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API crystallization with Secoya technology

Aspen API

DTS specialties

Erik ter Voert

CDMO Solutions

Established API Portfolio

Reliable Quality & Regulatory Support

Aspen API. **Nearly 100 years experience**

Content:

- Introduction Aspen API
- Why Secoya?
- Experimental
  - Cooling
  - Anti solvent
- Conclusion
- Questions

Introduction Aspen API

- The origins of Aspen API Oss date back to 1923, when the owner of a slaughterhouse initiated the extraction of animal pancreases for the use in the insulin production.
- Aspen API is a global supplier of APIs* and one of the world's best known producers of steroid hormones.
- Aspen API has around 600 employees and 2 production sites in Oss. One site in Boxtel.
- Aspen API specializes in the production of complex, highly potent APIs (HPAPIs) and peptides, in amongst others the therapeutic areas of gynecology / women's health, male health, muscle relaxation and the central nervous system.

  Estradiols, testosterone (esters), ganirelix, leuprorelin, mirtazapine, rocuronium bromide

* API = Active Pharmaceutical Ingredient

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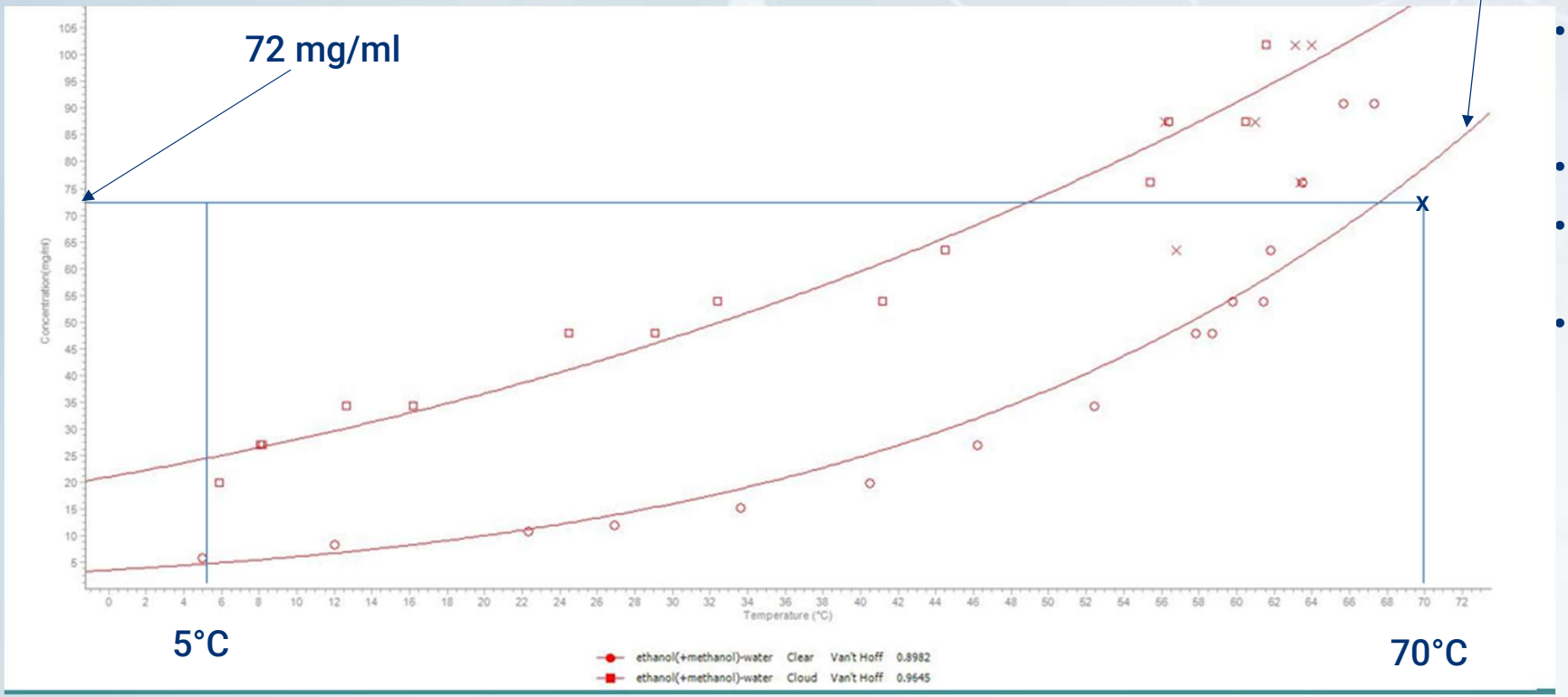
Why Secoya technology?

- We want a robustness in our crystallization processes.
- Reproducibility, each batch has the same PSD.
- We want to adept to modern technology like flow chemistry.
- Many of our products are micronized. Micronization is needed to reduce the particle size of the API. Smaller particles dissolve faster and therefore have better bioavailability.
- Micronization is done in a jet mill. However, many of our APIs are sticky (cohesive). Micronizing can give problems like clogging off the API in the jet mill.
- Ideal world would be to achieve the optimal particle size distribution during crystallization, so micronization is not necessary.
- These are the reasons for starting a research project with Secoya technology.

Cooling crystallization

- How to start:
  - We started with one of our API's which is difficult to micronize
  - Determination of the solubility curve of the API
  - Start with 3 ML reactor and cooling-0 reactor block
  - Perform some test runs without API
  - Cleaning of the lines

Solubility curve API by Crystal16



- Started with 72 mg/ml in ethanol: water 7:3
- At 70°C
- Below saturation point
- Cooling to 5°C

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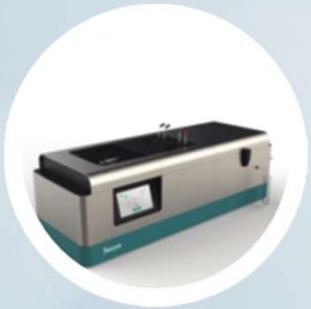
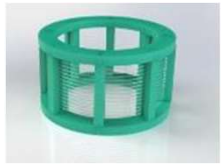
Setup for cooling crystallization experiment



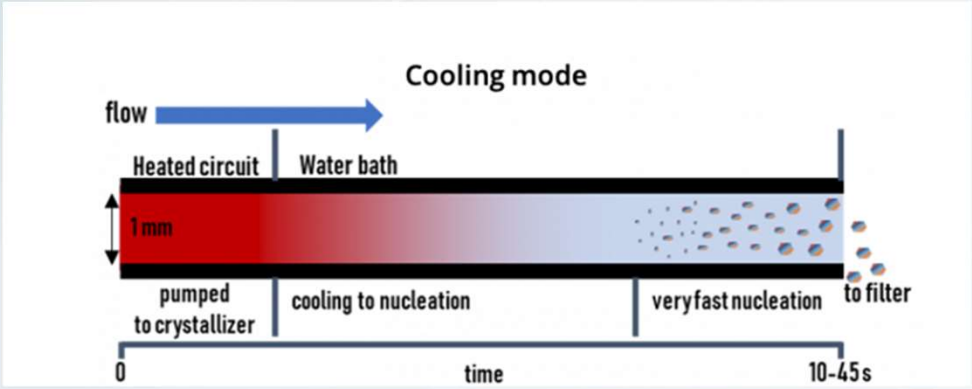
Secoya apparatus



3 ml reactor

Cooling bath

RS1050



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Crystallization using Cooling-0 vs Cooling-2

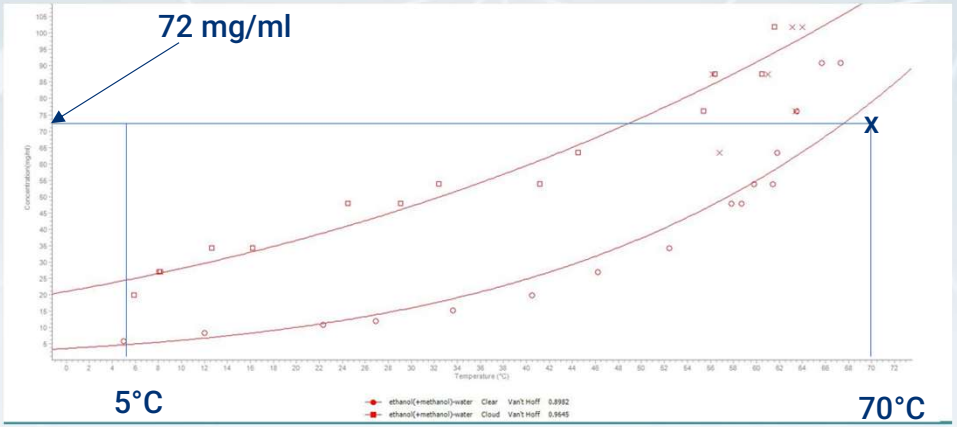
- There are two types of cooling reactors blocks: Cooling-0 and Cooling-2.
- First experiments were with cooling-0, later cooling-2.

Cooling-0

Cooling-2

Cooling crystallization - first experiments

Cooling-0

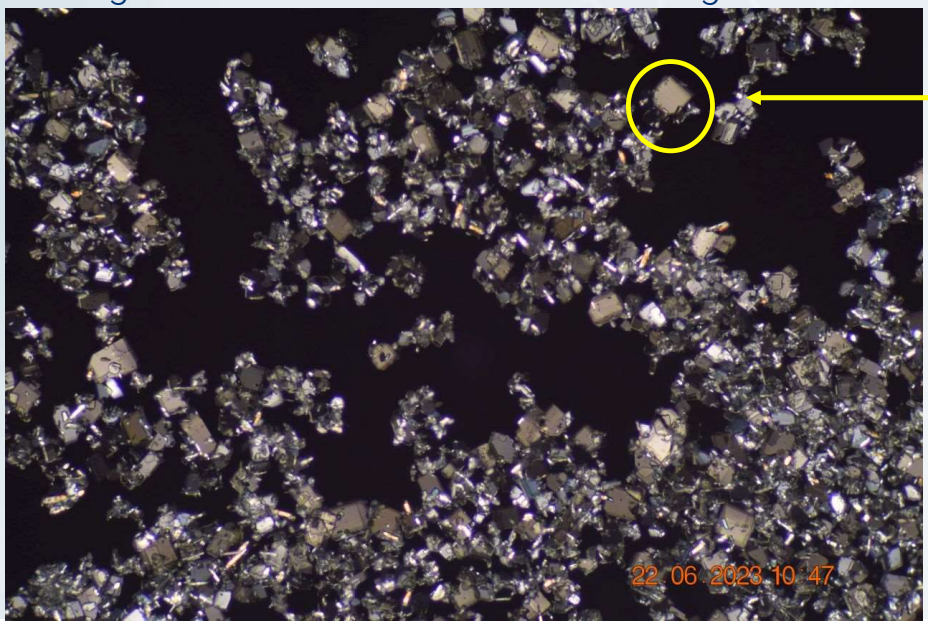


- Started with 72 mg/ml API in ethanol:water 7:3 at 75°C
- Syringe at 70°C, flow 20 ml/min, Cooling-0 reactor block and cooling unit at 5°C
- Material was collected at the end of reactor, no direct crystals. But nucleation did take part.
- “Solution” stirred at 5°C, after couple of minutes crystals are being formed.
- Material was isolated after 5 hours and overnight.
- First experiments no optimal cleaning → Cleaning was adjusted.
- Cleaning of the lines essential !

First experiments

Cooling-0

- Started with 72 mg/ml API in ethanol:water 7:3 at 75°C
- Syringe 70°C, flow 20 ml/min, Cooling-0 reactor block, cooling unit 5°C
- Material was collected at the end of reactor, no direct crystals. “Solution” stirred at 5°C after couple of minutes crystals are being formed. After 5 hours and overnight material was isolated.



± 60 µm

1000 µm

1500 µm

Suspension after 1½ hours stirring magnification 100x

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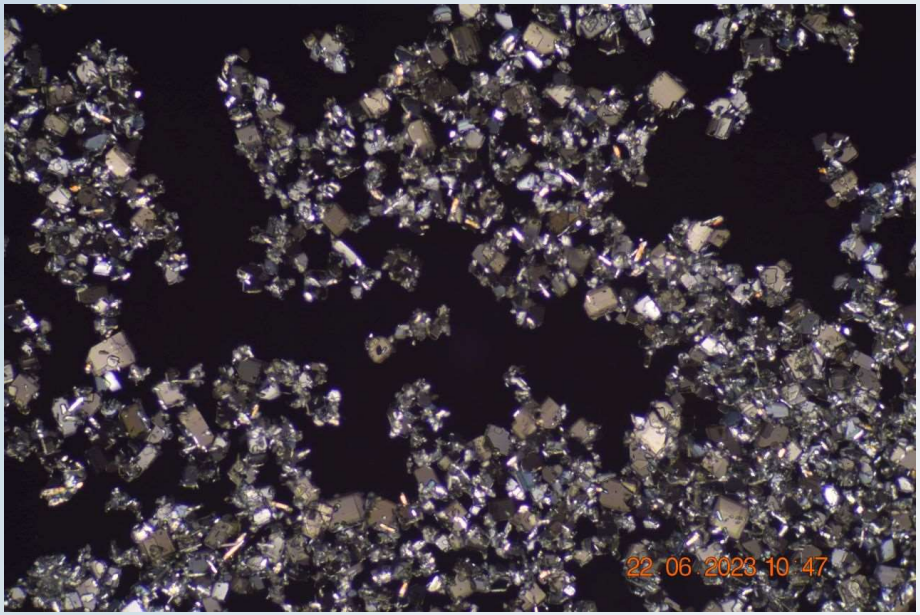
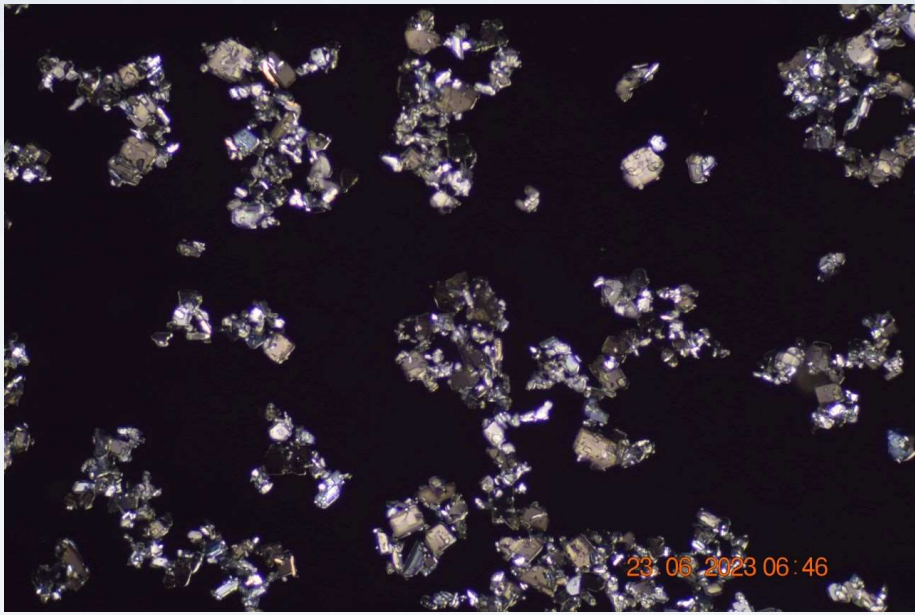
Growing of crystals ?

- Suspension after 1½ hrs. vs suspension after 21 hours,
  Photos for judgement, visual inspection, material was so small, later PSD measurement of isolated material.



1½ hours magnification 100x



21 hours magnification 100x

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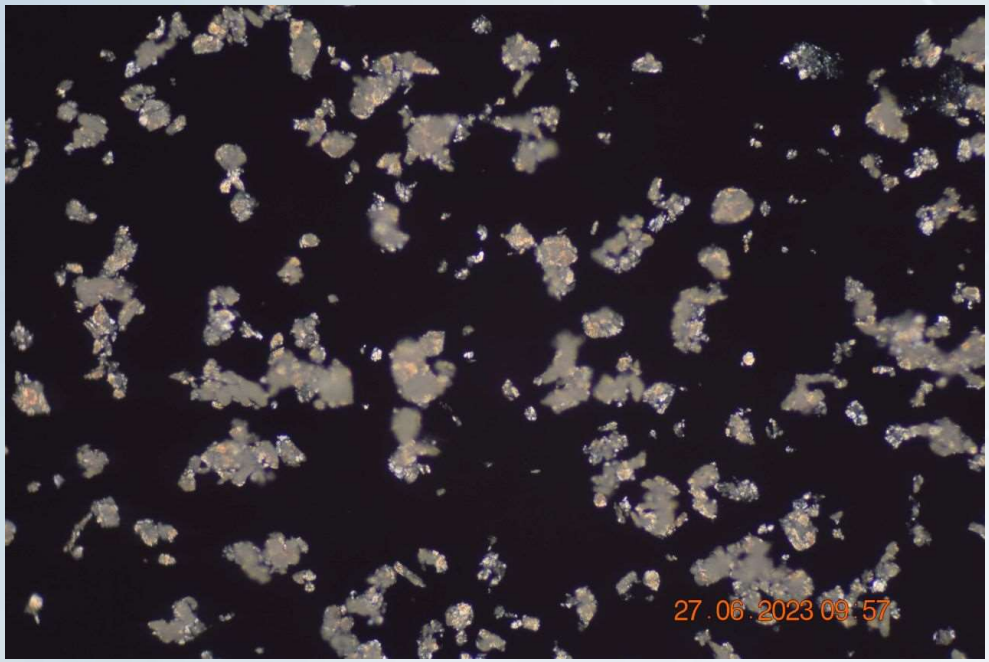
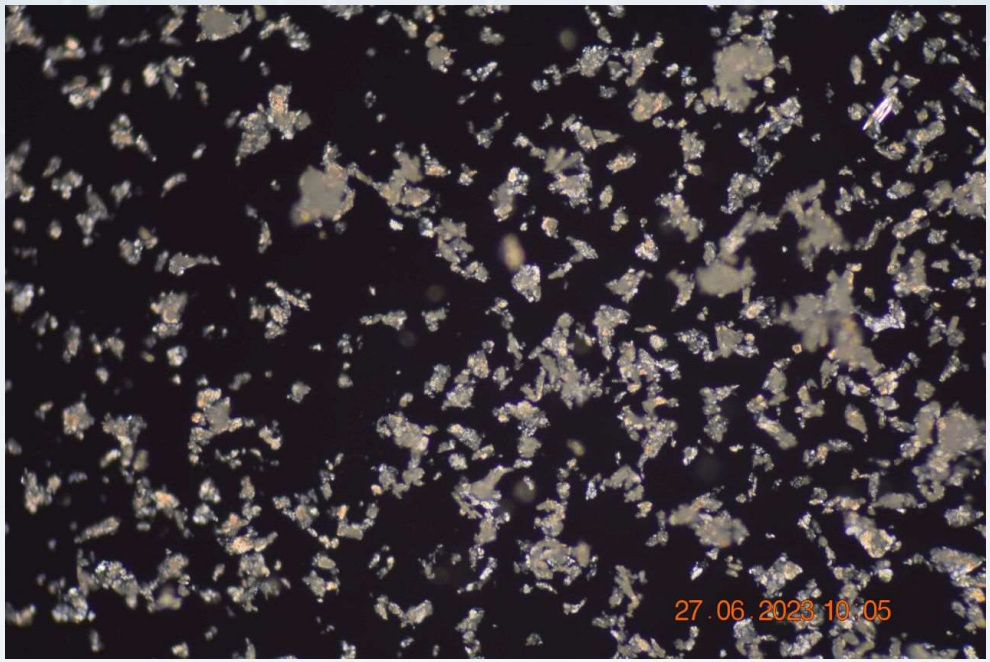
Growing of crystals ?

Cooling-0

- Isolated material, no visual difference. Material was coagulated. Later PSD measurement.



4½ hours magnification 100x



21 hours magnification 100x

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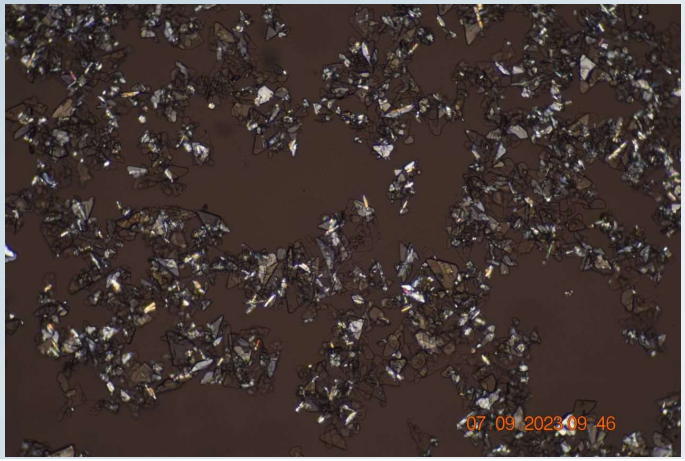
Cooling-2 crystallization, growing

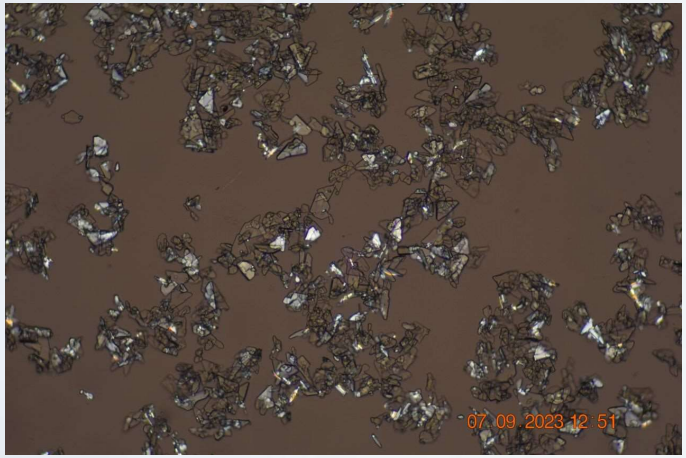
Cooling-2

- Set up same as with cooling-0 , but now reactor block cooling-2 was used.
- Concentration 72 mg/ml ethanol: water 7:3 reactor temperature 70°C.
- Run H4 reactor 70°C, Injection 15 ml ,Flow 20 ml/min, cooling 5.0°C direct stored at 5°C under stirring [RS1050] no direct crystals, crystals were formed after couple of minutes.

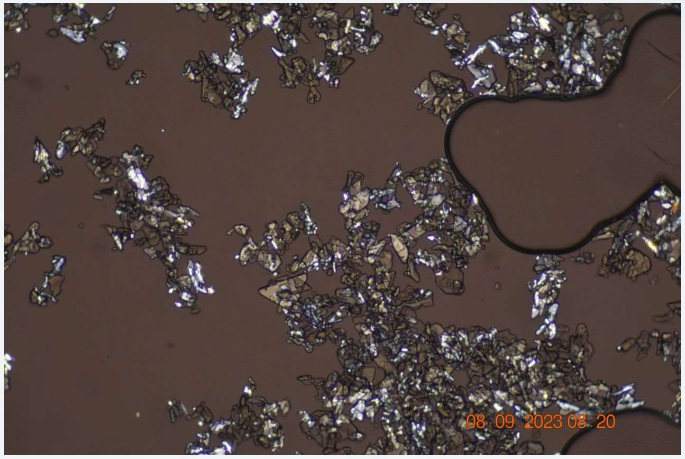
Run H4 after 1½ hrs. stirring at 5°C



Run H4 after 4 hrs. stirring at 5°C

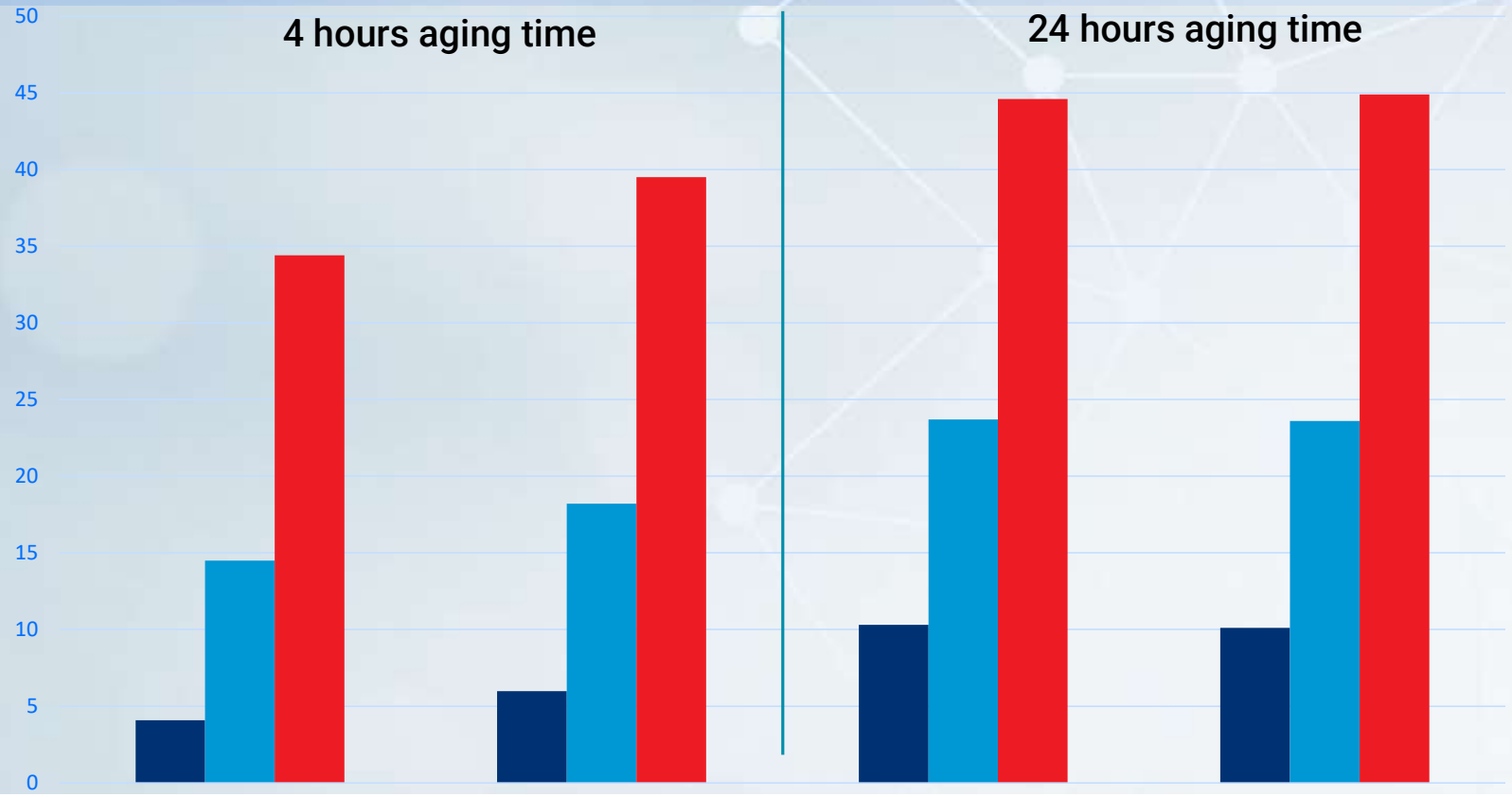


Run H4 after 24 hrs. stirring at 5°C



Particle size distribution cooling-2 at 5°C

Cooling-2



Duplo experiments

Growth of crystals over time

Increase in Dx (10), Dx (50) and Dx (90)

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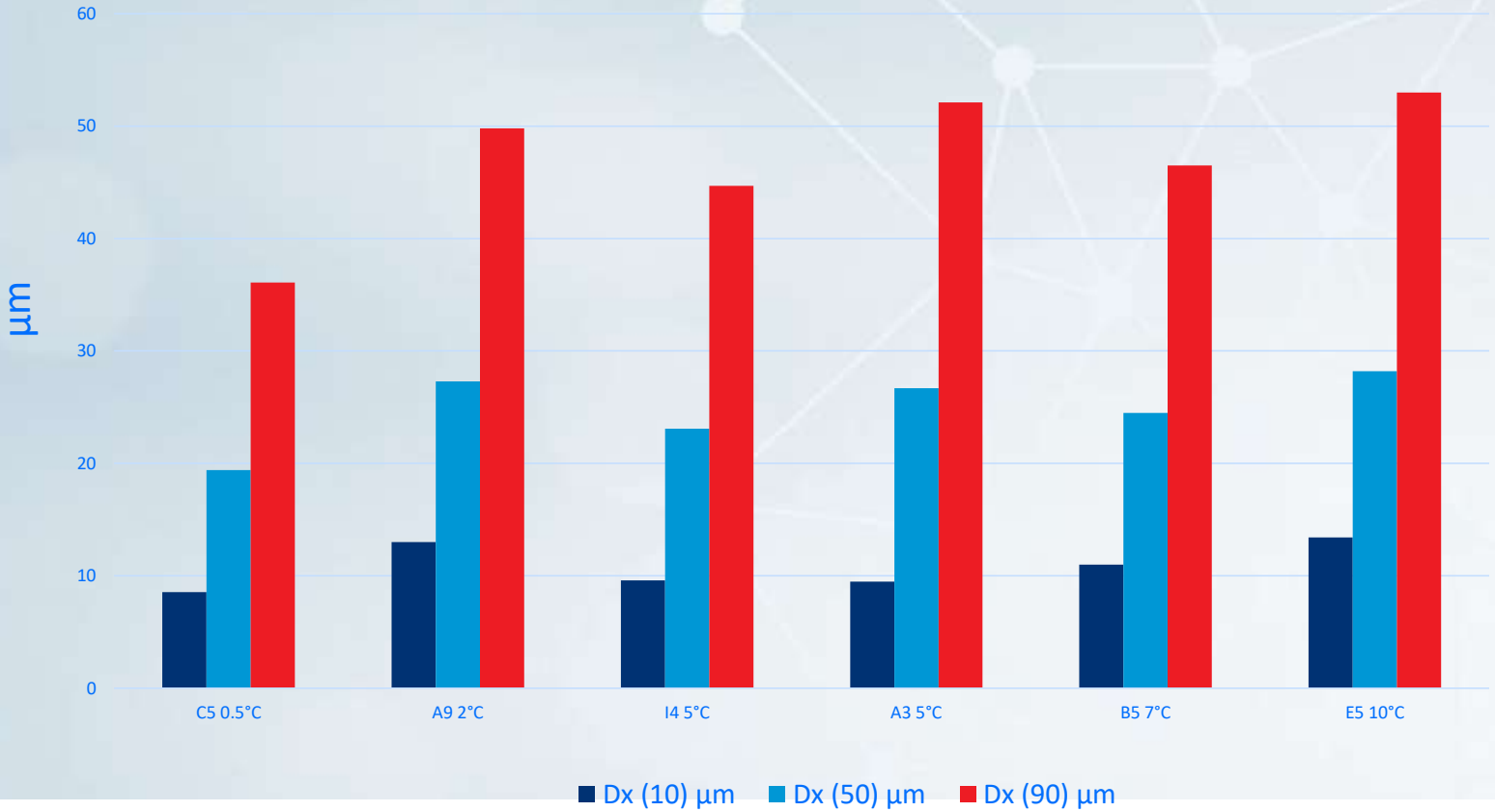
Particle Size distribution

Aging time 21-24 hrs

Cooling-2



Growth of crystals over time and temperature

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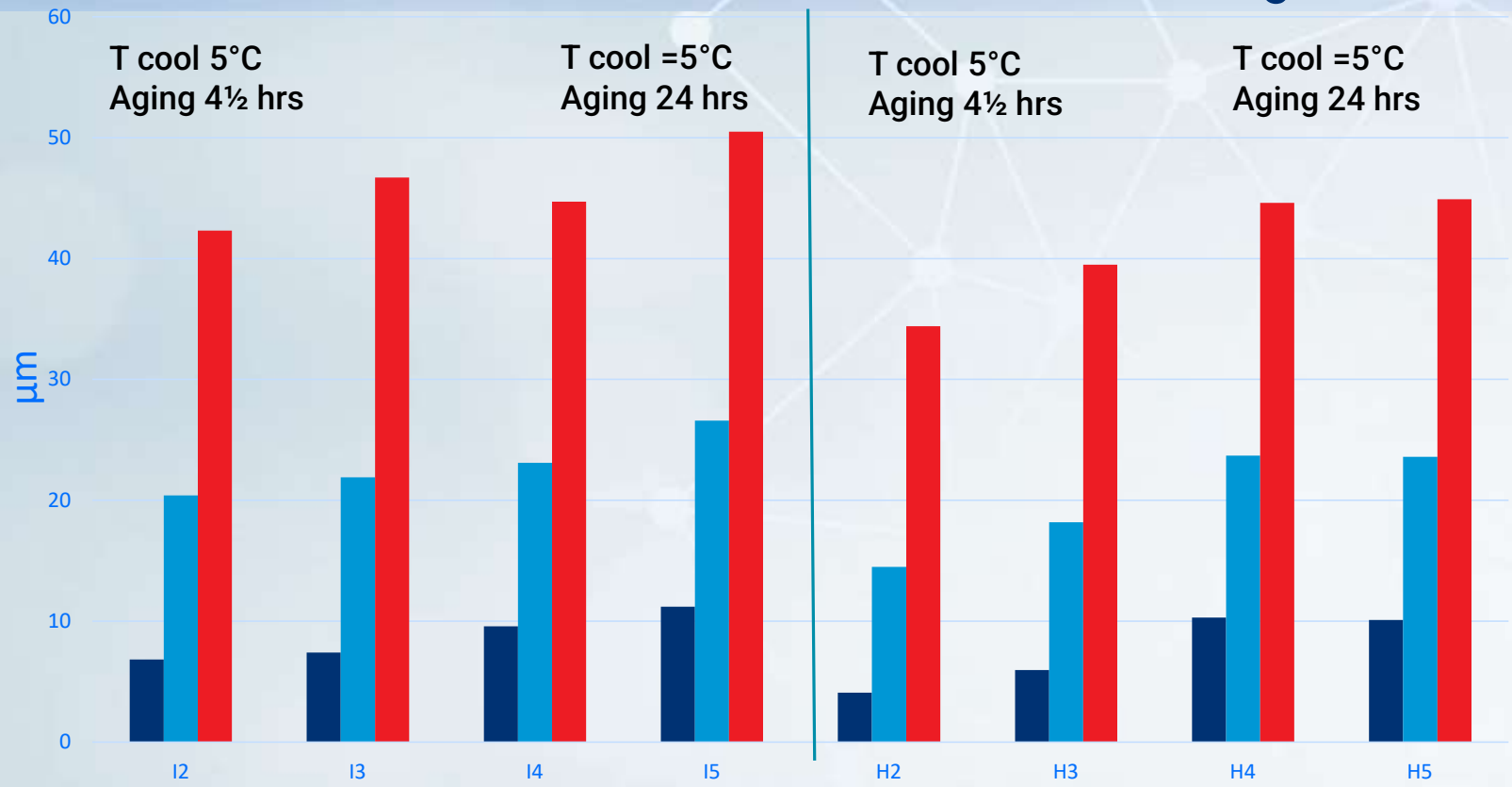
Particle Size distribution



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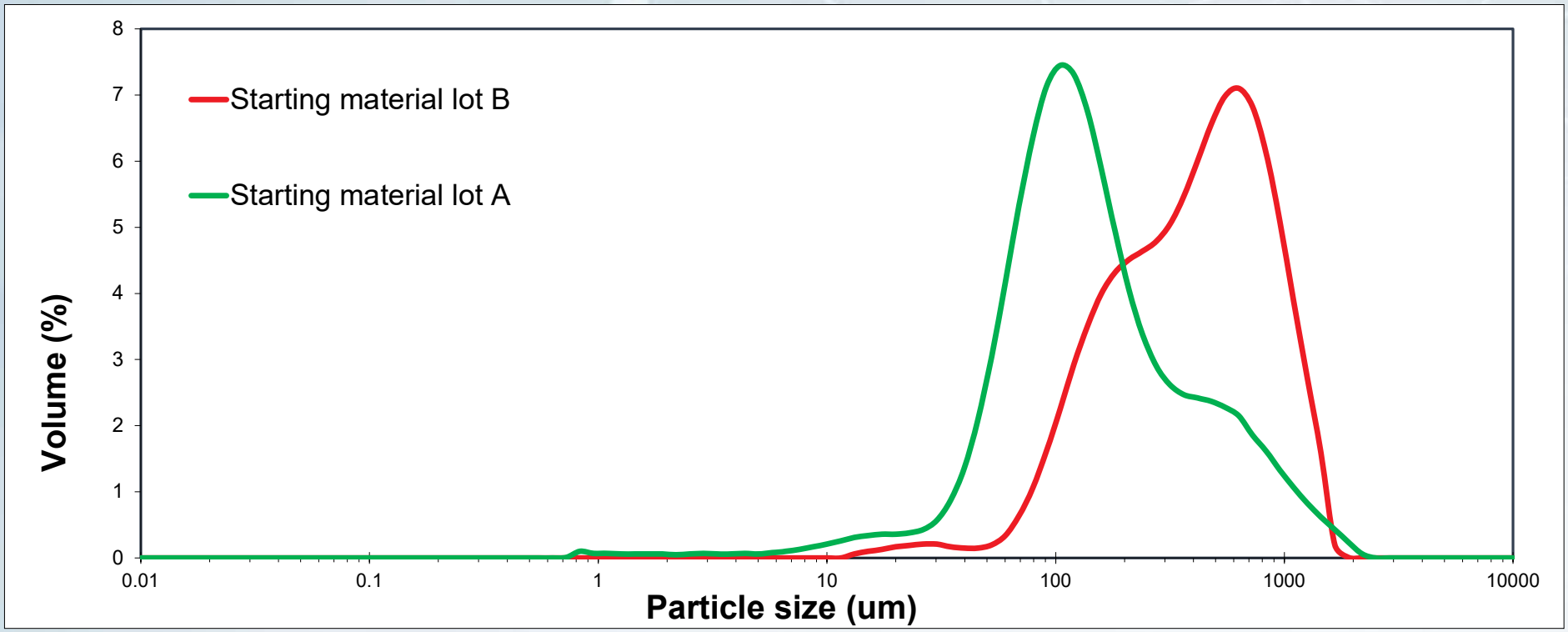
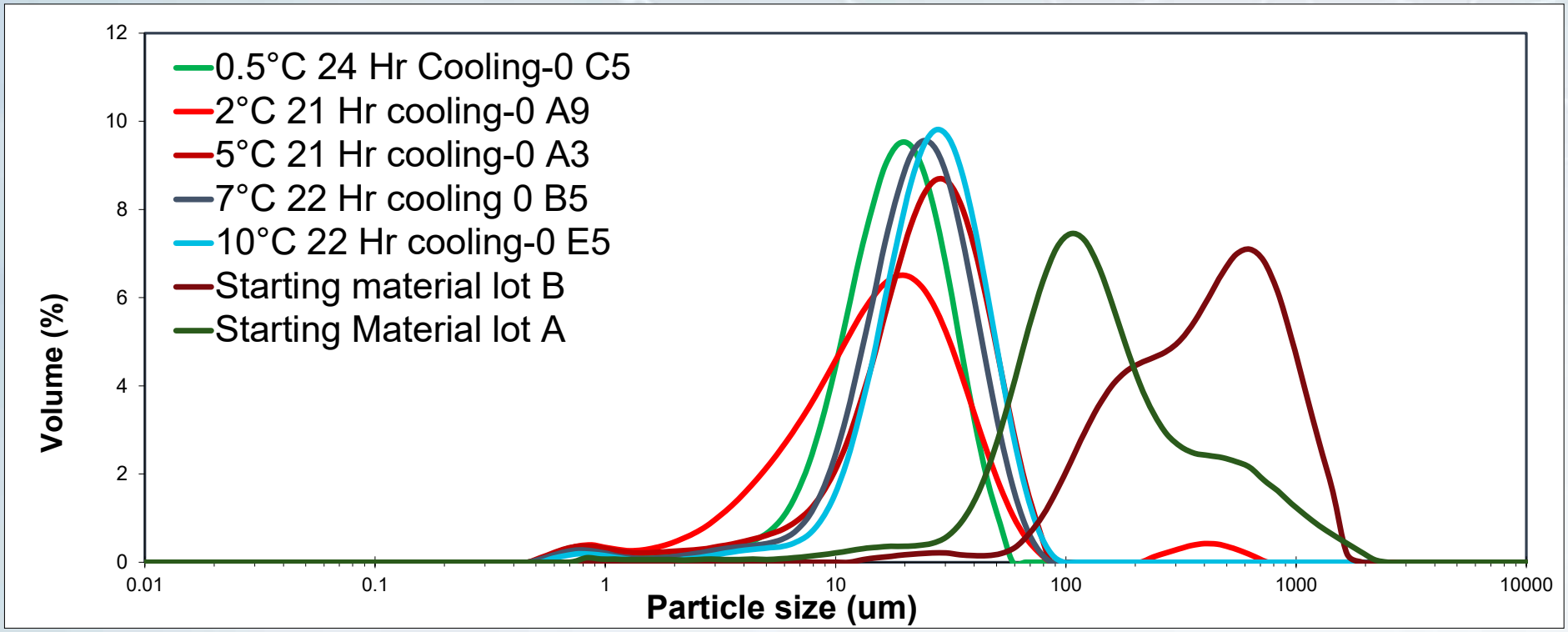
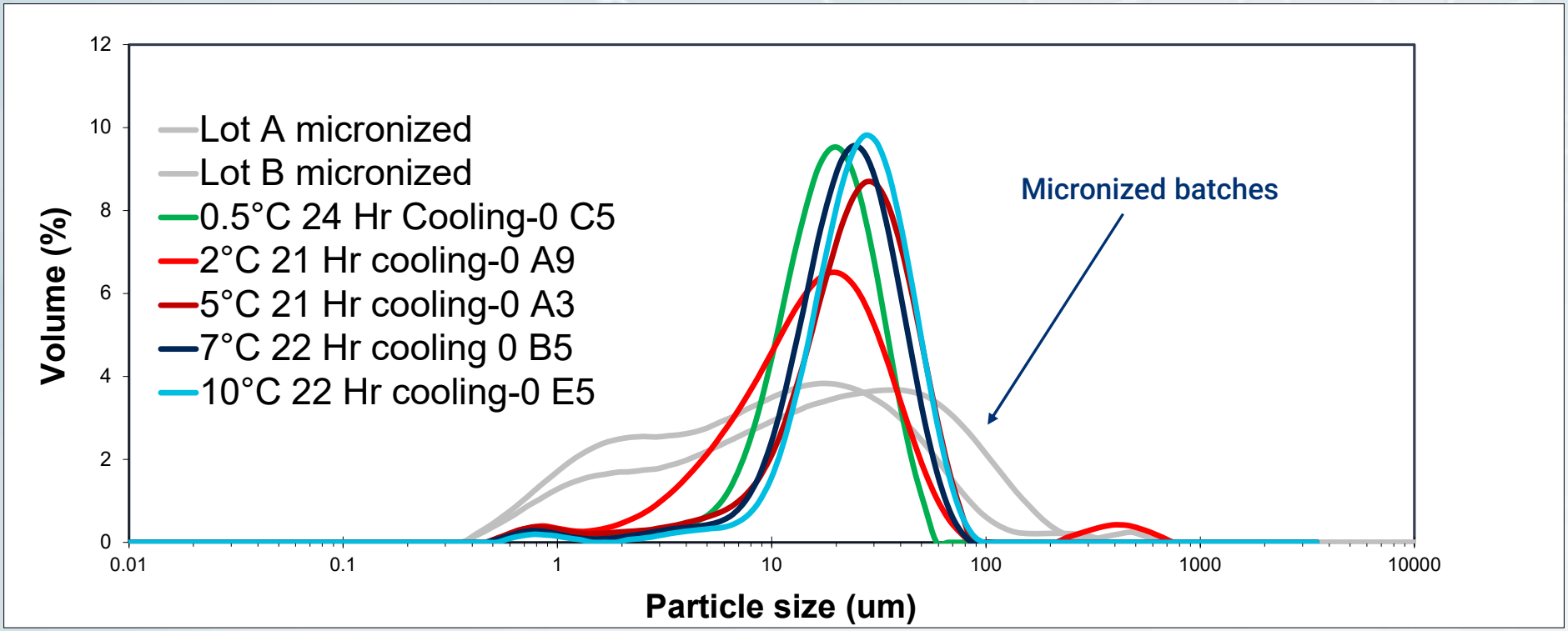
Particle size distribution



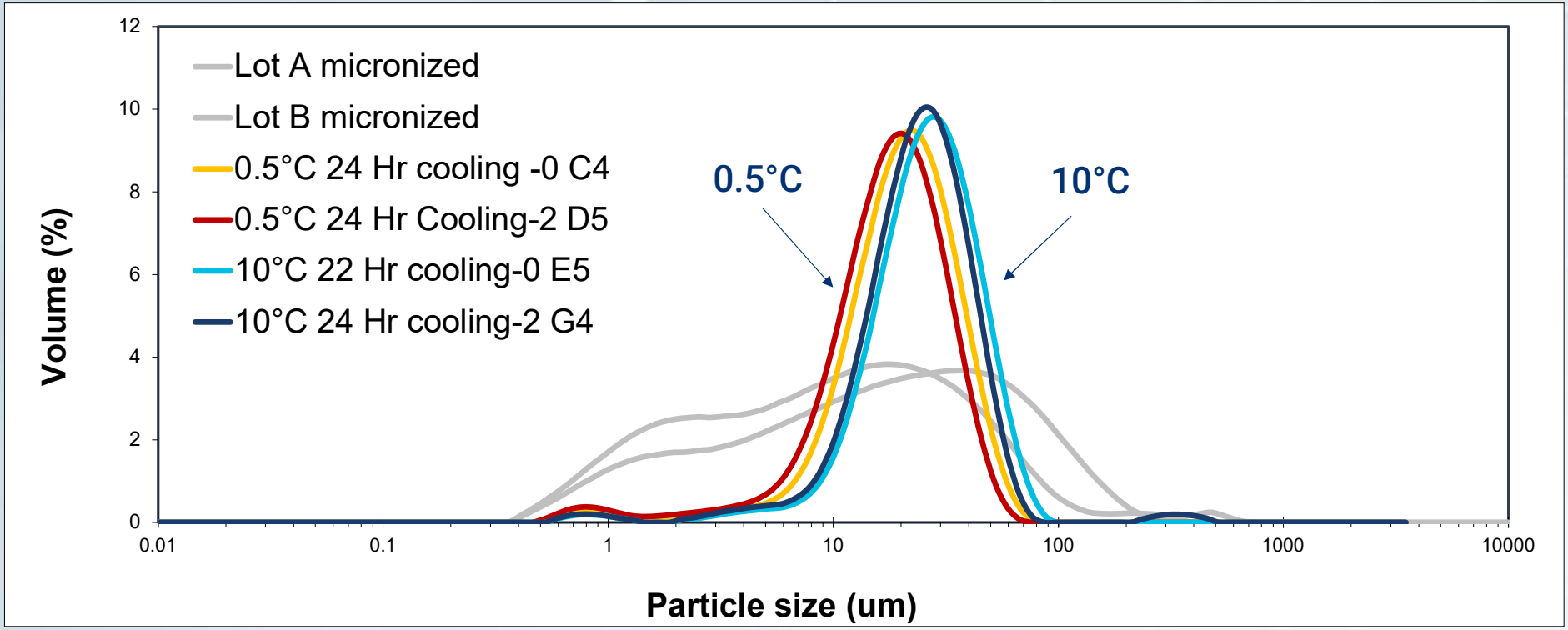
PSD commercial vs Secoya Cooling-0



PSD commercial vs Secoya Cooling-0

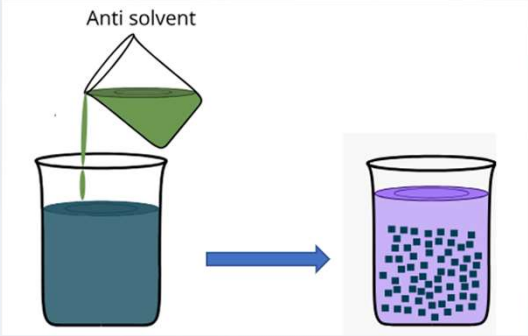


PSD cooling-0 vs cooling-2



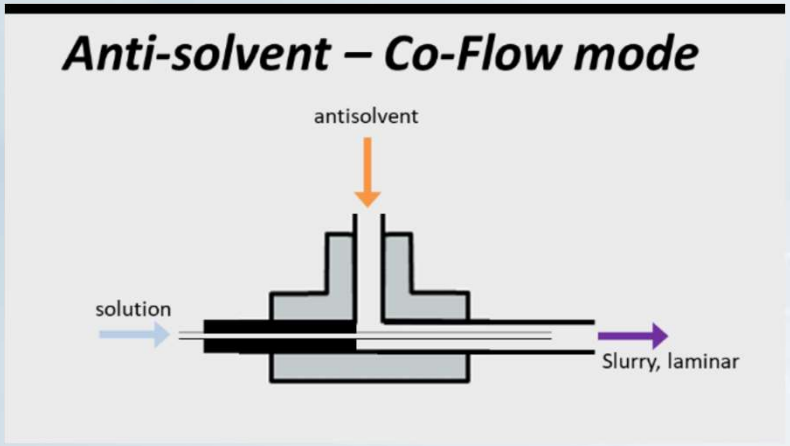
Antisolvent crystallization

- How to start:
  - We started with the same API as for cooling crystallization
  - Cleaning of the lines
  - Start with 1 ML reactor
  - Concentration inline with cooling. Cooling 72 mg/ml 7:3 ethanol: water antisolvent started with 100 mg/ml in ethanol
  - Perform test runs

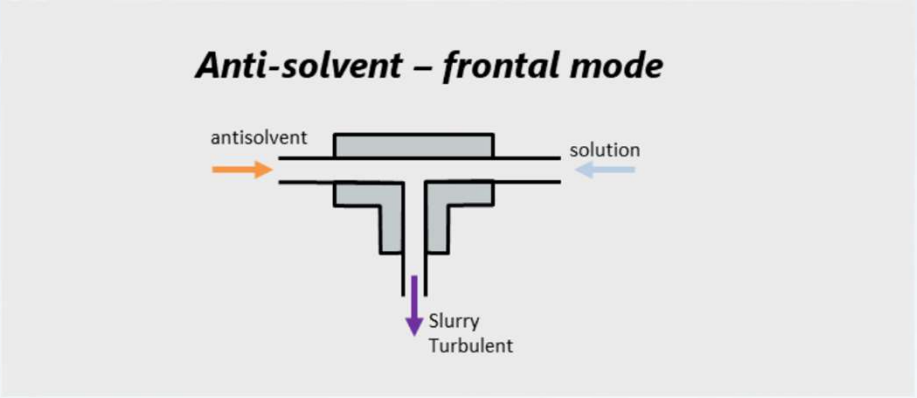


Antisolvent crystallization - first trials

- S1: API 100 mg/ml Ethanol:Water 95:5 S2: HPW water co-flow reactor KT
- Different proportions S1:S2 2:1 1:1 1:2 1:3 and 1:4



Slurry laminar

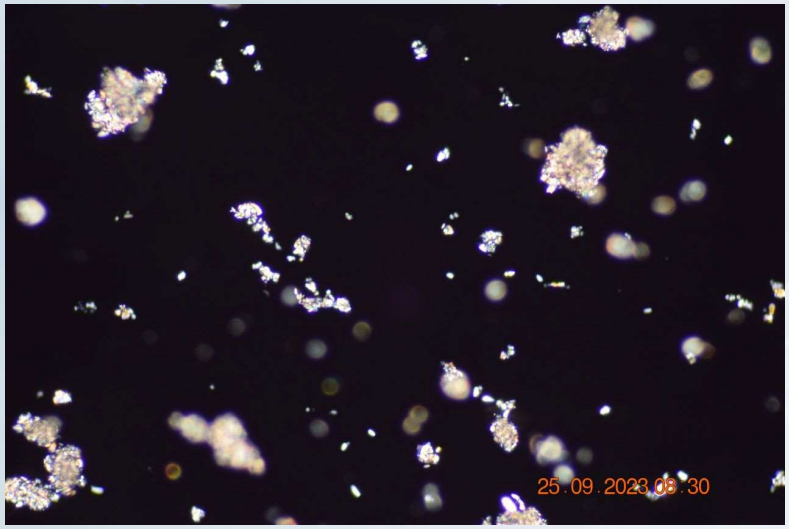


Slurry Turbulent

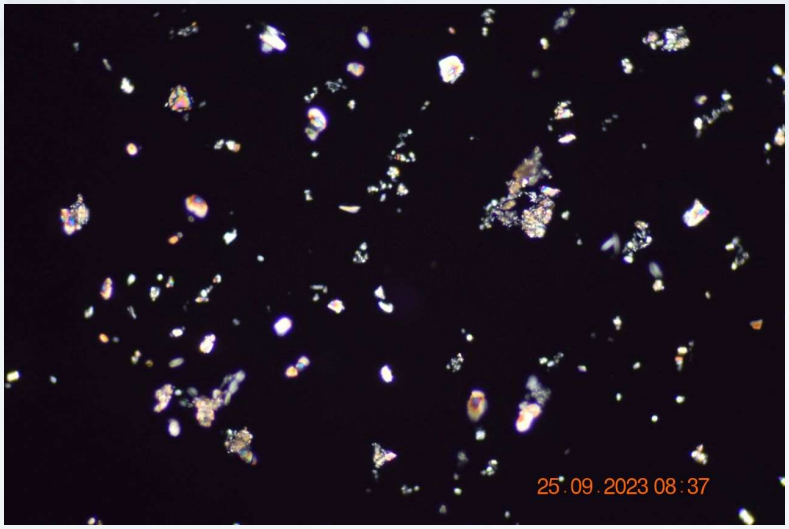
Source: Application note SCT. Secoya technologies SRL

Antisolvent crystallization first trials

- S1: API 100 mg/ml Ethanol:Water 95:5 S2: HPW water co-flow reactor KT
- Different proportions solute :anti solvent: 2:1 1:1 1:2 1:3 and 1:4



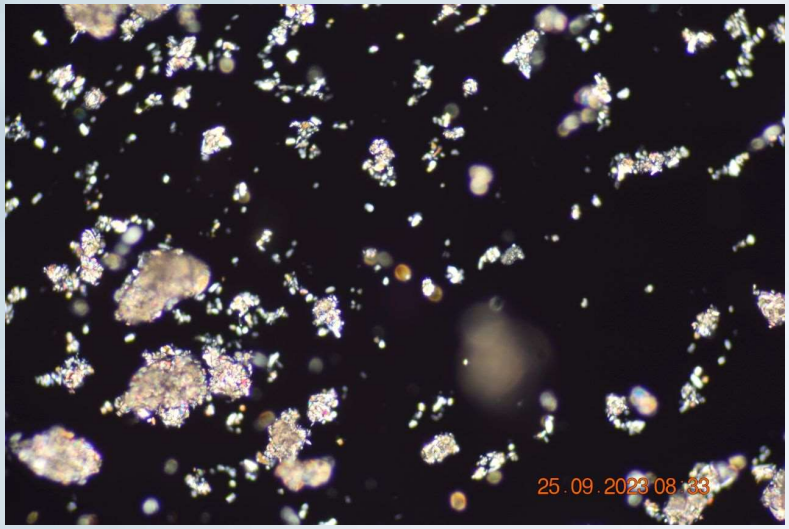
Antisolvent 2:1 Magnification 100x



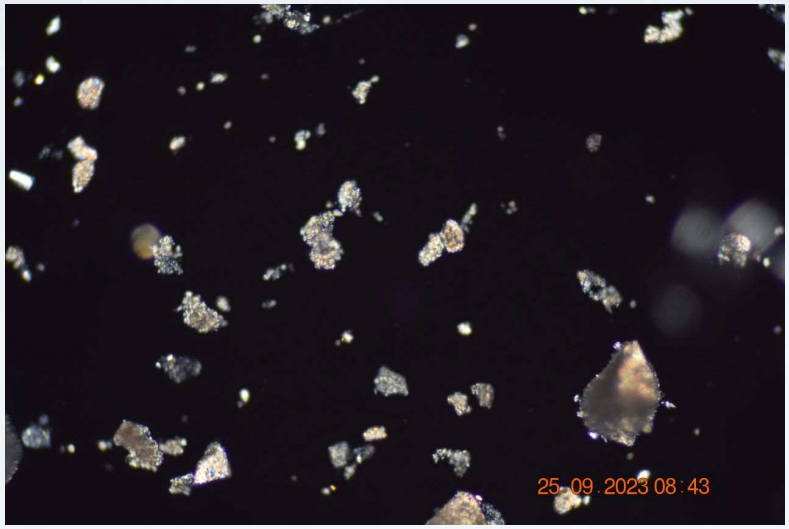
Antisolvent 1:2 Magnification 100x

Antisolvent crystallization first trials

- S1: API 100 mg/ml Ethanol:Water 95:5 S2: HPW water co-flow reactor KT
- Different proportions solute :anti solvent: 2:1 1:1 1:2 1:3 and 1:4

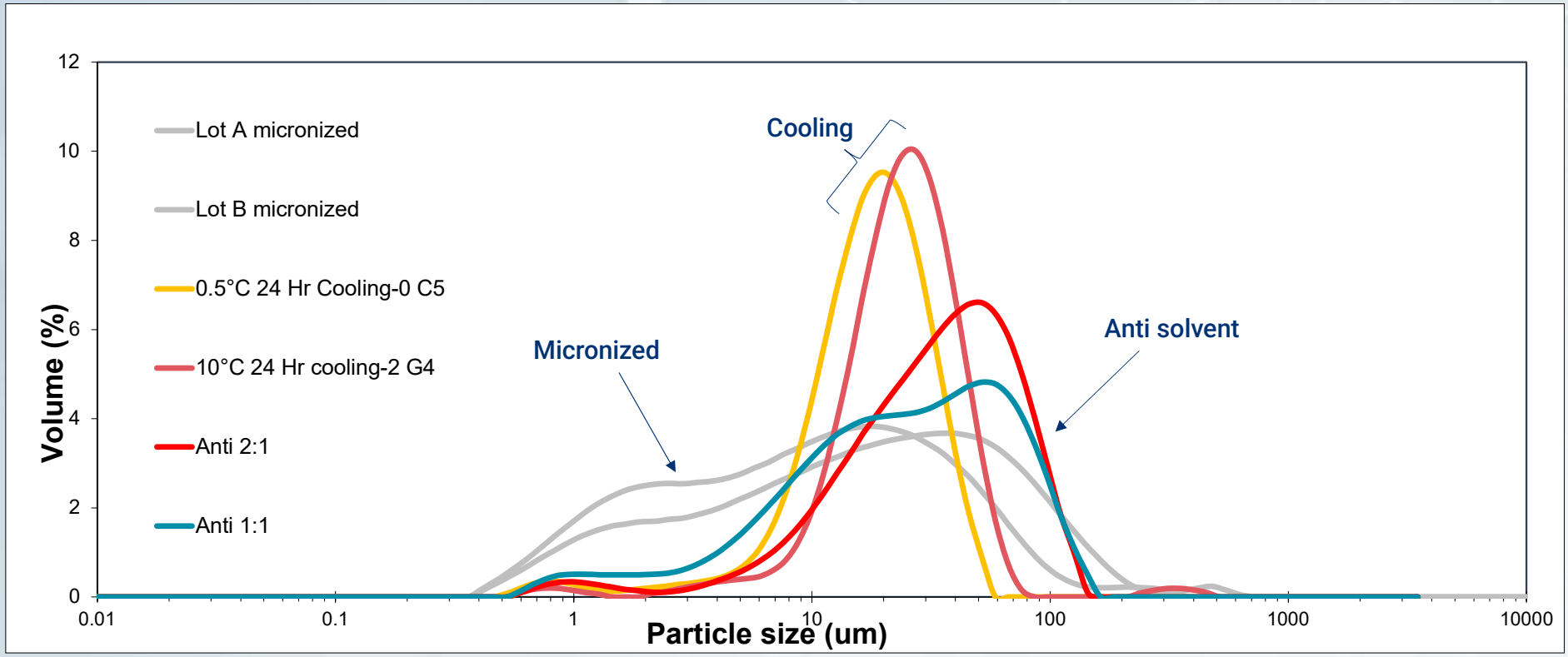


Antisolvent 1:1 Magnification 100x

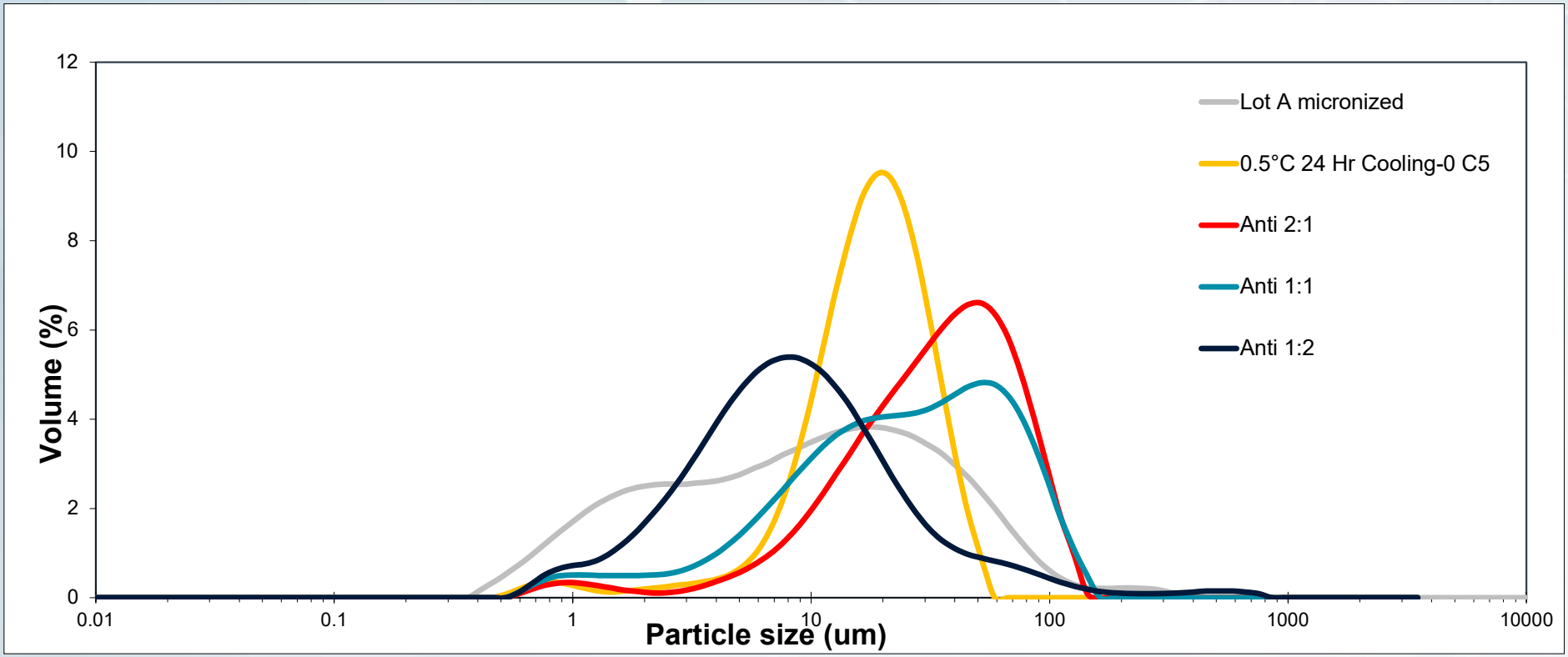


Antisolvent 1:3 Magnification 100x

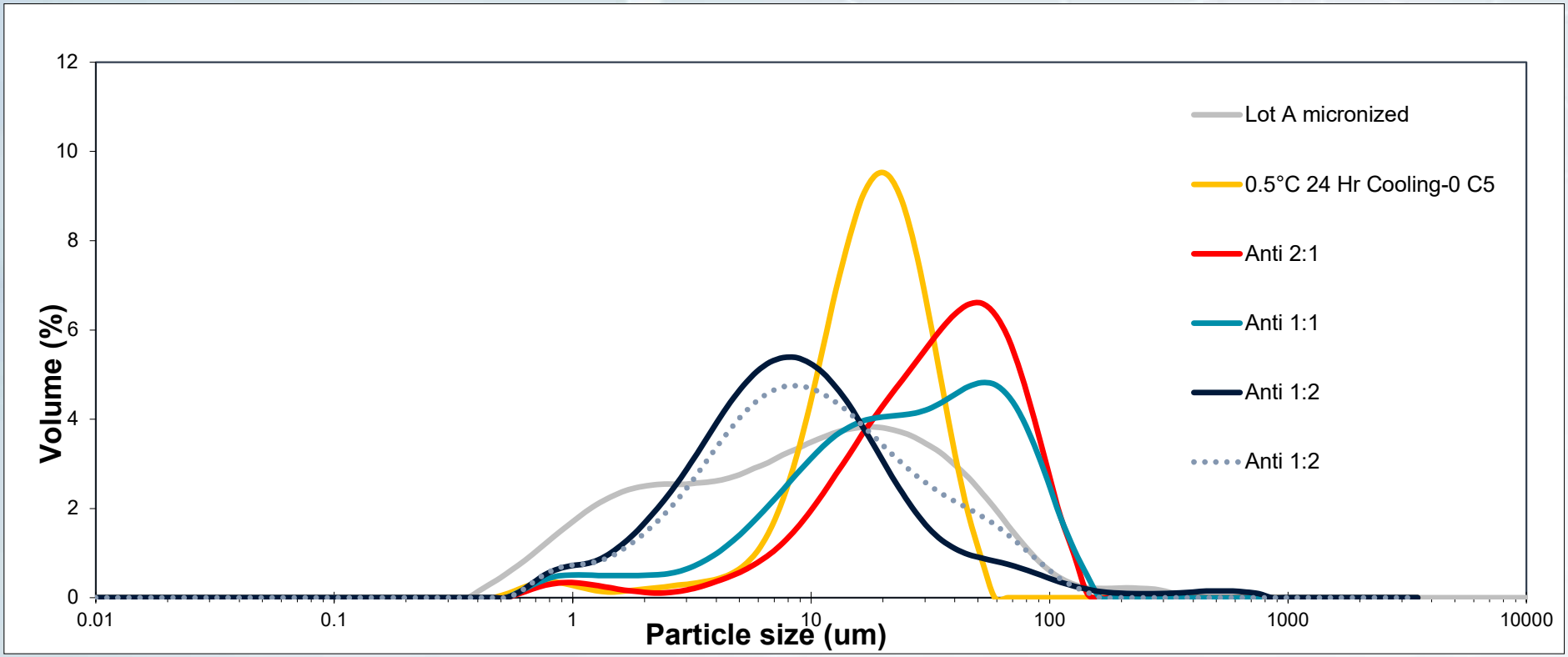
PSD antisolvent vs cooling



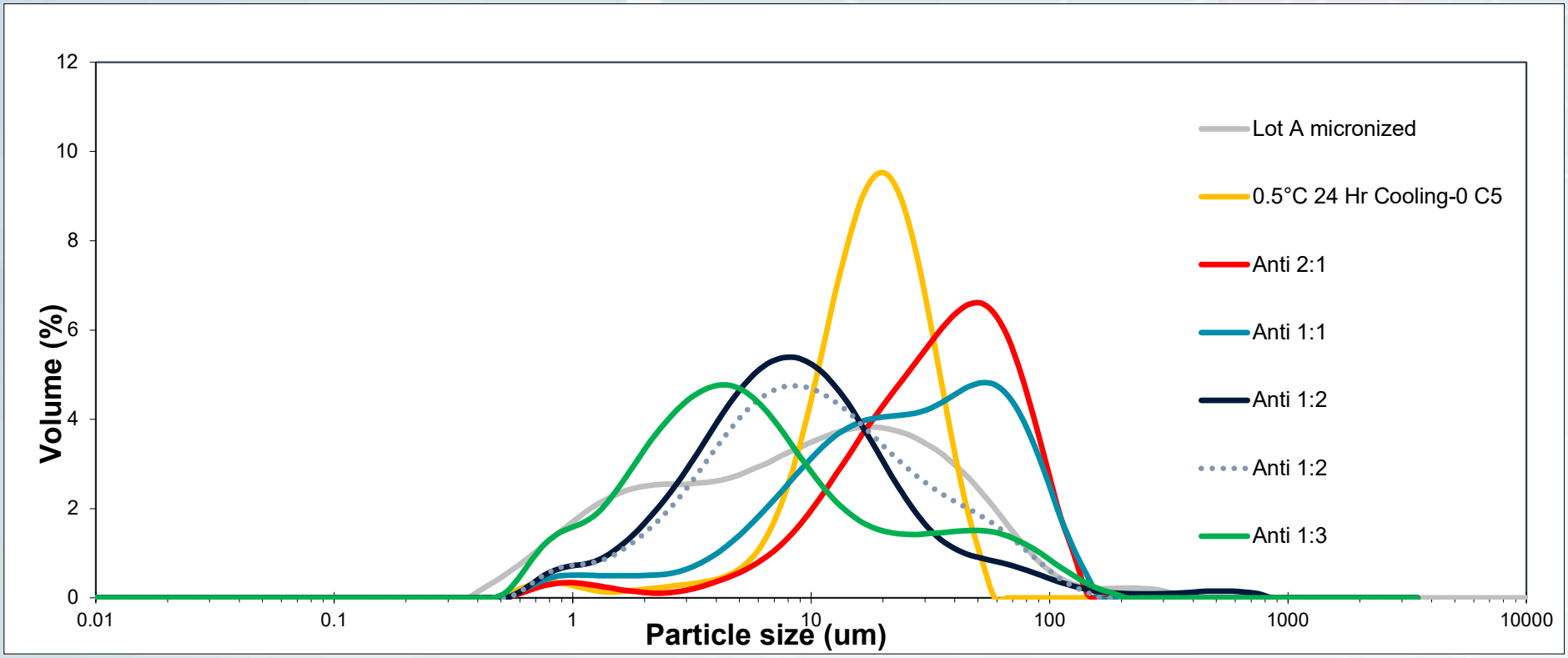
PSD antisolvent vs cooling



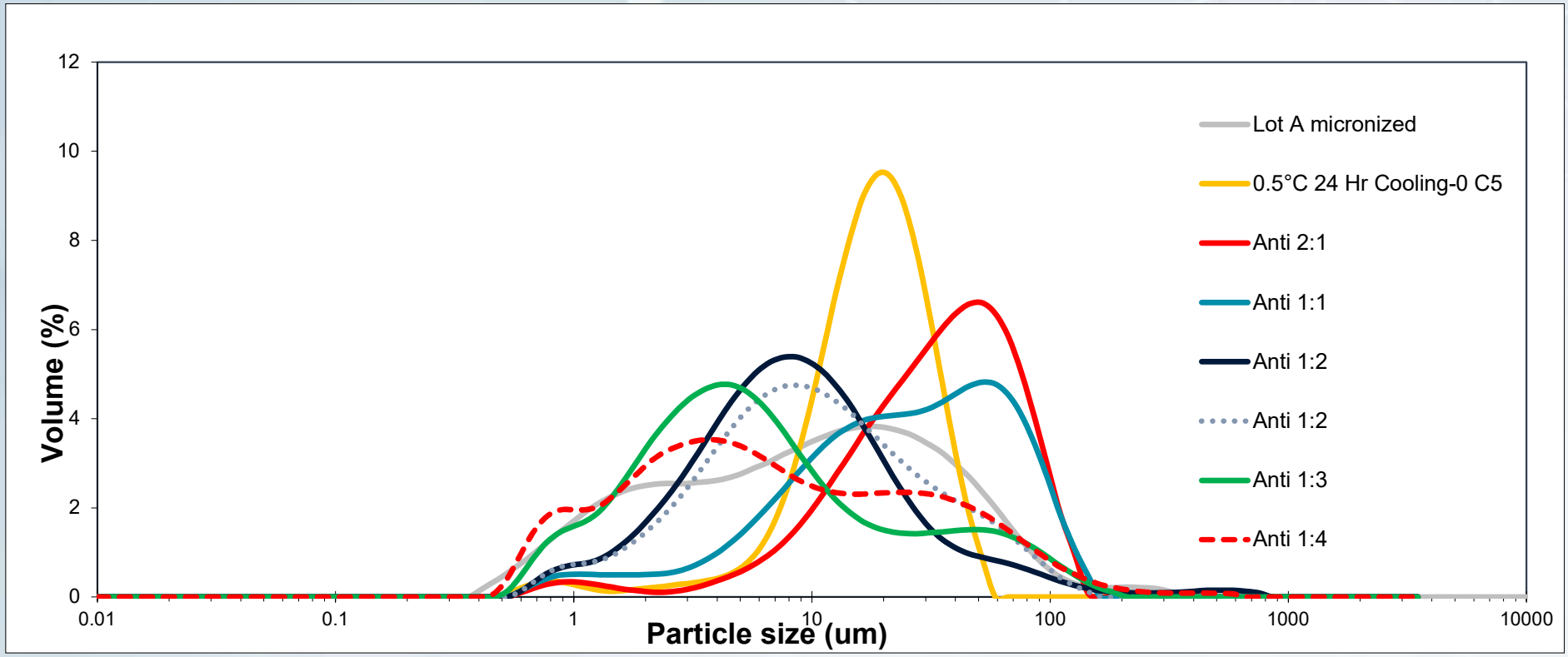
PSD antisolvent vs cooling



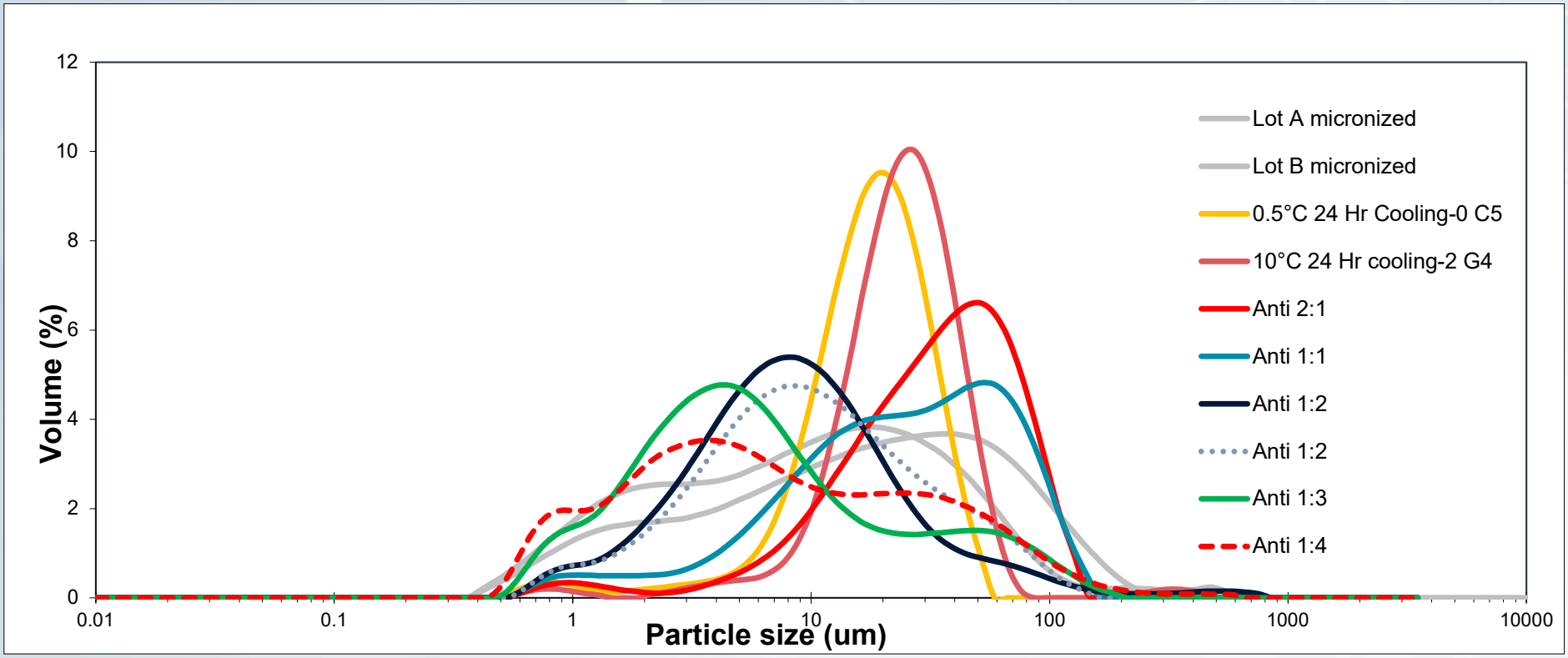
PSD antisolvent vs cooling



PSD antisolvent vs cooling



PSD antisolvent vs cooling



Conclusion

- Cooling crystallization gives a narrower distribution (PSD) than antisolvent for this API.
- Anti solvent gives a broader distribution (PSD) with smaller particles than cooling crystallization
- Antisolvent still in research phase.
- There is not much difference between cooling-0 and cooling-2 reactor.

- PSD of cooling crystallization is better than regular production → looks promising!

Acknowledgement

- Secoya technologies: Bart and this team, for all the support during the start up, and also the ongoing support

- Aspen colleagues

Back-up

Bad Cleaning