidic setting
- Impinging jet mixing with solvent IPAC at room temperature
- Impinging jet mixing with cooled solvent IPAC





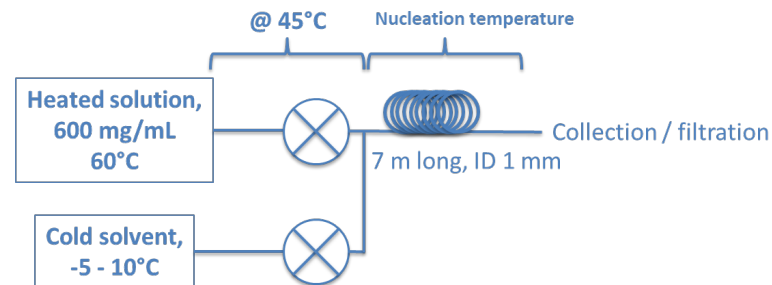
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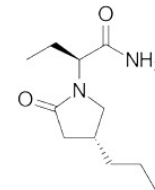
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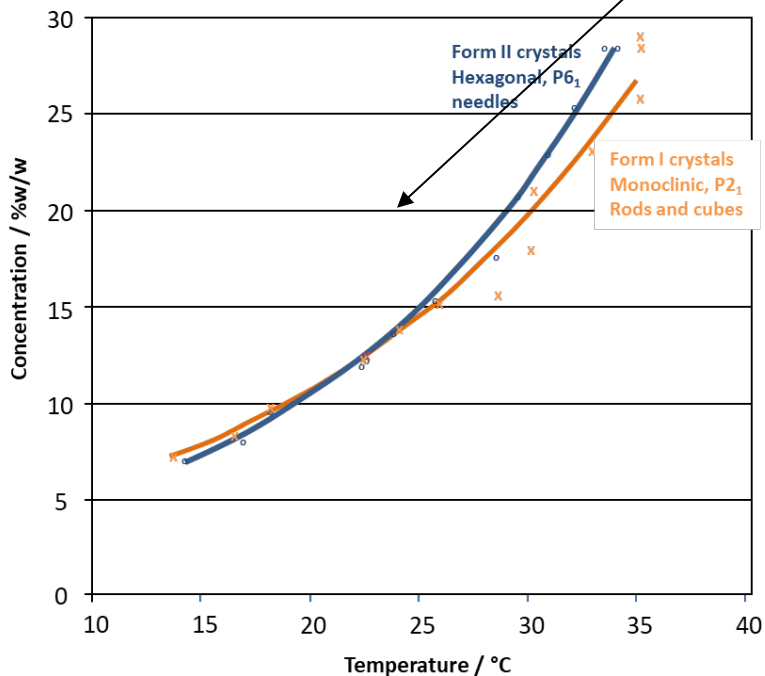
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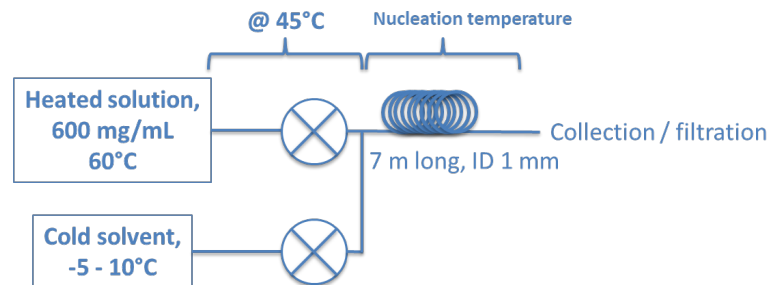
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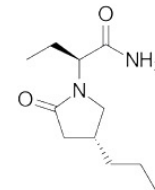
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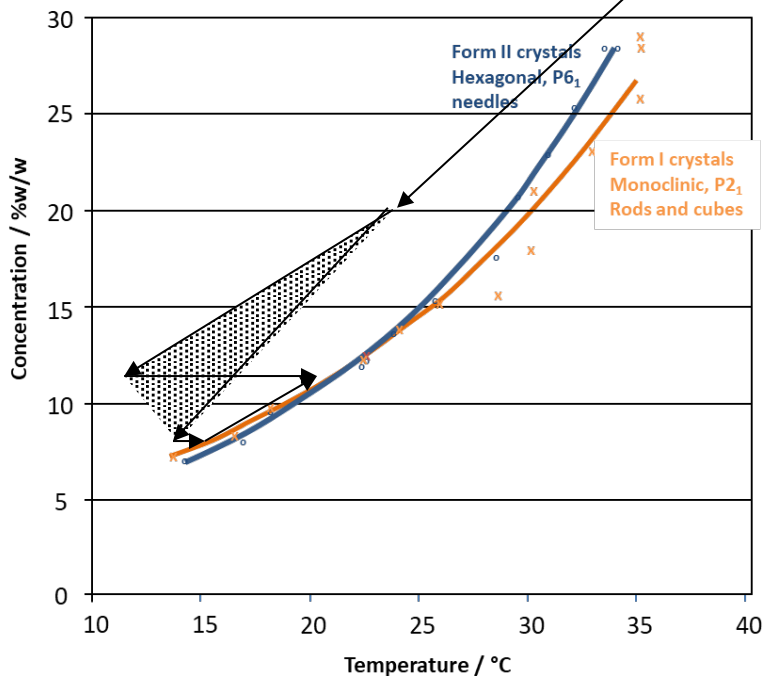
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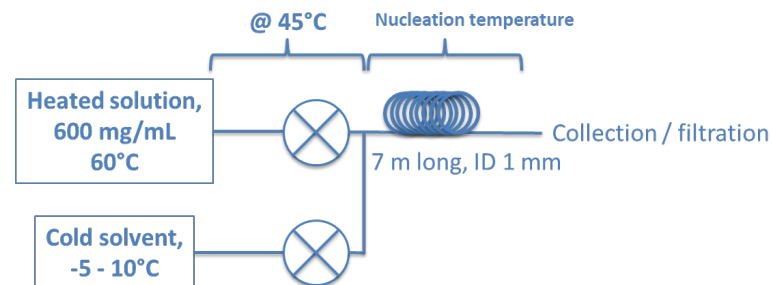
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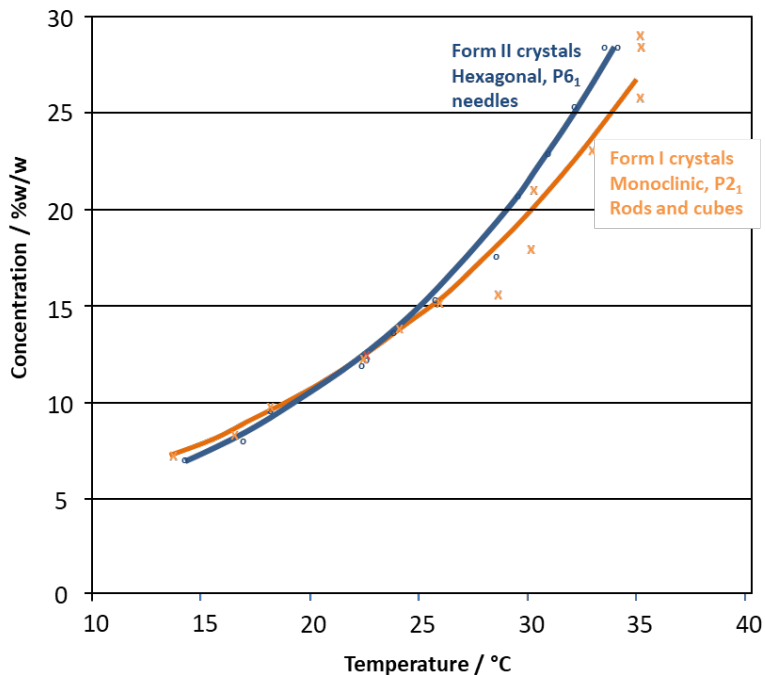
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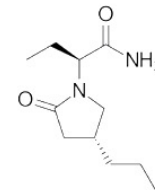
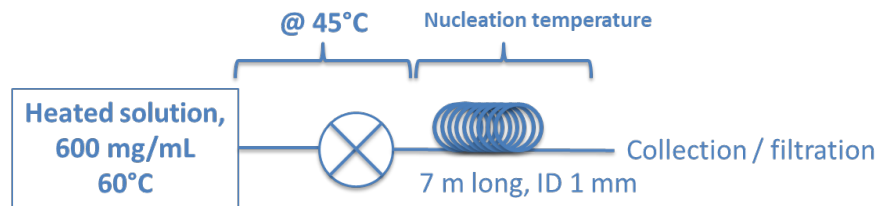
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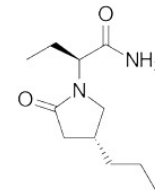


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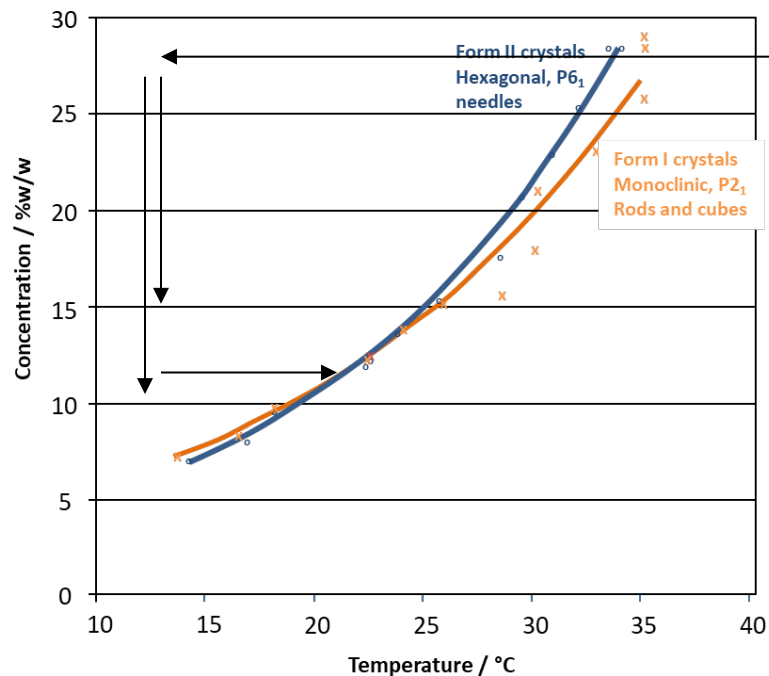






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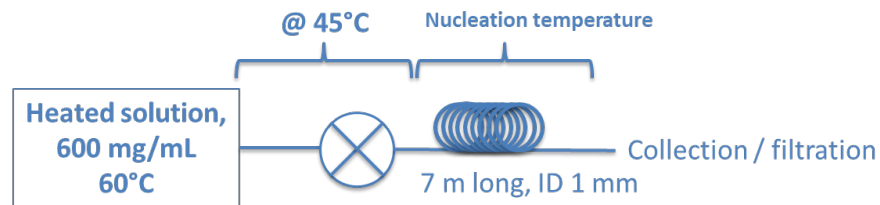
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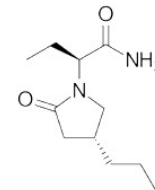


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**X**

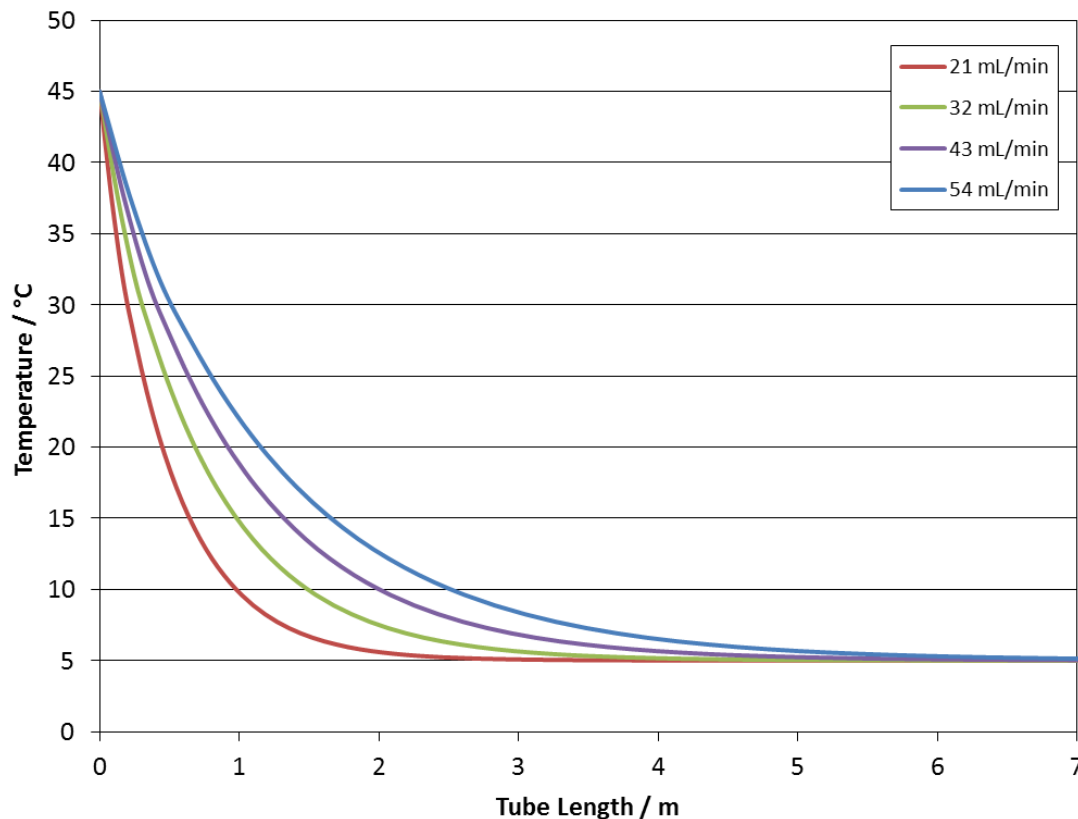
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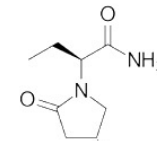
# Secoya Crystallization Technology

Residence time limitation?



## Residence time in tubing

Flow mL/min	Velocity cm/s	Residence time s
21	45	16
32	68	10
43	91	8
54	115	6

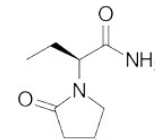


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Concentration mg/mL	Flow mL/min	Velocity cm/sec	Residence time sec	Temperature bath °C	Pressure bar	Crystallization result	Crystal sizes µm
600	21	45	16	0	8	Cubic	175± 100
600	32	68	10	0	12	Cubic	121 ± 33
600	43	91	8	0	16	Cubic	227 ± 64
600	54	115	6	0	22	Needles and cubic	

↑  
Too short residence times

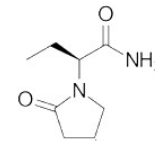


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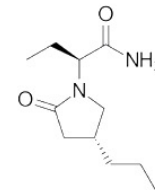
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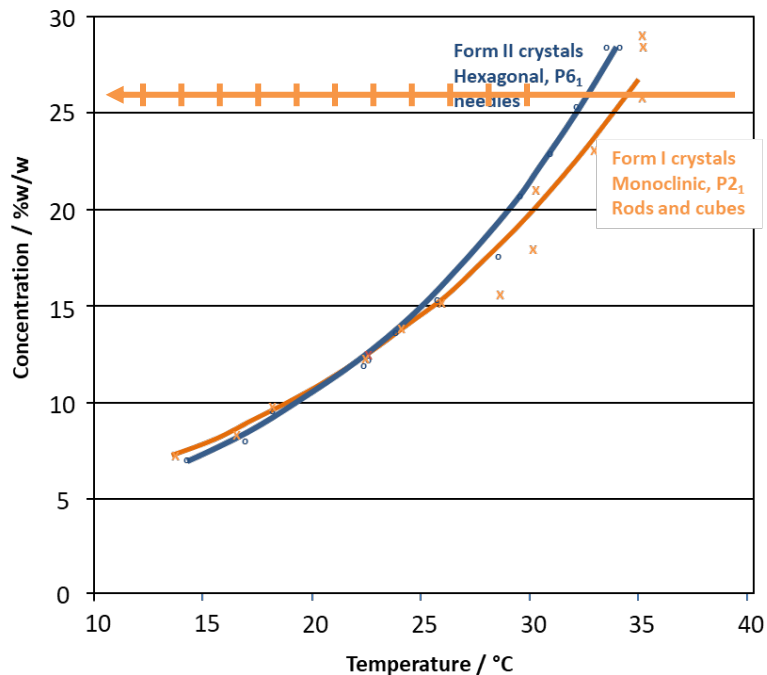
↑  
Too short residence times

↑  
Polymorph selection and smallest size



# Secoya Crystallization Technology

And what about about shear rate

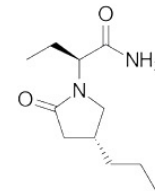


## Thermodynamics:

- Start with heated solution
- Cool down to desired temperature where nucleation may take inside reactor with fixed dimension
- Let slurry obtained after passage at different tested nucleation temperatures grow to equilibrium
- Analyze crystal appearance and size as a function of tested condition

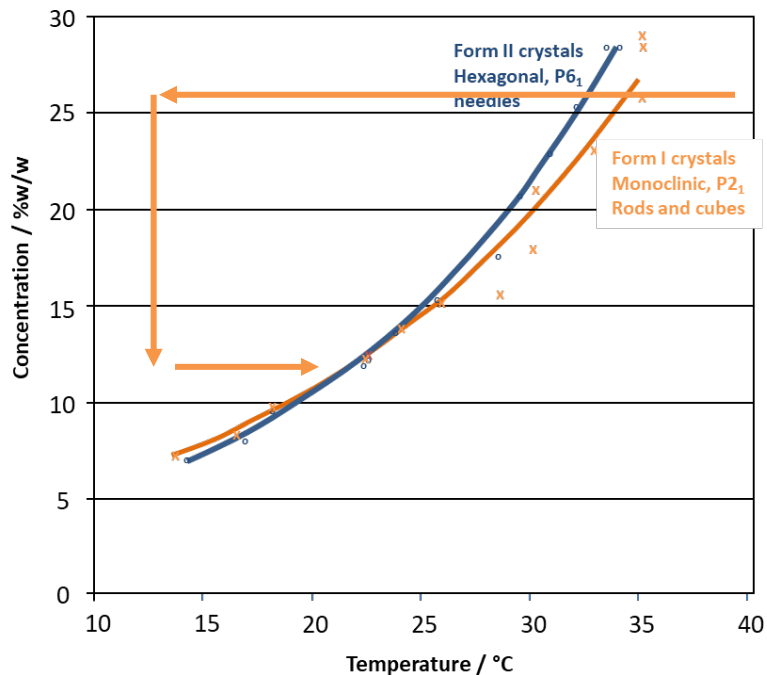
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- Each solute in solution has an optimum average shear rate
- Other types of behavior?



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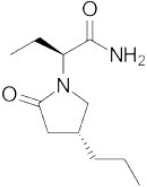


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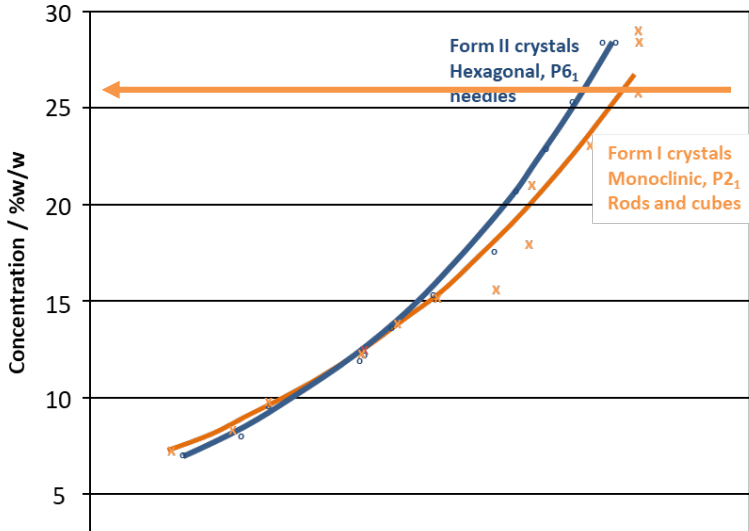
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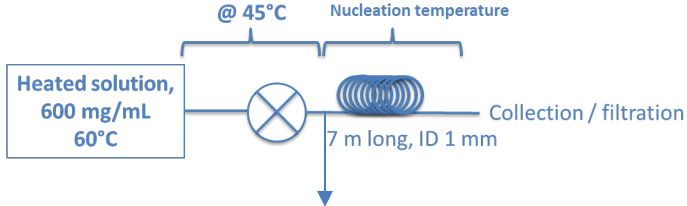
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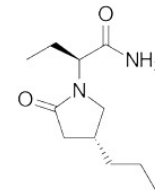
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Standard connector for 1/16" tubing

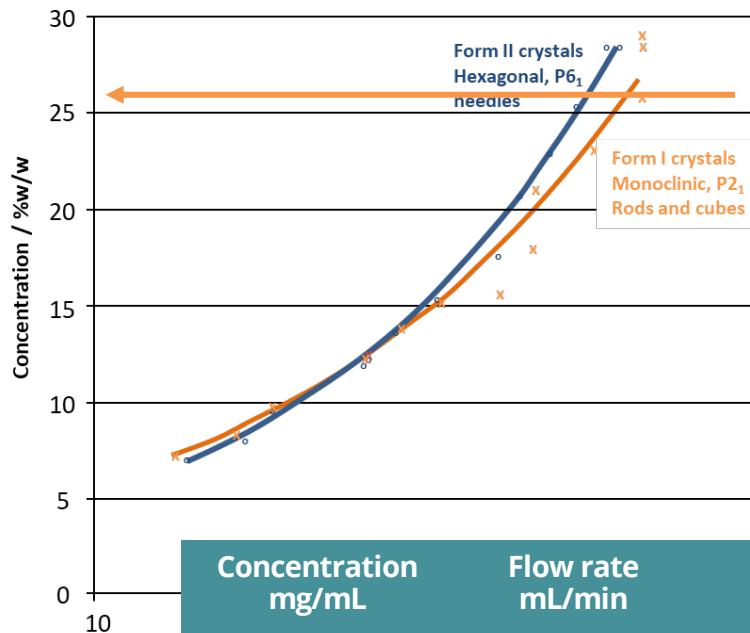
Concentration mg/mL	Flow rate mL/min	Restriction μm	Temperature bath / °C	Crystal sizes μm	Estimated nucleation rates / s <sup>-1</sup>
600	32	500	0	121 ± 33	625 000
600	32	1000	0	365 ± 106	23 000





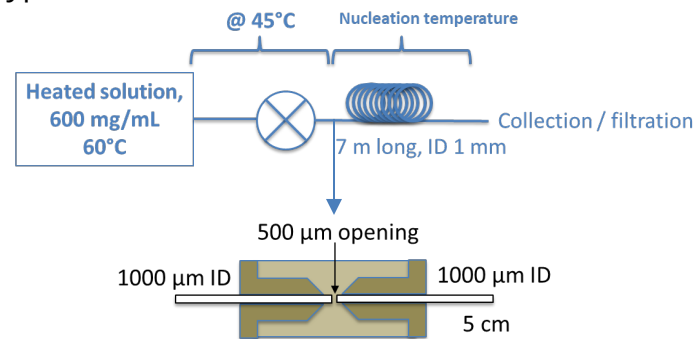
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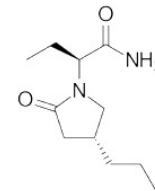
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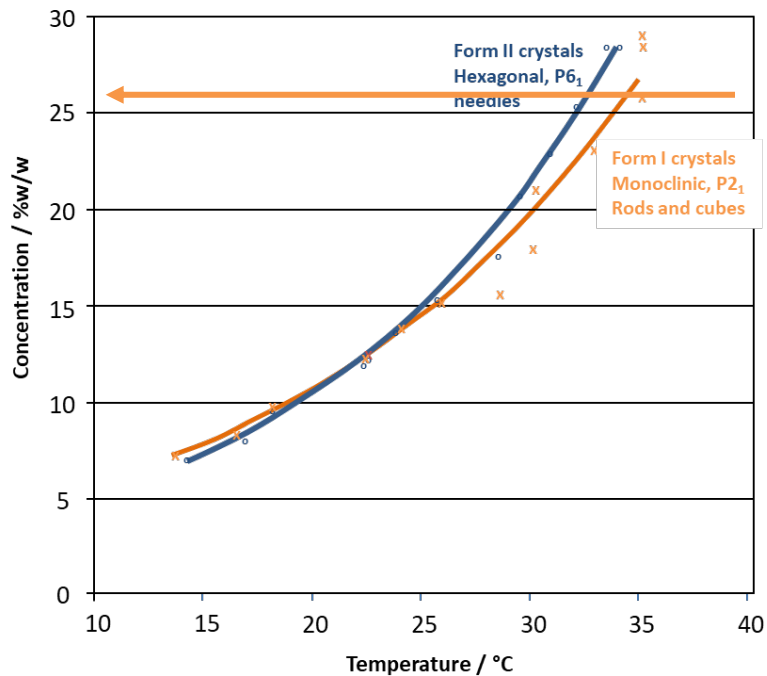
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Rimez et al. Cryst Growth Des 2018



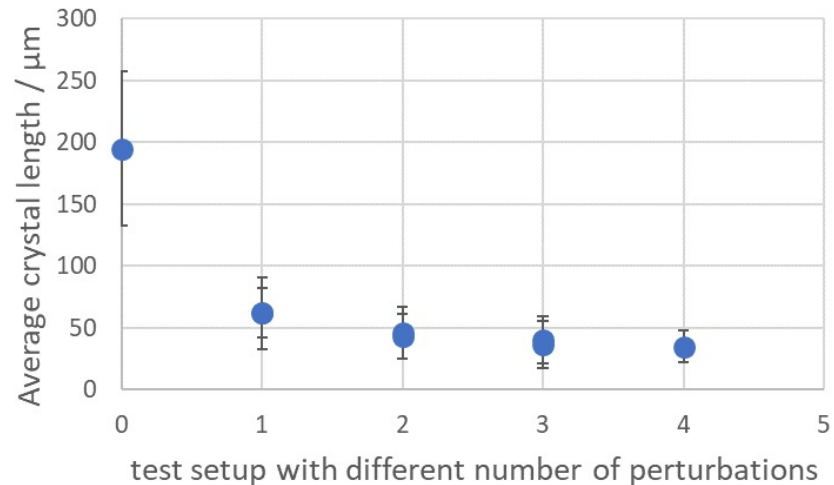
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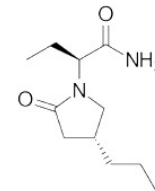
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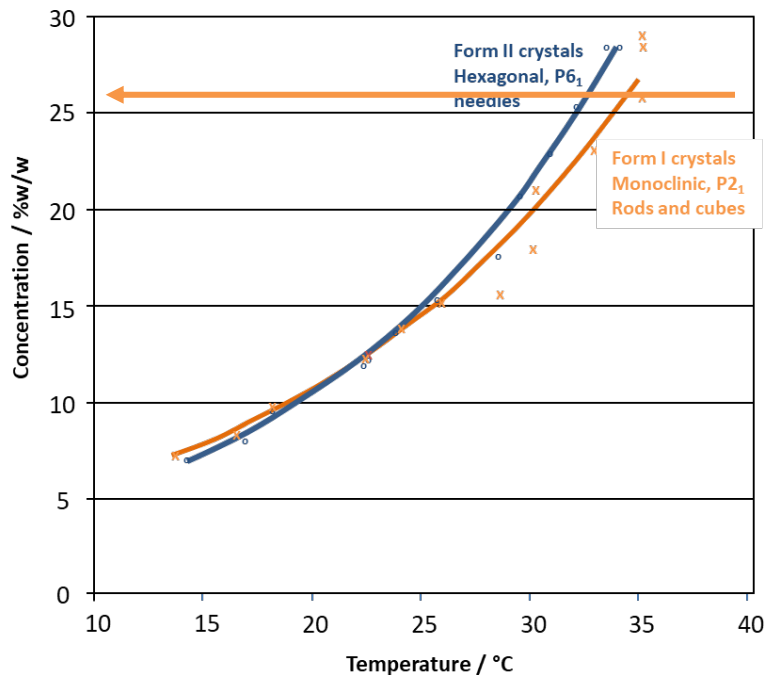
- Each solute in solution has an optimum average shear rate
- Repetitive placing of restrictions/openings/perturbations





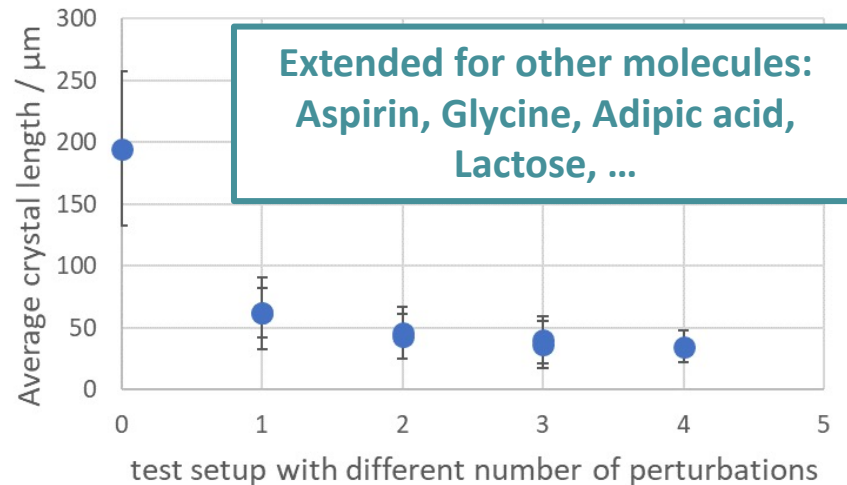
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# Secoya Crystallization Technology

Sometimes we couple this with a reaction

- Finalizing acetylation step in tubular reactor
- Quench with water
- Crystallization in neat conditions  
acetic anhydride as solvent

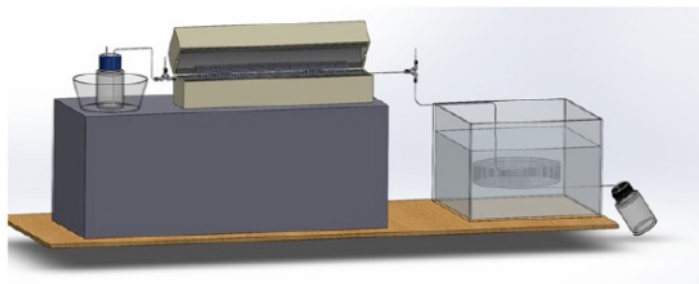
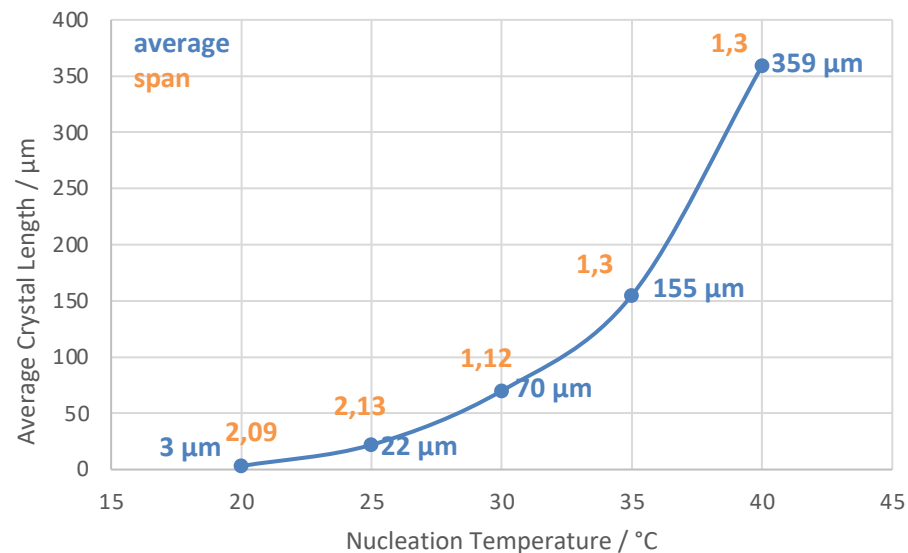
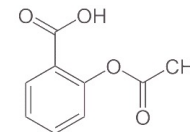


Fig. 7 Combined setup for the flow assisted synthesis and crystallisation of salicylic acid into aspirin, using identical connectors for sulphuric acid and water entry as shown in figure 1.

## Aspirin





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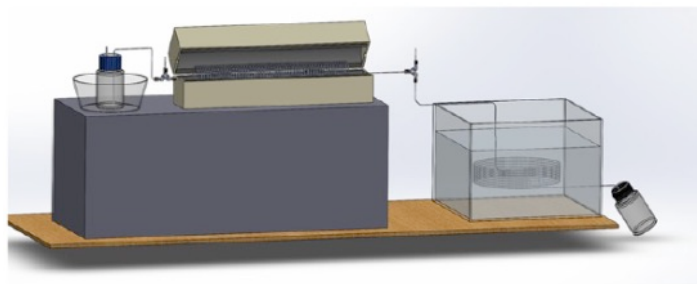
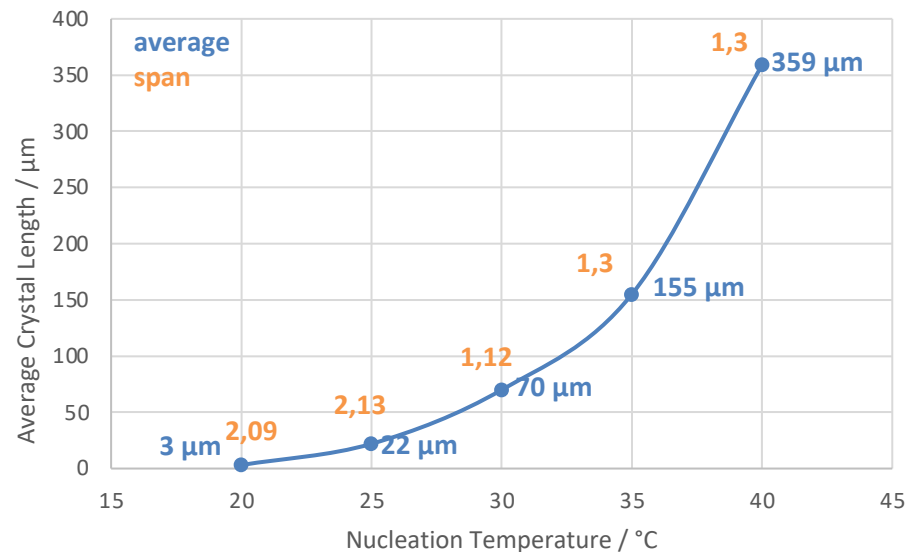
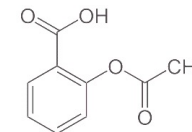


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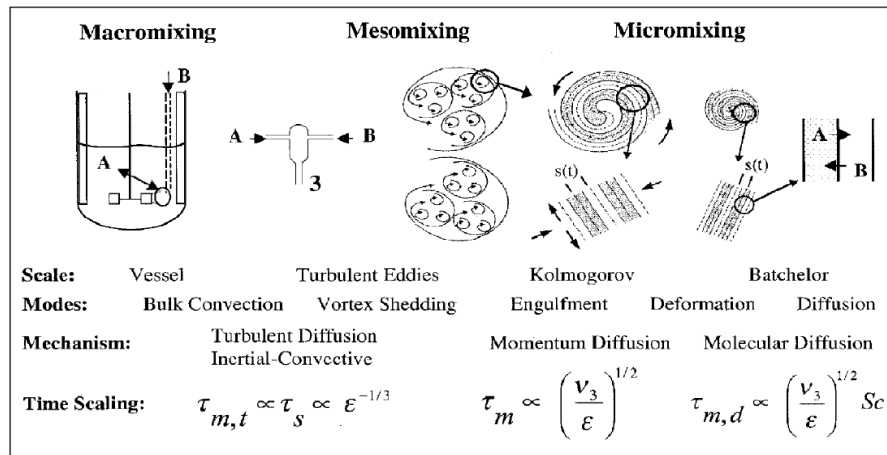


# Secoya Crystallization Technology

Then we started to mix with antisolvents – now on purpose

## Additional features with antisolvent

- Crystallization of organics at temperature between 0 and 70°C
- Precipitation of inorganic chemistries and salts: nanometric sizes
- Precipitation of APIs down to (sub-) micrometric sizes
- Co-crystallisation for enantiomeric purification - project foreseen with partner



Johnson, AIChE 2004

- ✓ mixing conditions without voids and dead volumes
- ✓ Mixing intensity determines nucleation rate
- ✓ Inherent small particle size

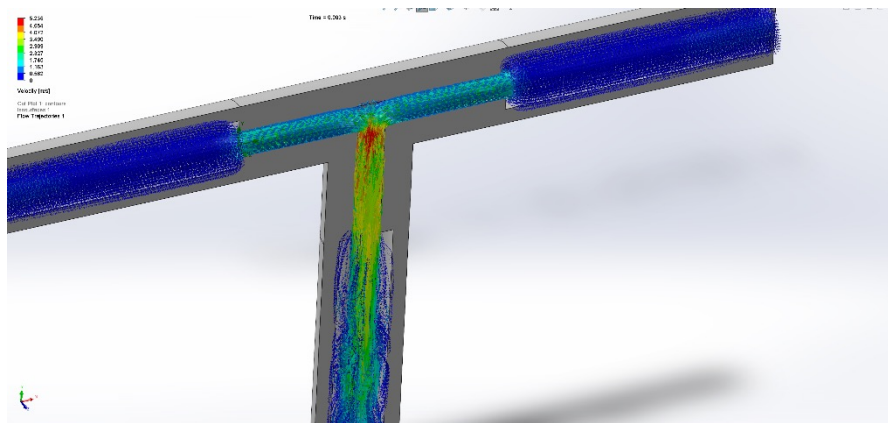


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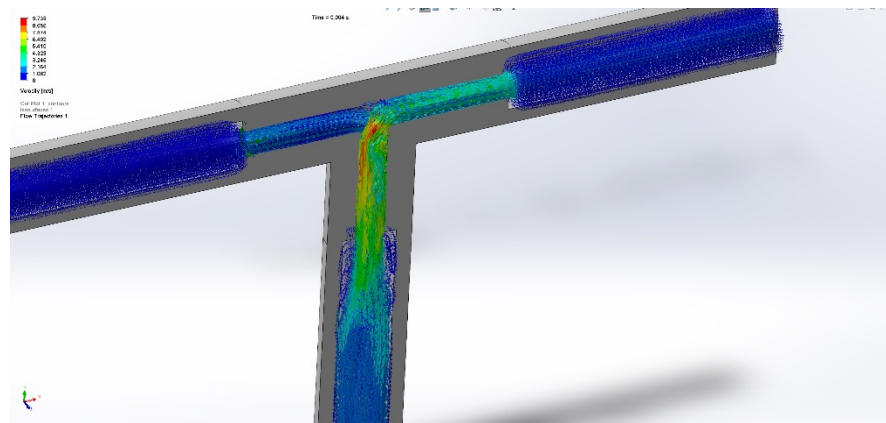
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**Frontal Collision mode:** high energy mixing for equal quantities solvent/antisolvent

20 and 20 mL/min



20 and 40 mL/min





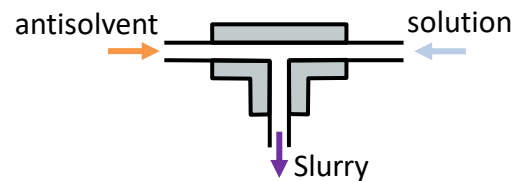
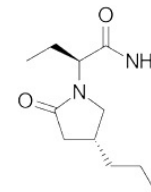
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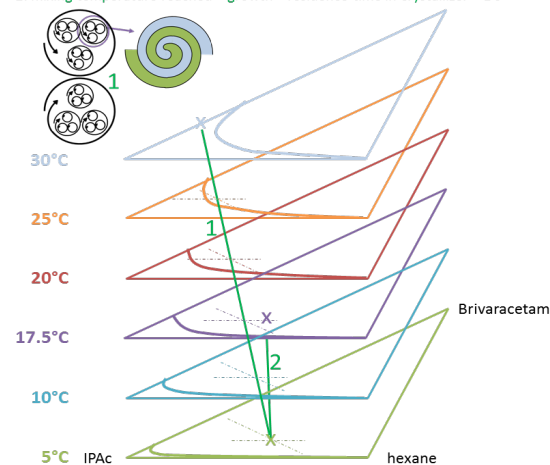
## Brivaracetam

- ✓ Difficult accessible chemistry and polymorphisms
- ✓ Excellent control of conditions

## Brivaracetam



- 1: frontal collision with cold antisolvent ~ 1 ms
- 2: mixing temperature reached + growth \*\* residence time in crystallizer < 1 s



Crystallization method	Initial concentration API/IPAc mg.mL <sup>-1</sup>	Tubular length mm	Mean $\mu$ m
Casted	150	500	10 $\pm$ 5
	200	500	9 $\pm$ 5
Filter paper	150	500	9 $\pm$ 4
	200	500	7 $\pm$ 3
	300	500	8 $\pm$ 3



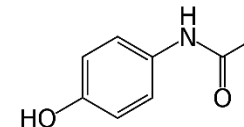


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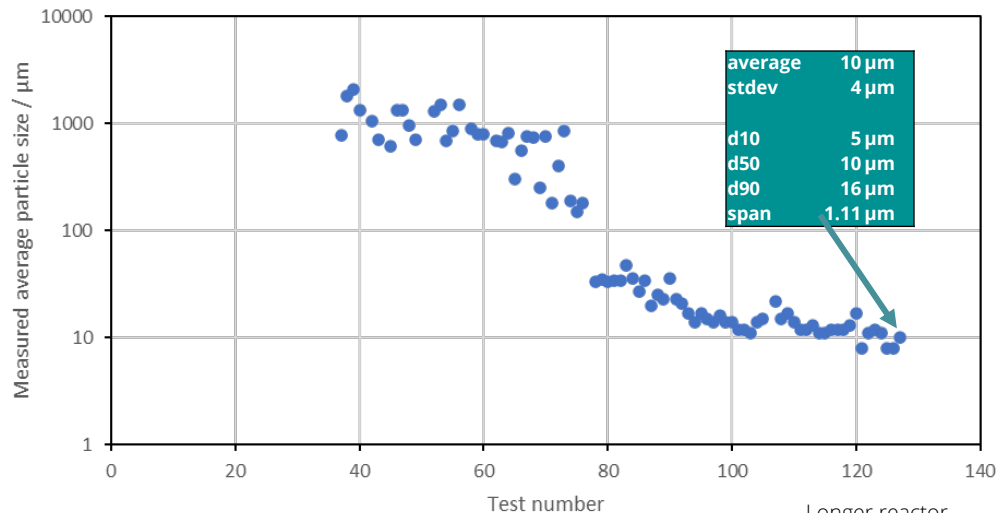
Then we started to mix with antisolvents – now on purpose

Paracetamol was dissolved in isopropanol (100 – 75 mg/mL)  
Water (unsuccessful) and heptane were tested as antisolvent

## Paracetamol



- For paracetamol, **127 tests and 130 g solids** on **three solvent/antisolvent systems** were necessary to arrive to particle sizes **down to 10 μm**
- SCT-LAB allows fast screening with low material consumption



Longer reactor  
of 5 mL and  
cooling applied

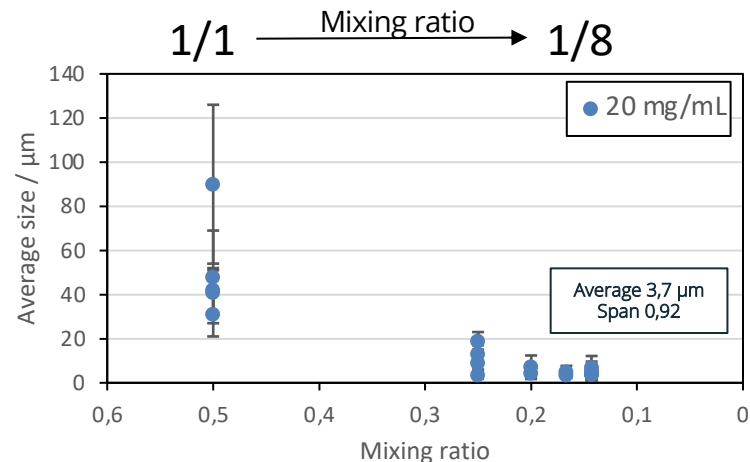
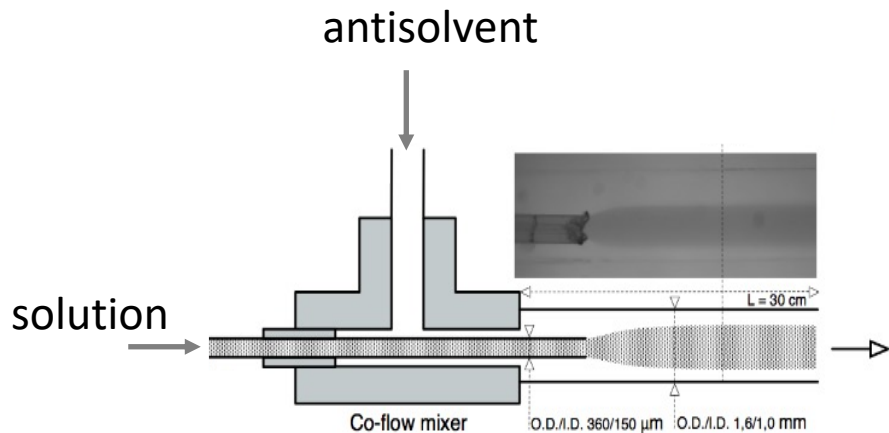


# Secoya Crystallization Technology

Then we started to mix with antisolvents – now on purpose

**Actual customer example  
Steroid compound**

**Co-flow mixing mode:** lowered energy of mixing, helps with increasing amount of antisolvent added



Down to 3  $\mu\text{m}$ , without the use of surfactant



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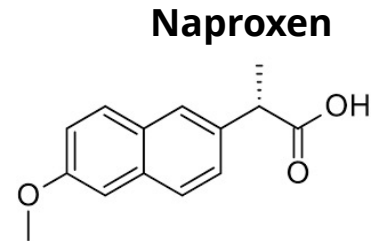
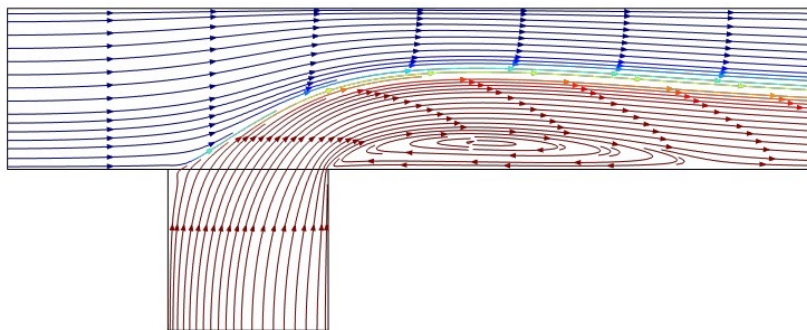
Then we started to mix with antisolvents – now on purpose

**side mixing mode:** go in-between

Naproxen was dissolved in isopropanol (12.5 mg/mL)

Water was used as antisolvent

Sample collected in known quantity with surfactant (HPMC)



Product number	insert	Mixing ratio	Mn nm	MI nm	PDI
S27	Tside 500µm	1/3	910	2199	0.17
S28	Tside 500µm	1/4	30	581	0.42
S37	Tside 250 µm	1/3	183	658	0.09
S38	Tside 250µm	1/4	182	658	0.13



# One Equipment that fits all needs

Obtain the crystal size of choice without hustle

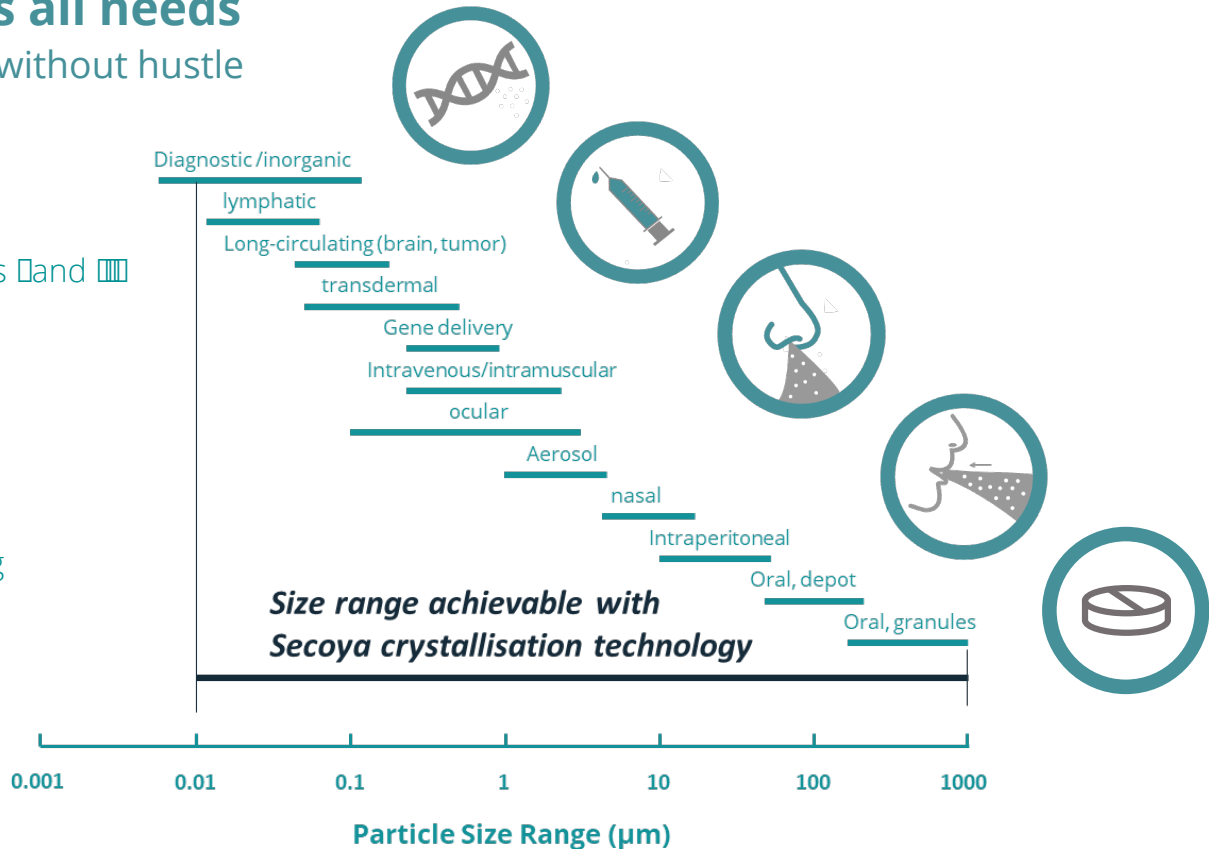
## Cooling crystallization

- Ideal for oral dosage forms
- Good soluble molecules – BCS Class I and II
- Optimised recycling and yield

## Antisolvent crystallization

### Frontal – co-flow – side mix

- Ideal solution for complex systems
- Reducing particle size under  $\mu\text{m}$
- Adjustable particle size upon mixing conditions
- BCS Class III and IV



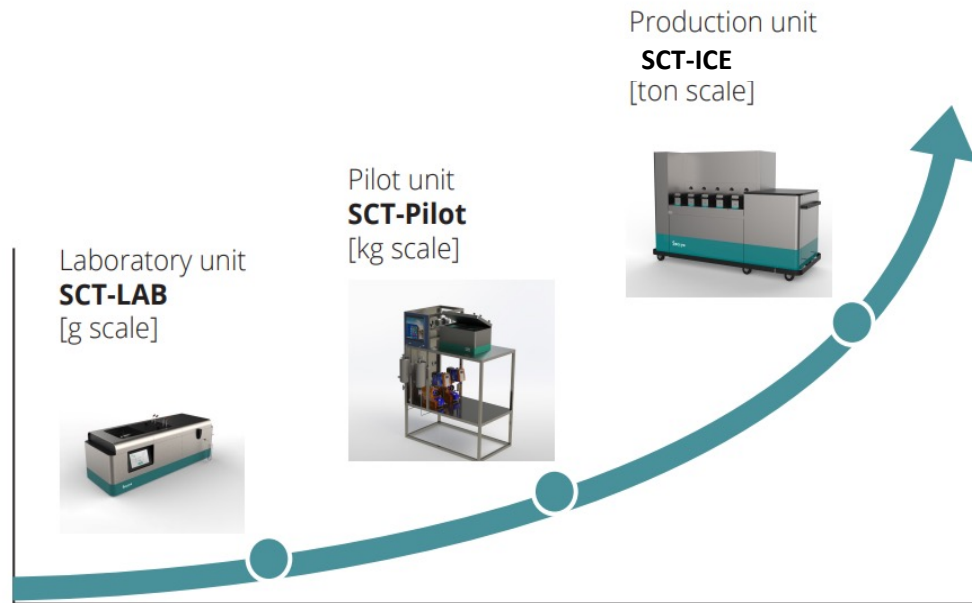


# Secoya Crystallization Technology

Reliable Upscaling with identical set of parameters

## Technology specifications:

- 3 temperature zones:
  - Solution: RT to 85°C
  - Antisolvent: 5 to 85°C
  - Reactor: 0 to 70°C
- Delivered with dedicated cooling/heating thermostat
- Single use inserts and reactors
  - 6 different inserts for cooling and antisolvent crystallization
  - 6 different integrated reactors with different volumes: 1 to 7mL
  - 1 specific reactor execution for highly viscous solutions
- Pump flow rates 1 to 60 mL/min
- Simplified collection of slurries
- Stand-alone 21 CFR part 11 software



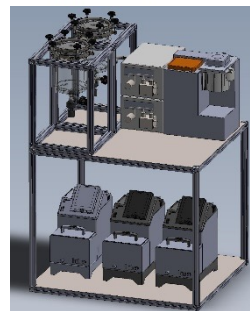


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Production unit  
**SCT-ICE**  
[ton scale]

