

Continuous crystallisation using oscillatory baffled plug flow crystalliser

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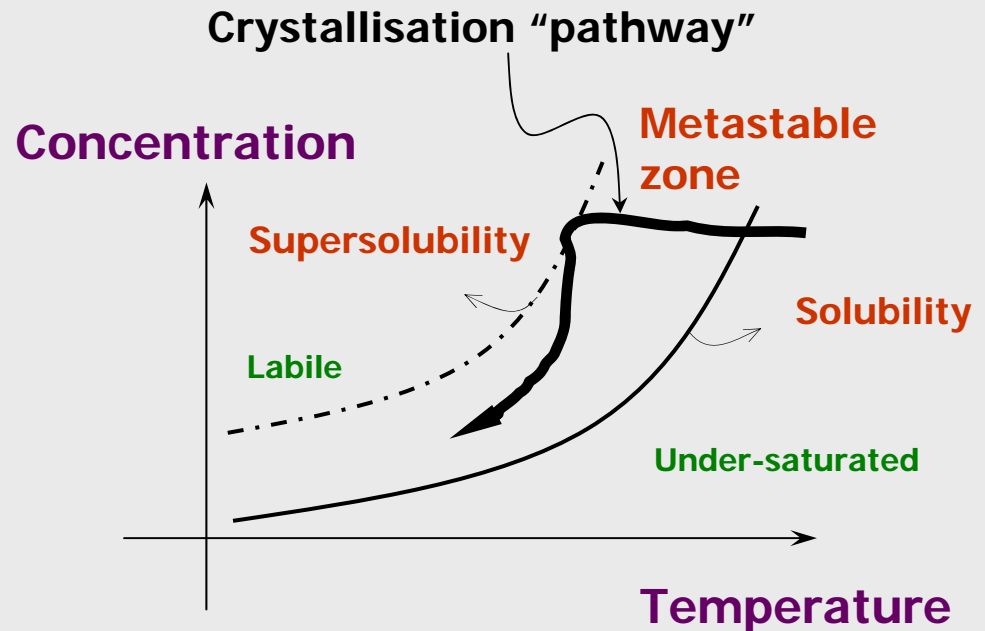
Structure

- 1. Crystallisation science**
- 2. Challenges in industrial crystallisation**
- 3. Continuous oscillatory baffled crystalliser**
- 4. Case studies**
- 5. Forward remarks**



1. Crystallisation Science

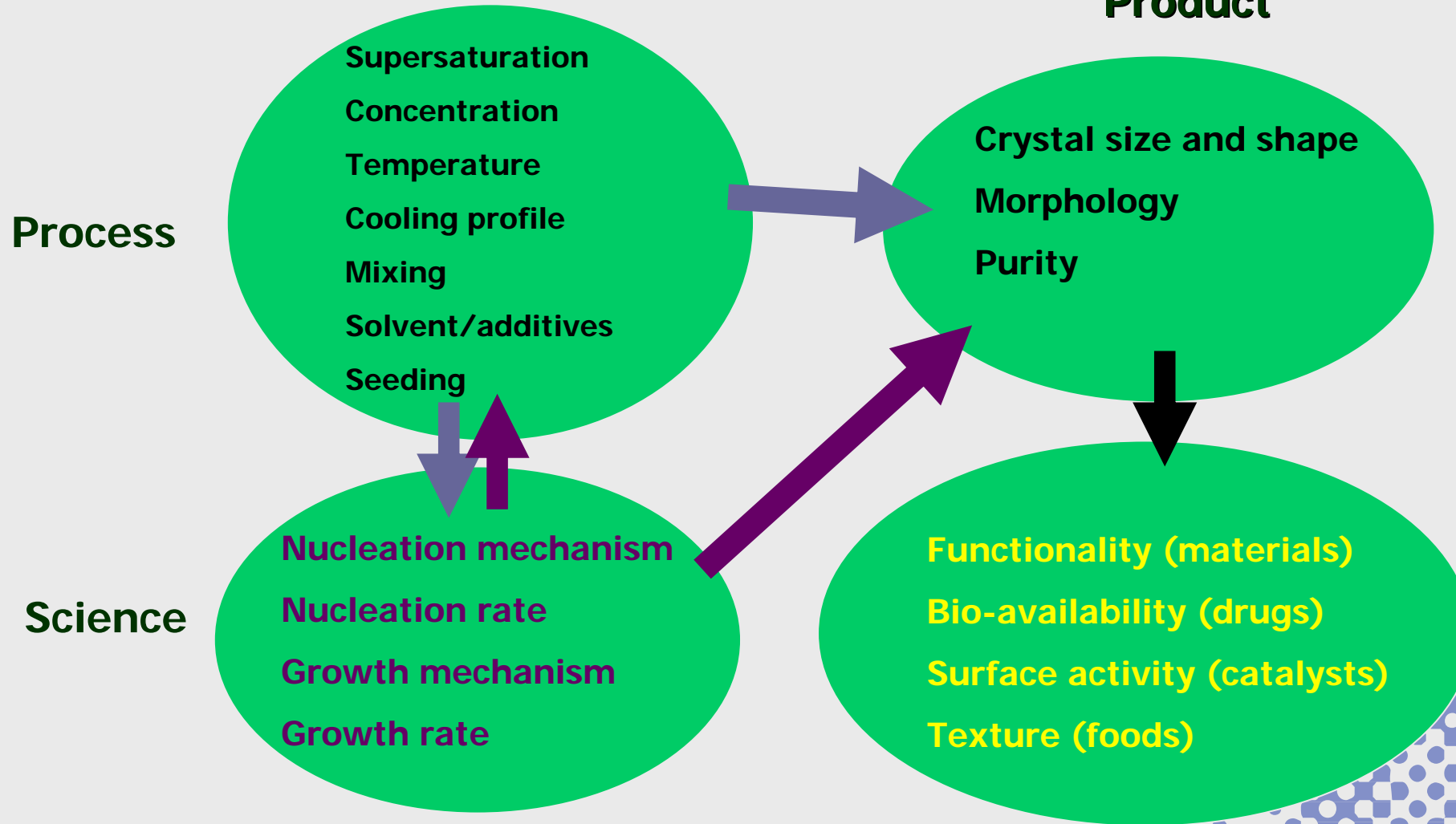
- Crystallisation is a relatively simple process
- But the underlying science and its control are very complex!
- In industrial scales, operators' experience still plays a major part



Supersolubility or metastable limit is thermodynamically not found and kinetically not well defined, depending on temperature, rate of generating supersaturation, solution history, impurities, fluid dynamics, scale and etc.

Science

Product



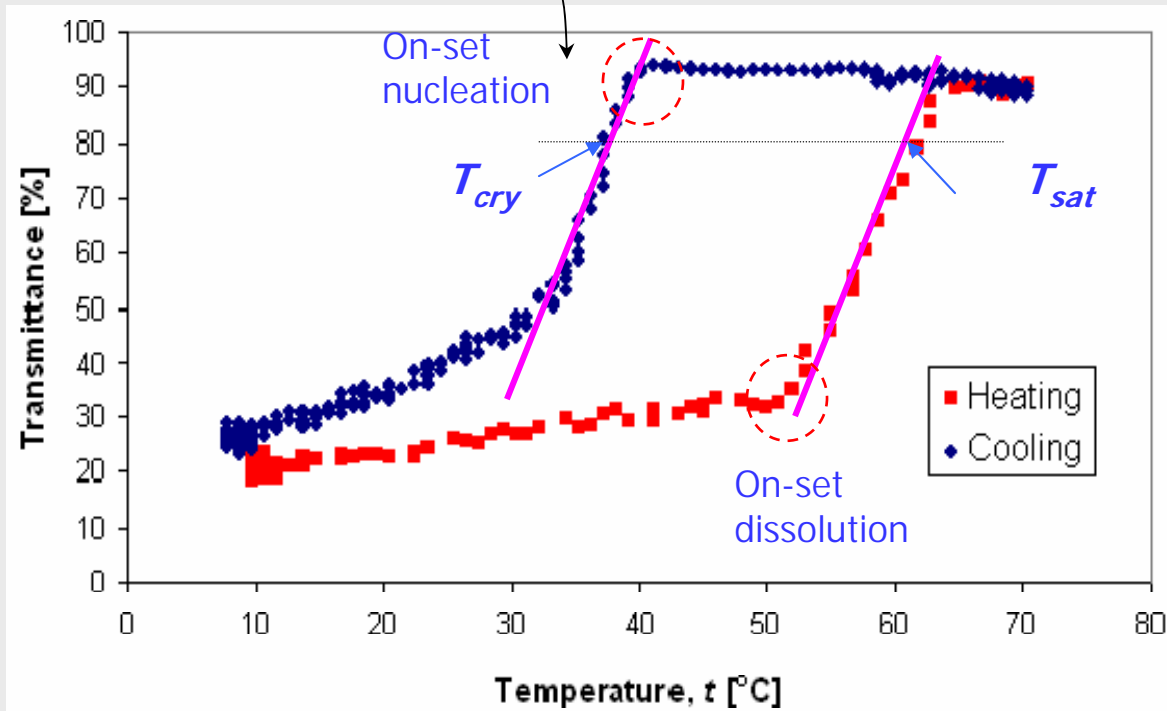
Nucleation

- **What initiates?**
 - not well understood
 - 3-D assembly of molecular clusters on nm scale
 - very fast kinetics
 - not easy to detect (soft X-ray absorption spectroscopy)
 - modelling available, lack of validation
- **How does it happen?**
 - Primary nucleation – without the presence of any crystalline matter
 - Secondary nucleation – collision breeding, seeding

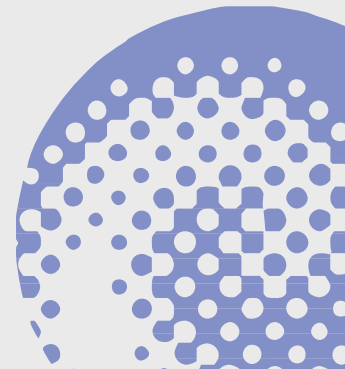


Determination of metastable zone width (MSZW) using a turbidity probe

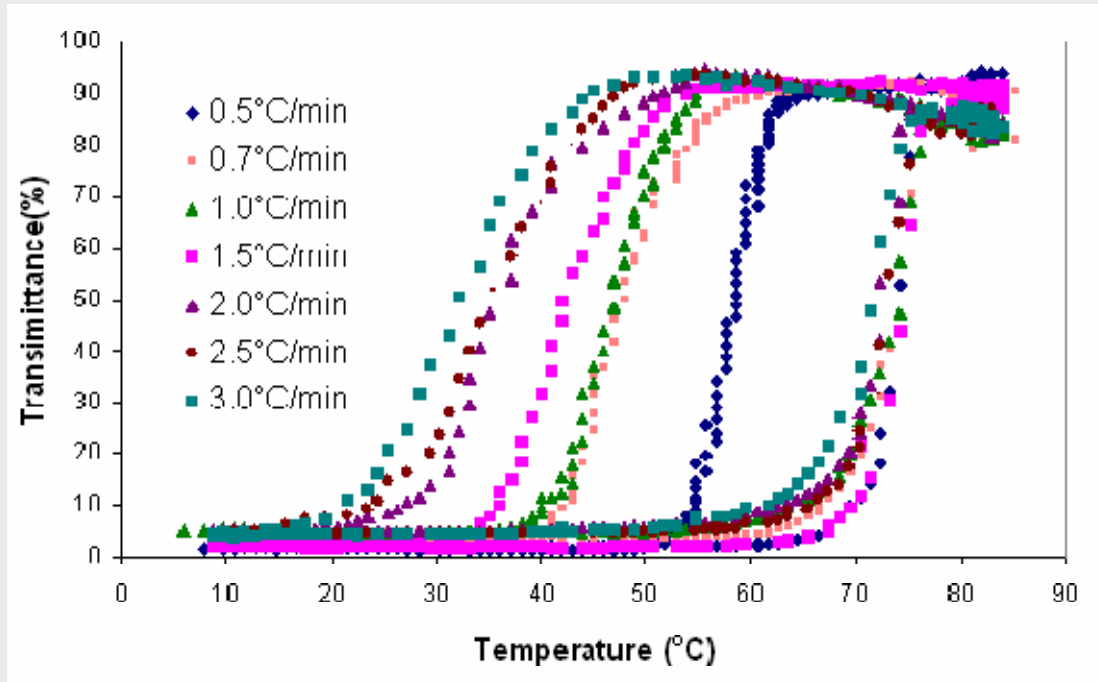
Detection of post-nucleation



$$MSZW = T_{sat} - T_{cry}$$



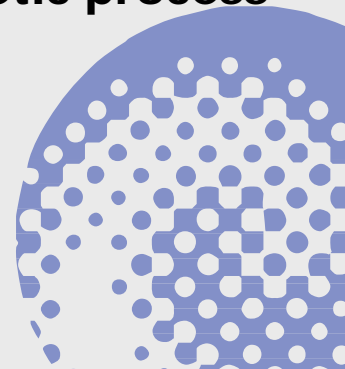
Metastable zone width (MSZW)



concentration = 45 g/L, $f = 2$ Hz, $x_0 = 10$ mm

MSZW depends on reactor, scale and operating conditions

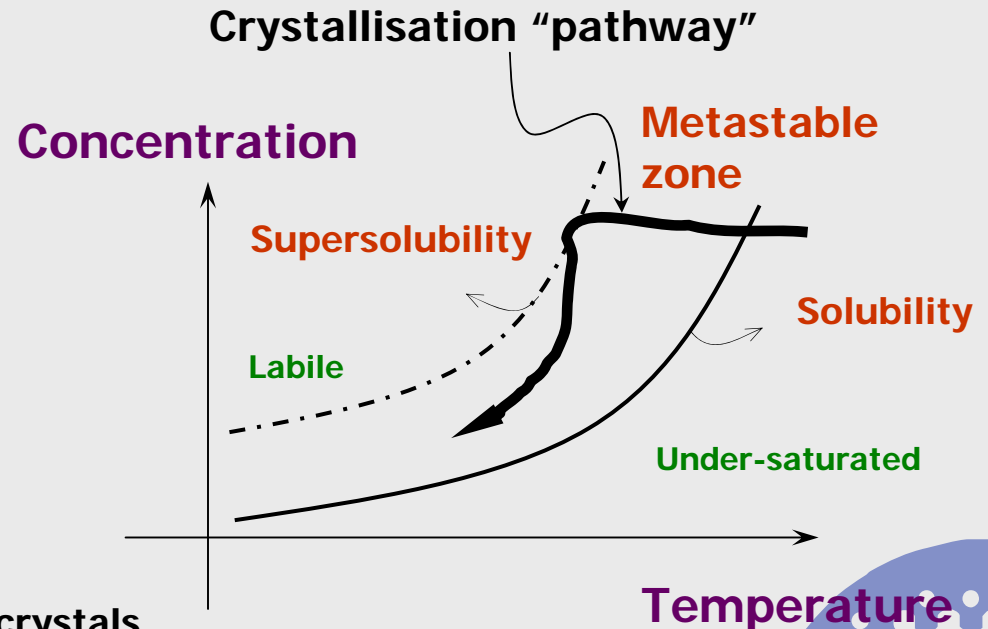
- Dissolution – a thermodynamic process
- Crystallisation – a kinetic process



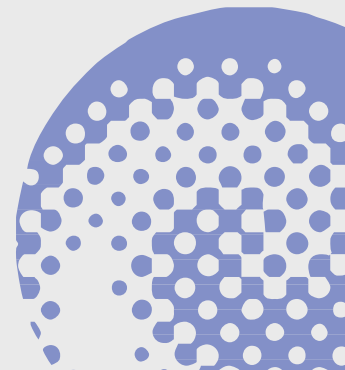
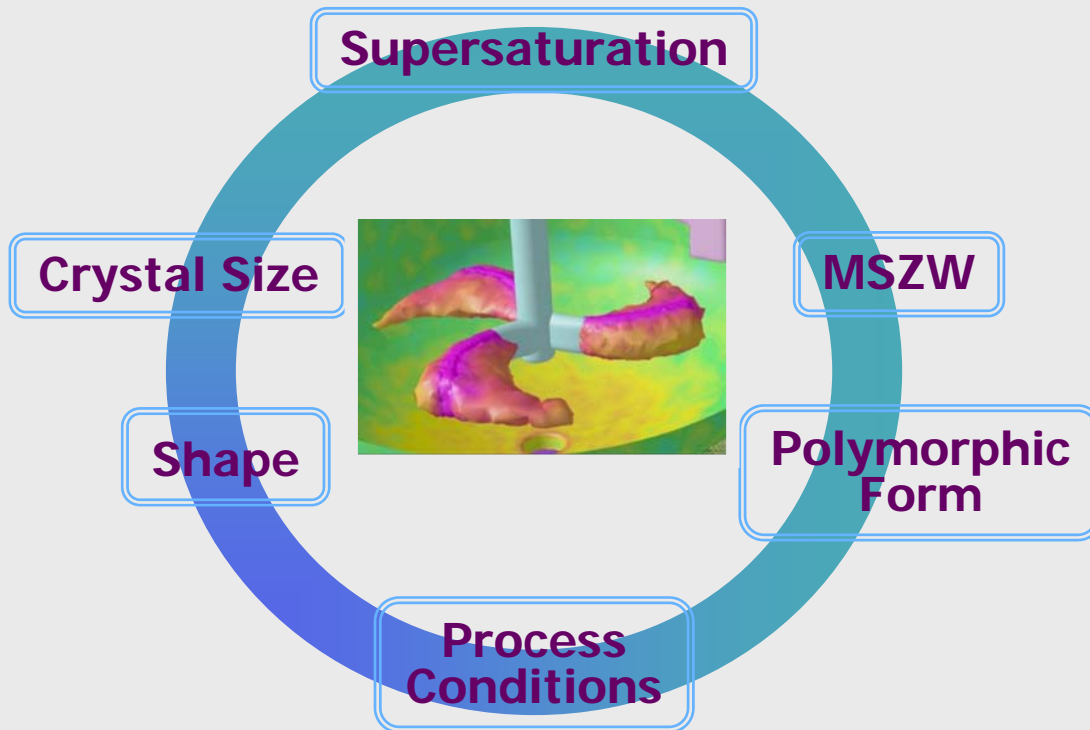
Crystal growth

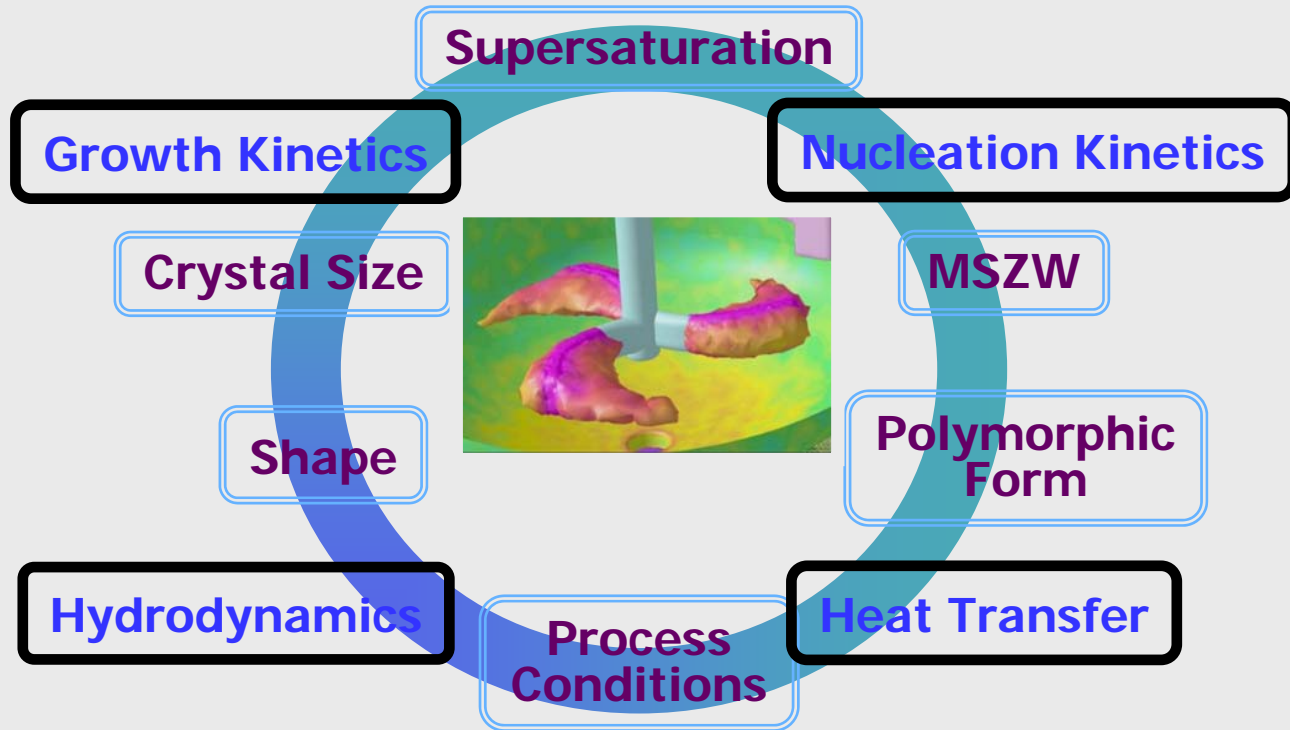
- Mass transfer phenomenon
- Crystal growth phase must take place within the MSZW

the degree of supersaturation is changed by crystal growth, simultaneously MSZW is altered due to different temperature levels and changes in impurity concentration

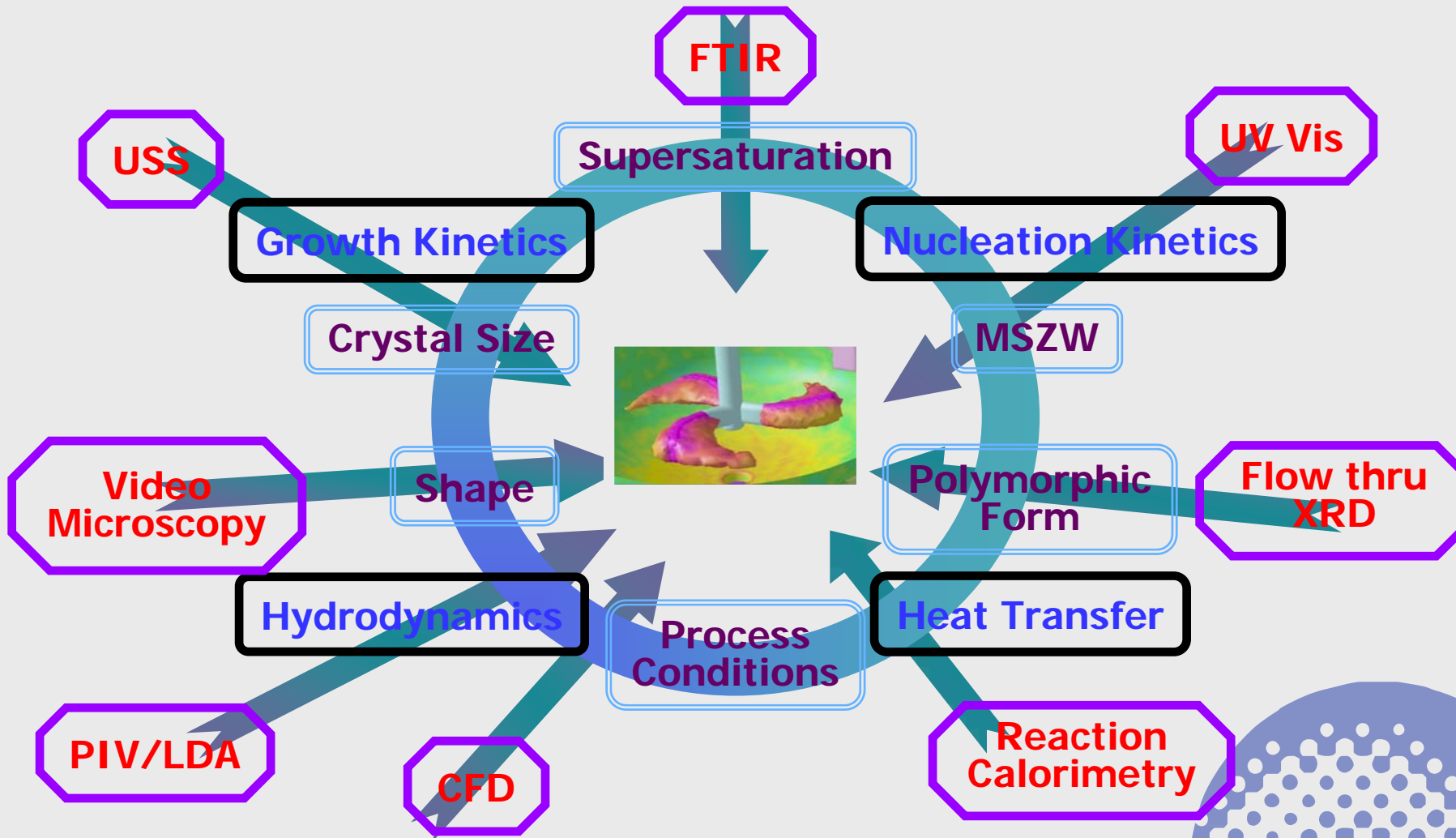


- Nucleation dominates → small crystals
- Growth dominates → large crystals





Chemicals Behaving Badly (CBB)



Lab scale batch crystallisation

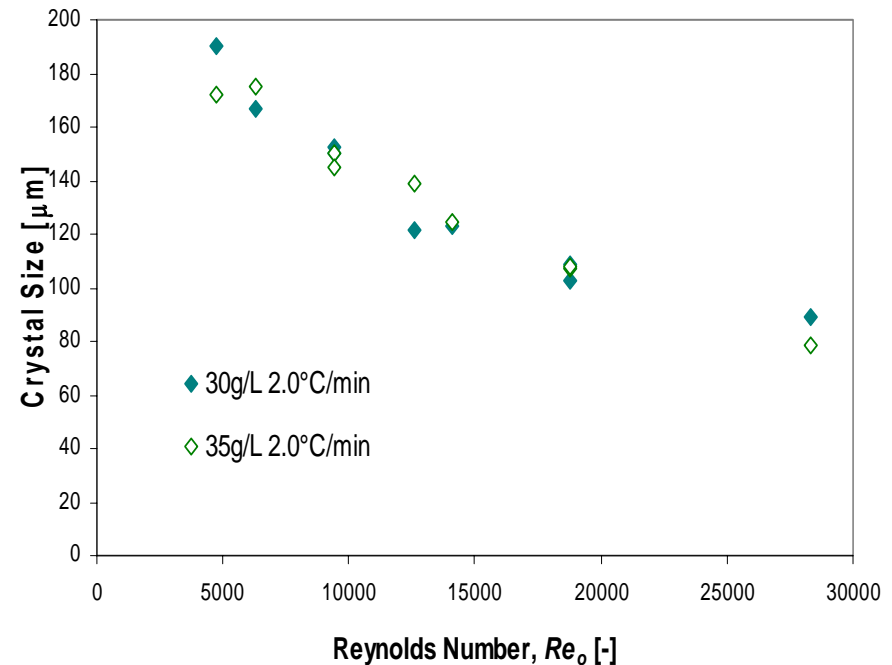
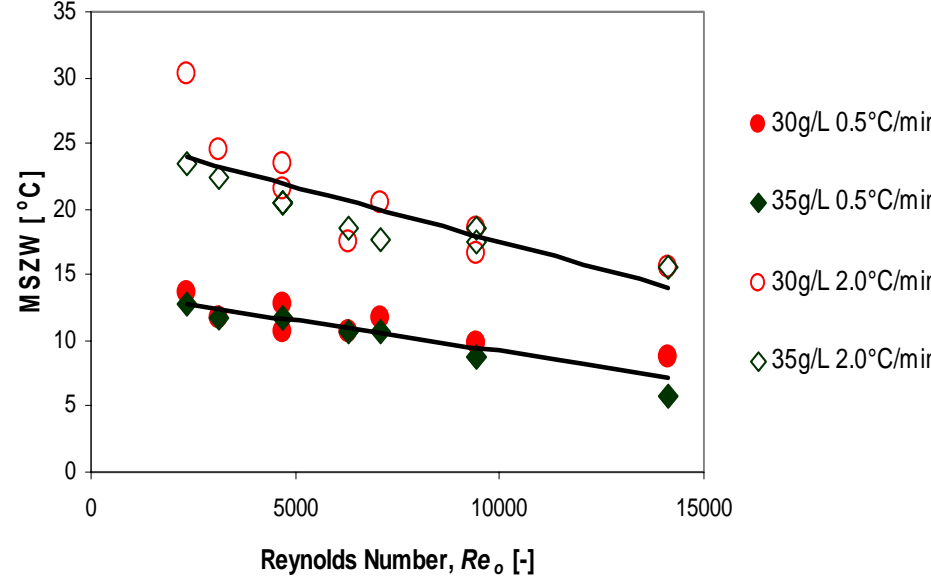
- Simultaneous multi-technique measurements during a crystallisation process
- Have promoted better understanding of crystallisation in lab scale
- Promoted better operation of crystallisation in small scale
- Linear cooling identified as one of the key operational parameters
 - Data rich
 - Lack of correlations between data
 - Disturbing flow conditions



Mixing affects

- Nucleation via collision breeding:

- Walls of vessel
- free surface of liquid
- internals, e.g. stirrer, baffle
- impurities, e.g. particulates, seeds
- crystal/crystal & crystal/vessel collision
- inhomogeneities due to mixing
- MSZW
- Crystal size distribution



2. Challenges in industrial crystallisation

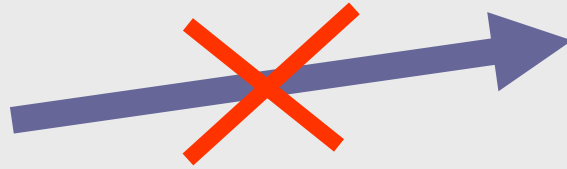
- Our understanding in scaling up STR is limited
- There is no agreed rule or parameter on scaling
- Velocity gradient or non-homogeneity increases with scale
- Mixing gradient leads to temperature and mass gradient



Scale-up of stirred tanks

Industrial scale

Laboratory



Kinetic control

Mass/heat transfer control

Mixing cannot linearly be scaled in STR

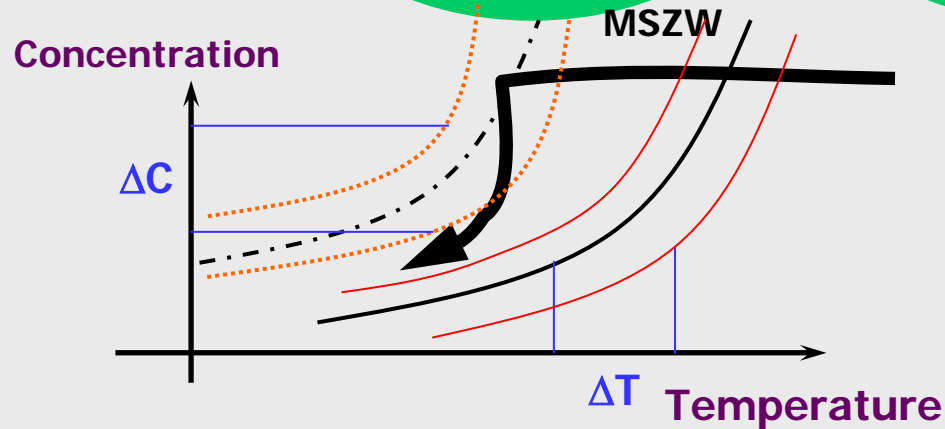
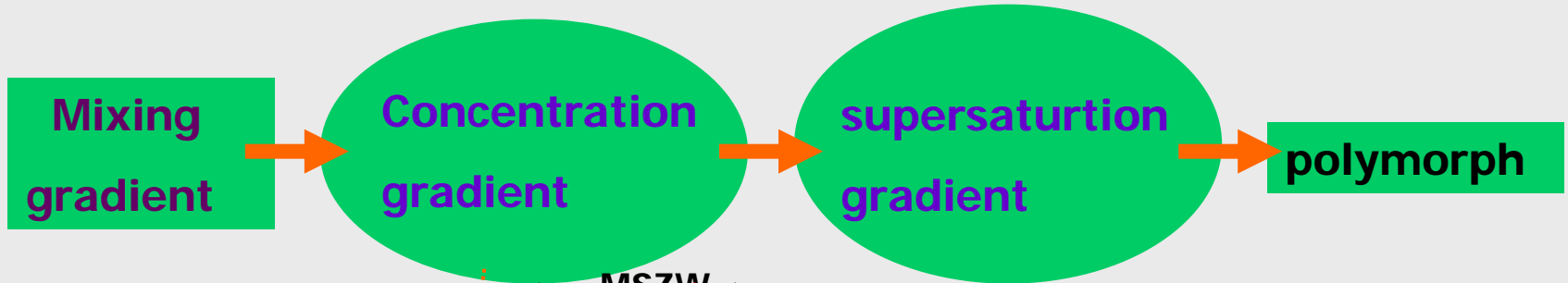
Heat Transfer on Scale-Up

	Volume (m ³)	Area (m ²)	Area / unit Volume (m ² /m ³)
Typical 90 litre STR	0.09	0.9	10
Typical 6500 litre STR	6.82	15.8	2.3

Specific heat transfer area decreases with scale



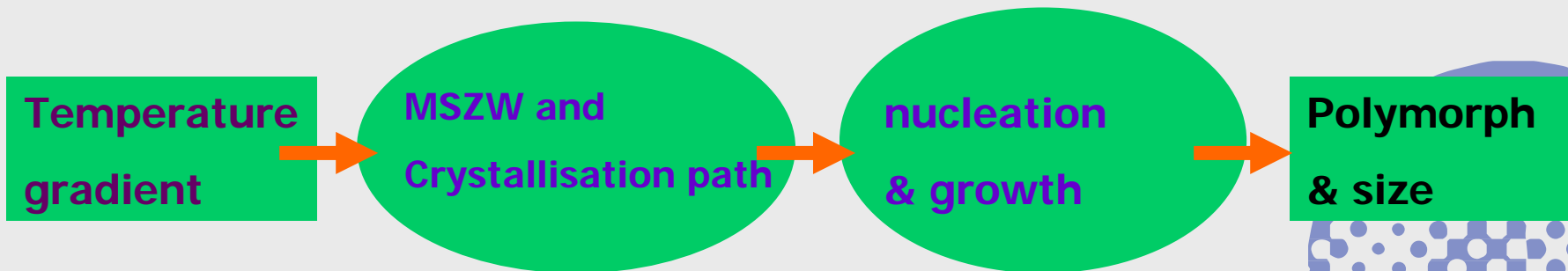
Industrial batch crystallisation



Inconsistent morphology

Wide size distribution

Difficult to filter



Practical issues

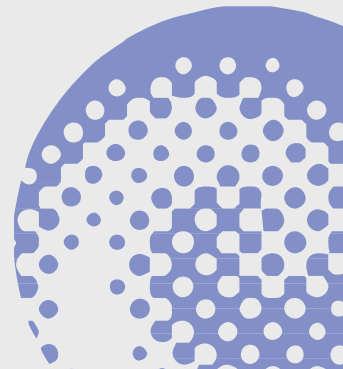
- **Linear cooling is difficult to achieve in large STR**
- **Implementation of lab multi-measurement techniques is practically impossible in industrial scale**



3. Continuous crystallisation

From the viewpoint of fluid mechanics

- i) consistent product quality can only be achieved in plug flows;
- ii) it is very rare to obtain plug flow conditions in batch STR!
- iii) Plug flow conditions can only be attained in continuous operation.

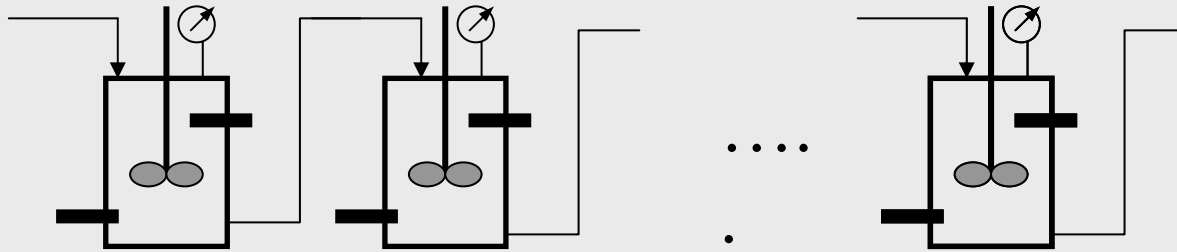


The conventional ways to achieve plug flow include

- a) Using a series of CSTRs
- b) Employing a tubular reactor

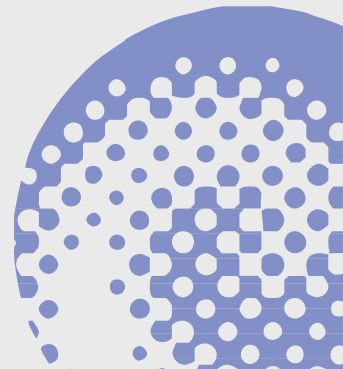


a) Using a series of CSTRs



Plug flow is achieved when the number of CSTRs goes to infinite

**Conclusions: a) significant increase in inventory, running and capital costs
b) far from plug flow**

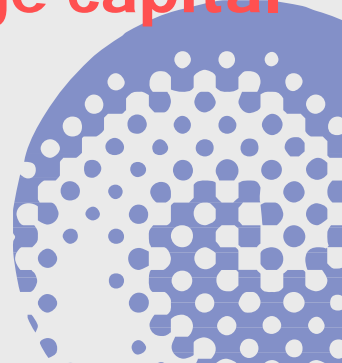


b) Employ a tubular reactor

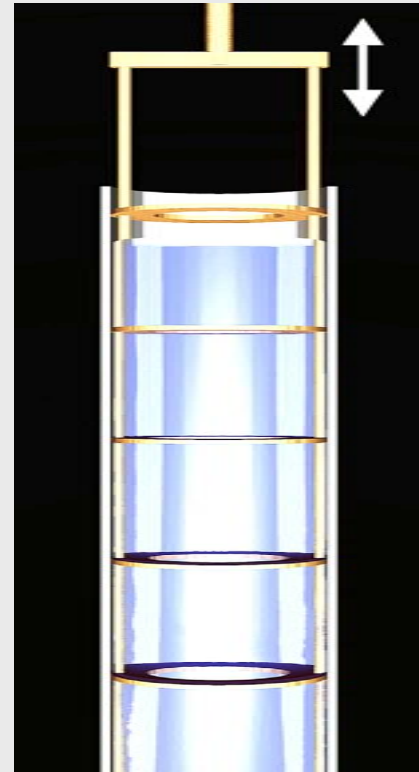
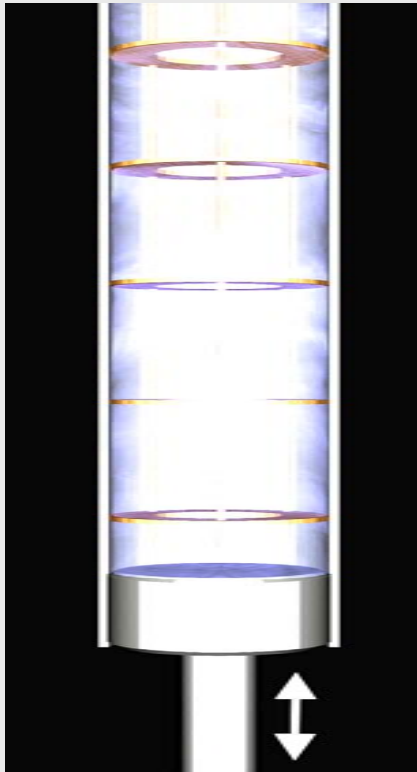


Operating a tubular reactor at turbulent flow regime in order to obtain near to plug flow

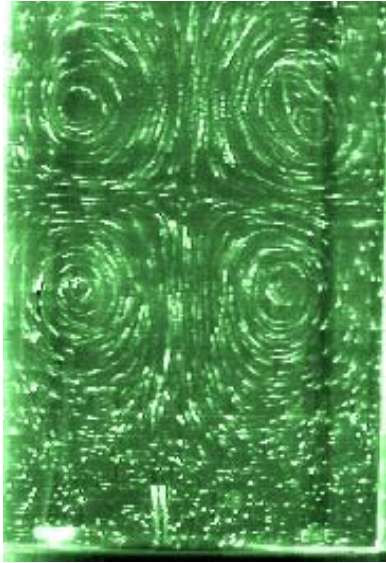
- Conclusion:**
- a) significant high flow rates, leading to very long reactor and large capital costs
 - b) very short residence time



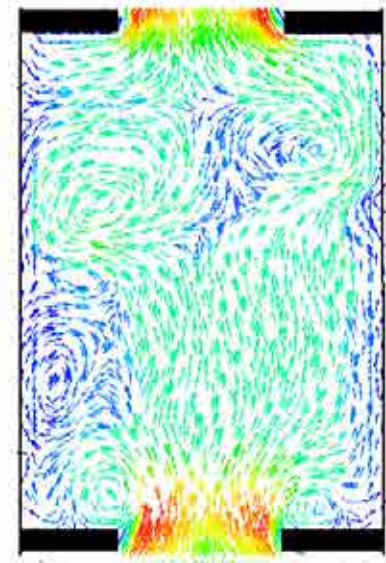
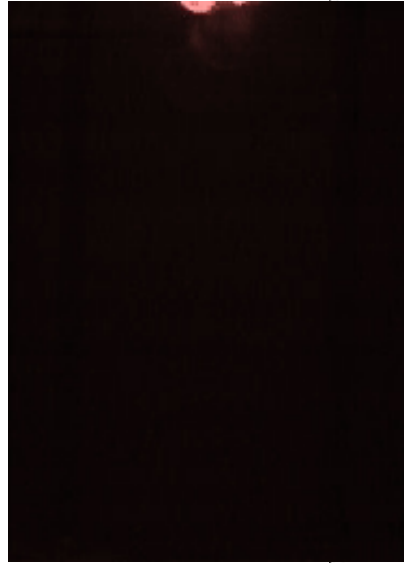
NiTech's oscillatory baffled reactor (OBR)



Demonstration of radial mixing with good dispersion



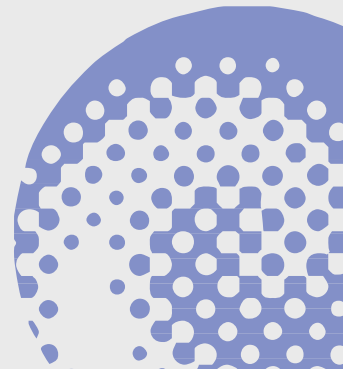
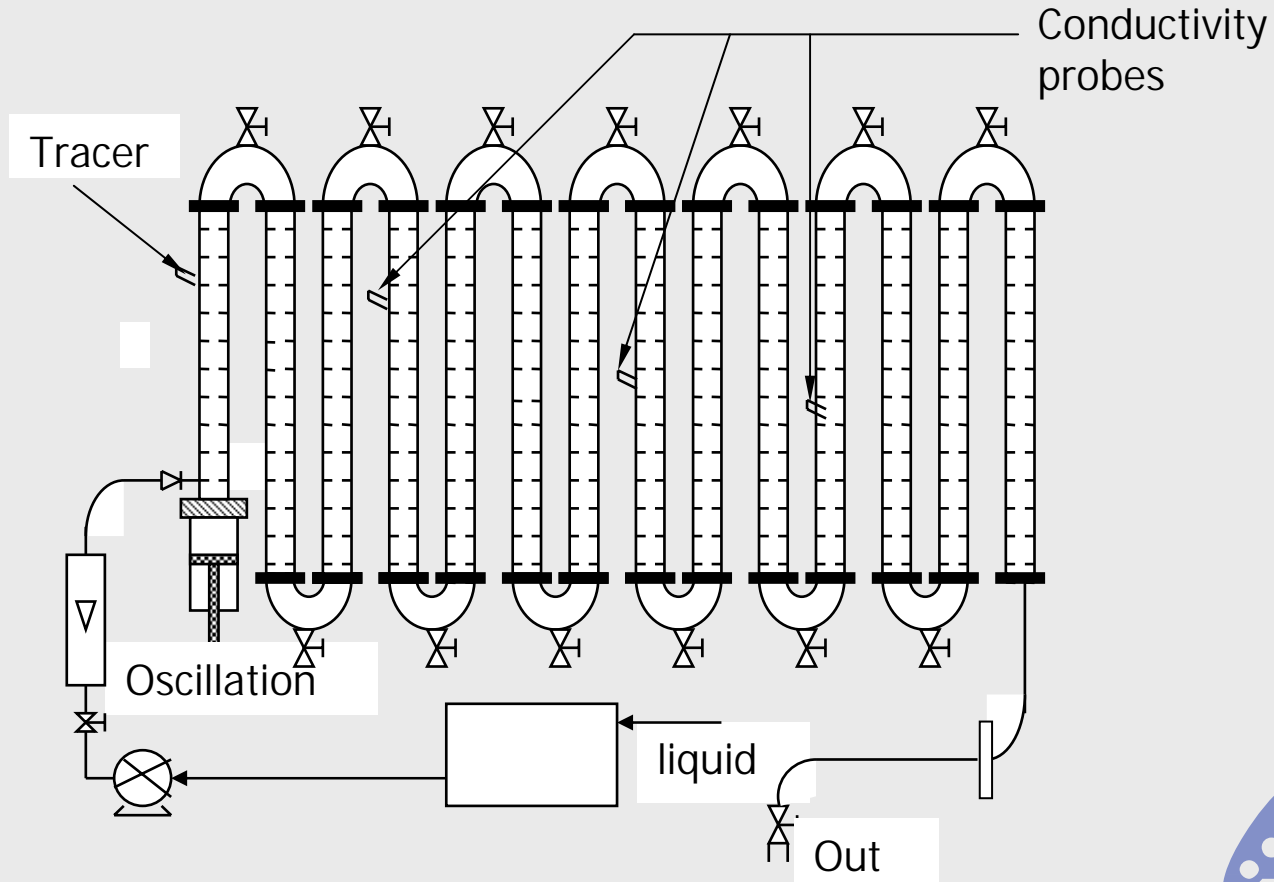
Real system



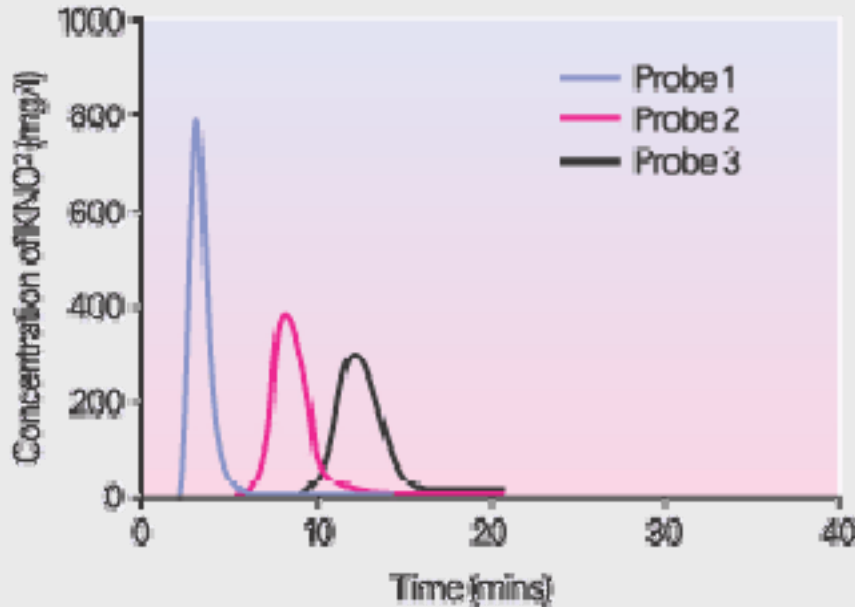
3-D CFD simulation

$$\text{Re}_0 = 1250 \quad (x_0 = 4 \text{ mm}, f = 1 \text{ Hz})$$

NiTech's Continuous OBR (COBR™)



Residence time distribution (RTD) in a COBR



Probe 1

3.7 meters away from injection

Probe 2

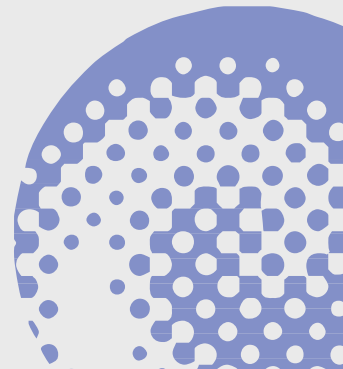
7.9 meters away from injection

Probe 3

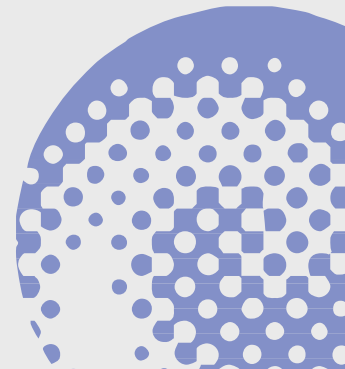
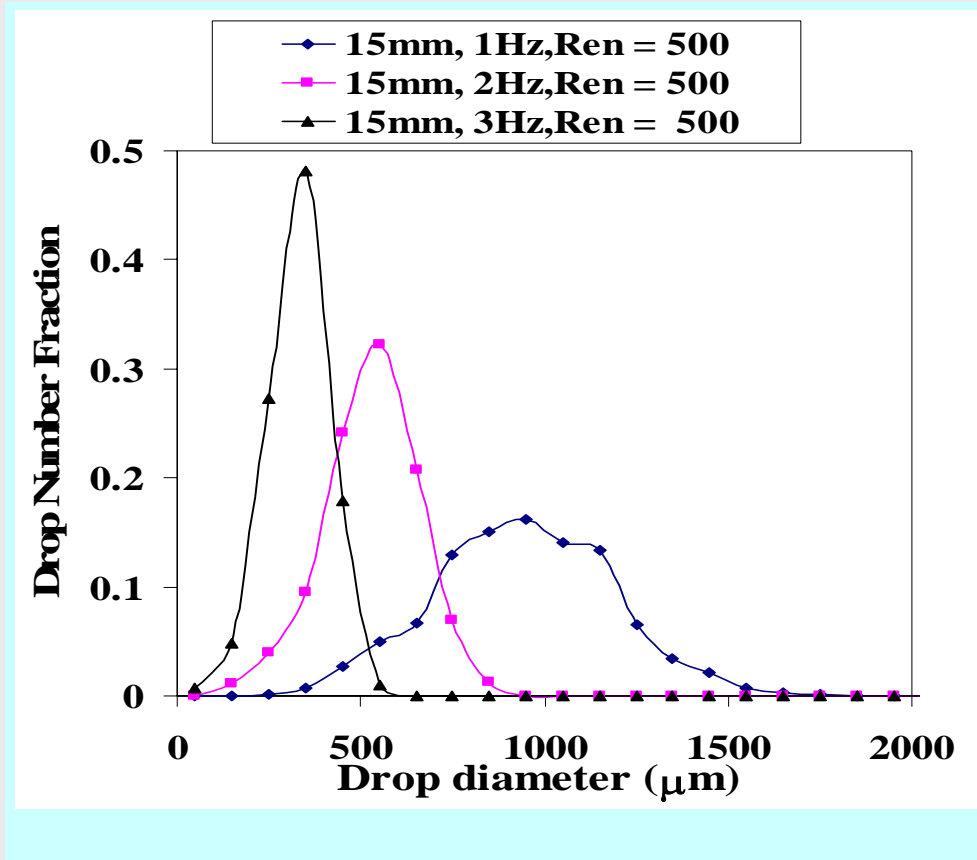
10.1 meters away from injection

- Mixing controlled by the combination of oscillation and baffles
- Each baffled cell is a CTSR
- Plug flow at laminar flows
- Handles particulates
- Long residence times

$$D = 0.00007 \sim 0.0003 \text{ m}^2/\text{s}$$

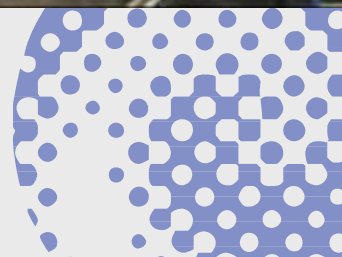
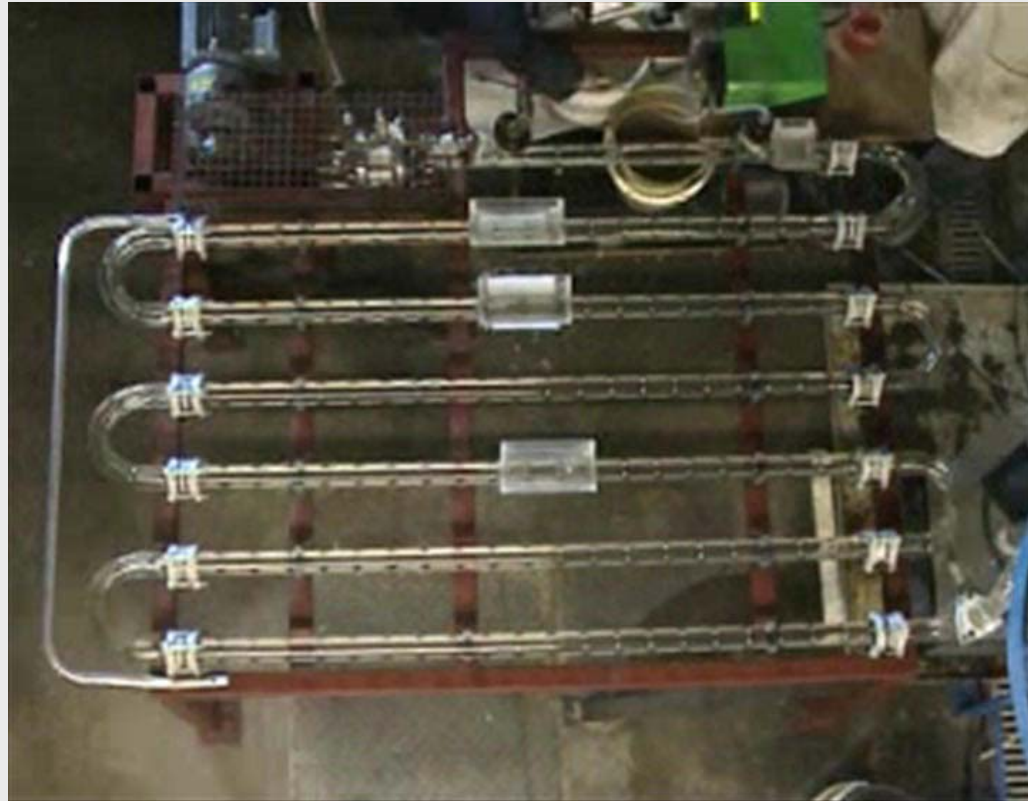


Drop/Particle/crystal size distribution obtained in a COBR



Key differences from other tubular devices on the market

- Mixing is not controlled by net flow
- Plug flow achieved at laminar flows
- Excellent heat & mass transfers
- No concentration gradients
- Good with solids



Continuous oscillatory baffled crystalliser (COBCTM)



Heat Transfer on Scale-Up

	Volume (m ³)	Area (m ²)	Area / unit Volume (m ² /m ³)
Typical 90 litre STR	0.09	0.9	10
Typical 6500 litre STR	6.82	15.8	2.3
Typical 72m long 100mm diameter COBC™	0.56	22.6	40

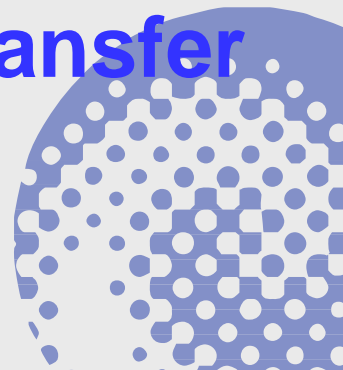
COBC™ has larger specific surface area for HT



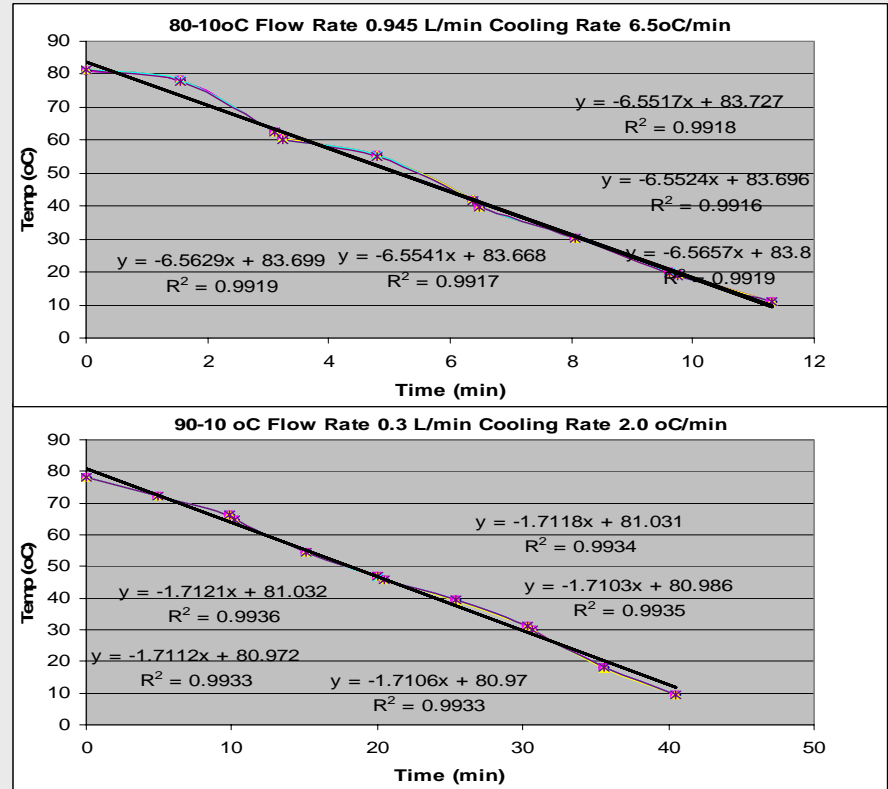
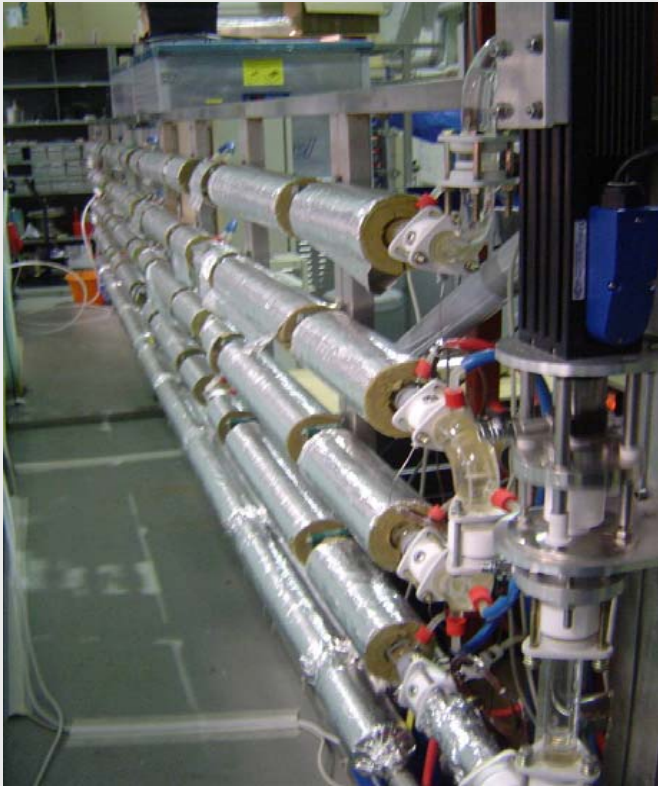
Tube side heat transfer coefficient (w/m^2K)

	1cp	10cp	100cp
600 kg/m^3	61,654 - 282,717	817 - 3,694	7 - 28
1000 kg/m^3	133,315 - 611,447	2,327 - 10,575	21 - 82
1500 kg/m^3	232,744 - 1,067,534	5,209 - 23,730	47 - 196

Plug flow delivers excellent heat transfer



Control over cooling profile



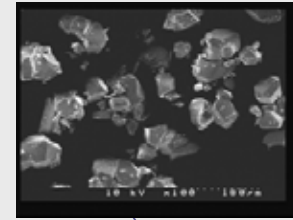
Any cooling profile, e.g. linear, parabolic, non-continuous, step-wise and etc, can be obtained along COBC™

Multi-monitoring techniques in lab scale can be implemented along COBC™

4. Case studies

a) Morphology of a pharma crystal

$\alpha + \beta$ crystals

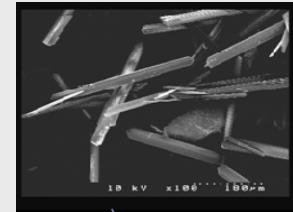
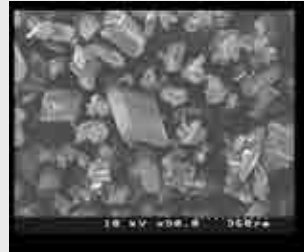


Seed β crystals



COBC™ enables greater control over crystallisation path

α crystals

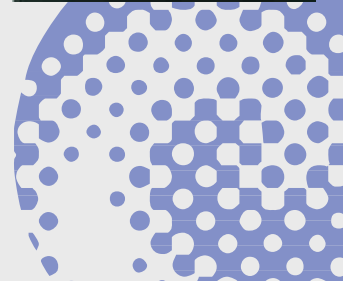
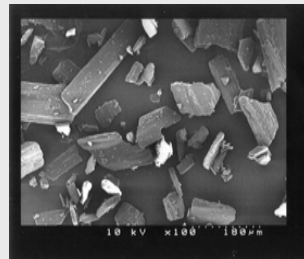


Seed α crystals



Able to be more selective on crystal morphology

β crystals



b) Pharma API - size on filtration

- Change on crystal size
- Impact on filtration

The residence time in the COBC translates to 12 minutes, compared to a batch cycle time of 8 hours, demonstrating a significant potential improvement in throughput relative to a batch manufacturing facility.

Shaken, Not Stirred: Taking Crystallisation from Pots to Pipes

Demonstrating the use of a Continuous Oscillatory Baffled Reactor for crystallisation of an API

Oliver Lortie*, Ian Loh*, Vikal Kaur†, PVE Ghosh†, Gary Webb†, Lina Zhao†

*Advanced R&D Chemist, †Advanced Engineering, ‡Batch Operations Ltd



Introduction

Pharmaceutical products have been traditionally isolated by batch operations followed by filtration and drying. This approach improves available in terms of the degree of isolation and consistent temperatures prior to collection of crystals.

Crystallisation, in batch mode however, is intrinsically difficult to make-up crystallisation or manufacturing systems.

Traditionally it is possible to achieve uniformity through the use of a plug flow crystalliser, or low cost oscillatory baffled reactor, popular for a soluble crystallisation.

Historically, around driven and further investigation of continuous crystallisation technology.

The delivery of well-defined crystal quality, such as morphology, size and size distribution, that cannot be easily achieved in large batch operations.

Investigation of additional manufacturing approaches (e.g. Continuous API plant scale) for crystallisation in continuous and semi-continuous modes e.g. Shortening residence of crystallisation being subjected to uniform mixing and energy consumption and the provision of cooling or heating paths throughout the run.

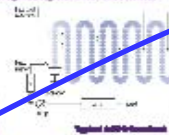
COBC Technology

A novel development that offers the promise of continuous at low cost, in the continuous oscillatory baffled reactor (COBC).

The system consists of a string of reactor vessels along the length of a tube to promote mixing through the generation and production of vortices in the fluid medium in the tube. An inlet is primarily fed in a continuous manner from a reservoir of a crystallising solution. The tube, high mixing can be achieved with low and linear, enabling processes requiring good mixing in systems of the low flow-rates typically required for the dosage manufactured by the pharmaceutical industry.



The practical implementation of this technology is to use a piston to move back and forth, hence changing the volume of the tubular reactor and causing the fluid contents to flow backwards momentarily to produce a progressing wave-like movement.



The key differences between the COBC and other tubular devices are:

- Mixing is governed by the excitation and not the net flow
- Superior heat transfer coefficients are obtained under plug flow

These factors enable the delivery of cooling rates of up to 3°C min⁻¹ – far in excess of the 0.3°C min⁻¹ attainable in a batch stirred tank reactor.

- The use of COBC technology for crystallisation offers several potential benefits:
- Increased: Higher throughputs from given volume of plant → lower capital investment
- Crystal Engineering: Enables better control of morphology & particle size
- Access to conditions not possible in a batch crystalliser such as high cooling rates (>0.3°C min⁻¹)

Materials & Methods

A soluble API was prepared to demonstrate the potential benefits of this technology using the scheme below to identify potential candidates.

• Ready Supply of raw materials. (~12kg)

• Product is already manufactured at multi-tonne scale and so would be a commercially viable candidate for continuous processing.

• Capital cost comparison possible for existing and new technology.

An experimental programme was drawn up to evaluate the potential benefits of applying COBC on a real pharmaceutical product, consisting of batch screening experiments followed by continuous flow trials.

Batch Results

Batch runs were carried out using a 300mm diameter oscillatory baffled reactor (OBR) to determine the quality of material required. This equipment replicates the conditions used in commercial batch plants in a batch cycle. The results of the batch runs were used to investigate key parameters.

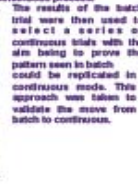
Maximum Agglomerate	Maximum Crystallite	Batch Cooling	Mixing (Reactor)
API Concentration	API Amount		
Stirring Rate	Mixing for crystallisation		

The material resulting from the trial was analysed to ensure that it complied with the API specification, with additional optical and scanning electron microscopy (SEM) and Focused Beam Reflectance Spectroscopy (FB-RM, Leica). Some parameters were also analysed by Sievers Mastersizer to provide particle size distribution data.

The batch results indicated that significantly higher cooling rates were possible, whilst still generating the rod morphology that has traditionally been produced in batch production. Additionally a plate morphology was produced by reduction in thickness of the rods. Agglomeration of rods and plates were formed due to the higher nucleation rates occurring as a consequence of higher cooling rates. These agglomerates appear to be loosely held together, and so could be expected to break up when upon stirring, whilst their greater size could be expected to have filtration performance proving the agglomerates did not break during the isolation process. An unexpected result was the production of large rods at high cooling rates (during the jacket from 50°C to 20 °C in approx. 5 seconds) which was used. This discovery lends itself to the use of recycling of fines in a continuous process.



API particles (rod morphology)



Agglomerates (plate morphology)

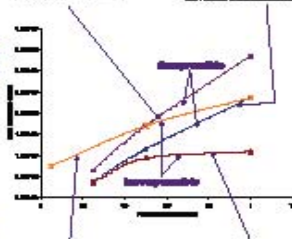
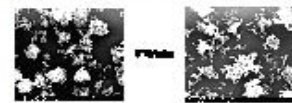
The results of the batch trial were then used to select a series of continuous trials with the aim being to prove the patterns seen in batch could be replicated in continuous mode. This approach was taken to validate the move from batch to continuous.

Continuous Results

The continuous trial was conducted with the aim of providing crystal of a particular size range to demonstrate the benefits of crystal engineering.

Run	Media	Media	Crystallite	Crystallite	Media
Small	Fast	High	High	High	None
Large	Slow	0.25°C min ⁻¹	Low	Std	None
Large Agglomerates	Fast	Low	Std	Std	None
Std size	7°C min ⁻¹	Std	High	High	None
Small	Fast	High	High	High	Media ID 10°C

Each run was analysed as previously with the addition of a filtration study at varying pressures to characterise the performance and permit an evaluation of potential plant performance.



The agglomerates showed evidence of compressible cake behaviour, whilst the rod shaped crystals showed incompressible behaviour. Agglomerates and rods exhibited specific cake resistances that are at the lower end of the range typically seen in pharmaceutical manufacture. The residence time in the COBC translates to 12 minutes, compared to a batch cycle time of 8 hours, demonstrating a significant potential improvement in throughput relative to a batch manufacturing facility.

Further trials have been carried out exploring a number of the agglomerates formed as a result of high cooling rates which exhibited agglomerate structures to varying degrees.

Conclusions

APIs have been developed using a novel technology for the crystallisation of active pharmaceutical ingredients and low volume quantities for crystal engineering. The potential increase in throughput was not lost to capital cost saving.

The COBC responded to changes in conditions in a predictable manner.

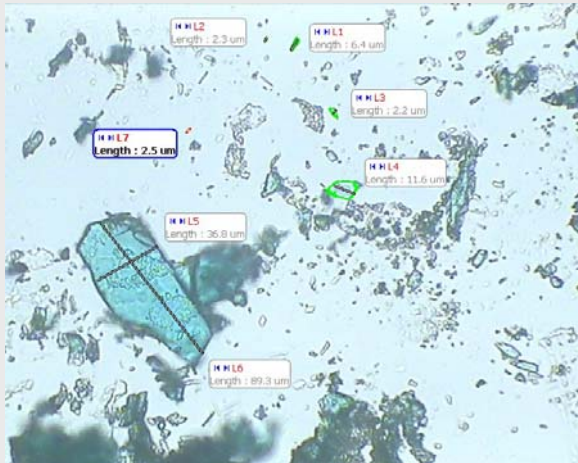
Authors: Oliver Lortie, Ian Loh, Vikal Kaur, PVE Ghosh, Gary Webb, Lina Zhao
 Contact: Gary Webb, Gary.Webb@az.com
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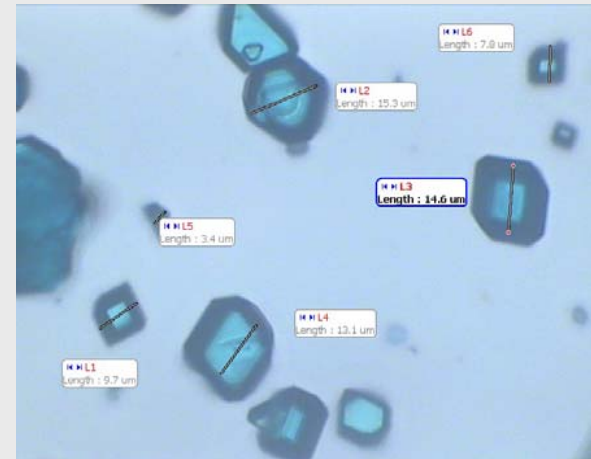
c) Filtration index for a pharma product

COBC™ affects outcomes achieved

- Product characteristics/performance
- Consistent filtration index of 25



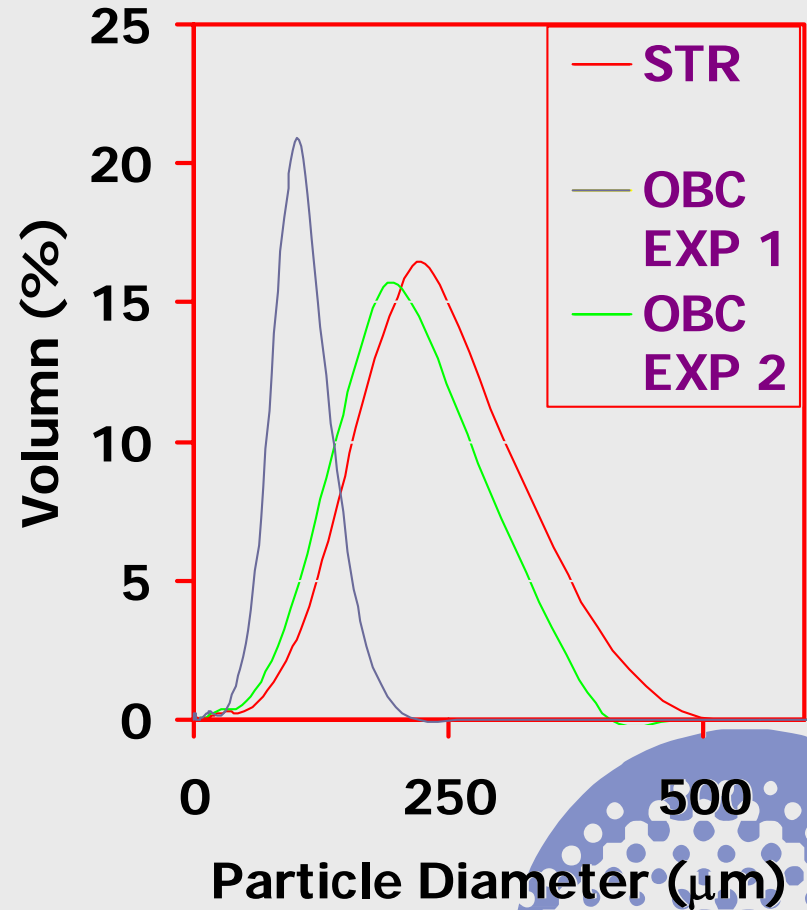
STR



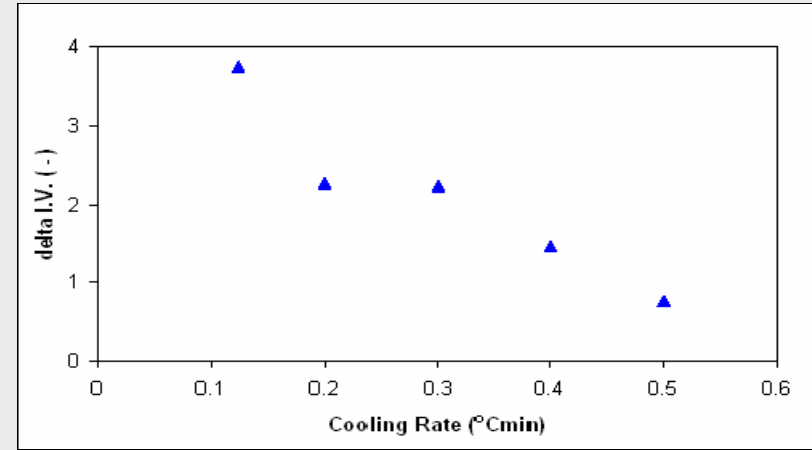
COBC™

d) Crystal size distribution of a fine chemical product

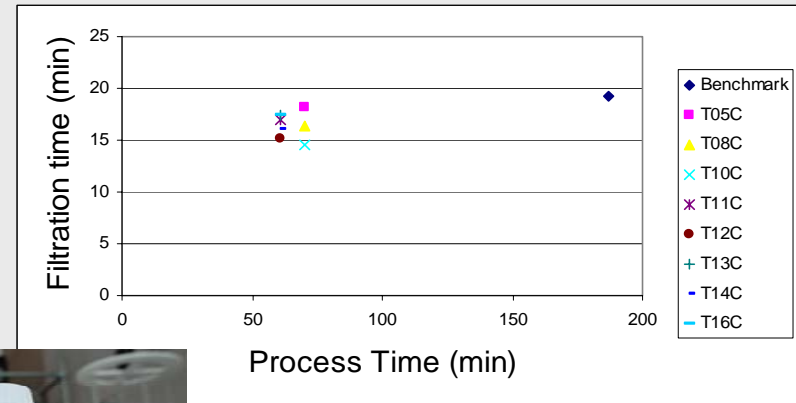
- More uniform size can be achieved
- Greater control on outcome



e) Fractionation of edible oils

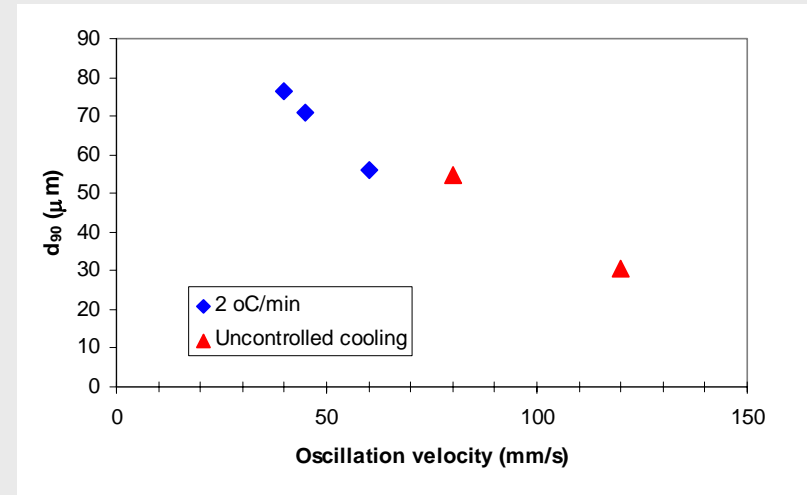


- Two stage cooling (17 and 0.3 °C/min)
- Consistent IV achieved
 - Significant reduction of crystallisation time
 - Improved filtration time

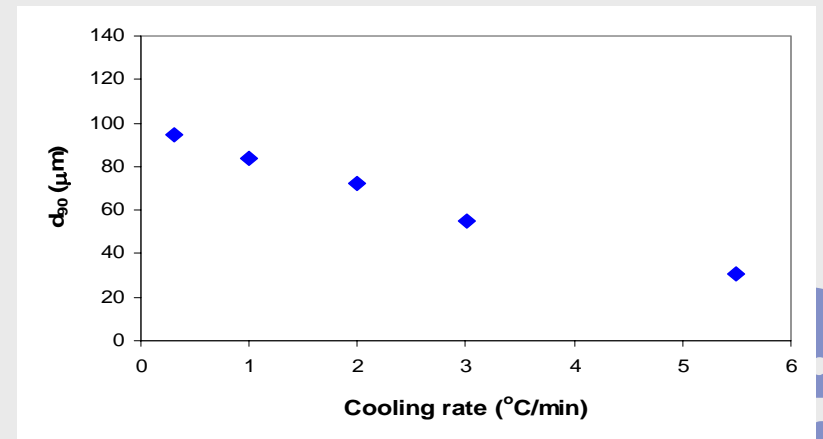


f) Combined reaction & crystallisation

- **Crash cooling**
- **Variable mean sizes from crystallisation after a reaction**
- **Crystals stuck to the walls of the vessel and surfaces of the impeller**



- ◆ **Consistent mean crystal size**
- ◆ **Linear cooling profiles in COBC™ eliminated the events of crystal-sticking**
- ◆ **Minimise the down-time of washing/cleaning**



4. Forward remarks

- Plug flow tubular crystallisation technology, such as COBC™, can be used to bridge the gap between lab and industrial scale crystallisation operations
- Multi-monitoring techniques from lab scale crystallisation can directly be fitted along the COBC™
- COBC™ can be incorporated into existing plants
- Continuous filtration could also be implemented in COBC™



Acknowledgement

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Ruth Lane

