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Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

CMAC

Modular test bench for continuous crystallisation

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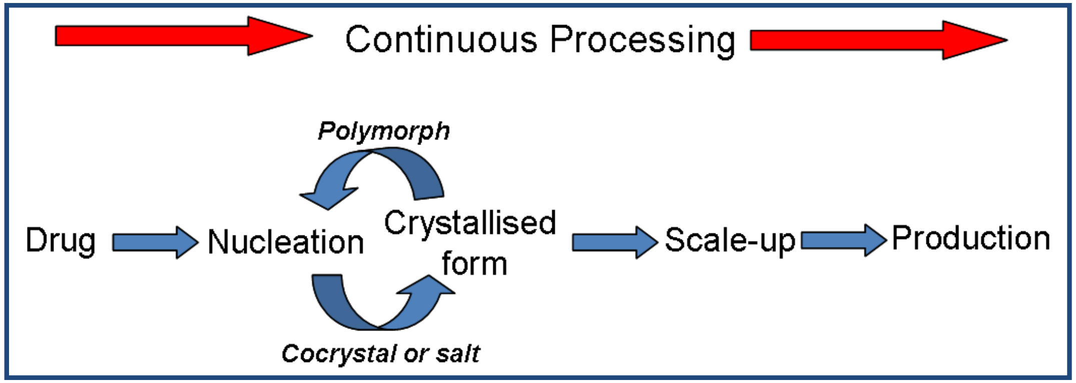
EPSRC

Engineering and Physical Sciences Research Council

Overview

1. Why continuous processing?
2. Modular test bench for continuous crystallisation: mixing, nucleation and growth
3. Deconstructing continuous crystallisation: nucleators and growers
4. Continuous generation of seed suspensions
5. Continuous growth of seed crystals
6. Conclusions

Why continuous processing?



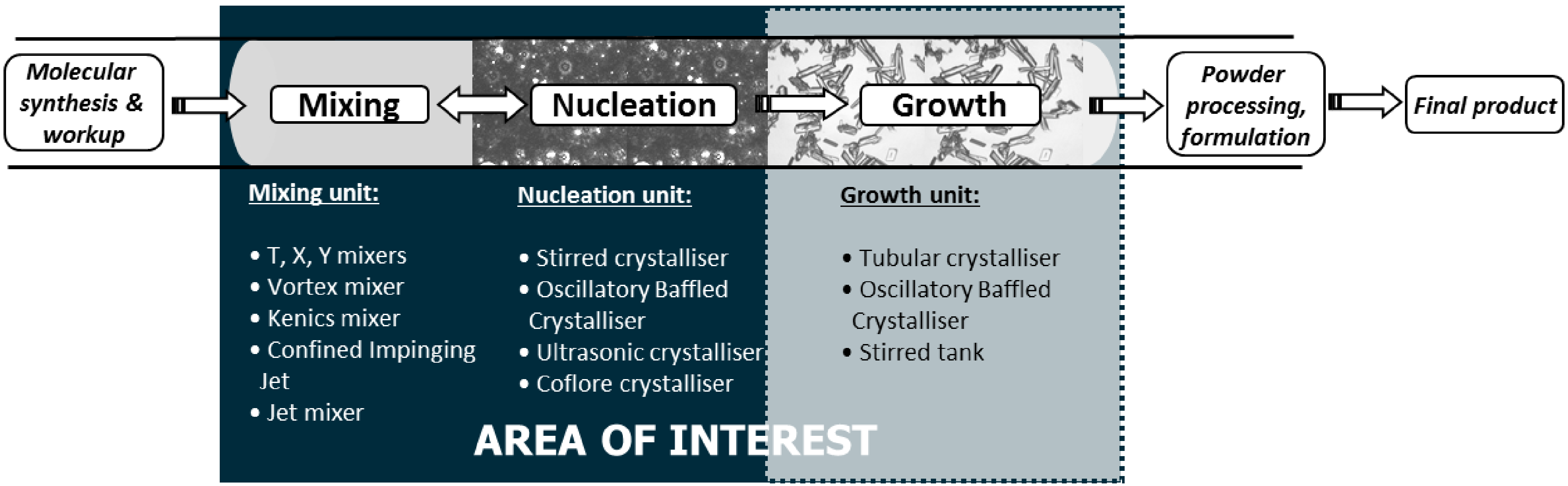
Benefits of continuous processing

- Lower costs, more sustainable
- Potential to exploit faster/ more selective/ hazardous
- Increased flexibility (moving processes between sites)
- Steady state operation (consistent product quality)
- Continuous on-line quality measurements to build understanding
- Better control of product (particle size, polymorphism…)
- Reduced plant scale (manufacture using laboratory equipment, no scale-up risk)
- Improved process robustness (greater control, producing the same product every time)

Chen, Sarma, Evans & Myerson (2011) *Crystal Growth & Design* **11**, 887-895.
Tung (2012) *Organic Process Research & Development* **17**, 445-454.

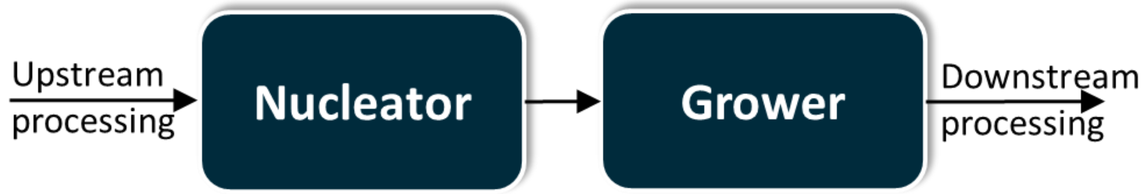
Modular test bench for continuous crystallisation

Development of flexible modular test bench including mixing, nucleation and growth units which enable better control over key product particle attributes (form, size, yield, purity) through continuous crystallisation

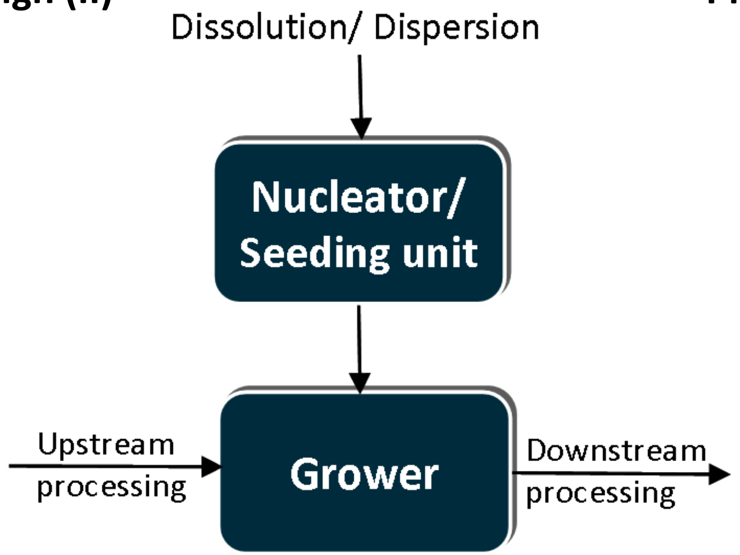


Deconstructing continuous crystallisation: Nucleator (in situ production of seeding suspensions) & Grower

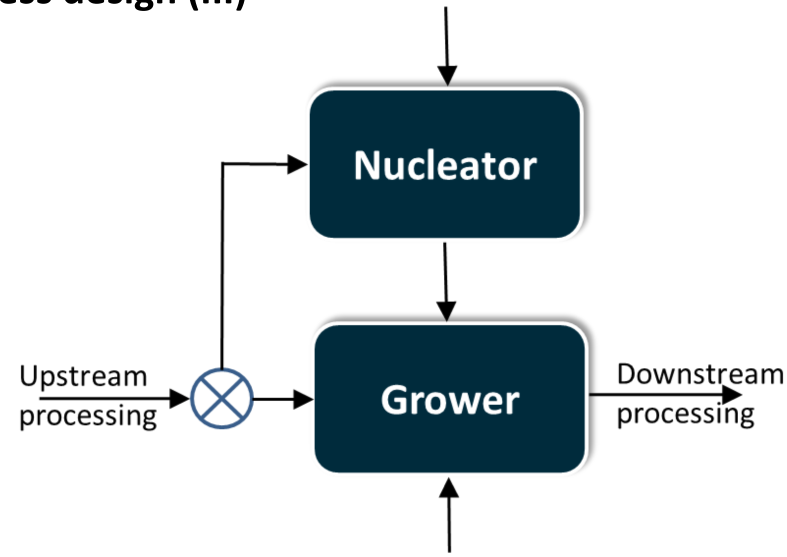
Process design (I)



Process design (II)

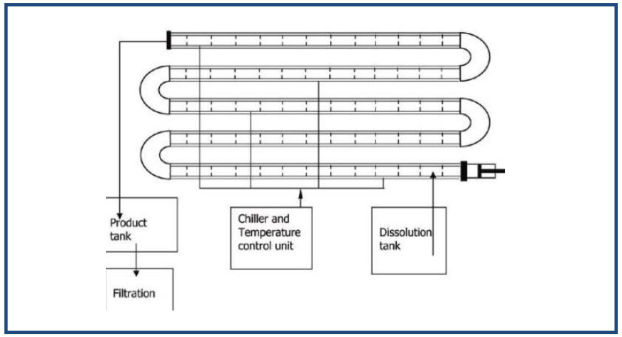


Process design (III)



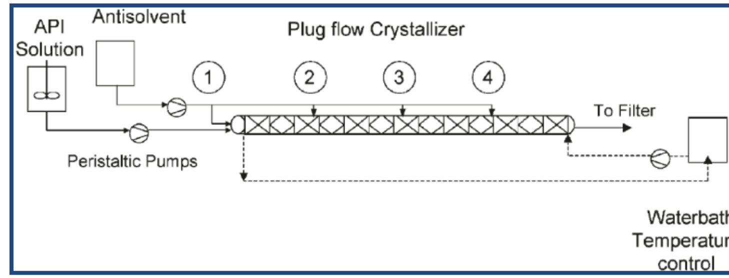
Continuous crystallisation- review

Continuous oscillatory baffled crystalliser



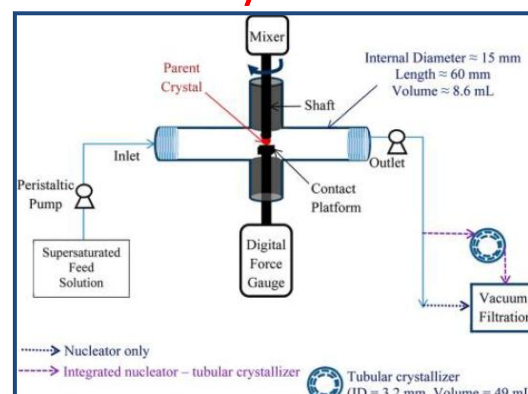
Lawton, Steele, et al. (2009) Organic Process Research & Development **13**, 1357-1363.

Static mixer (Kenics)



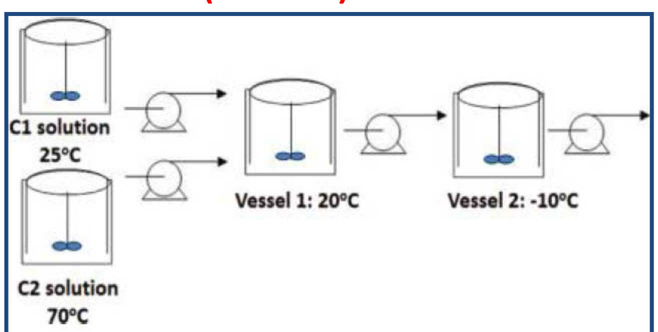
Alvarez & Myerson (2010) Crystal Growth & Design **10**, 2219-2228.

Continuous secondary nucleator and tubular crystalliser



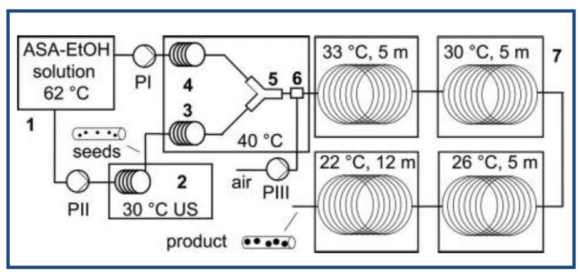
Wong, Cui, et al. (2013) Crystal Growth & Design **13**, 2514-2521.

Stirred tank (MSMPR) cascade



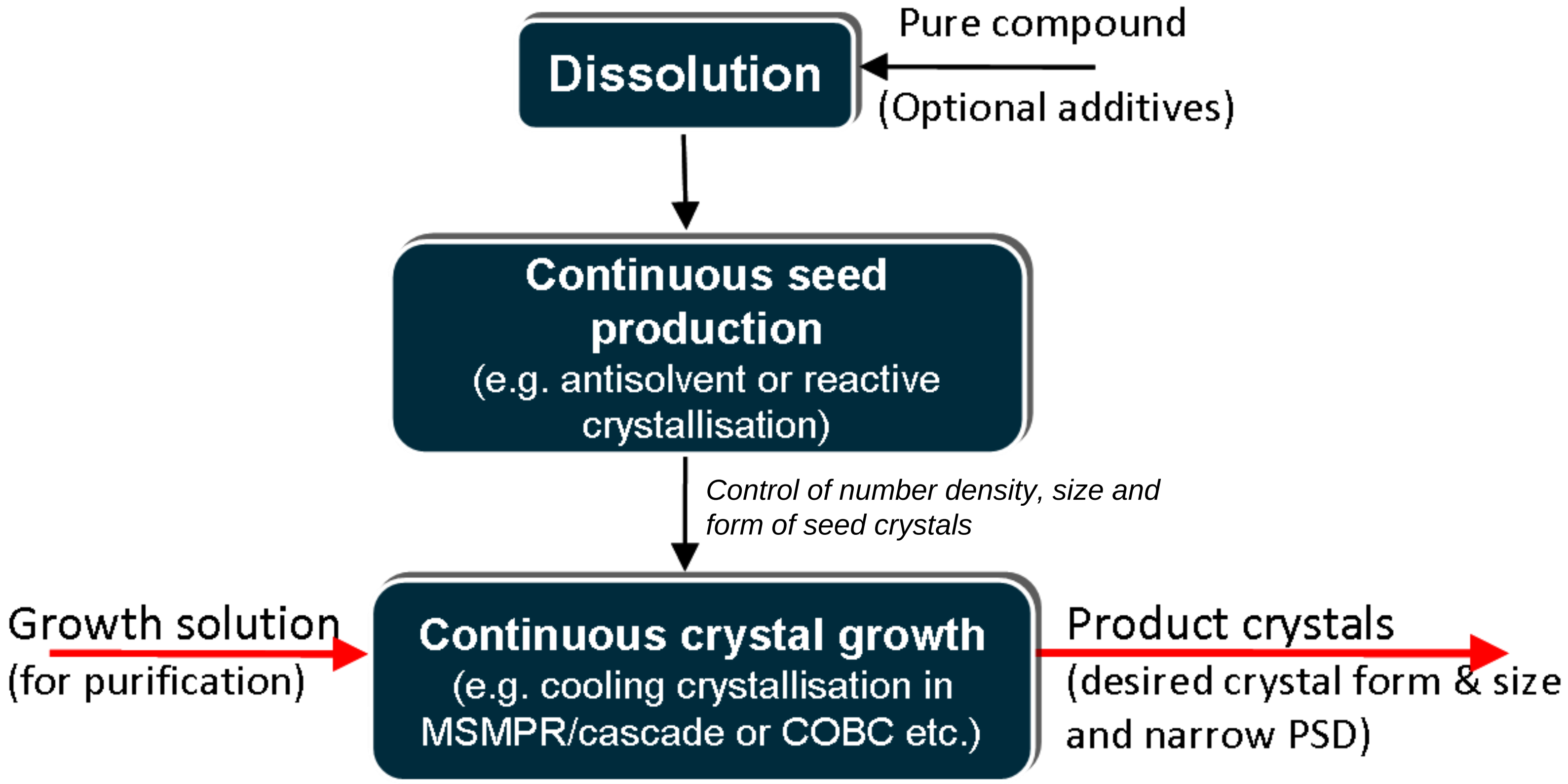
Quon, Zhang, et al. (2012) Crystal Growth & Design **12**, 3036-3044.

Continuous tubular crystalliser

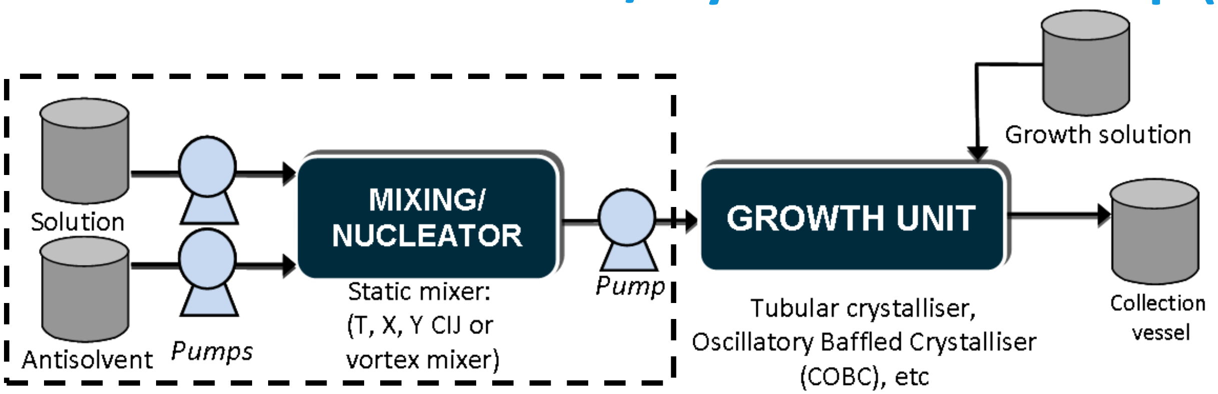


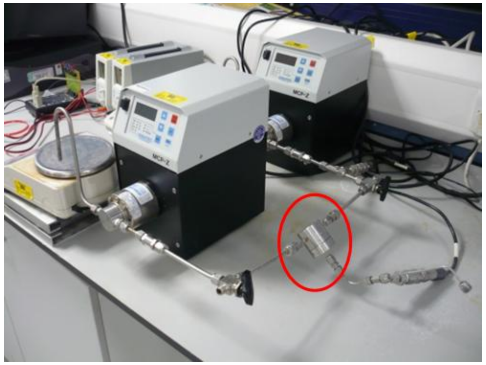
Eder, Schrank, et al. (2012) Crystal Growth & Design **12**, 4733-4738.

Example arrangement of continuous nucleation and growth units

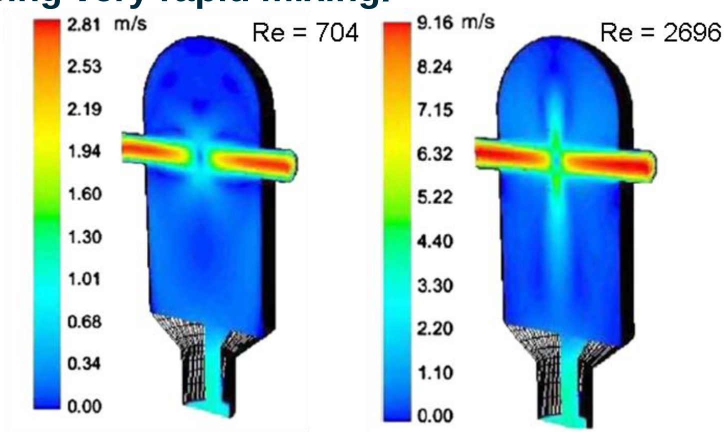


Continuous nucleation/crystallisation setup (I)

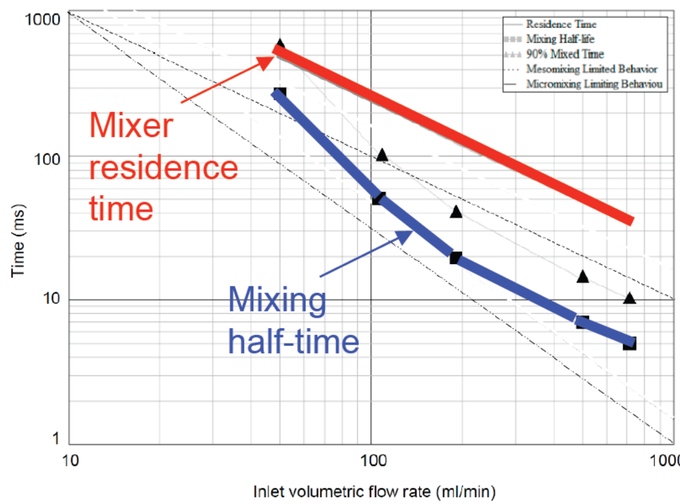




Confined Impinging Jet (CIJ) mixer: Turbulent kinetic energy is generated and then quickly dissipated, inducing very rapid mixing.



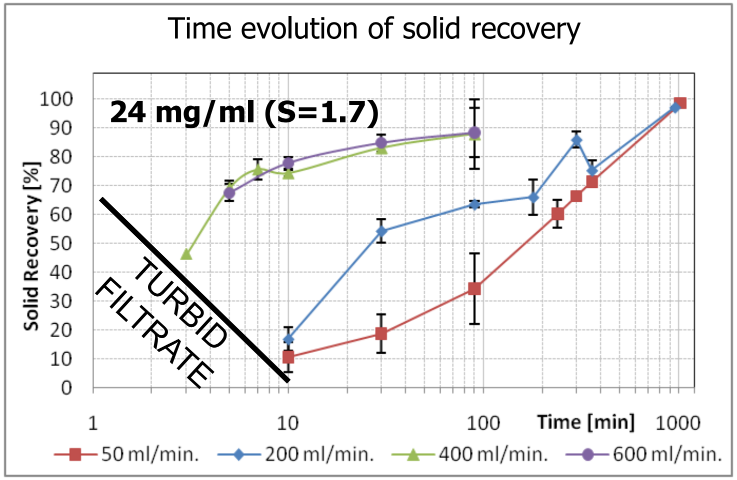
Mixing times estimated using Bourne IV reaction scheme were of order of 10-100 ms
Total mixer residence times were less than 1 s, but always longer than mixing times

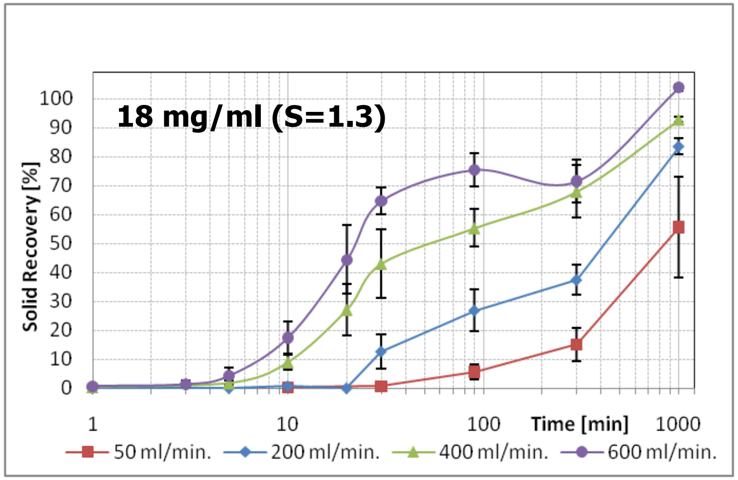


Marchisio, Rivautella, Barresi (2006) AIChE Journal **52**, 1877-1887.
Gavi, Marchisio, et al. (2007) Chemical Engineering Science **62**, 2228-2241.

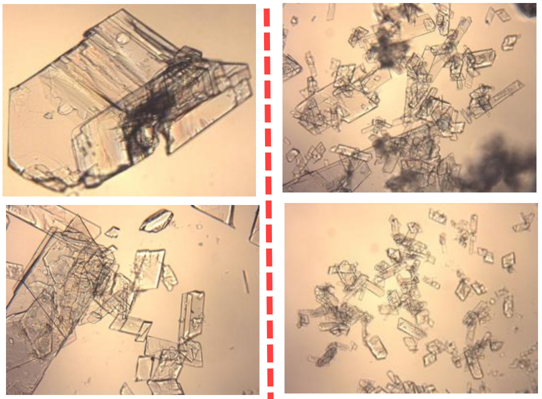
Effect of flow rate through static mixer (CIJ)

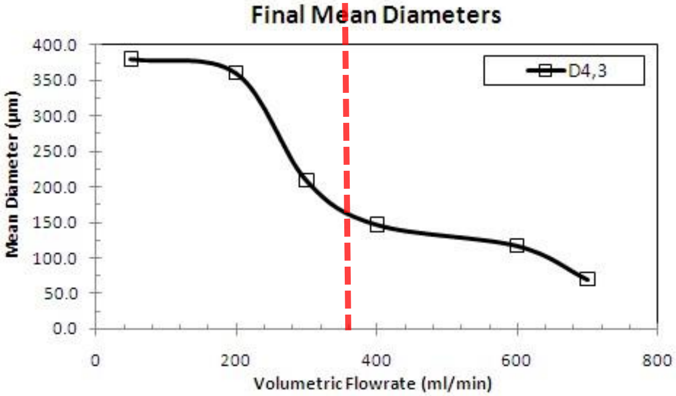
Antisolvent crystallisation of DL-valine (IPA:water, 1:1, w%)





All mixing completed in less than 1 sec: no stirring afterwards



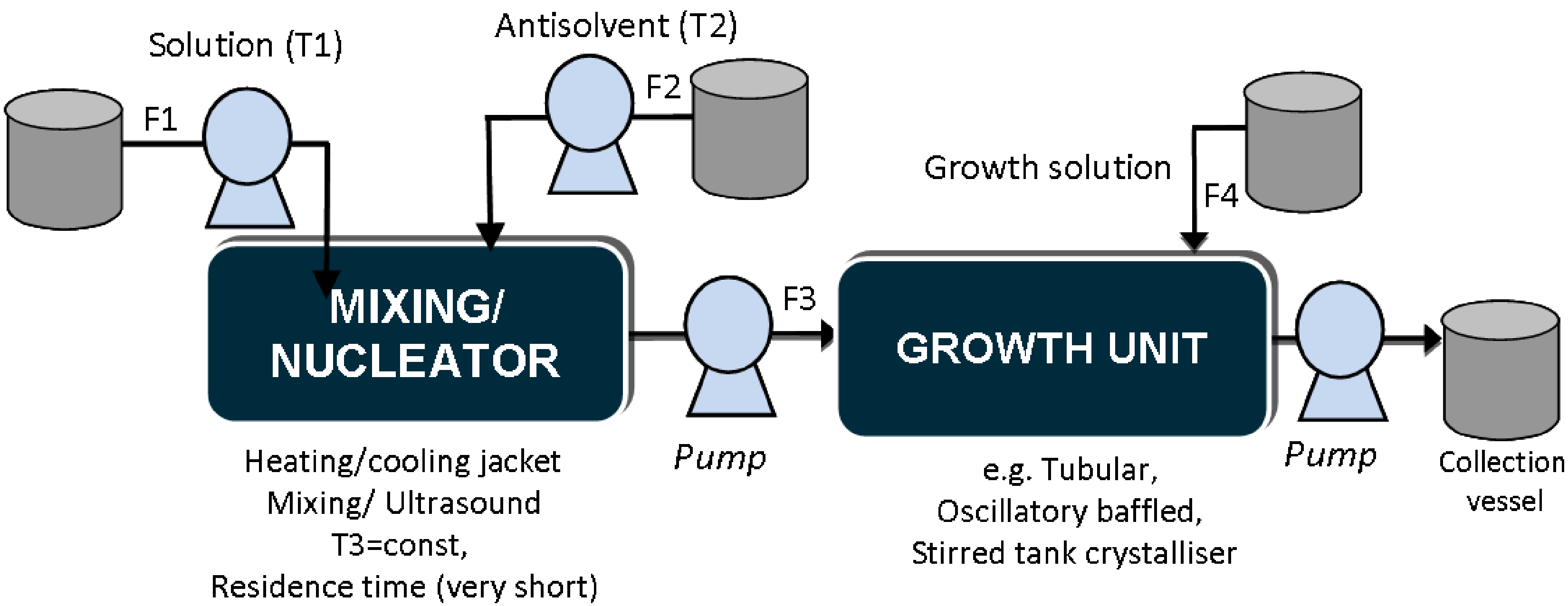


- Lower flow rate
- Fewer nuclei
- Larger crystals

- Higher flow rate
- More nuclei
- Smaller crystals

Continuous nucleation/crystallisation setup (II)

Nucleator design:



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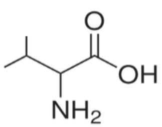
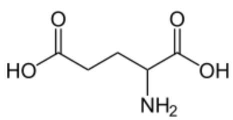
Continuous generation of seed crystals by antisolvent precipitation

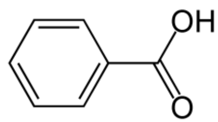
The continuous crystal nucleation units were tested using four model compounds:



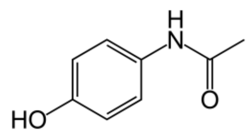
DL-valine



L-glutamic Acid

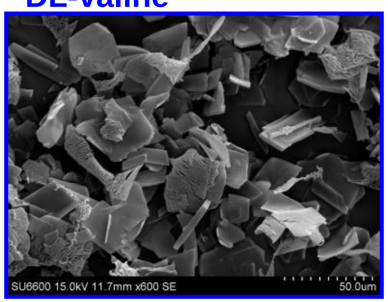


Benzoic Acid

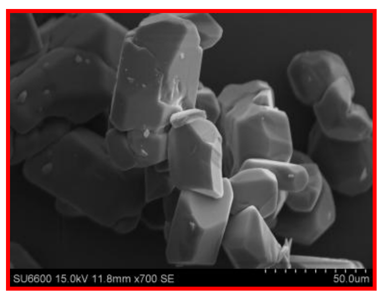


Paracetamol

DL-valine

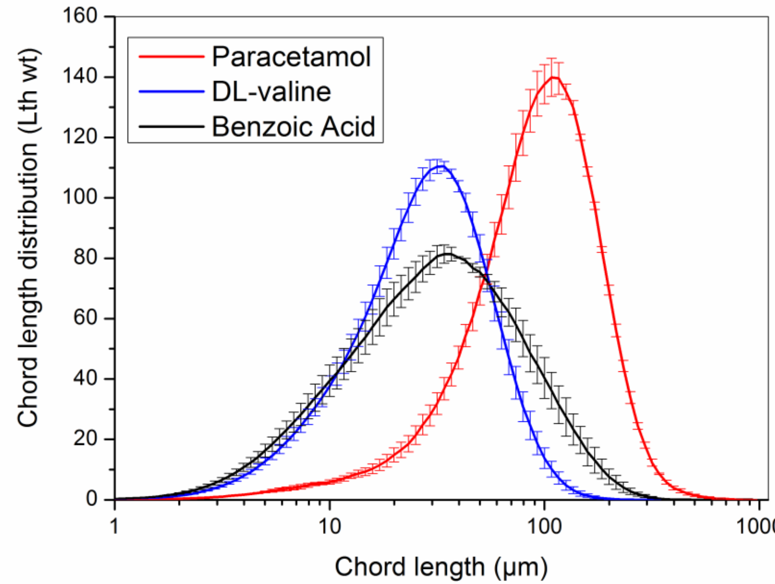


Paracetamol



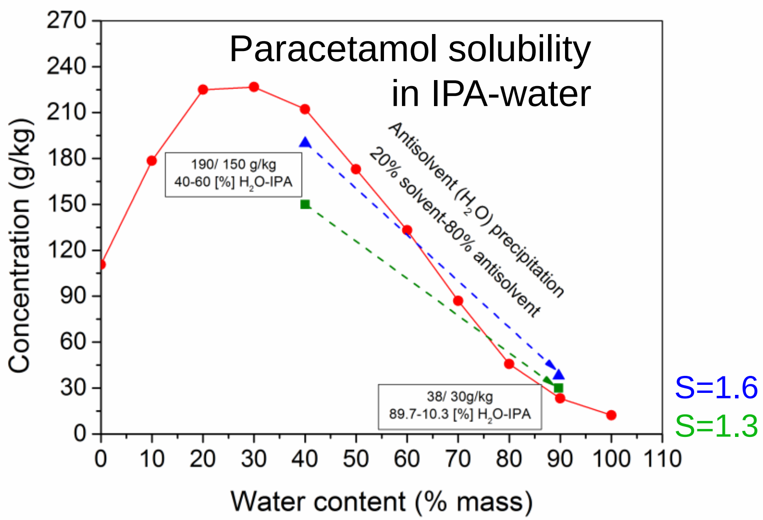
Benzoic Acid

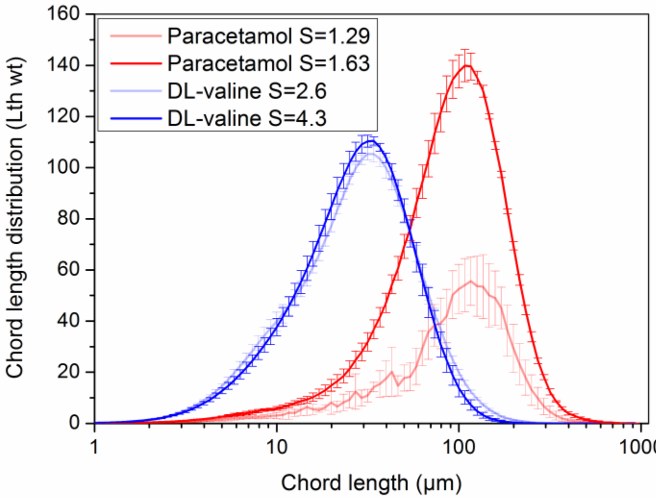
L-glutamic Acid

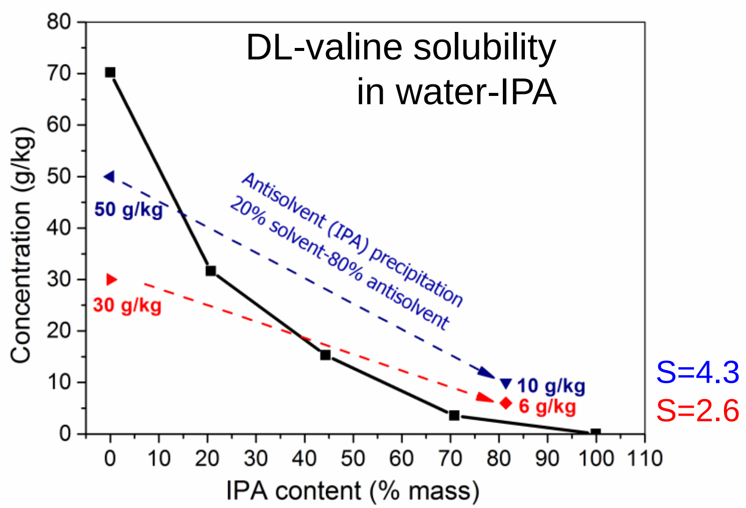


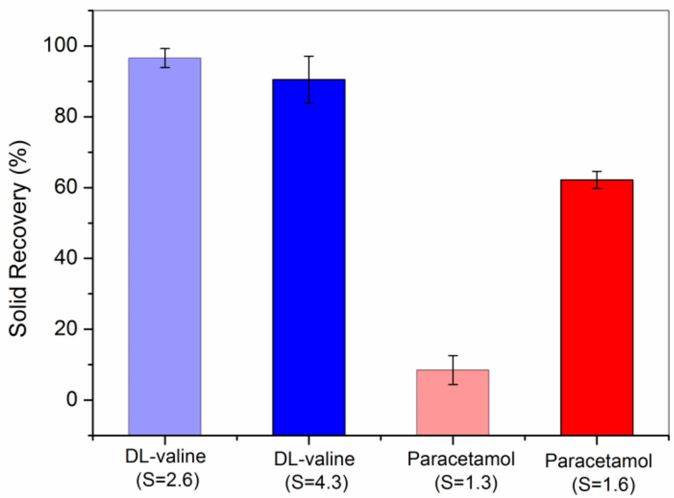
Compound	Mean size [µm]	Solid Recovery [%]
DL-valine (S=4.3)	33.9 ±1.7	90.5 ±6.6
Benzoic Acid (S=3.7)	35.2 ±4.6	76.4 ± 10.5
Paracetamol (S=1.6)	89.9 ±11.1	62.2 ± 2.4
L-glutamic Acid (S=13)	10.1 ± 0.9 (LD)	98.0± 1.2

Continuous generation of seed crystals: *effect of supersaturation*

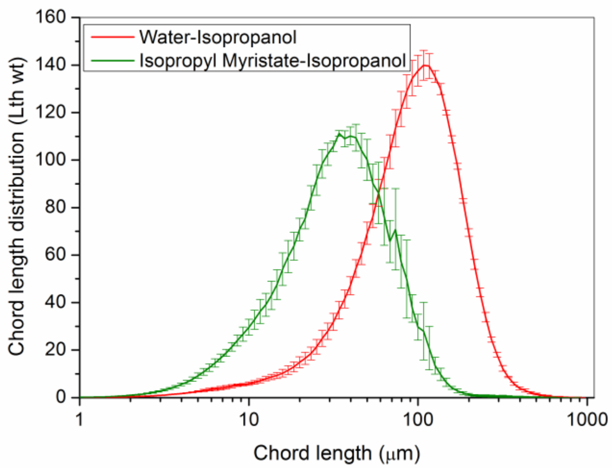


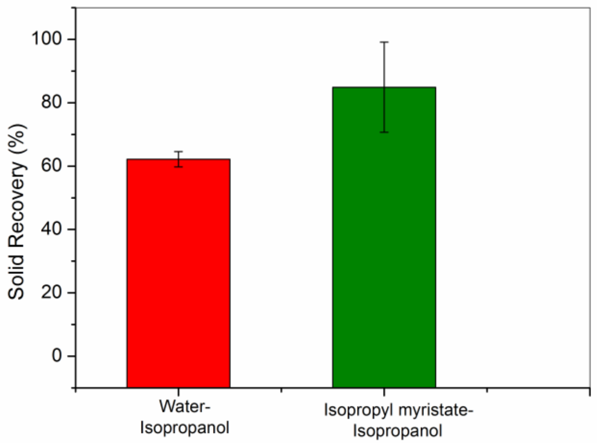




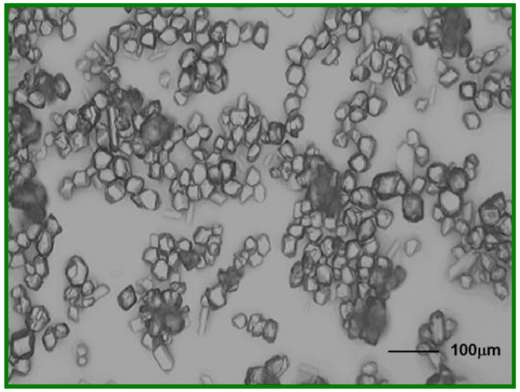


Continuous generation of seed crystals: *effect of solvent*

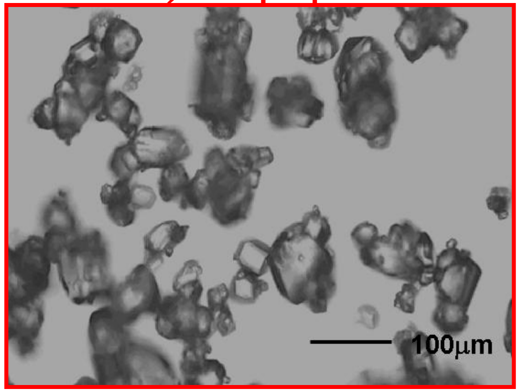




Isopropyl Myristate-Isopropanol

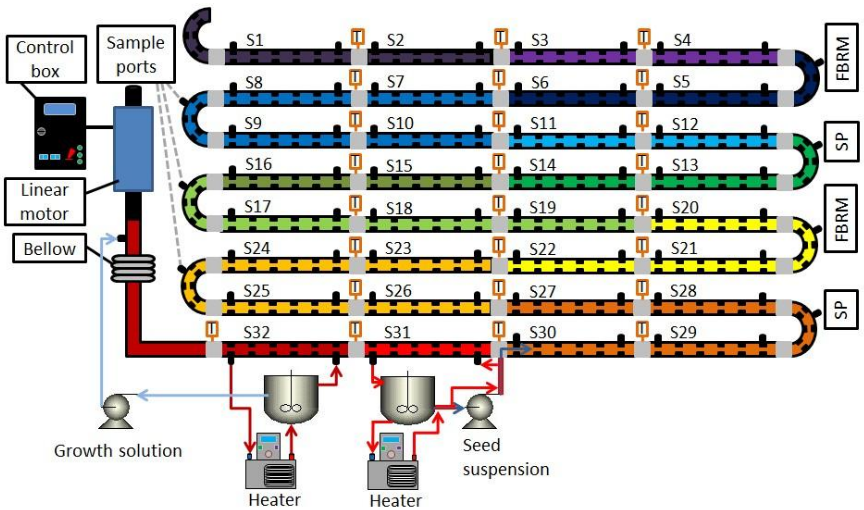


H_2O-Isopropanol



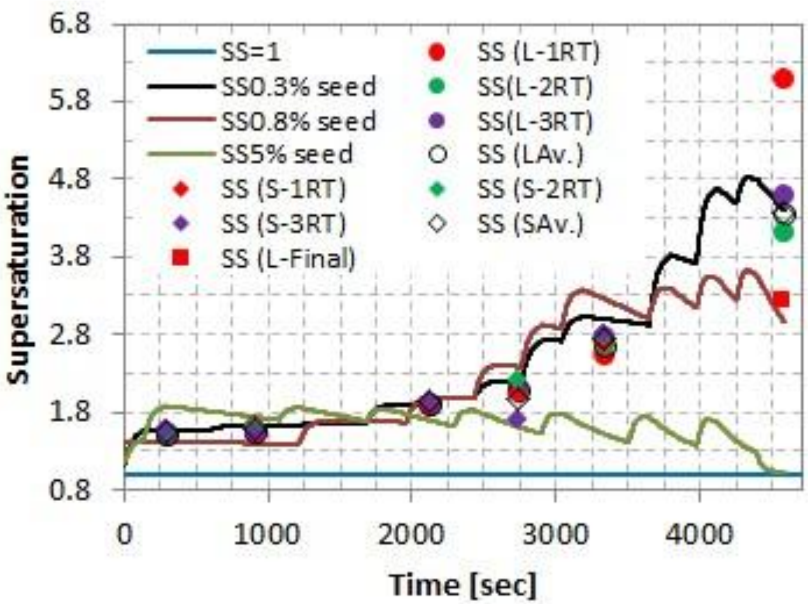
Compound	Solvent/ Antisolvent	Mean size [μm]	Solid Recovery [%]
Paracetamol	Water-Isopropanol (S=1.6)	89.9 ±11.1	62.2 ±2.4
	Isopropyl myristate-Isopropanol (S=2.6)	40.4 ±3.3	84.9 ± 14.2

Continuous growth of seed crystals: *L-glutamic acid* *(Naomi Briggs/Ulrich Schacht)*

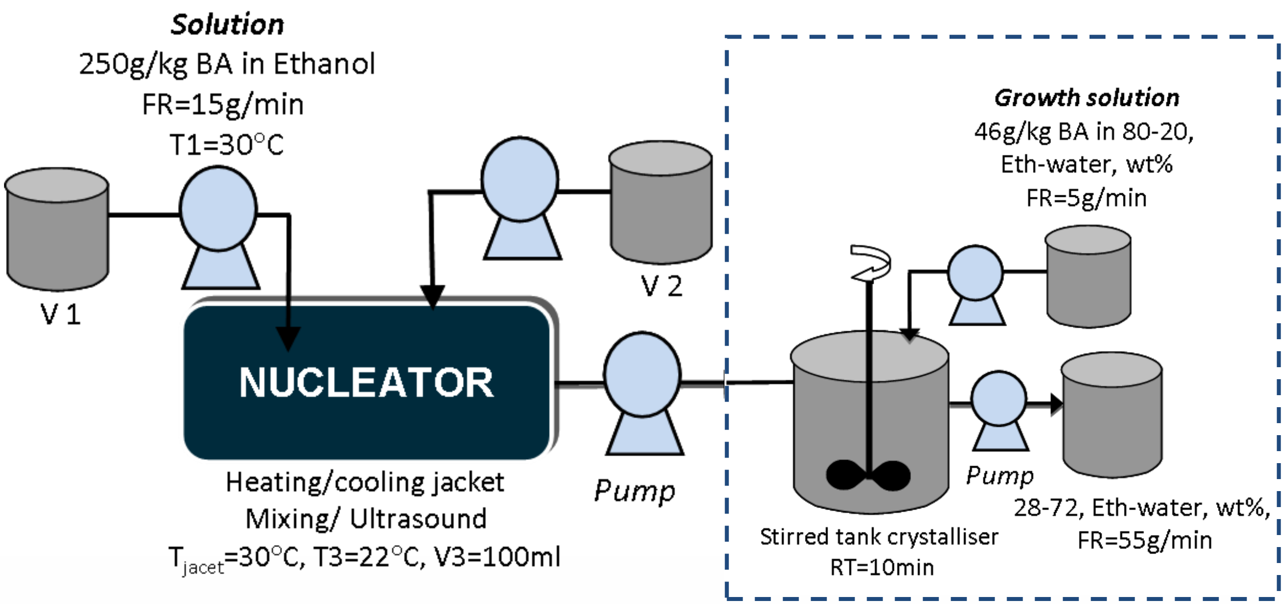


L-Glutamic Acid (β polymorph) seeding suspensions prepared by continuous nucleation unit

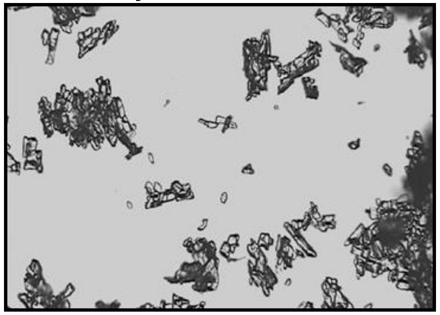
Operation	Mean size [µm]
Seed crystals	10.1 ±0.9
1 RT	150 ±8.0
2-5 RT	230 ±11.0



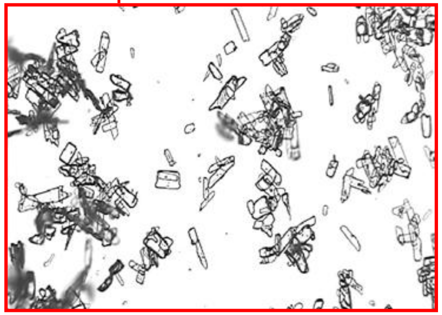
Growth of seed crystals: *benzoic acid*

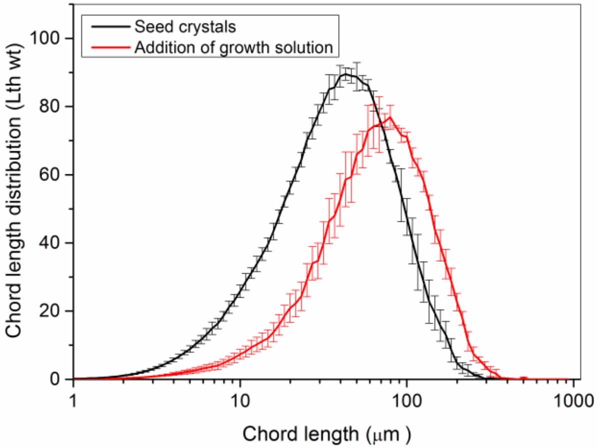


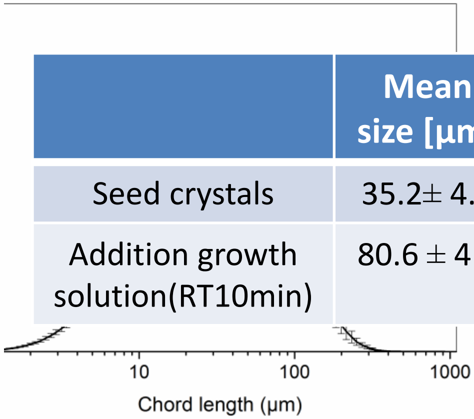
Seed crystals



Final product







	Mean size [μm]	Solid Recovery [%]
Seed crystals	35.2± 4.6	76.4± 10.5
Addition growth solution(RT10min)	80.6 ± 4.1	75.5± 0.9

Summary

1. Separation of nucleation process (formation of seed crystals) from subsequent growth helps to better control the final product attributes in continuous crystallisation
2. Modular test bench provides range of units tailored for specific mixing, nucleation and growth requirements of particular systems
3. Examples of continuous generation of seeding suspensions have been demonstrated through rapid antisolvent crystallisation for a wide range of systems
4. Continuous feeding of seeding suspensions into continuous crystal growth units (MSPMPR, COBC, etc.) will allow for fully continuous crystallisation process
5. Using in situ PAT will improve understanding and control of continuous nucleation/crystallisation process

Acknowledgements

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Thank your for your attention