Continuous crystallisation using oscillatory baffled plug flow crystalliser

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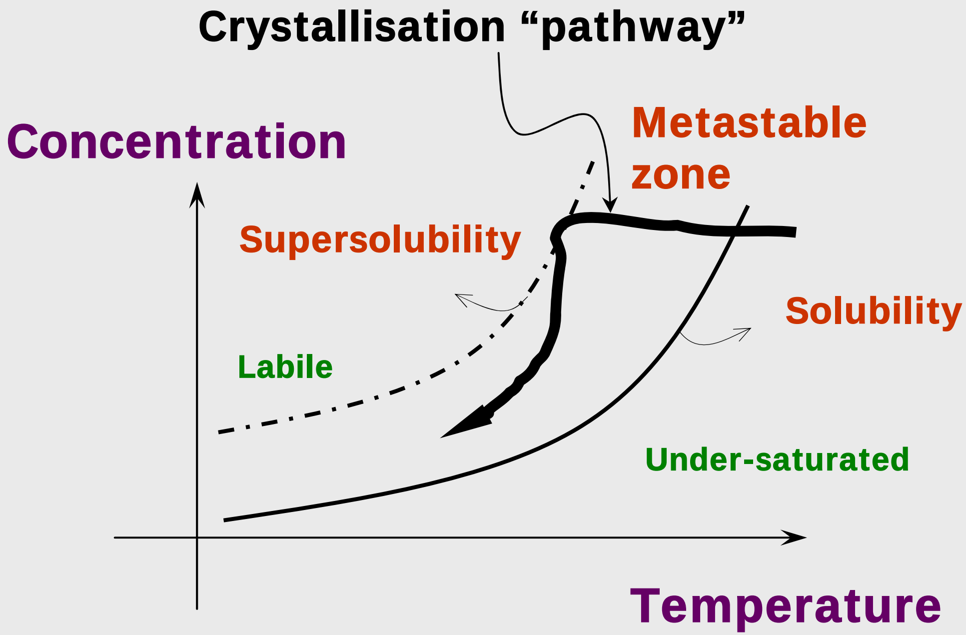
Structure

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

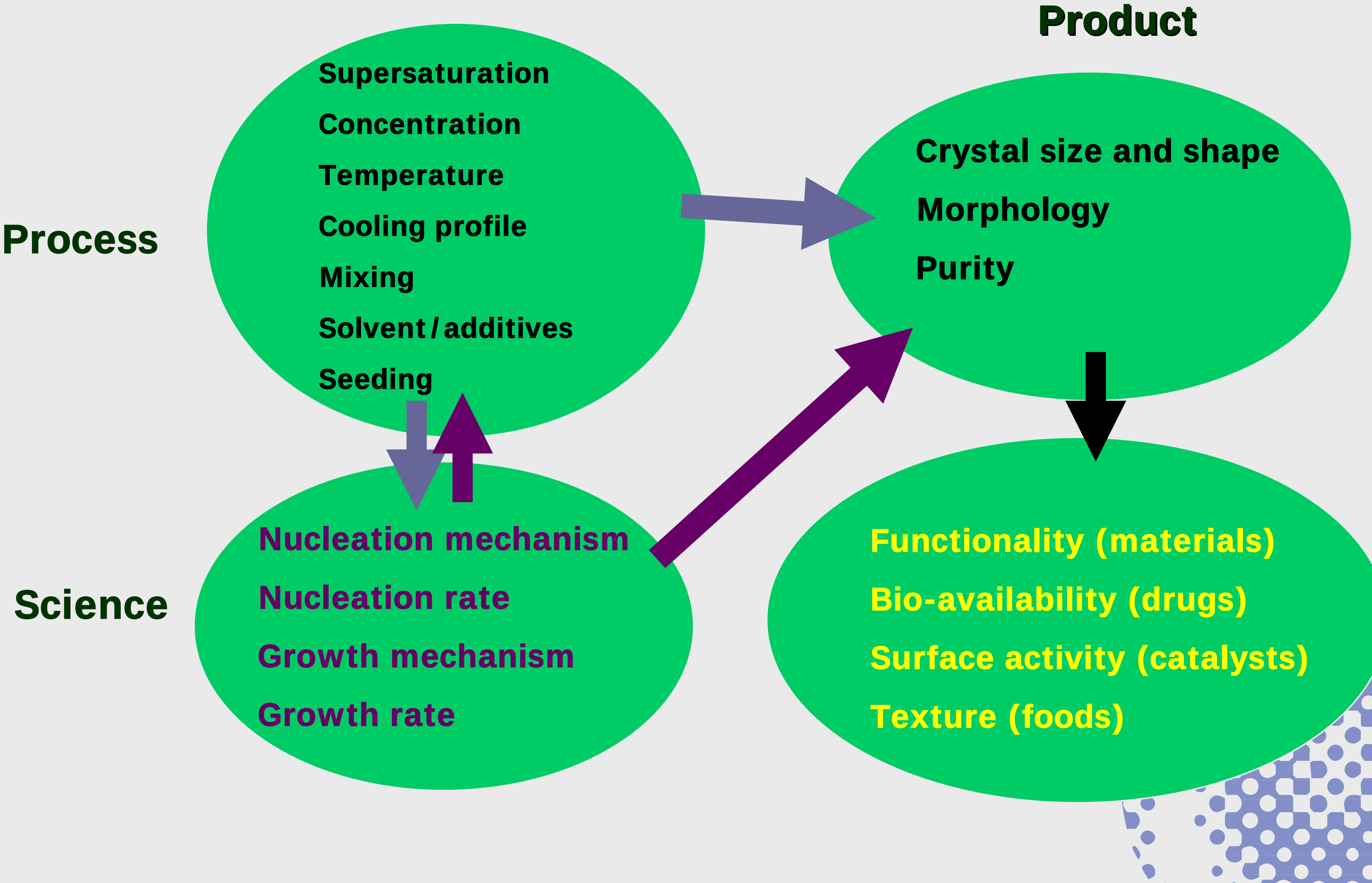
1. Crystallisation Science

- 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
Process
Supersaturation
Concentration
Temperature
Cooling profile
Mixing
Solvent / additives
Seeding
Crystal size and shape
Morphology
Purity
Science
Nucleation mechanism
Nucleation rate
Growth mechanism
Growth rate
Functionality (materials)
Bio-availability (drugs)
Surface activity (catalysts)
Texture (foods)

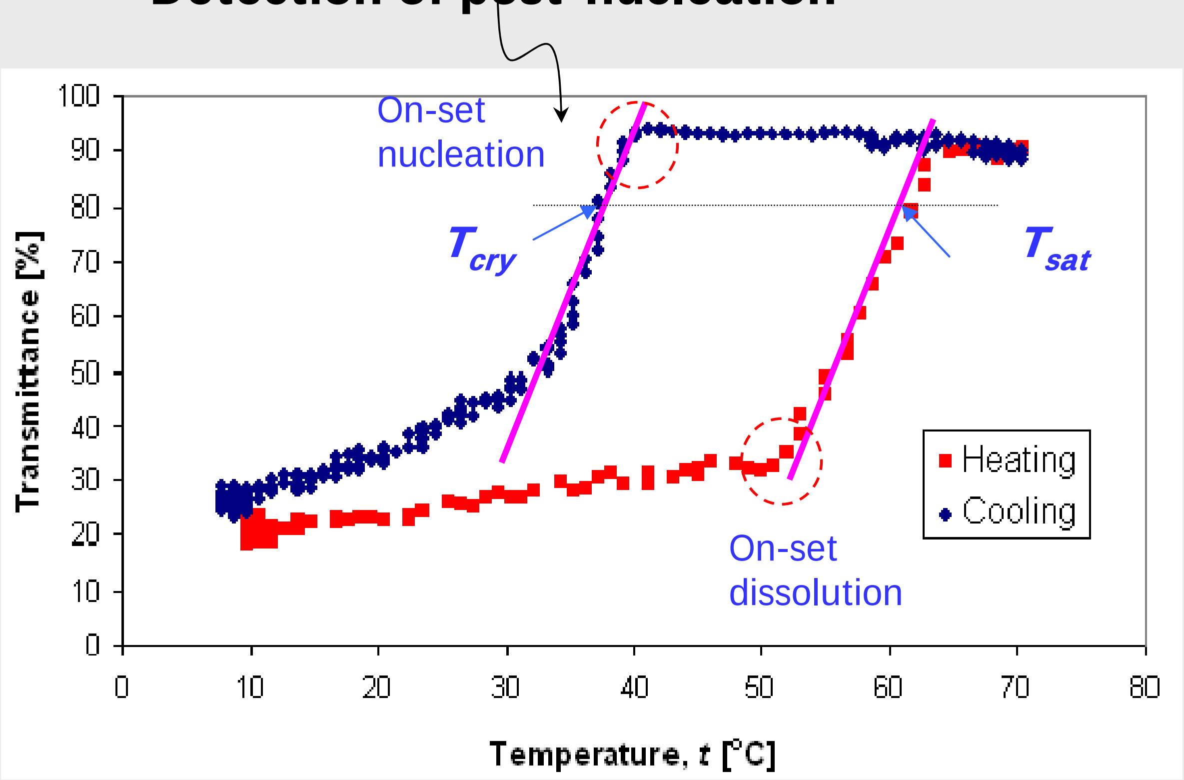
Nucleation

- **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**

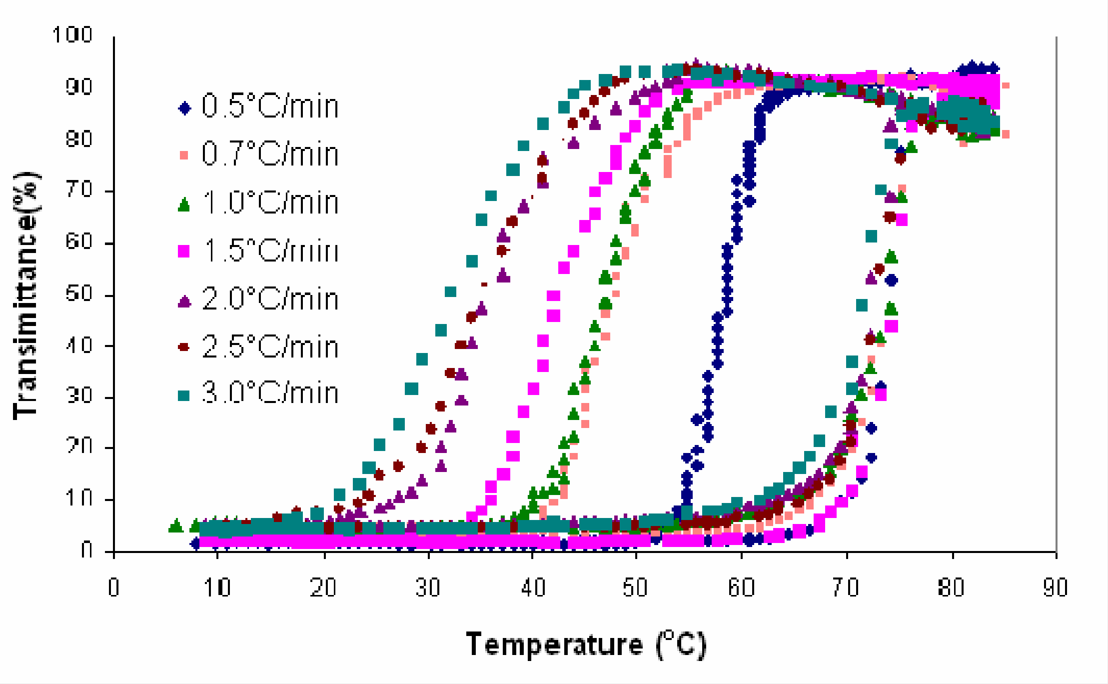
Determination of metastable zone width (MSZW) using a turbidity probe

Detection of post-nucleation



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

Metastable zone width (MSZW)



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

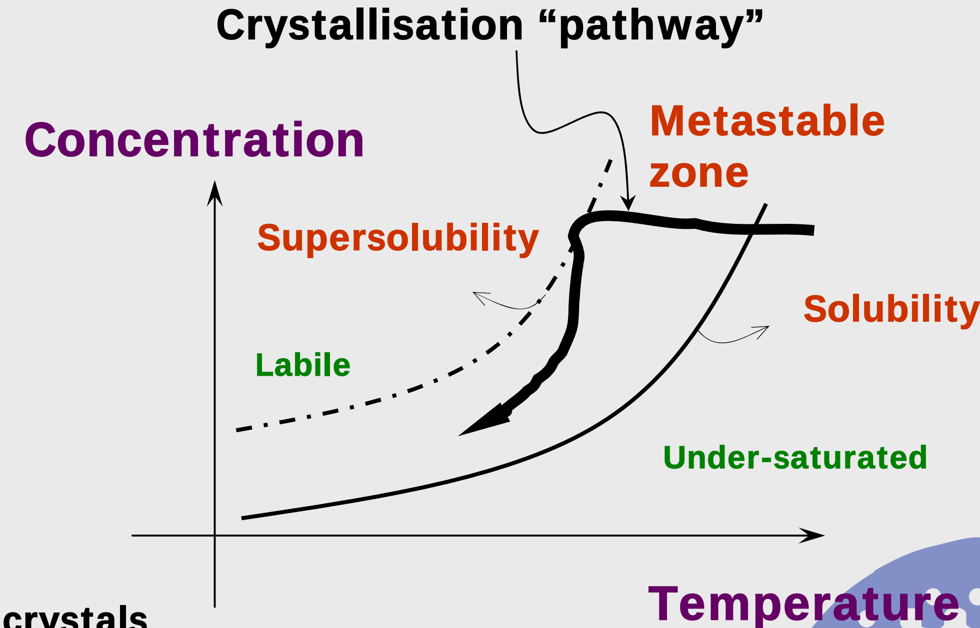
MSZW depends on reactor, scale and operating conditions

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

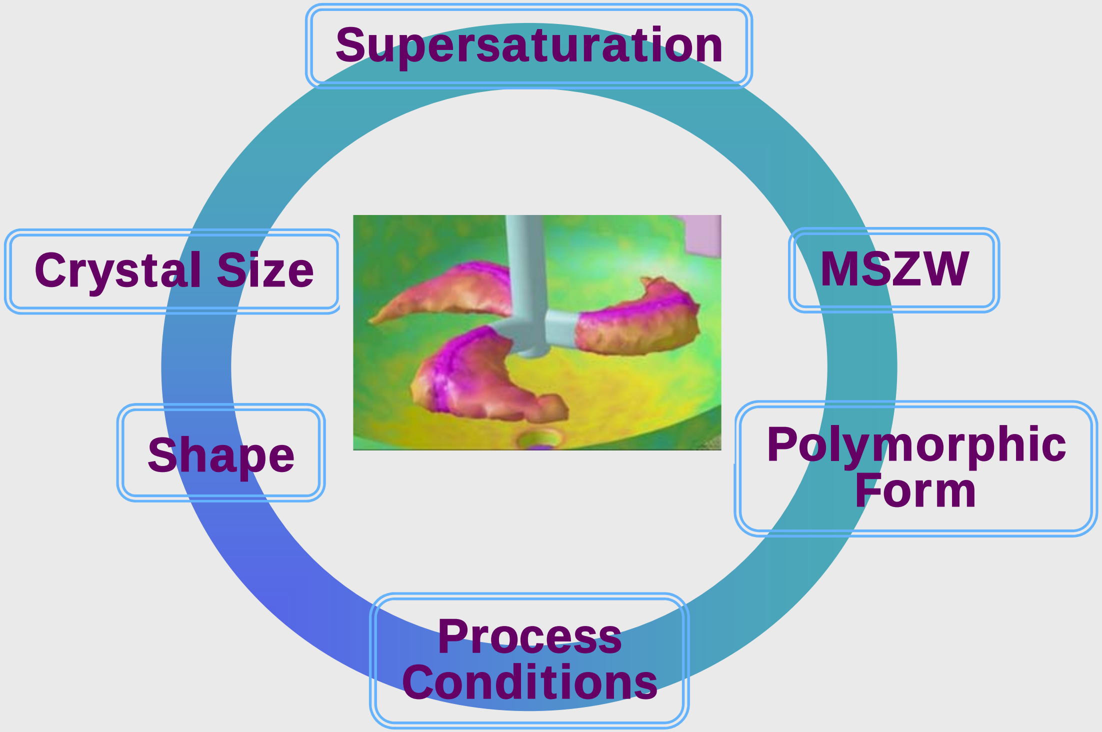
Crystal growth

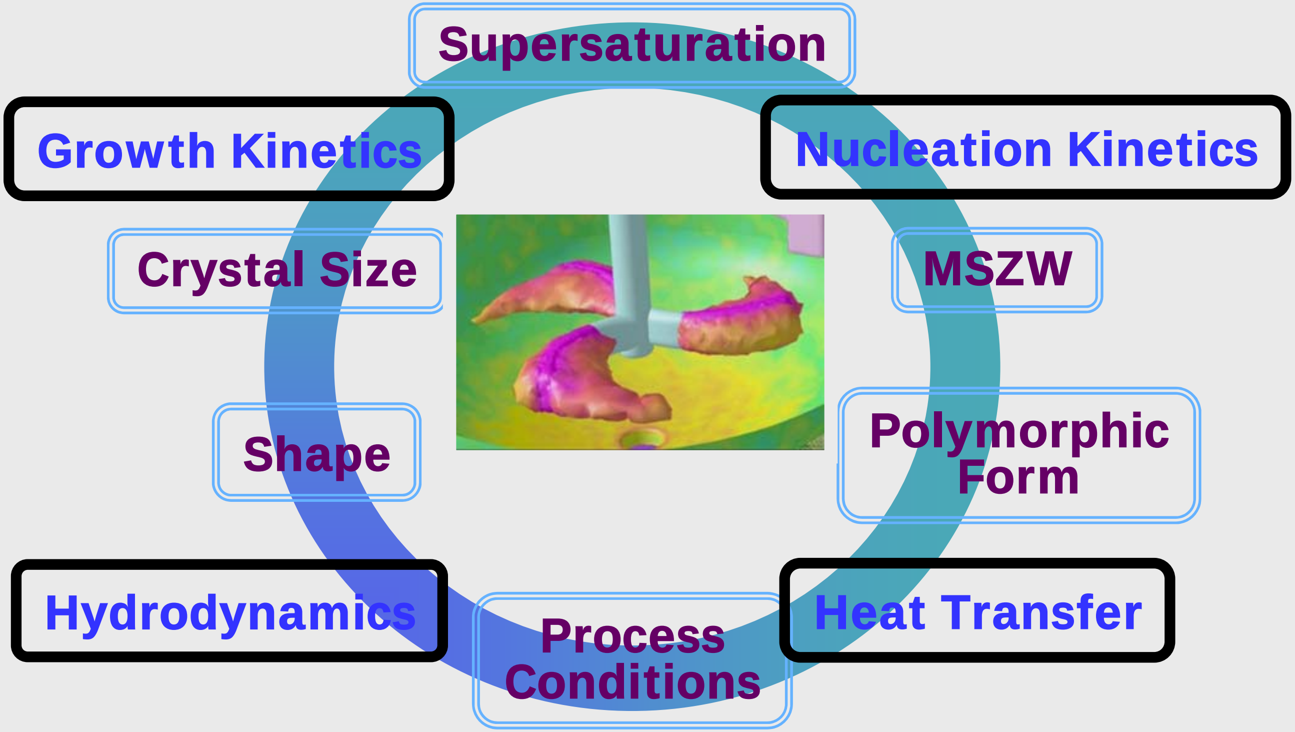
- **Mass transfer phenomenon**
- **Crystal growth phase must take place within the MSZW**

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

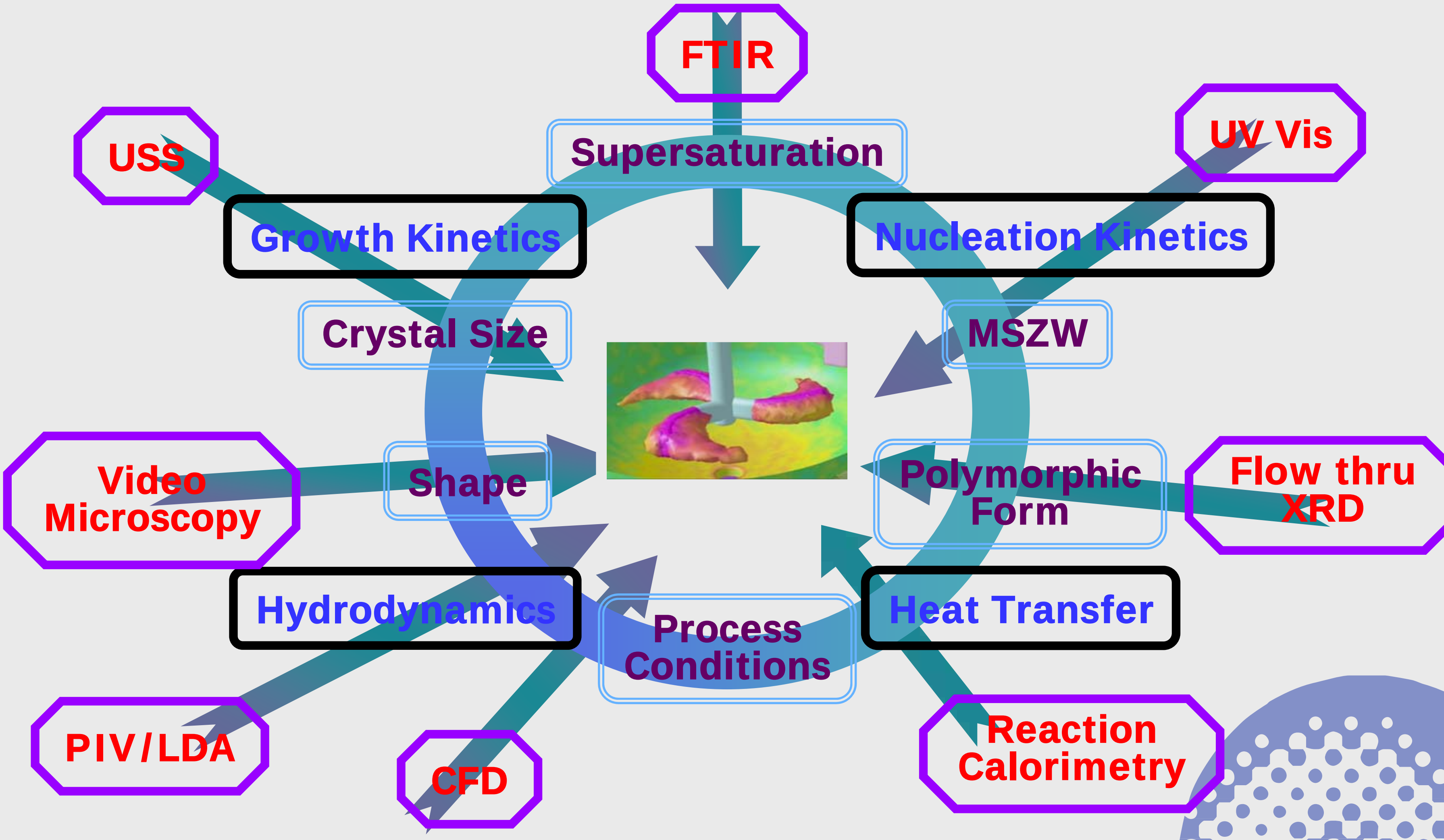


- **Nucleation dominates → small crystals**
- **Growth dominates → large crystals**


Supersaturation
Crystal Size
MSZW
Shape
Polymorphic Form
Process Conditions


Supersaturation
Growth Kinetics
Nucleation Kinetics
Crystal Size
MSZW
Shape
Polymorphic Form
Hydrodynamics
Process Conditions
Heat Transfer

Chemicals Behaving Badly (CBB)



Courtesy of Dr White, Heriot-Watt University

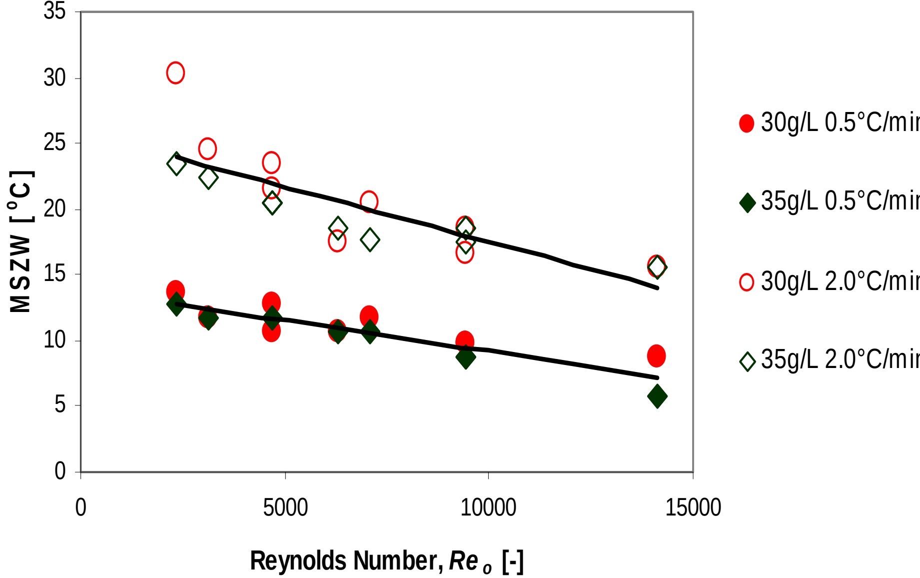
Lab scale batch crystallisation

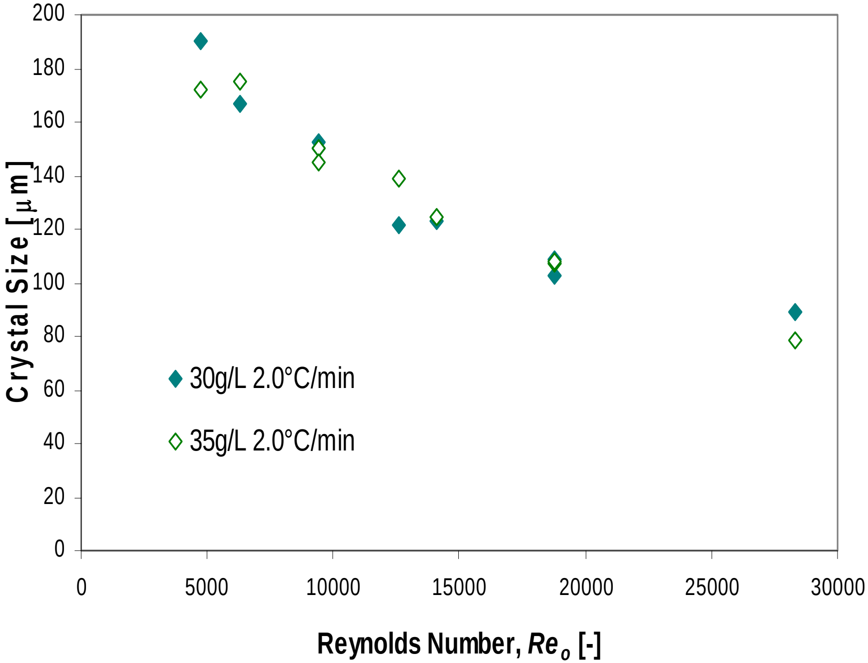
- Simultaneous multi-technique measurements during a crystallisation process
- Have promoted better understanding of crystallisation in lab scale
- Promoted better operation of crystallisation in small scale
- Linear cooling identified as one of the key operational parameters

    - 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

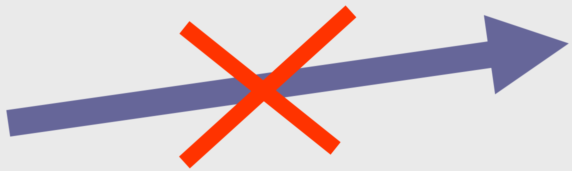
- Our understanding in scaling up STR is limited
- There is no agreed rule or parameter on scaling
- Velocity gradient or non-homogeneity increases with scale
- Mixing gradient leads to temperature and mass gradient

Scale-up of stirred tanks

Industrial scale

Laboratory

Kinetic control



Mass/heat transfer control

Mixing cannot linearly be scaled in STR

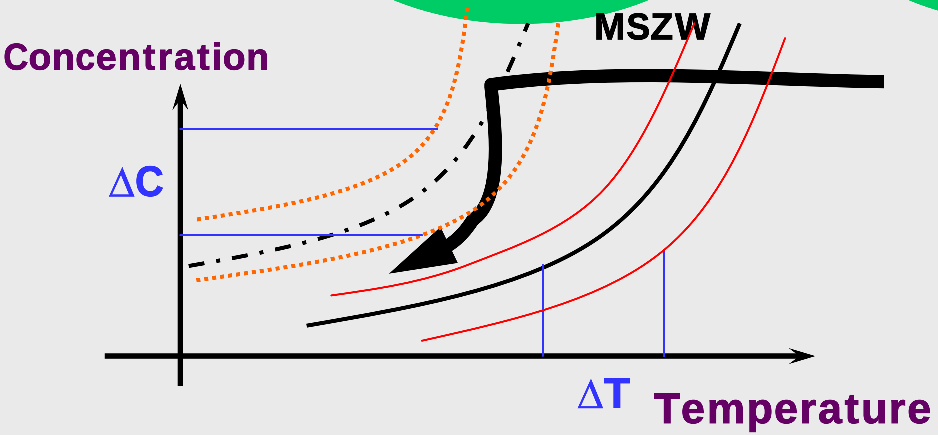
Heat Transfer on Scale-Up

	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

Mixing gradient → Concentration gradient → supersaturtion gradient → polymorph



Inconsistent morphology

Wide size distribution

Difficult to filter

Temperature gradient → MSZW and Crystallisation path → nucleation & growth → Polymorph & size

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!

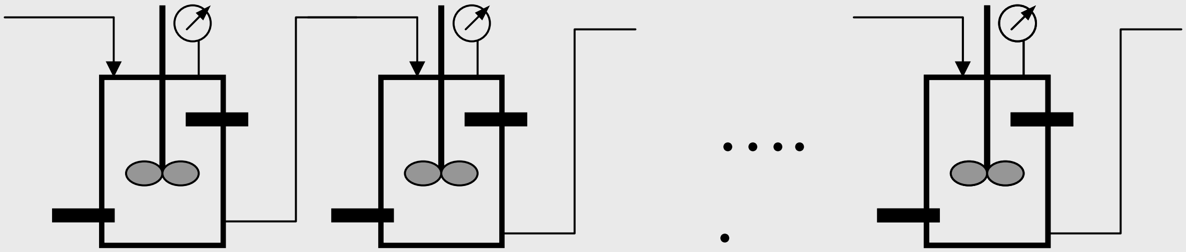
iii) Plug flow conditions can only be attained in continuous operation.

The conventional ways to achieve plug flow include

a) Using a series of CSTRs

b) Employing a tubular reactor

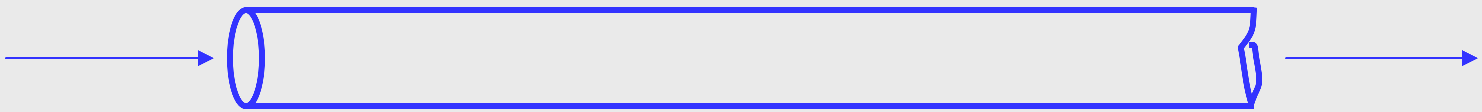
a) Using a series of CSTRs



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

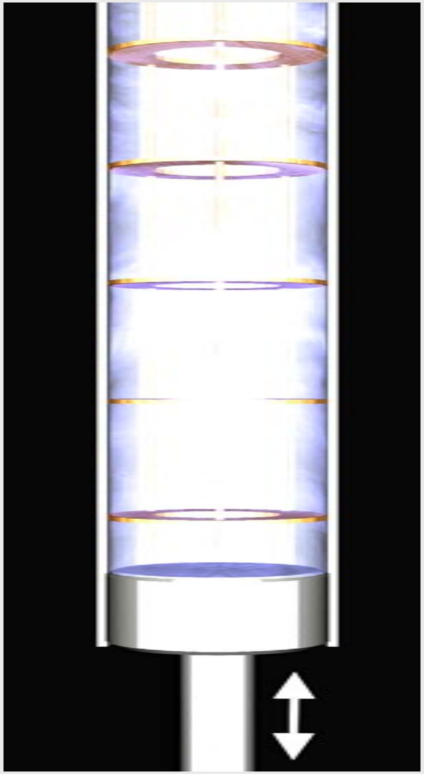


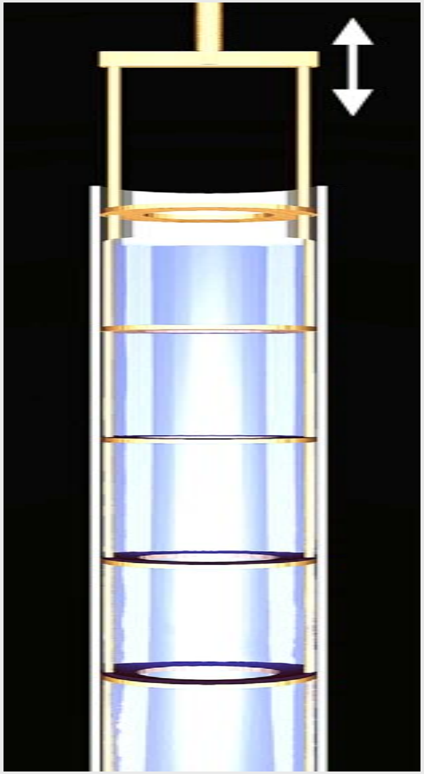
Operating a tubular reactor at turbulent flow regime in order to obtain near to plug flow

Conclusion: a) significant high flow rates, leading to very long reactor and large capital costs

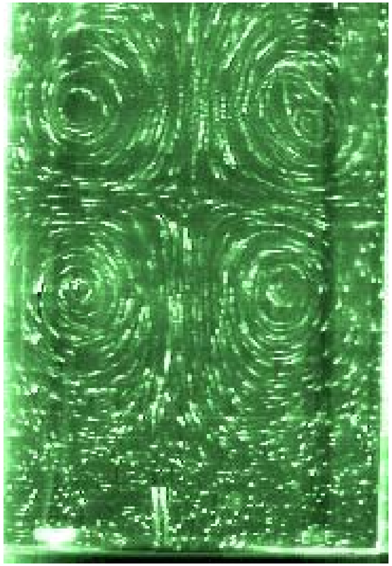
b) very short residence time

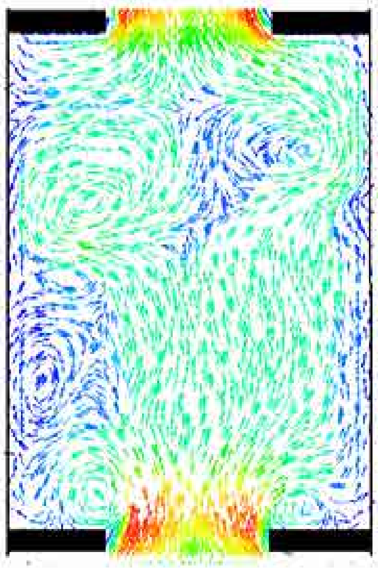
NiTech's oscillatory baffled reactor (OBR)





Demonstration of radial mixing with good dispersion



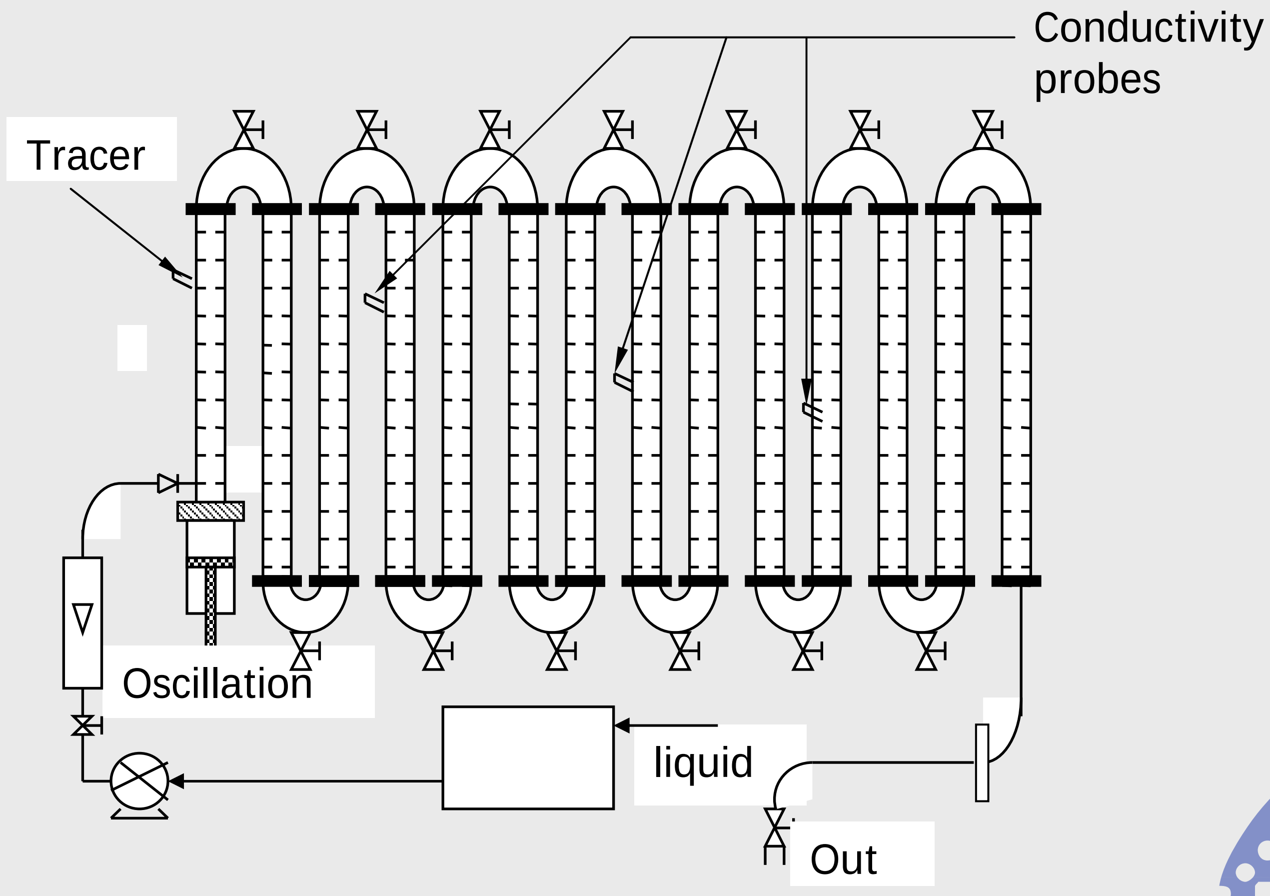


Real system

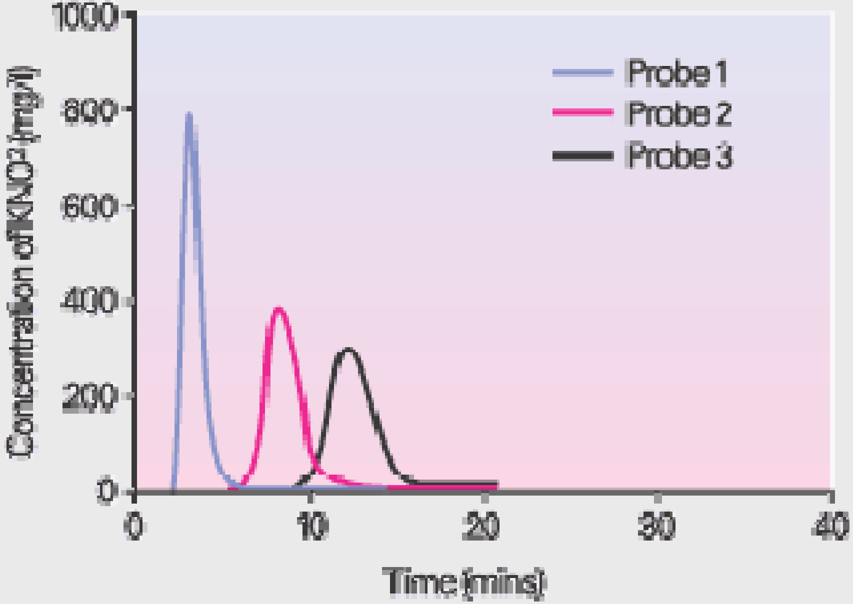
3-D CFD simulation

Re_o = 1250 (x_o = 4 mm, f = 1 Hz)

NiTech's Continuous OBR ($COBR^{TM}$)



Residence time distribution (RTD) in a COBR

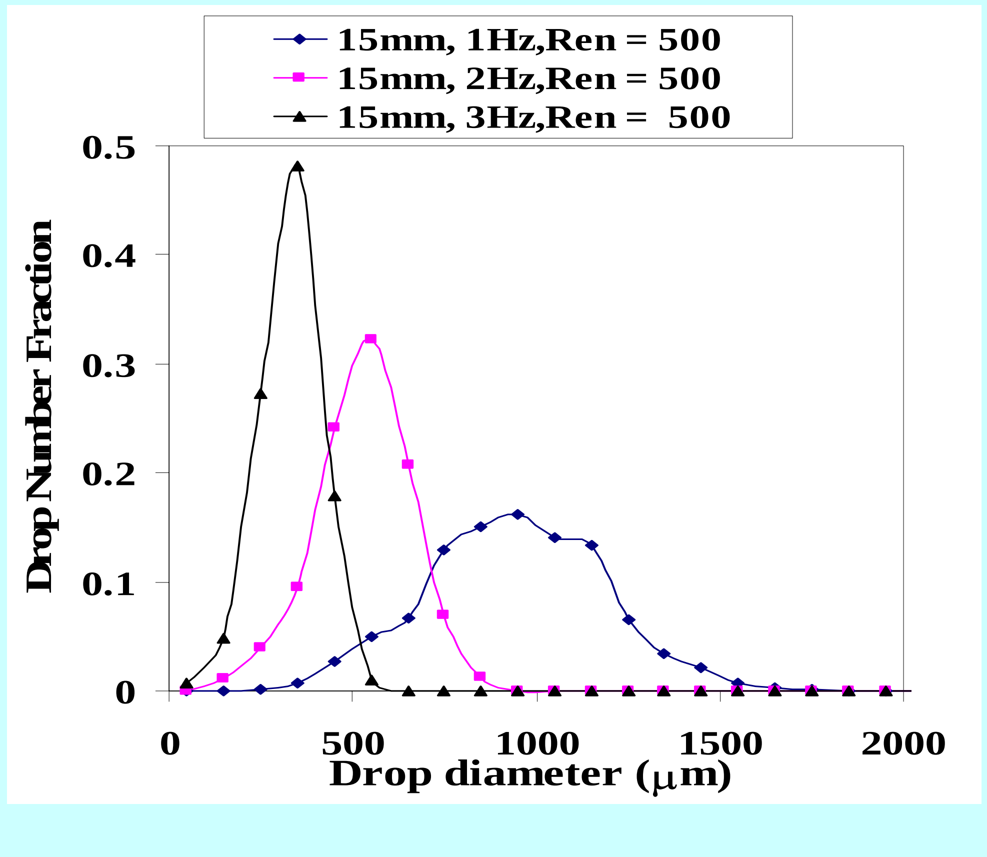


Probe 1
3.7 meters away from injection
Probe 2
7.9 meters away from injection
Probe 3
10.1 meters away from injection

- 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

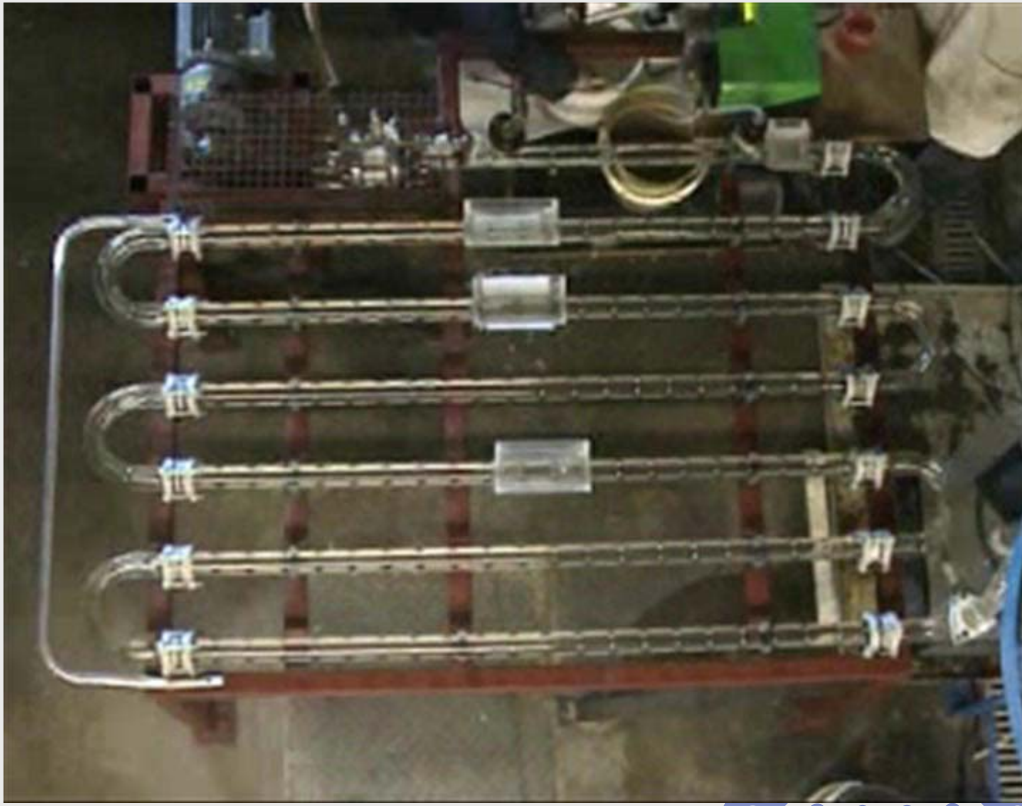
D = 0.00007~0.0003 m^2/s

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 (COBC™)

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

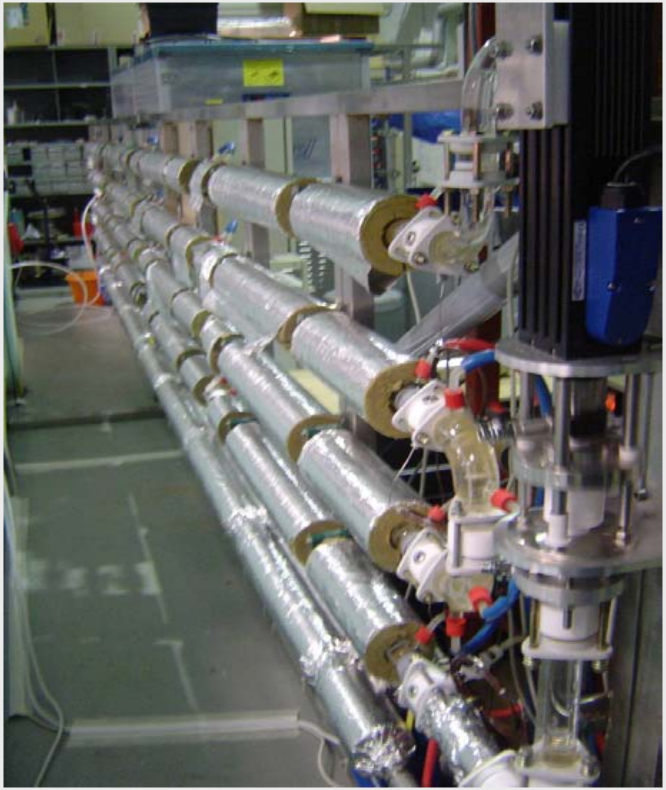
COBC™ has larger specific surface area for HT

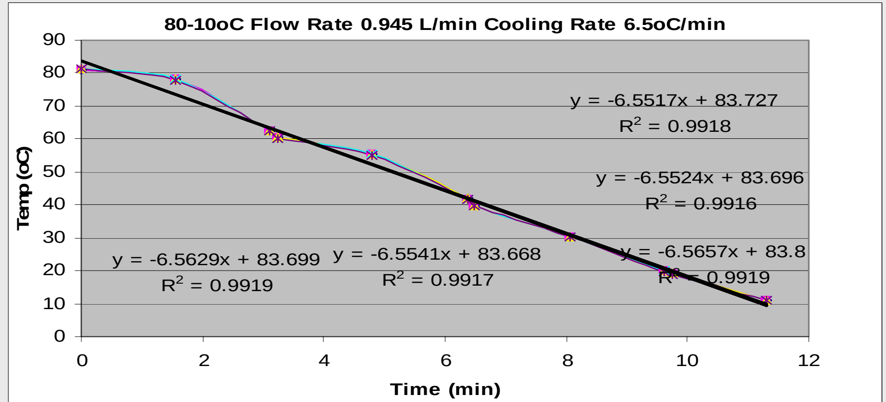
Tube side heat transfer coefficient (w/m^{2}K

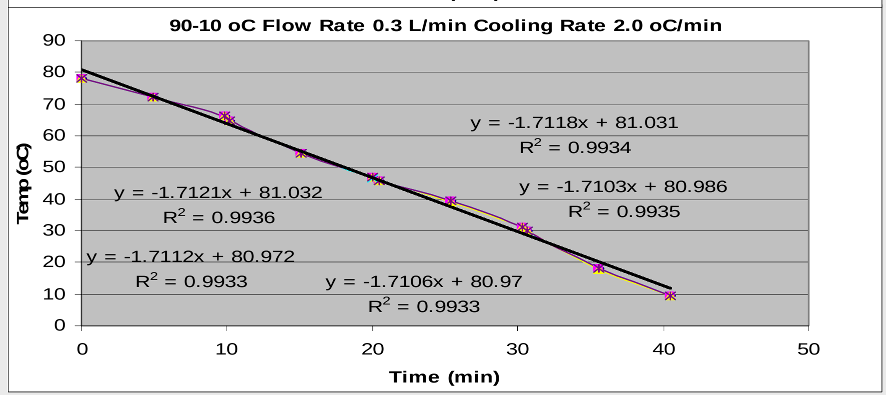
	1cp	10cp	100cp
600 kg/m^3	61,654 - 282,717	817 - 3,694	7 - 28
1000 kg/m^3	133,315 - 611,447	2,327 - 10,575	21 - 82
1500 kg/m^3	232,744 - 1,067,534	5,209 - 23,730	47 - 196

Plug flow delivers excellent heat transfer

Control over cooling profile







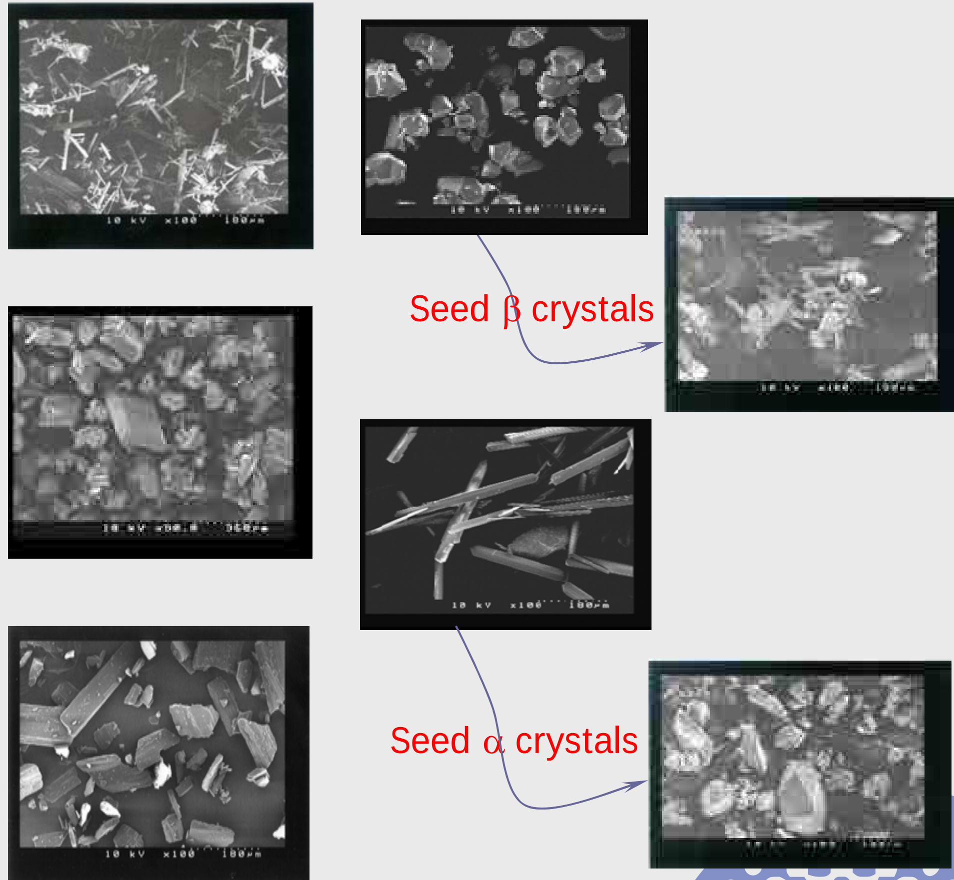
Any cooling profile, e.g. linear, parabolic, non-continuous, step-wise and etc, can be obtained along COBC™

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

4. Case studies

a) Morphology of a pharma crystal

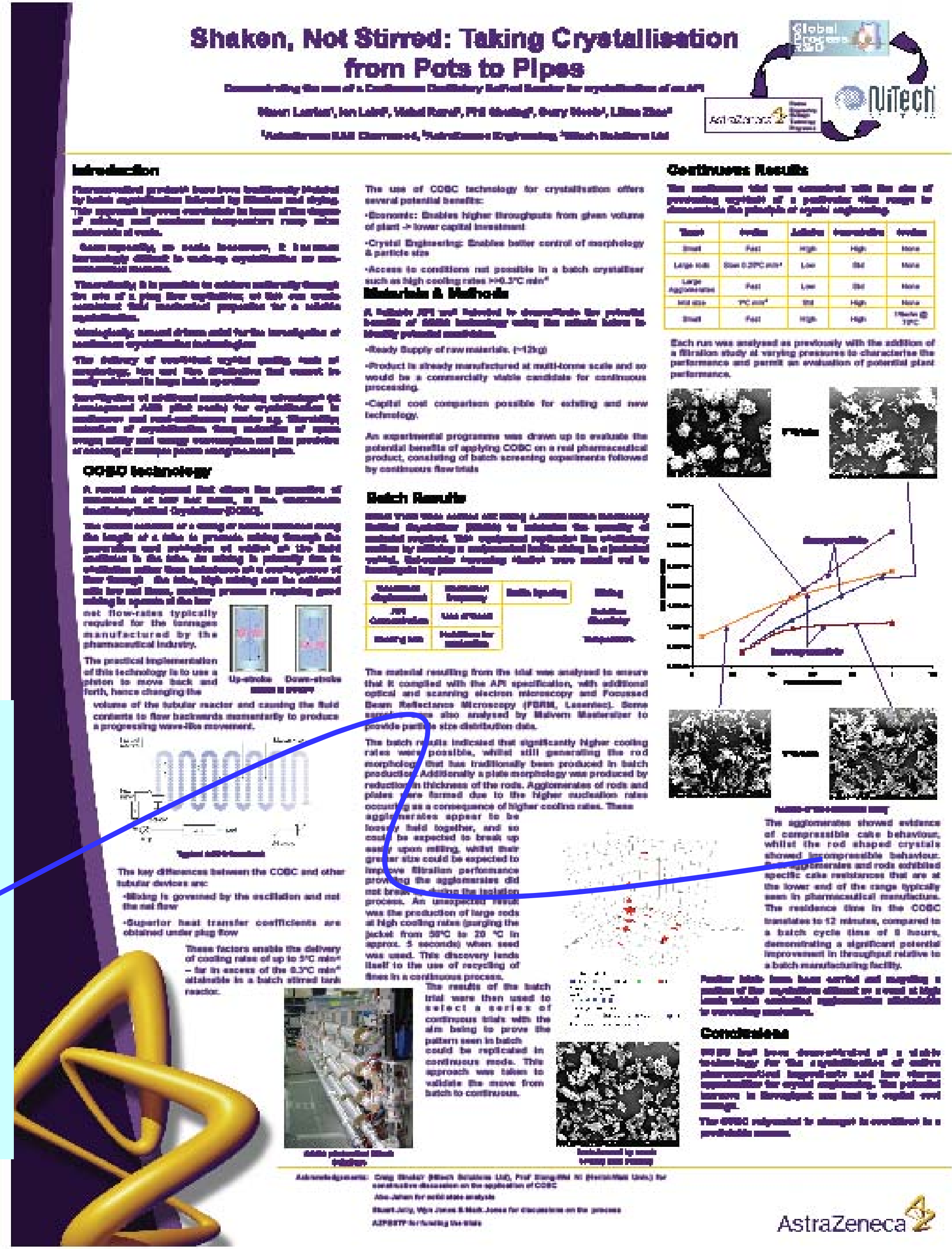
- COBC™ enables greater control over crystallisation path
- Able to be more selective on crystal morphology



b) Pharma API - size on filtration

- Change on crystal size
- Impact on filtration

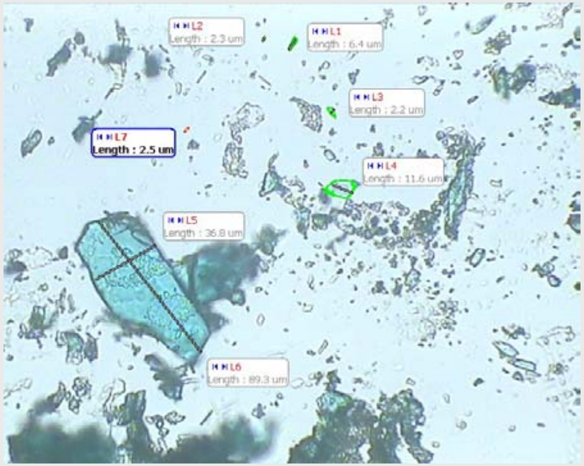
The residence time in the COBC translates to 12 minutes, compared to a batch cycle time of 8 hours, demonstrating a significant potential improvement in throughput relative to a batch manufacturing facility.



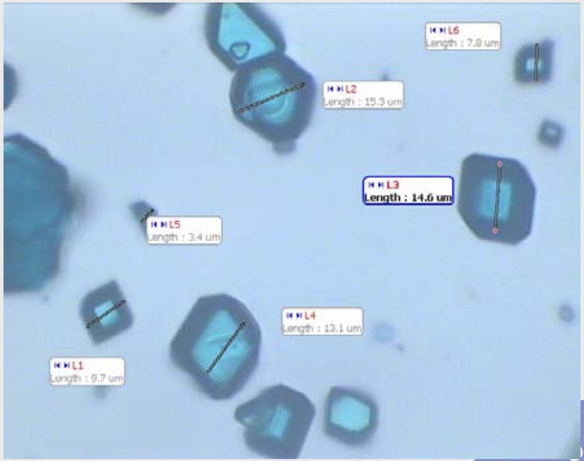
c) Filtration index for a pharma product

COBC™ affects outcomes achieved

- **Product characteristics/performance**
- **Consistent filtration index of 25**



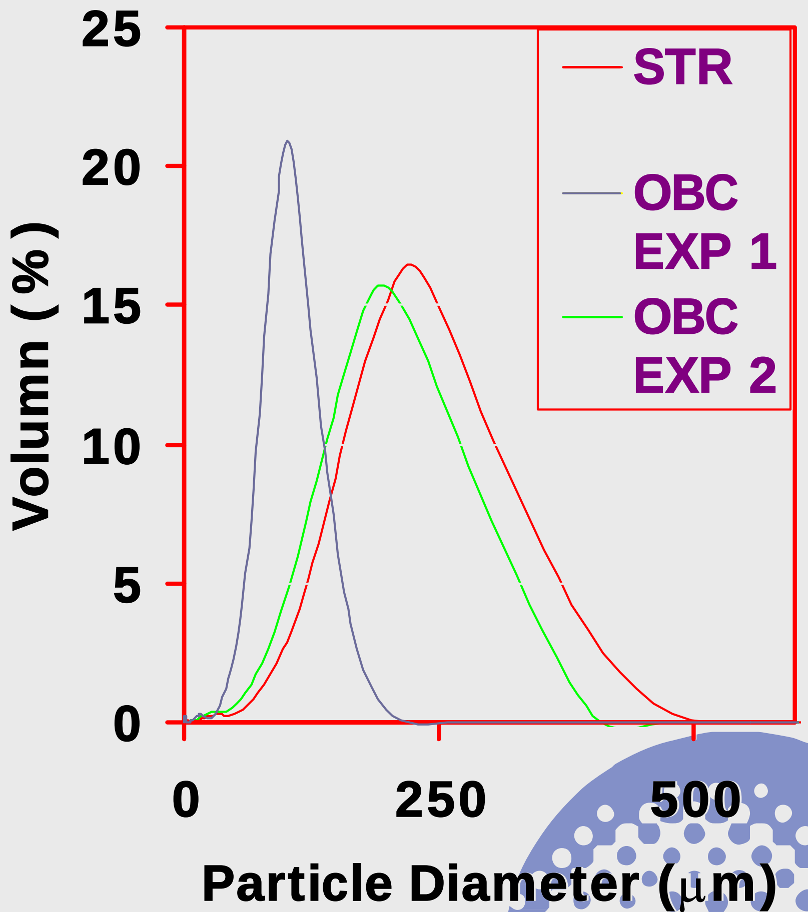
STR



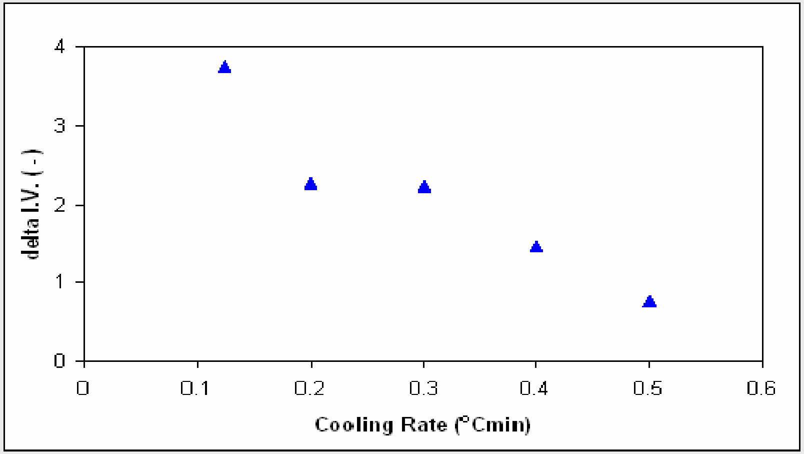
COBC™

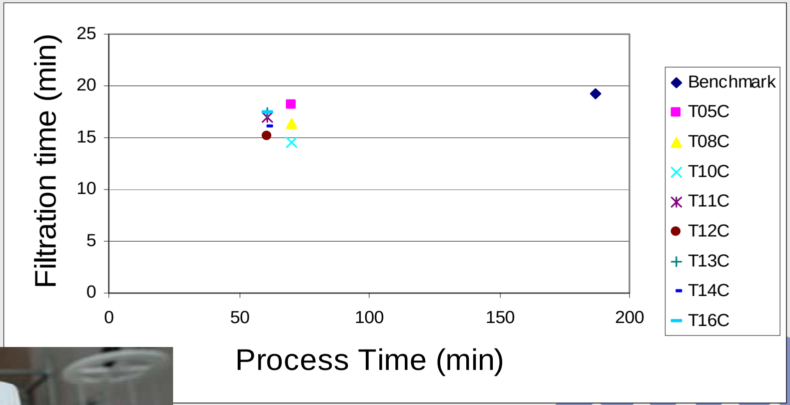
d) Crystal size distribution of a fine chemical product

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



e) Fractionation of edible oils





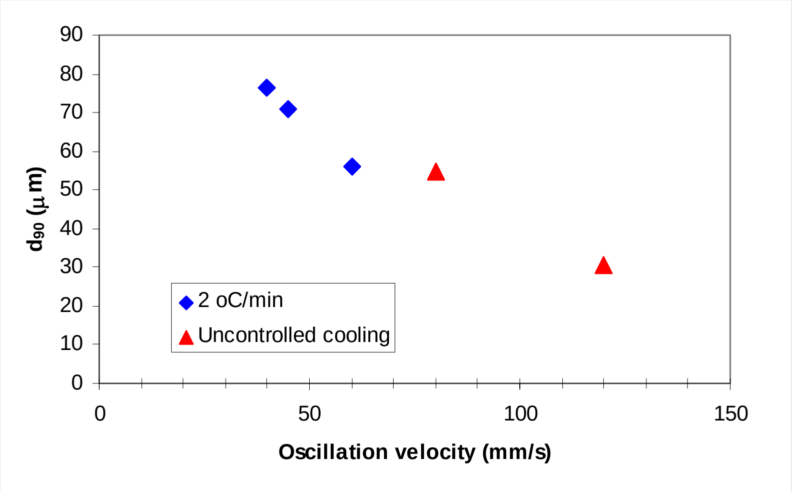
- **Two stage cooling (17 and 0.3 °C/min)**
- **Consistent IV achieved**

• **Significant reduction of crystallisation time**

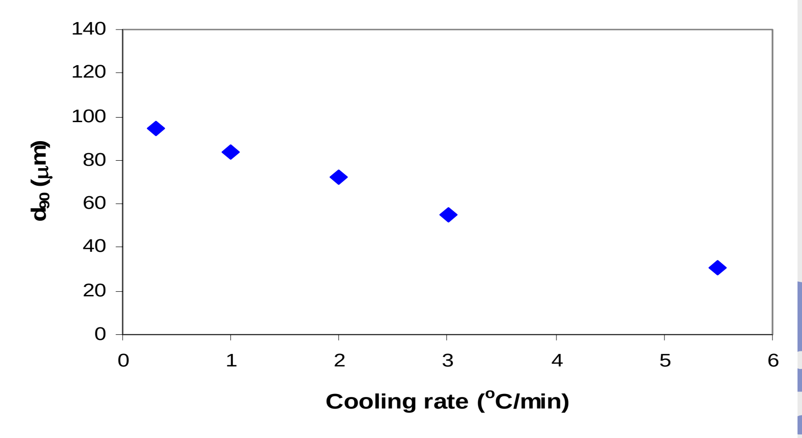
• **Improved filtration time**

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^{TM}, 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^{TM}
- COBC^{TM} can be incorporated into existing plants
- Continuous filtration could also be implemented in COBC^{TM}

NiTech SOLUTIONS

Acknowledgement

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