Partners in Pharmaceutical Process Engineering

Engineering process performance.....

from development to manufacture

Engineering Particles – the Key to Deliver Better Drug Product

QbD/PAT Conference 2013

Professor Brian Glennon

APC Introduction

APC was formed in 2011 by Prof. Brian Glennon and Dr. Mark Barrett in the School of Chemical and Bioprocess Engineering and is located in University College Dublin in Ireland.

APC delivers streamlined process engineering solutions and technologies to large & small pharma, and CMOs, to ensure the delivery of robust and scale-independent processes.

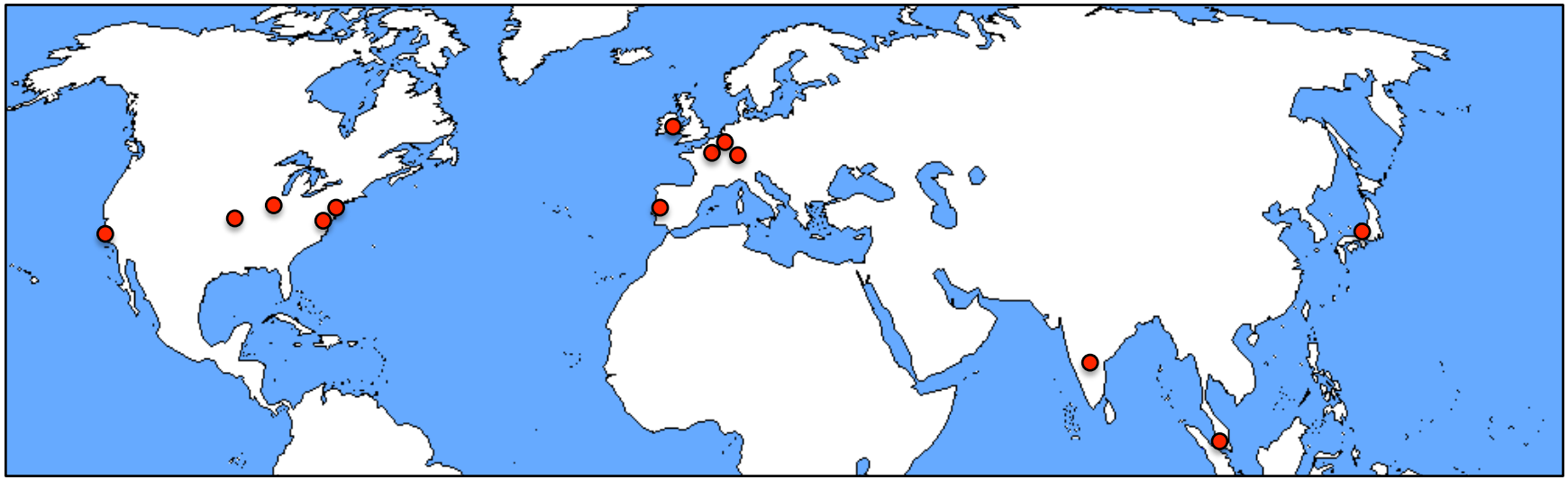
APC engineers process performance into development & manufacture of biopharmaceutical compounds.

APC Introduction

Currently APC works globally with 8 of the top 10 pharmaceutical companies and 5 of the top 10 biotechs in R&D, commercialization, manufacturing and technology development.

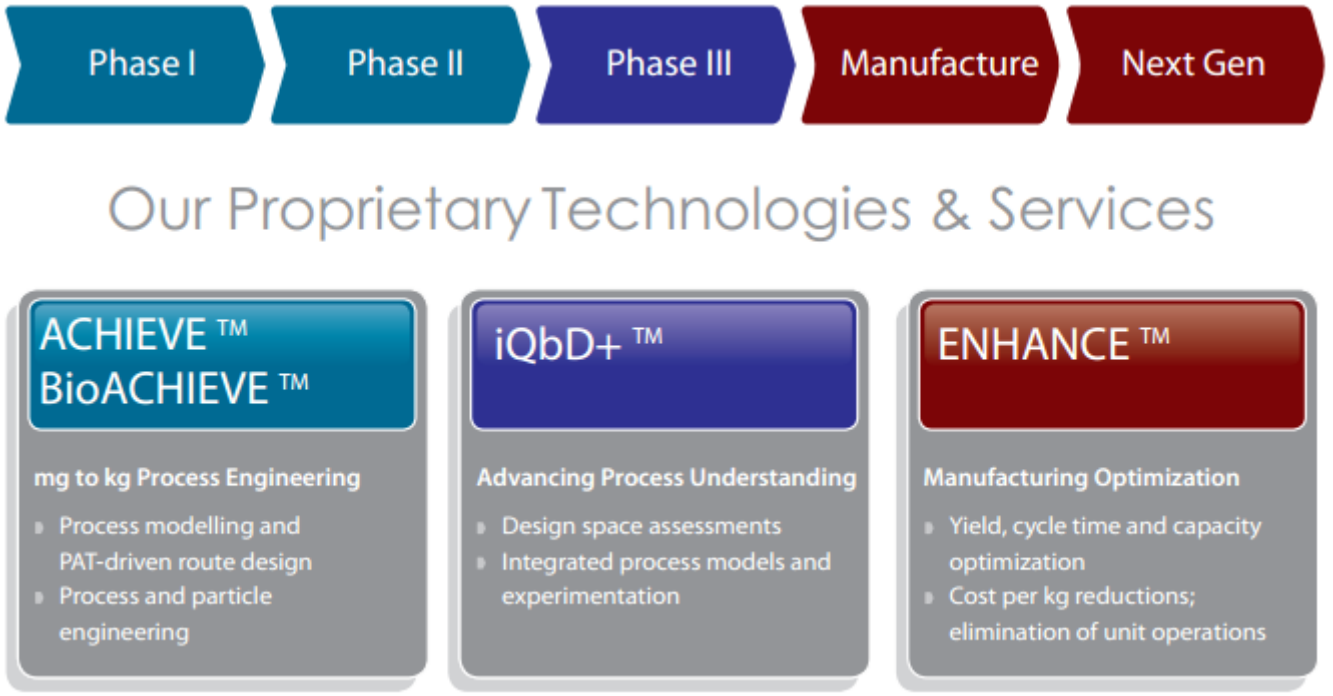
To date APC has delivered process engineering and technology solutions on over 100 projects. 80 of which are in GMP manufacture are the world.

APC's highly experienced team consists of 25 chemical engineers, and process and analytical chemists. Team currently expanding to 30.

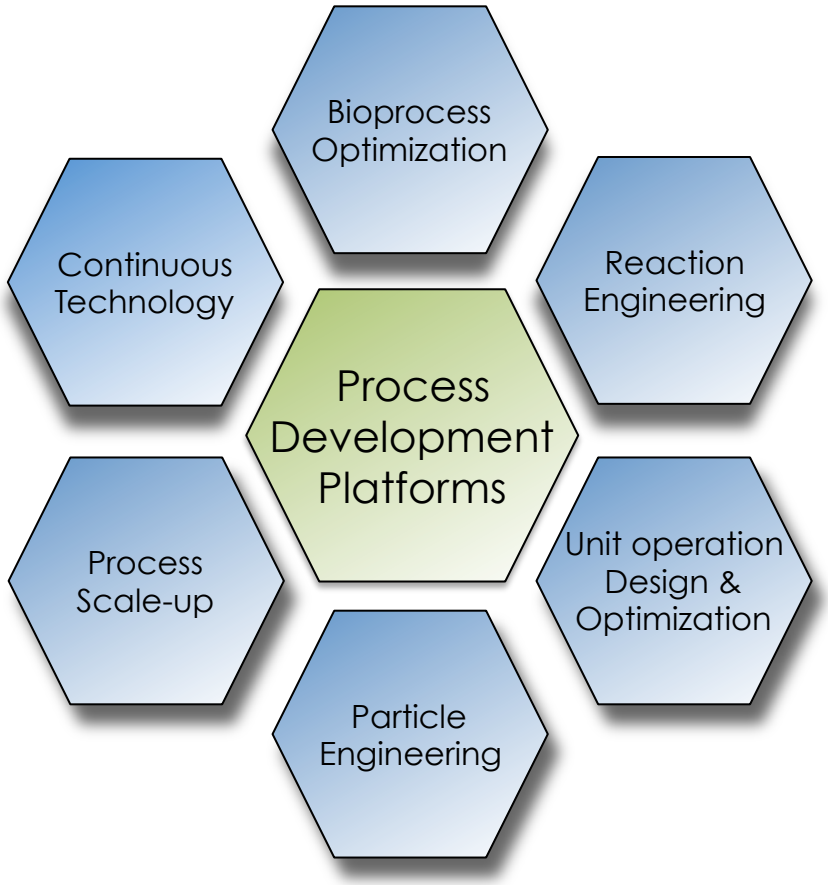


APC Introduction

APC interfaces its proprietary and novel research and technology programs across the entire lifecycle of pharmaceutical compounds



Process Development Platforms



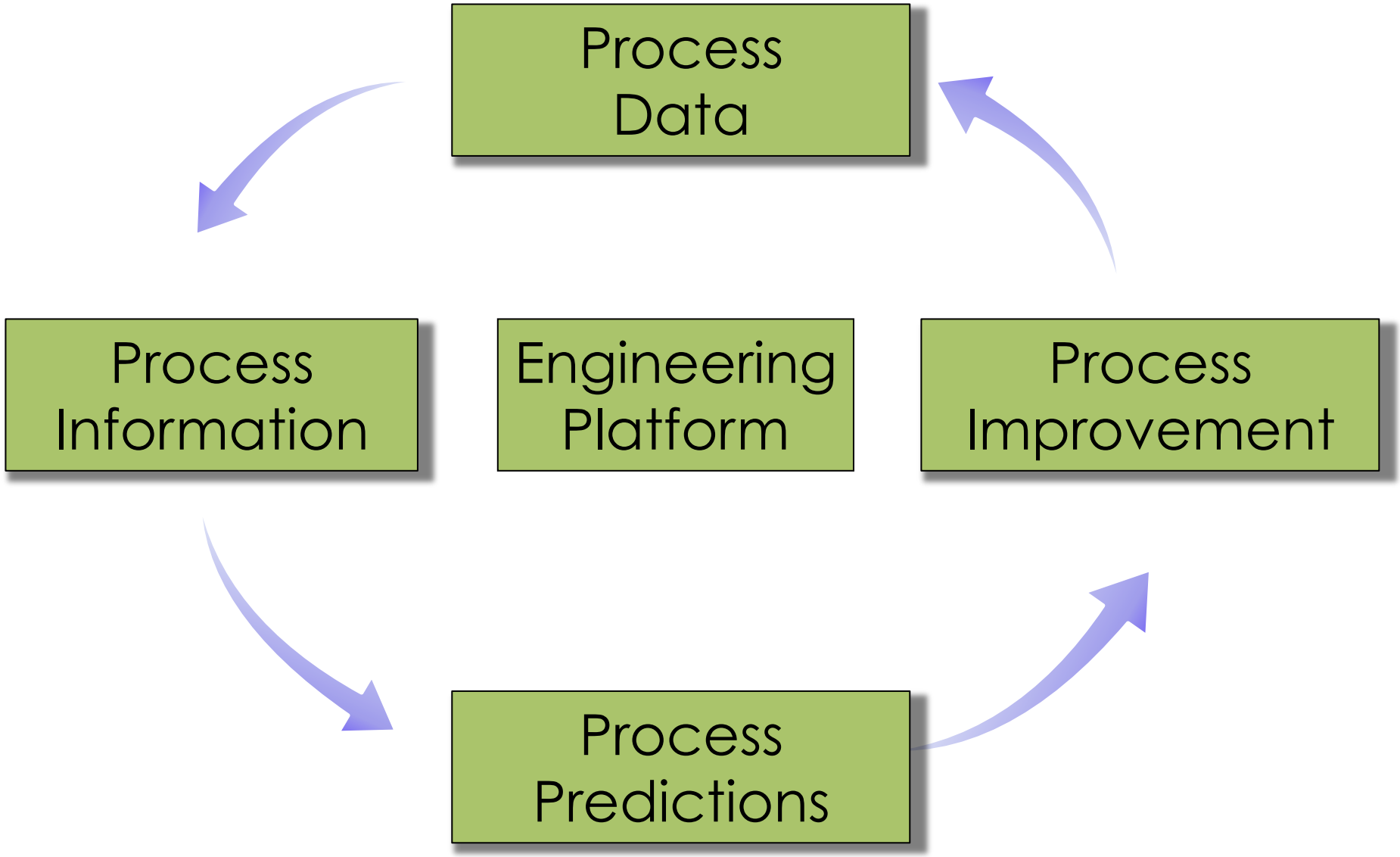
Objective:

Use Engineering tools (PAT, modelling, control etc) to provide
- better understanding
- more robust scale-up
- reliable risk analysis
- reliable identification of CPPs.

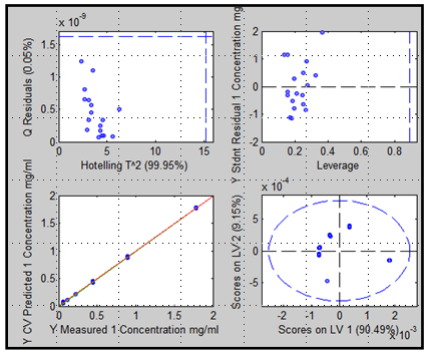
Focus on

- directed process development strategies
- robust processes for drug substance
- highly engineered characteristics
- directly address drug product requirements.

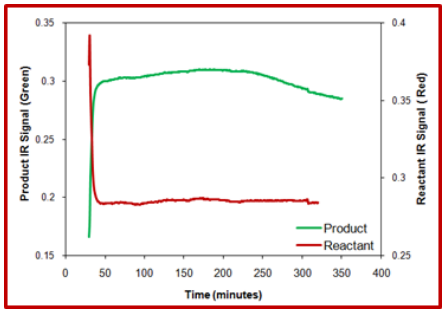
APC Platforms



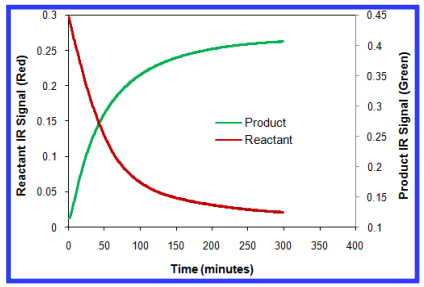
Reaction Eng & Optimization Platform



Chemometric method & model development



In Situ Process Monitoring



Model Inferred Reaction Optimization

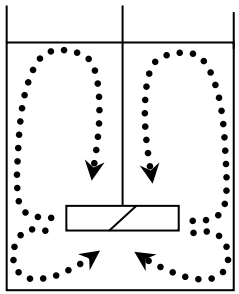
$$r_A = k[C_A]^a[C_B]^b$$

Kinetic & Engineering Process Modelling

Reaction Eng & Optimization Platform

- Impact of process environment, such as turbulent mixing and heat transfer, on process performance
- Engineering of process performance across lab and manufacturing scales

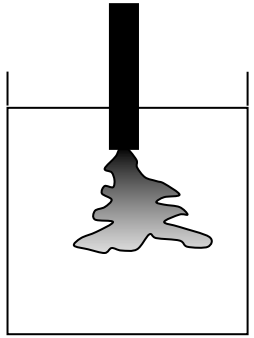
Macro-Mixing



Scale of tank, blend time

$\tau_c = V/Q_C$

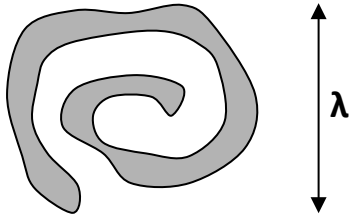
Meso-Mixing



Scale of feed pipe
- Reaction plume

$\tau_D = Q_{FEED} / u\ D_T$

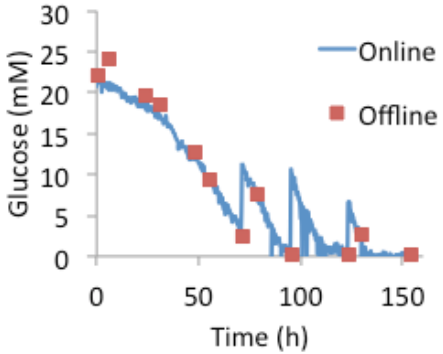
Micro-Mixing



Smallest scale of mixing
- Molecular diffusion

$\tau_E = 17.24(v/\varepsilon)^{0.5}$

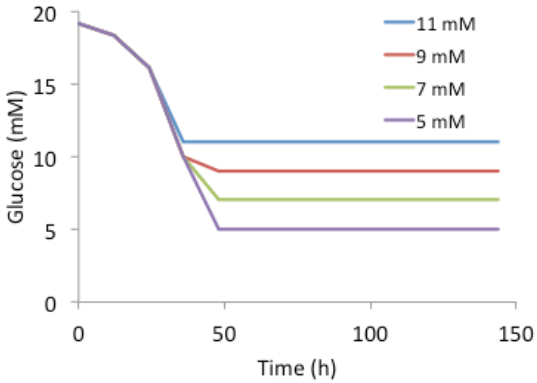
Bioprocess Optimization Platform



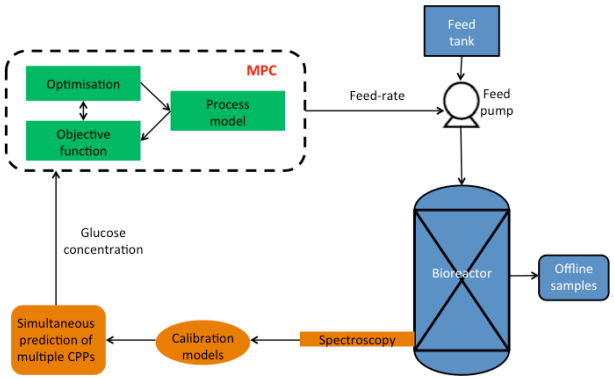
Advanced monitoring

$$\mu = \frac{\mu_{max}(G)(Q)}{(K_G + G)(K_Q + Q)\left(\frac{L}{K_L} + 1\right)\left(\frac{N}{K_a} + 1\right)}$$

Process Monitoring

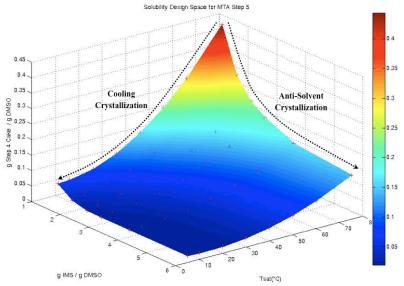


Bioprocess Optimization

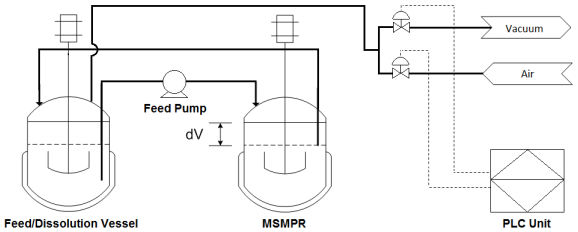


Bioprocess Development Platform

Particle Engineering

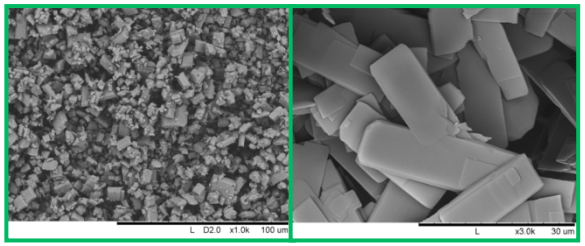


Solubility Design Space Assessment



APC Reactor Technology

ACHIEVE ™



Engineered Particle Attributes

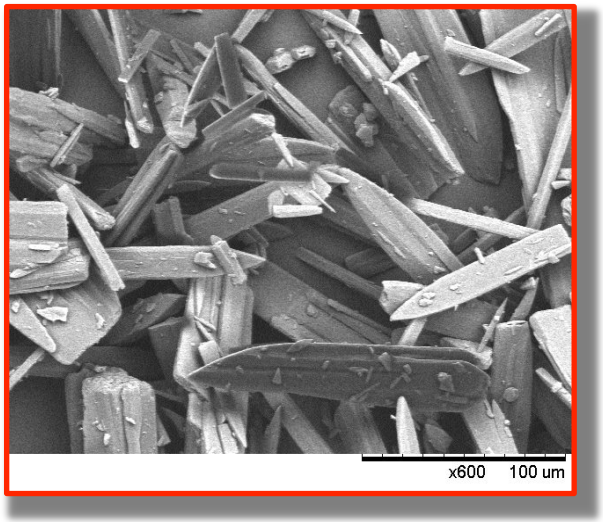
$$B_j = 7.49 x 10^{-8} \left(\frac{C_j - C_j^*}{C_j} \right)^{2.04} \quad [\#/\mu m^3 s]$$

Transient and Kinetic Data Extraction

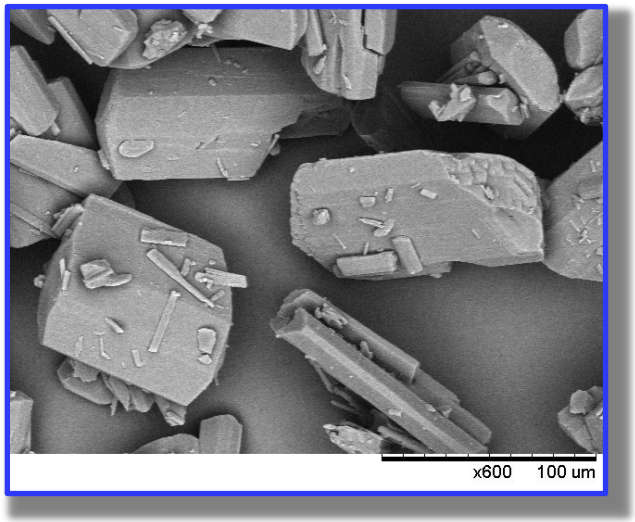
Case Study

Problem statement: Compound with poor shape control for consistent wet milling.
Requirement to change crystal shape and aspect ratio.

Current Process



New process



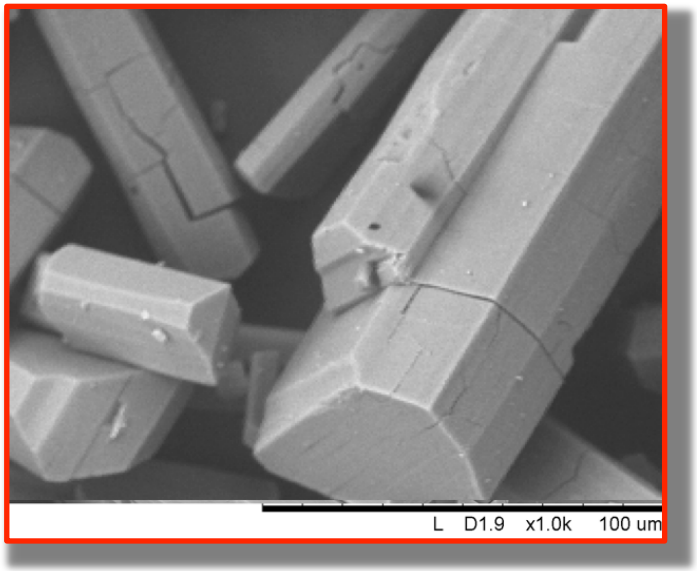
Outcome: Process improved to provide required crystal aspect ratio for milling.
Wet milling process successfully scaled-up to GMP manufacture.
Material characteristics for optimal formulation performance provided.

Duration: 12 weeks

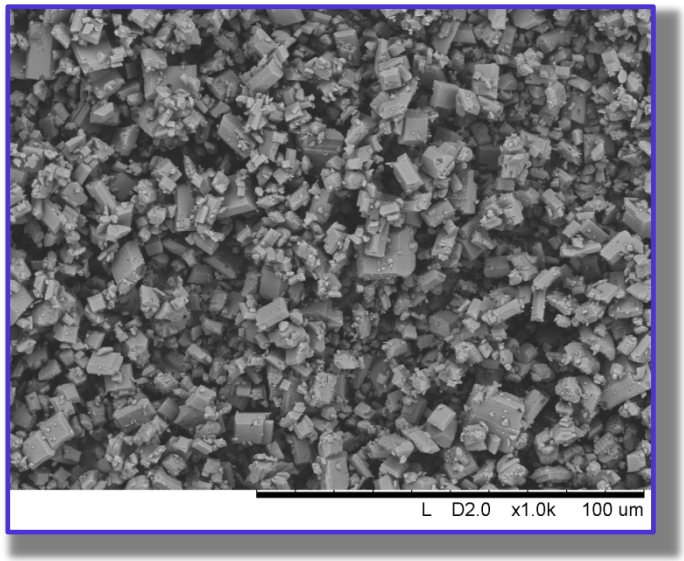
Case Study

Project Objective: Compound with micronization as rate limiting step.
Capacity issue for future manufacturing of compound.

Current Process



New Process



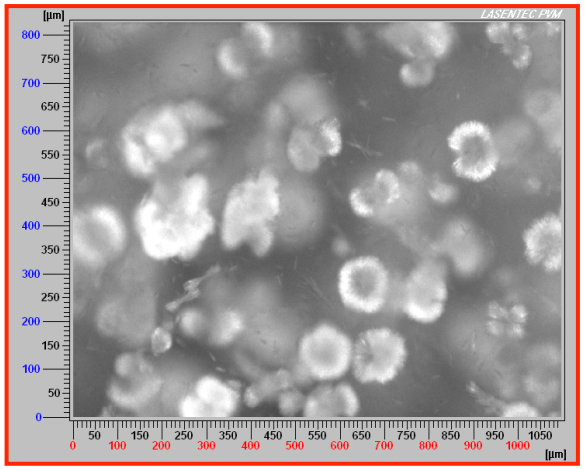
Outcome: Process modified within filing.
Micronisation eliminated.
Process scale-up enabled.

Duration: 14 weeks

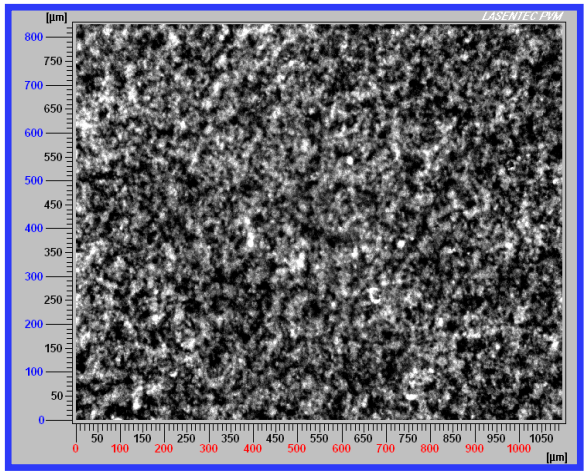
Case Study

Problem statement: 2nd generation process with cost intensive re-crystallization & milling operations.

Current batch process



New semi-continuous process



Outcome: Cost per kg production reduced significantly by elimination of re-crystallization and milling steps.

Purity & PSD delivered directly from crude step.

Applied to GMP manufacture.

Duration: 20 weeks

IR Applications

Novel Calibration Free Technique

Based on single peak height.

No empirical chemometric model required.

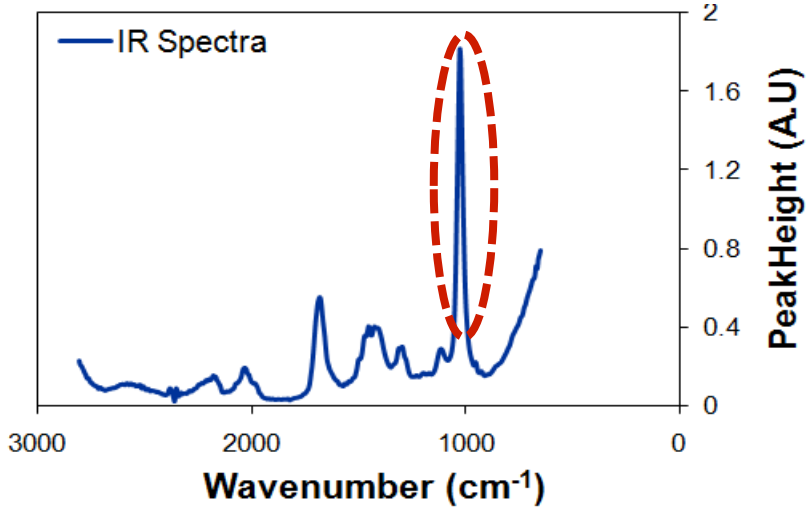
Solubility measurement integrated into method.

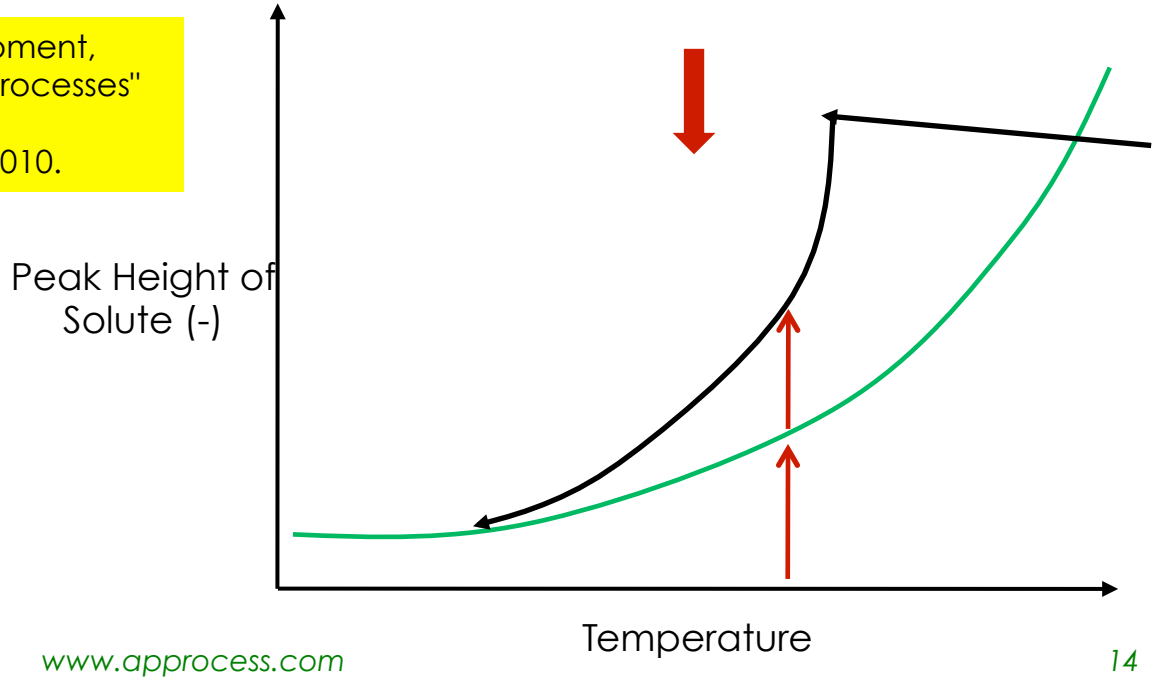
Independent of location in metastable region.

Temperature effects irrelevant.

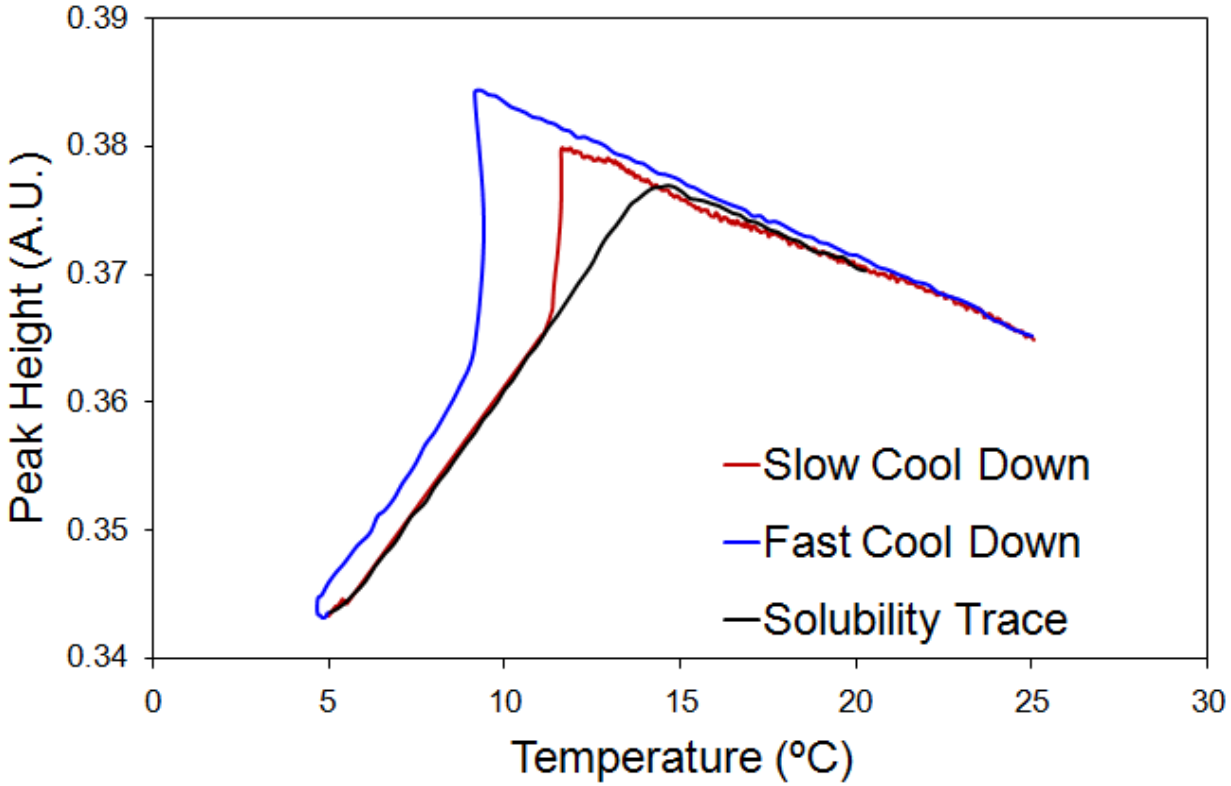
Concentration expressed in terms of peak height.

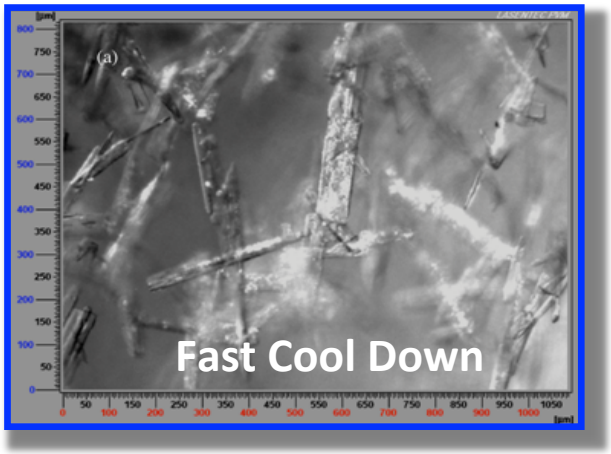
"Supersaturation tracking for the development, optimization and control of crystallization processes"
Barrett, M. *et al.*
Chem. Eng. Res. Des., **88**, 1108-1119, 2010.

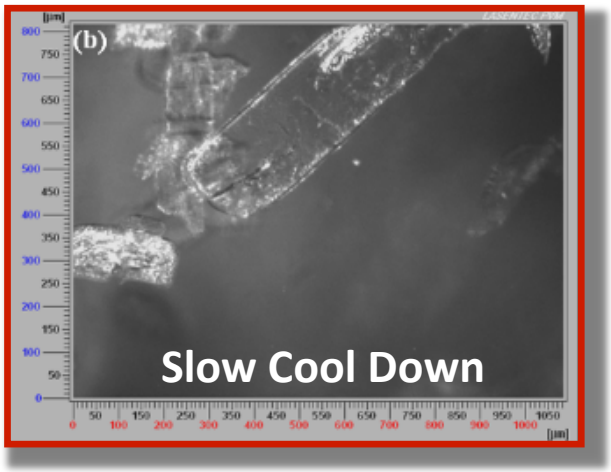




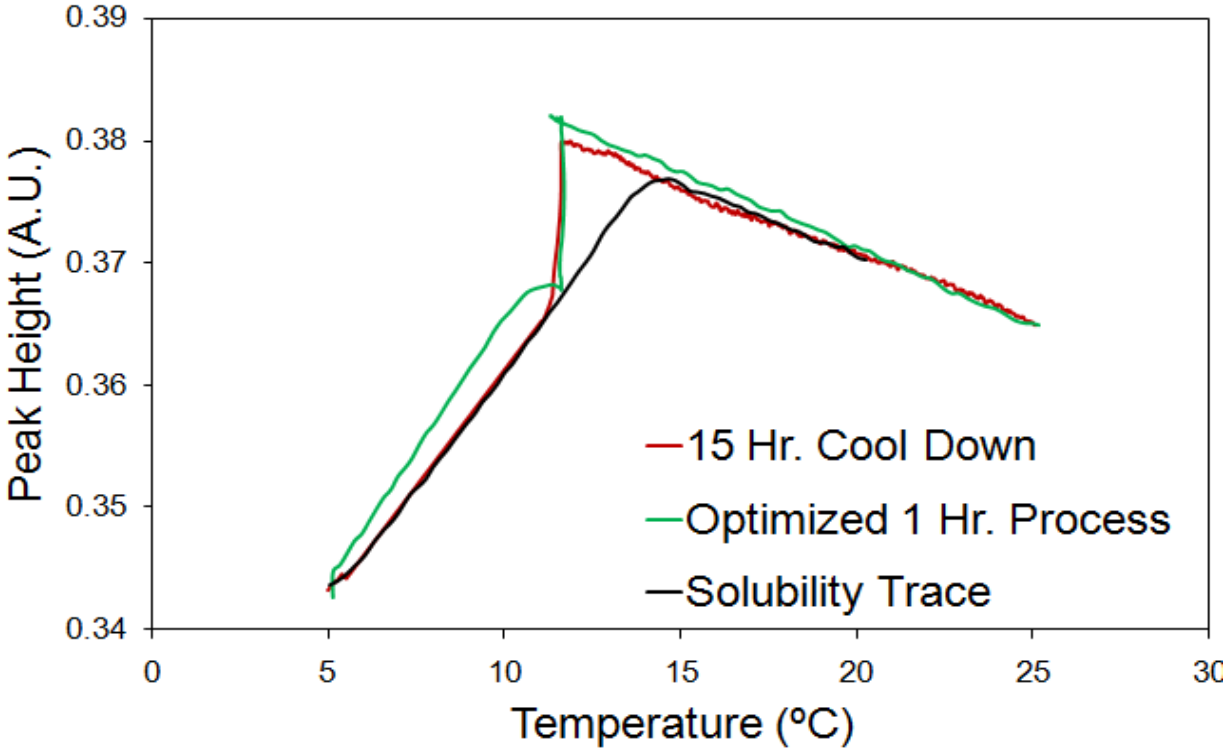
IR Applications

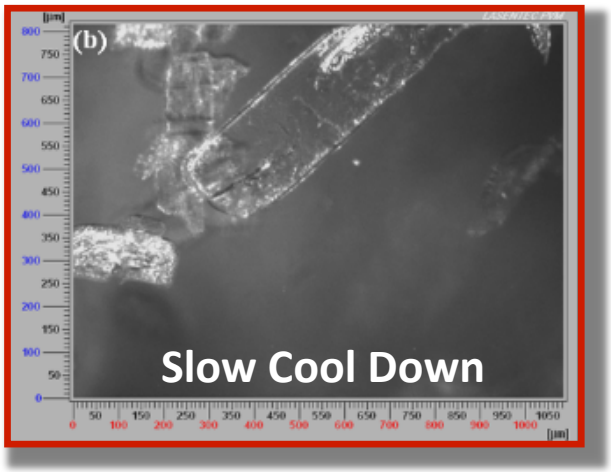






IR Applications



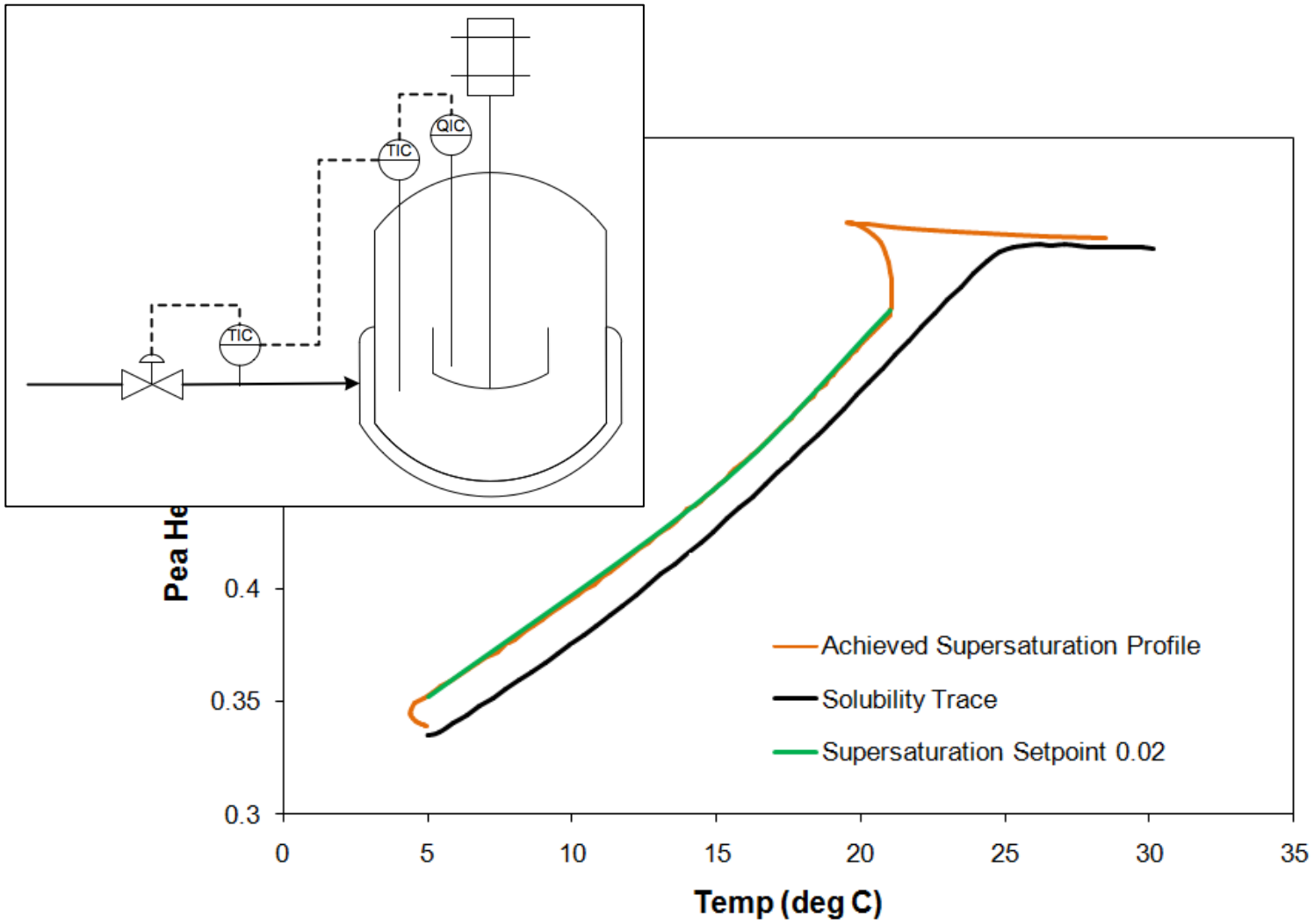


Rapid process evaluation & design method.

- days vs months

Case Study

Problem statement: Develop lean process to deliver consistent PSD



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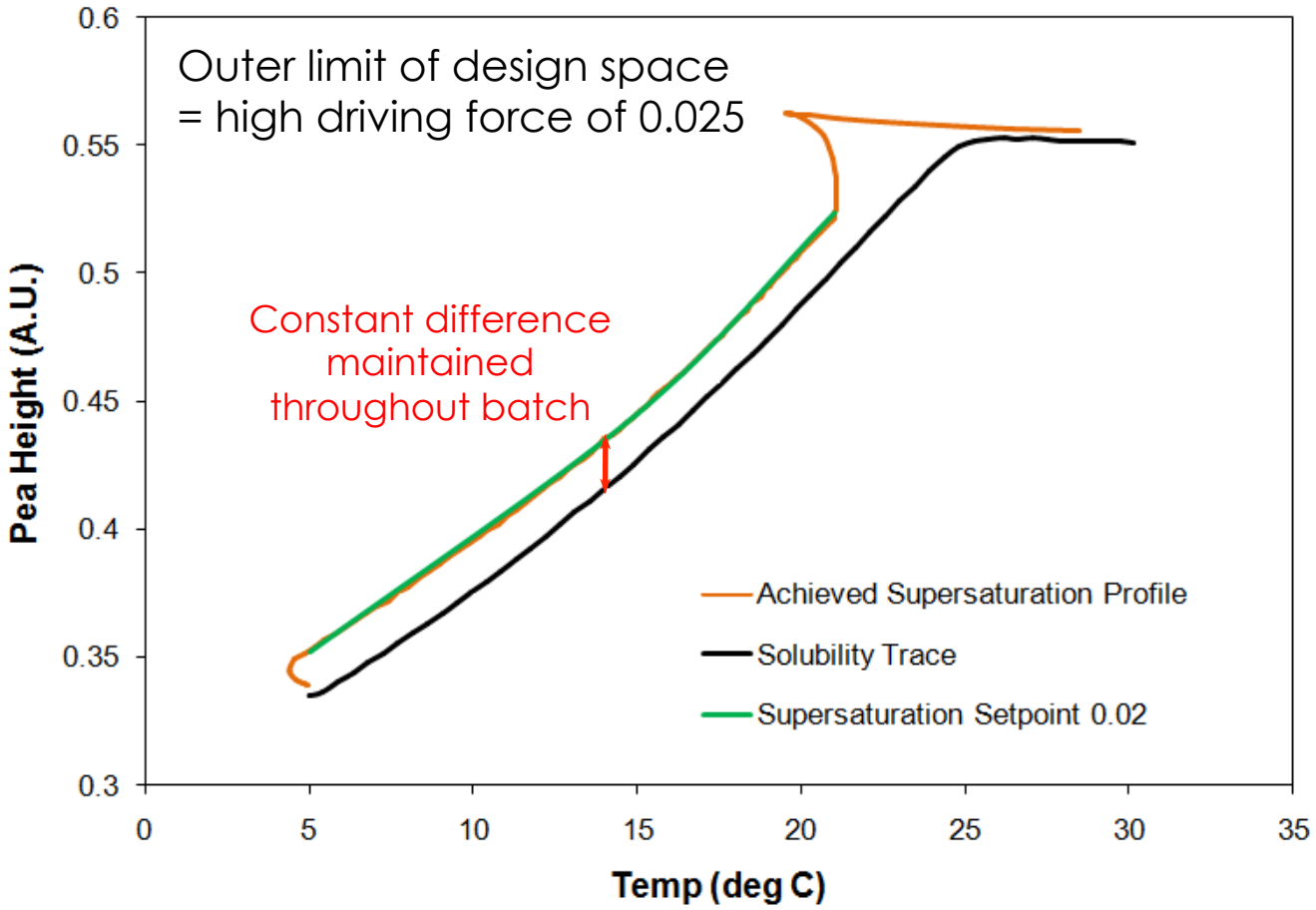
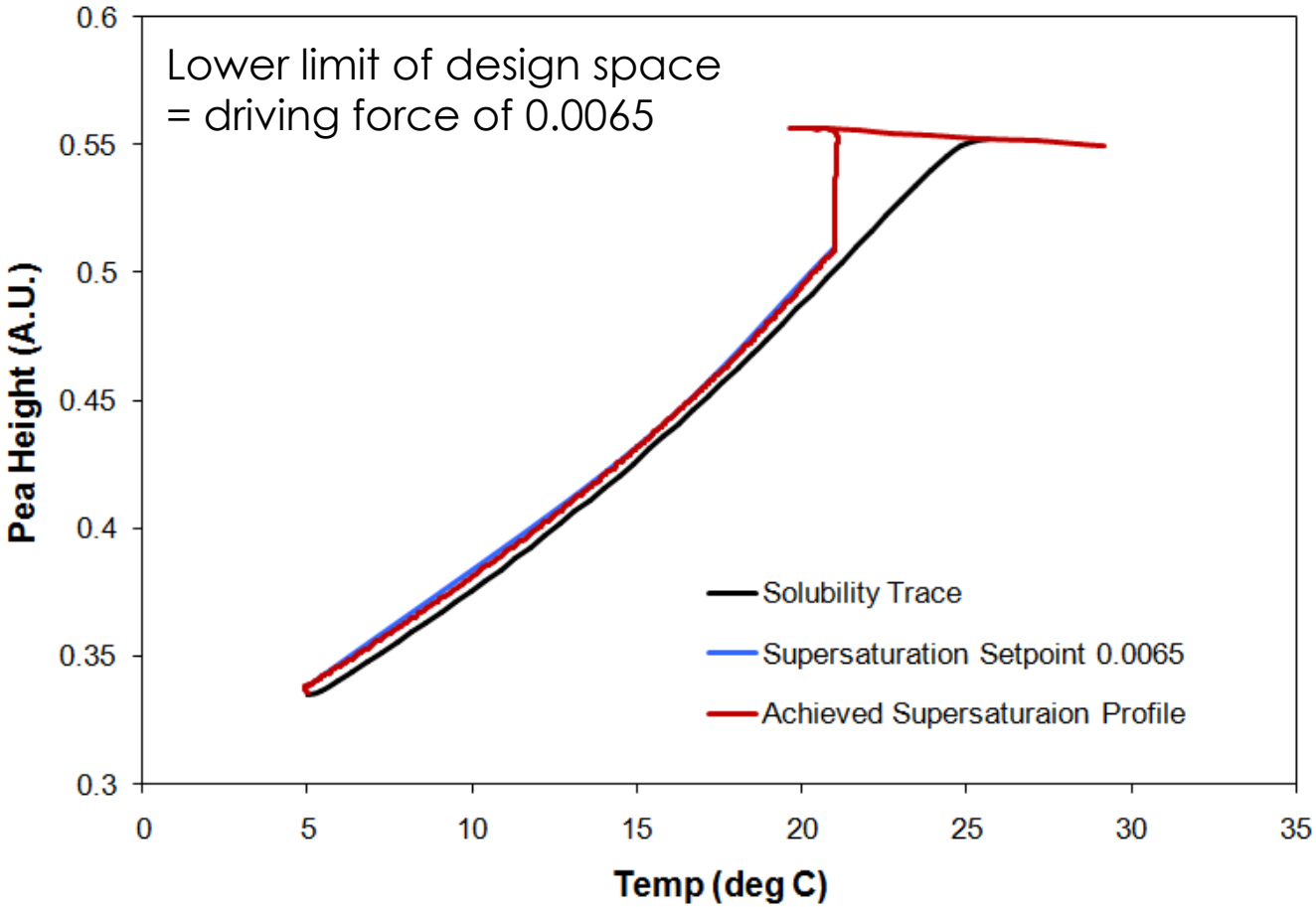


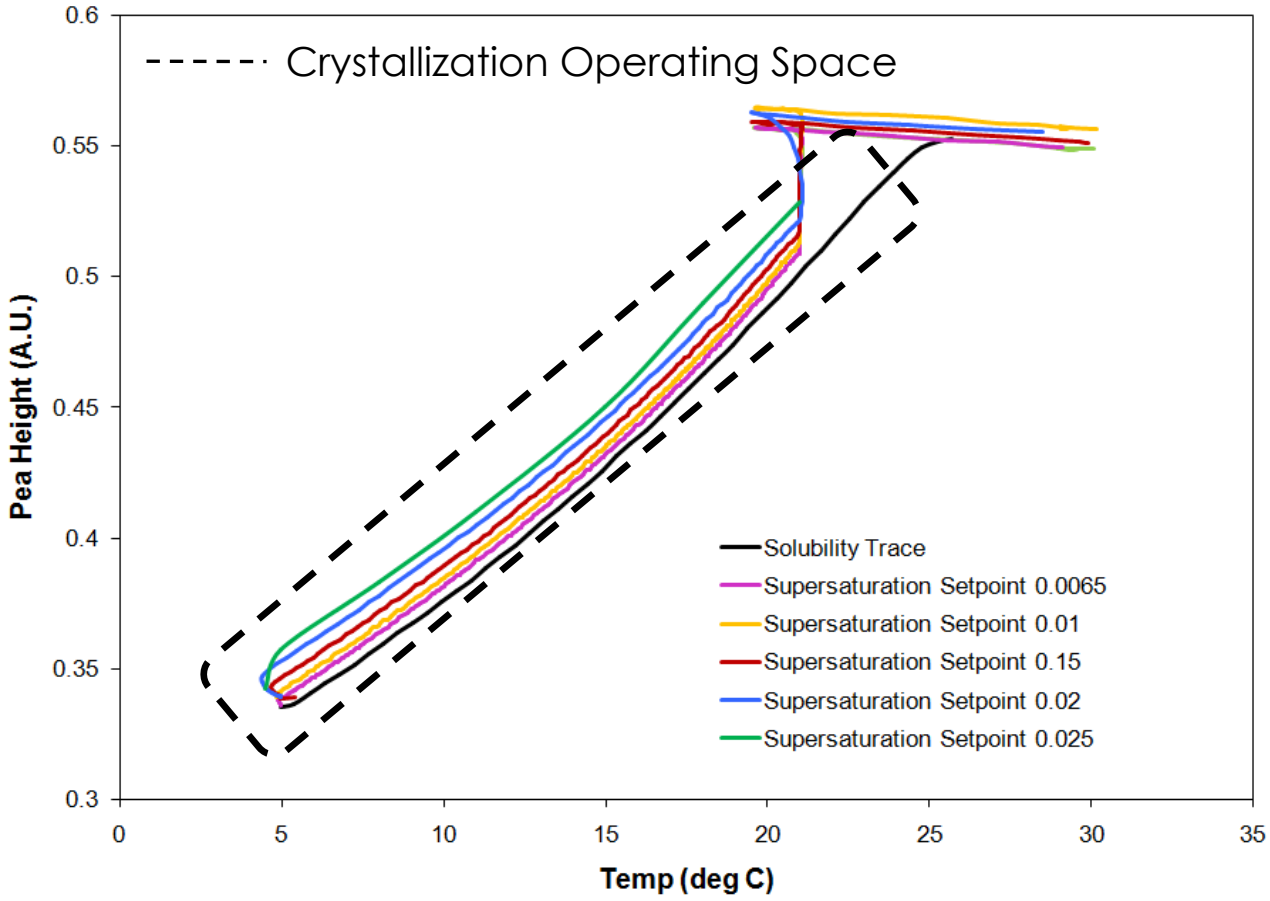
Case Study

Interrogate various supersaturation trajectories using feedback control



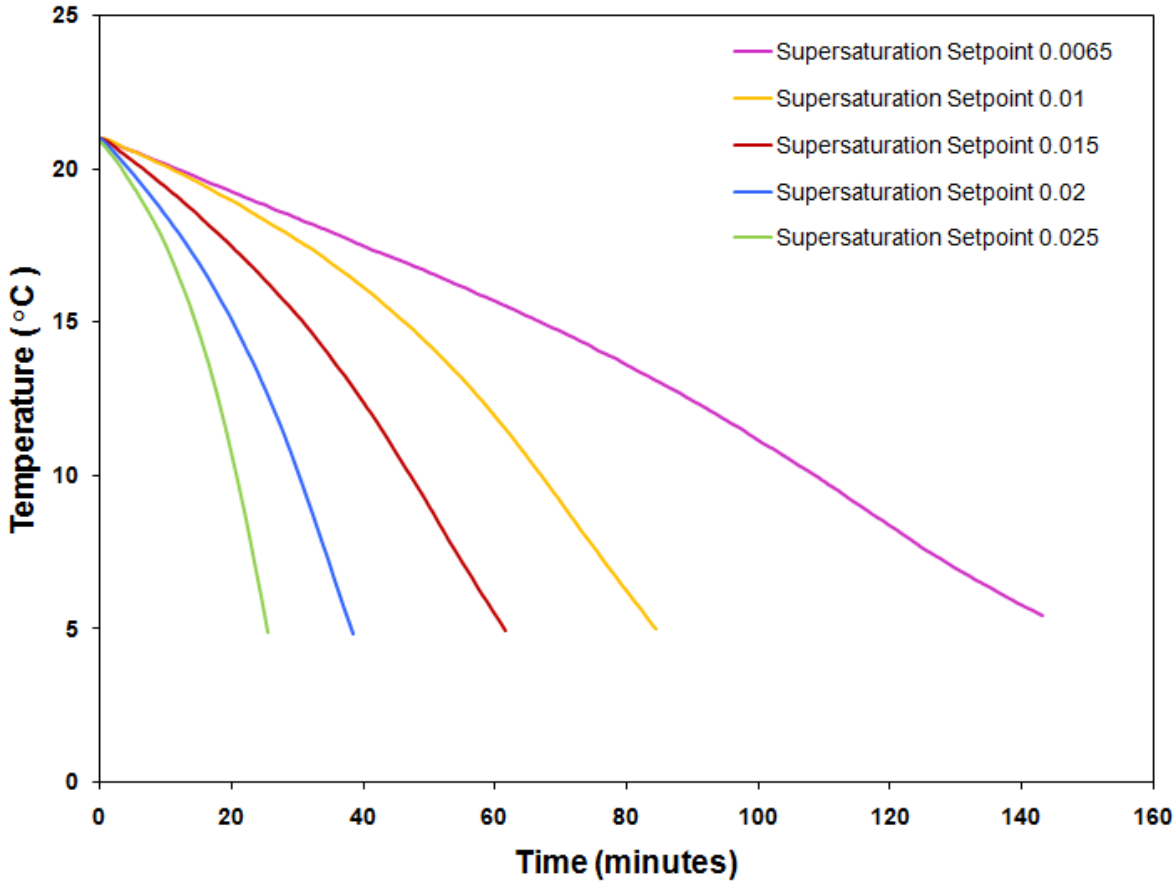
Case Study

Rapidly establish operating space for crystallization process



Case Study

Optimum cooling profile developed systematically



Case Study

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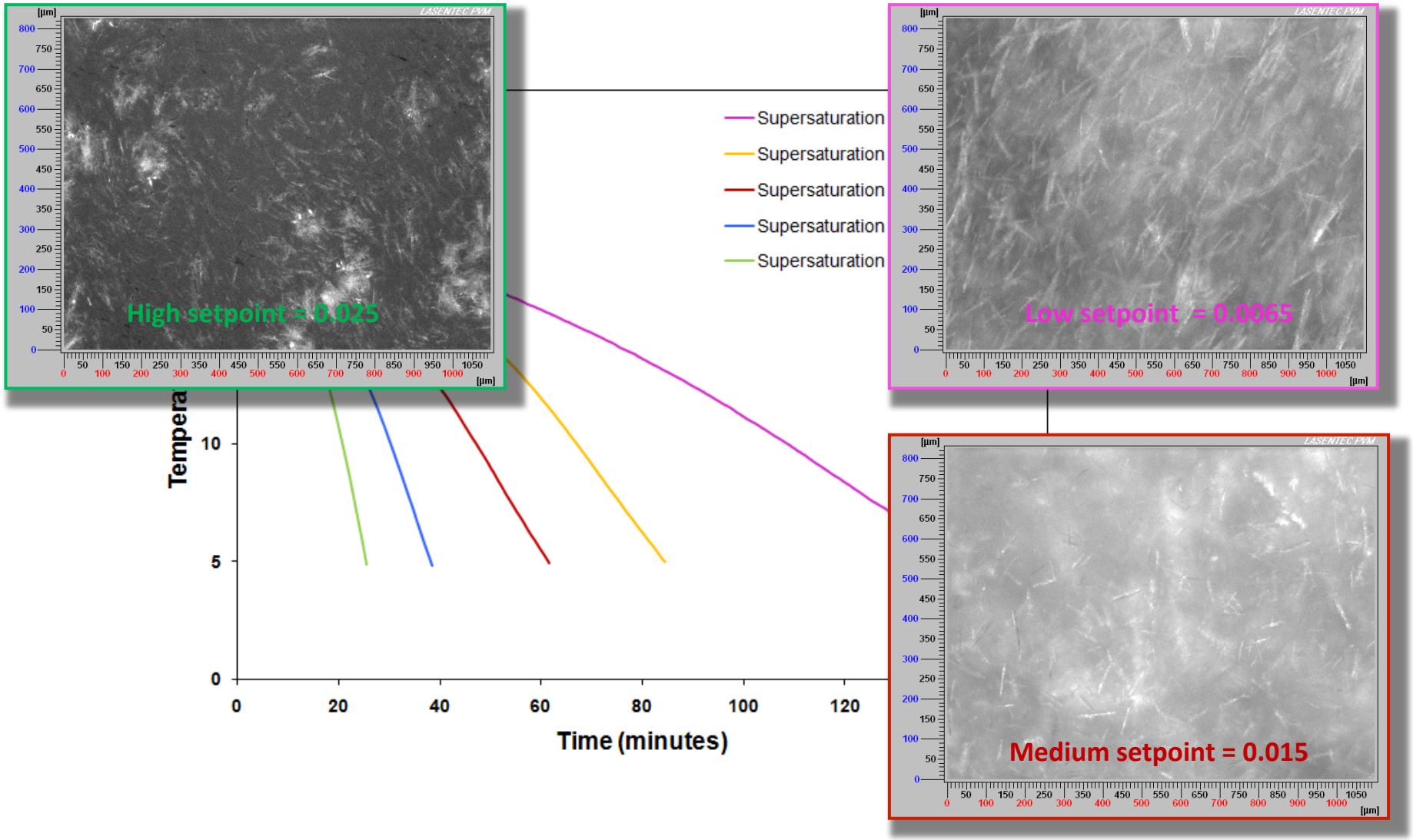
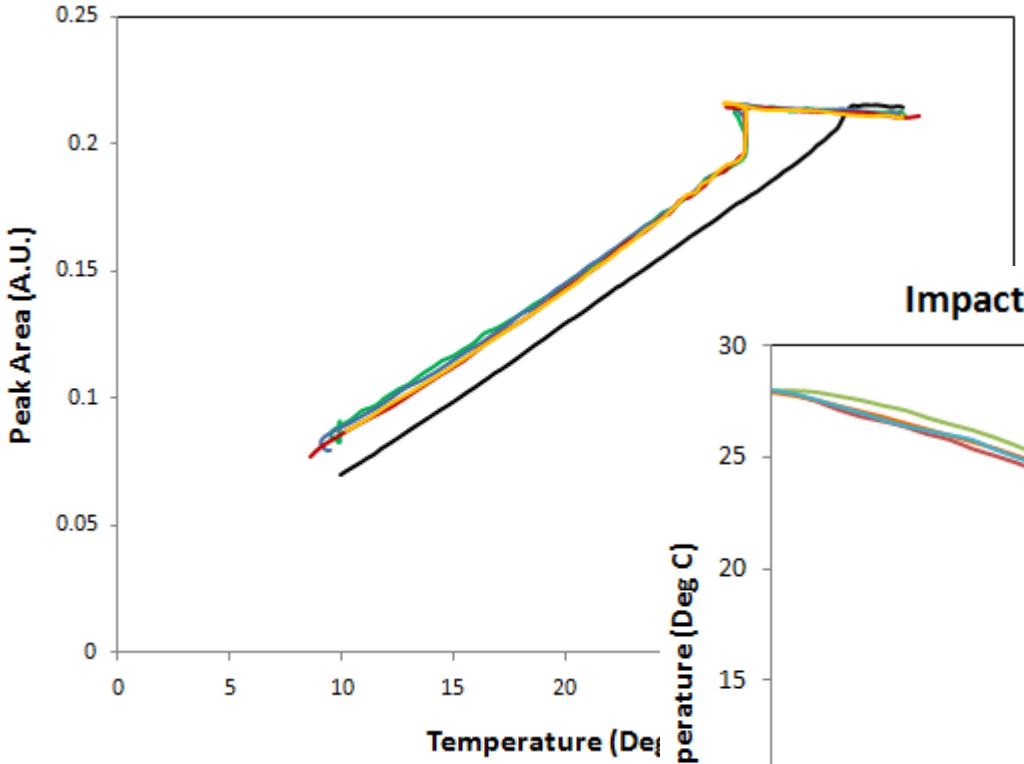
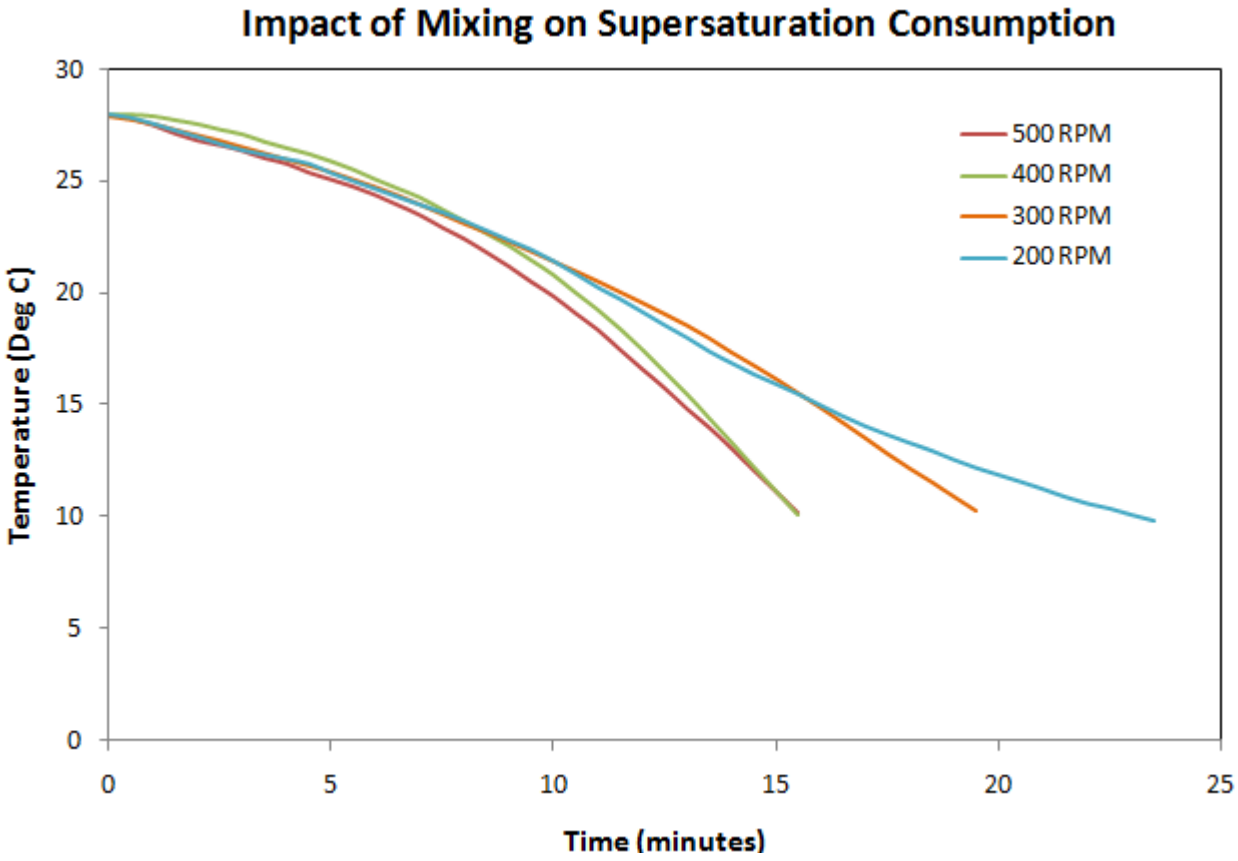


Case Study

Develop of protocols to identify the scalability of crystallization process





Case Study

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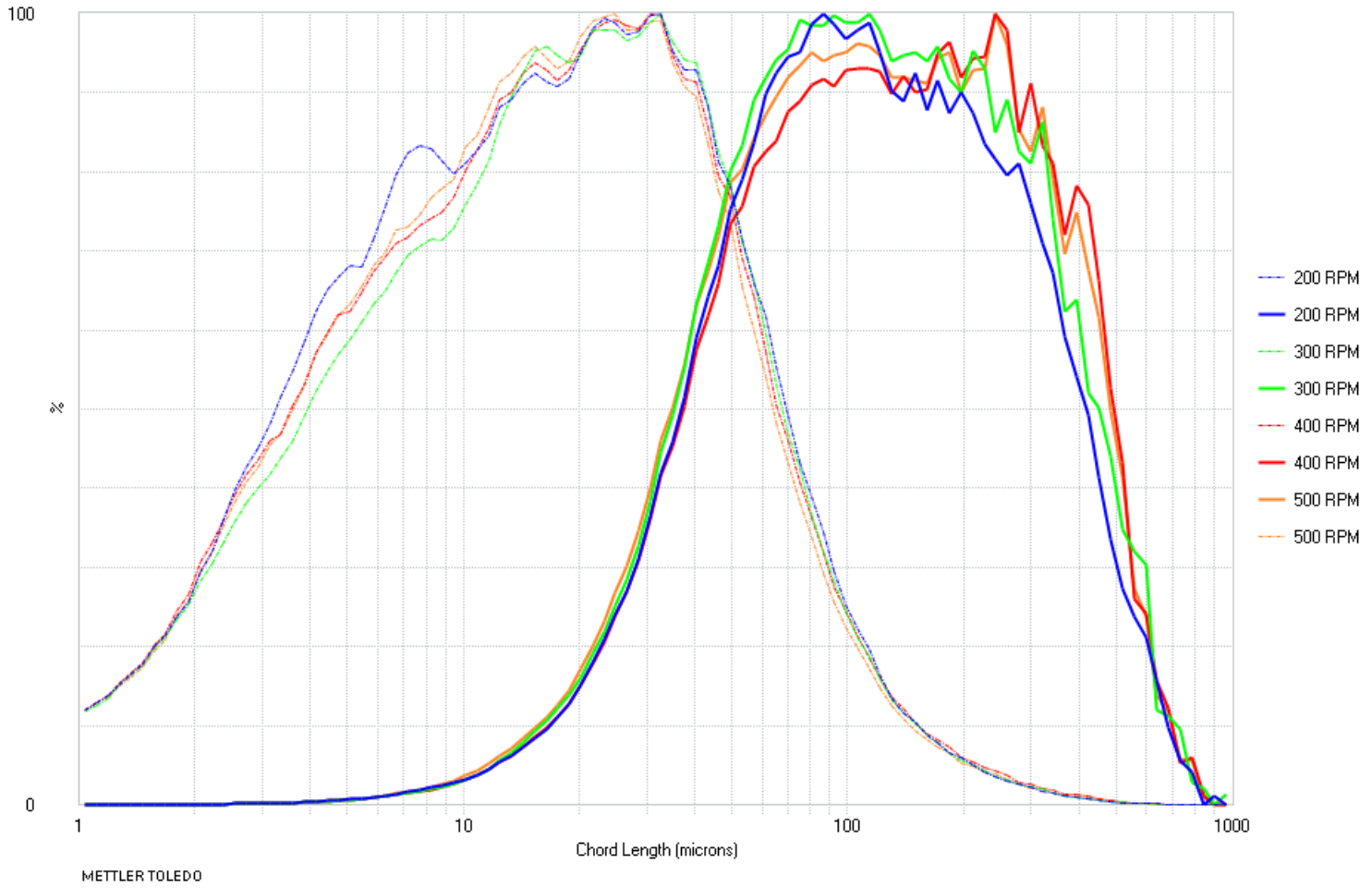
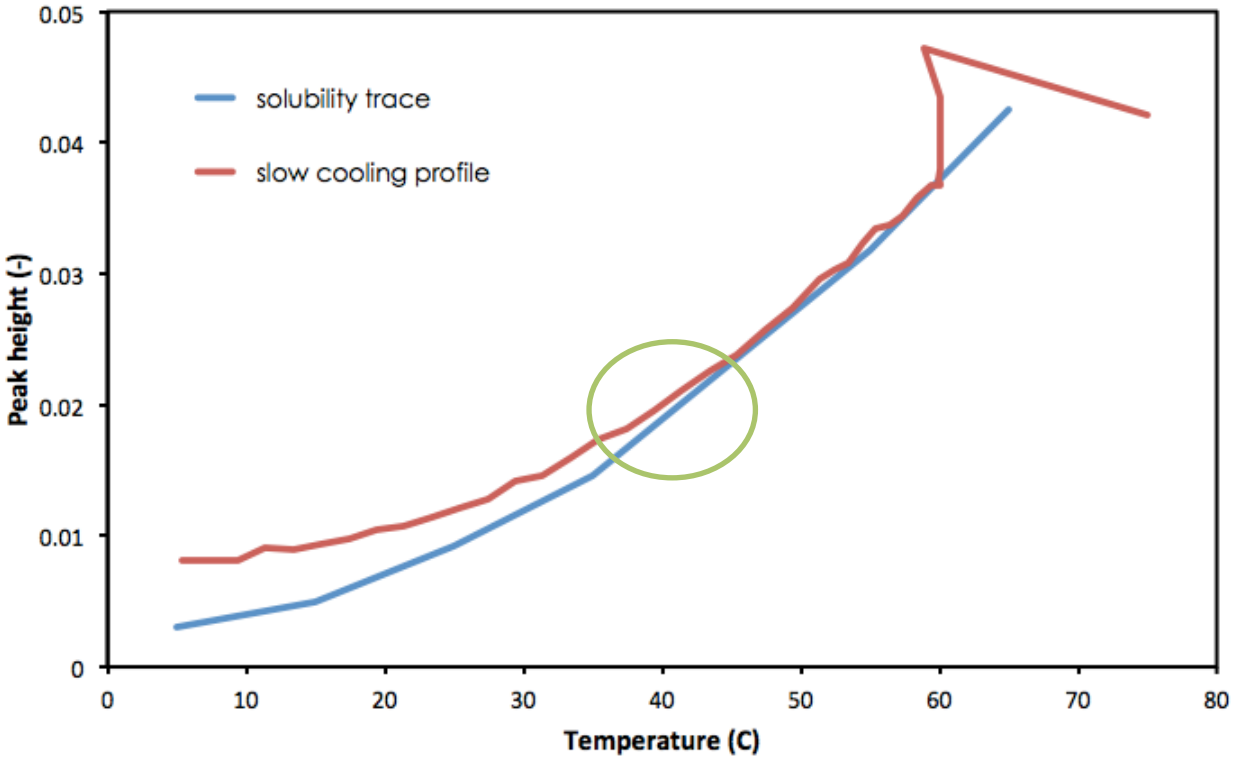
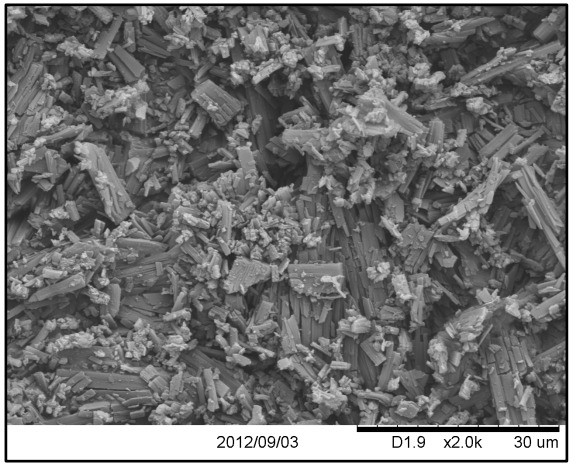
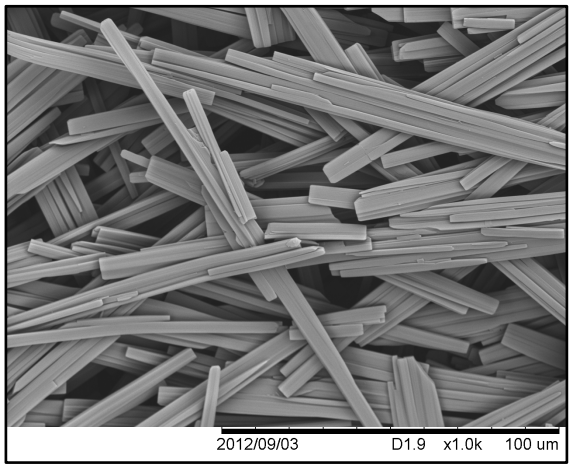


Case Study

Problem statement: Develop robust batch process to deliver consistent product







Outcome: Kinetic limitations identified using continuous operation.

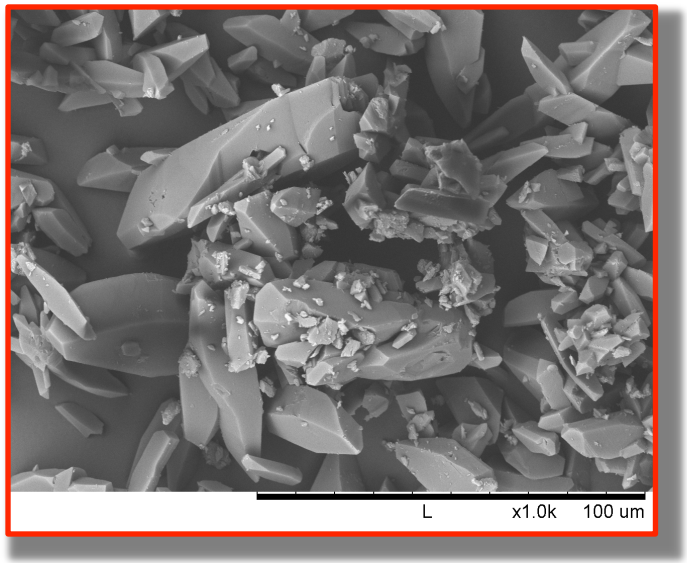
Batch process redesigned to eliminate kinetic limitations.

Duration: 20 weeks

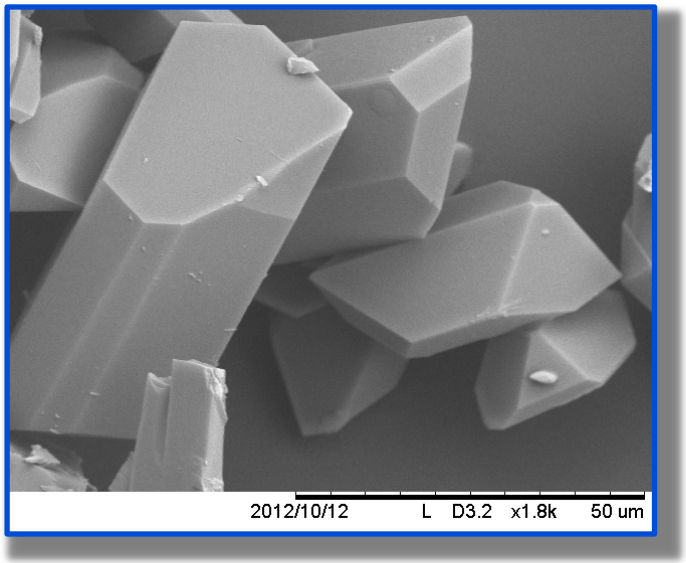
Case Study

Problem statement: Compound with poor PSD control for formulation.
D_{90} varying from 10 to 60 µm.
Batch failures on PSD and composition.

Current Process



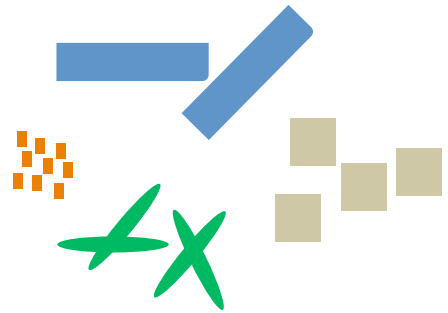
New Process



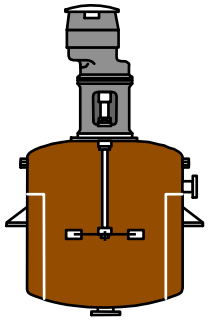
Outcome: Intermediate forms identified.
Batch trajectory designed based on phase diagram.
Solid state characteristics routinely delivered.

Duration: 16 weeks

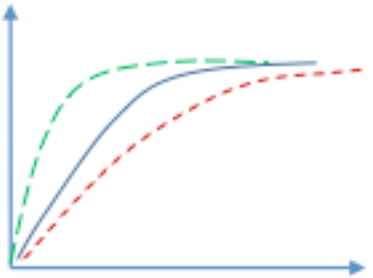
API / Drug Product Interface



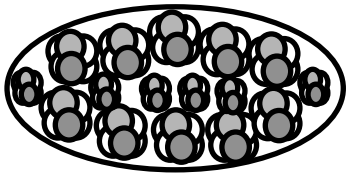
5-100 mL API Particle Design



Scale-up Validation
Formulation Supply



APC Tablet Performance Platform

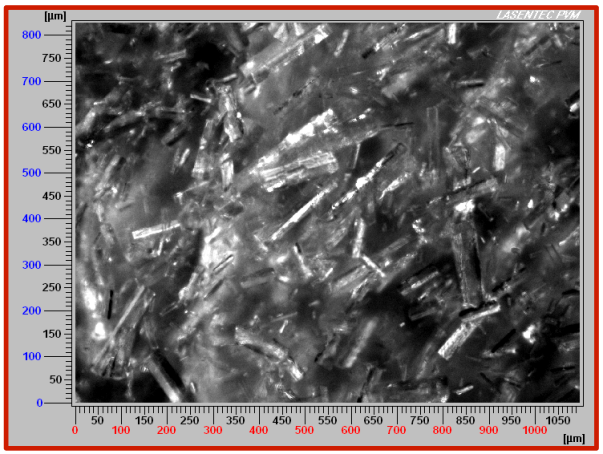


Tableting of API Options

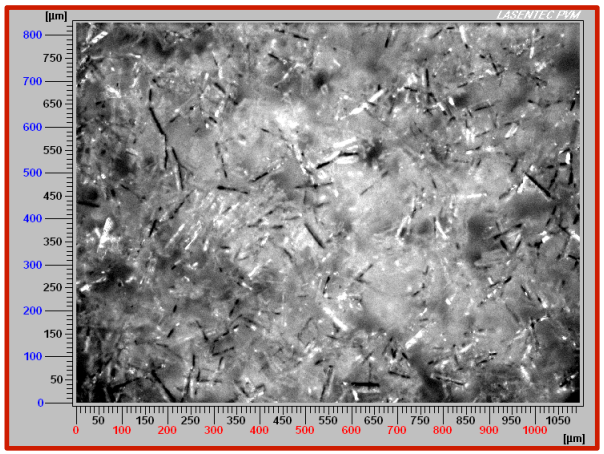
Case Study

Problem statement: Deliver drug substance to deliver targeted excipient and API release profile.

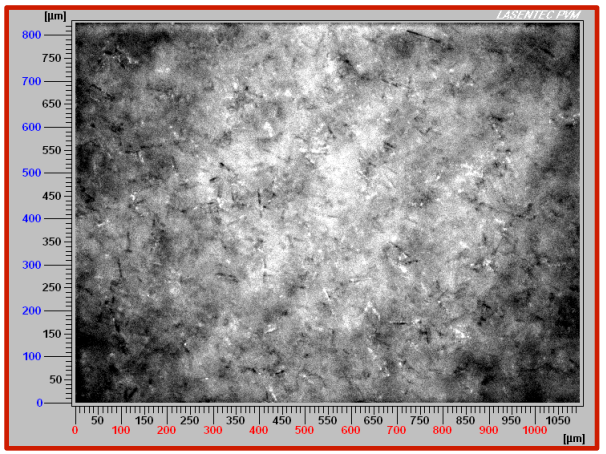
Option 1: D_{90} = 250 µm

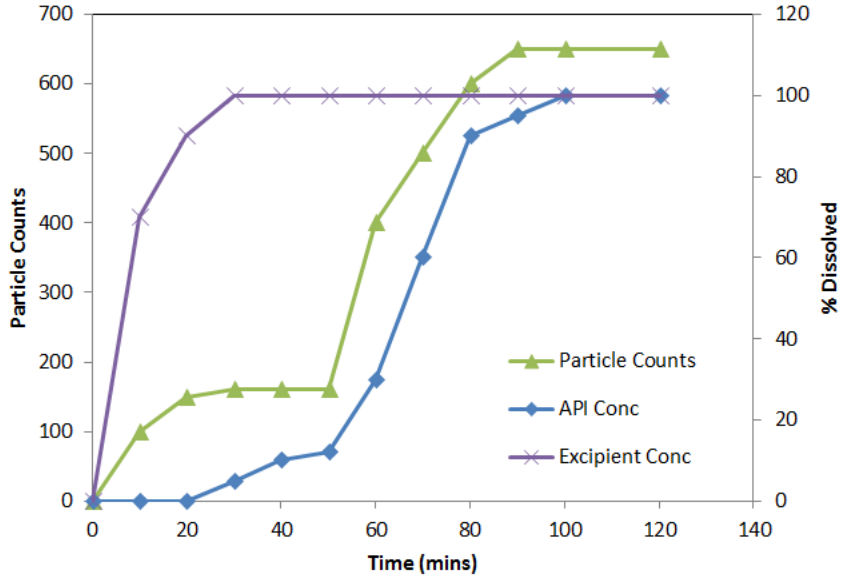


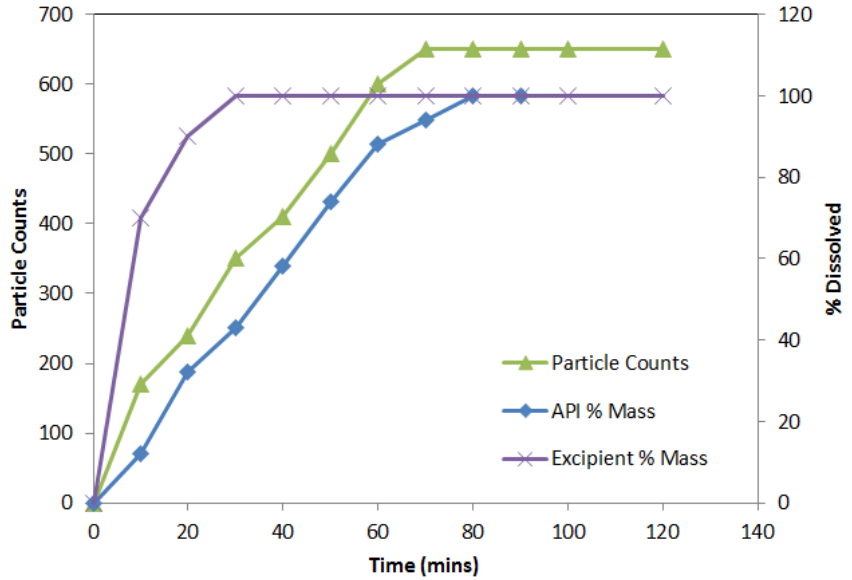
Option 2: D_{90} = 30 µm



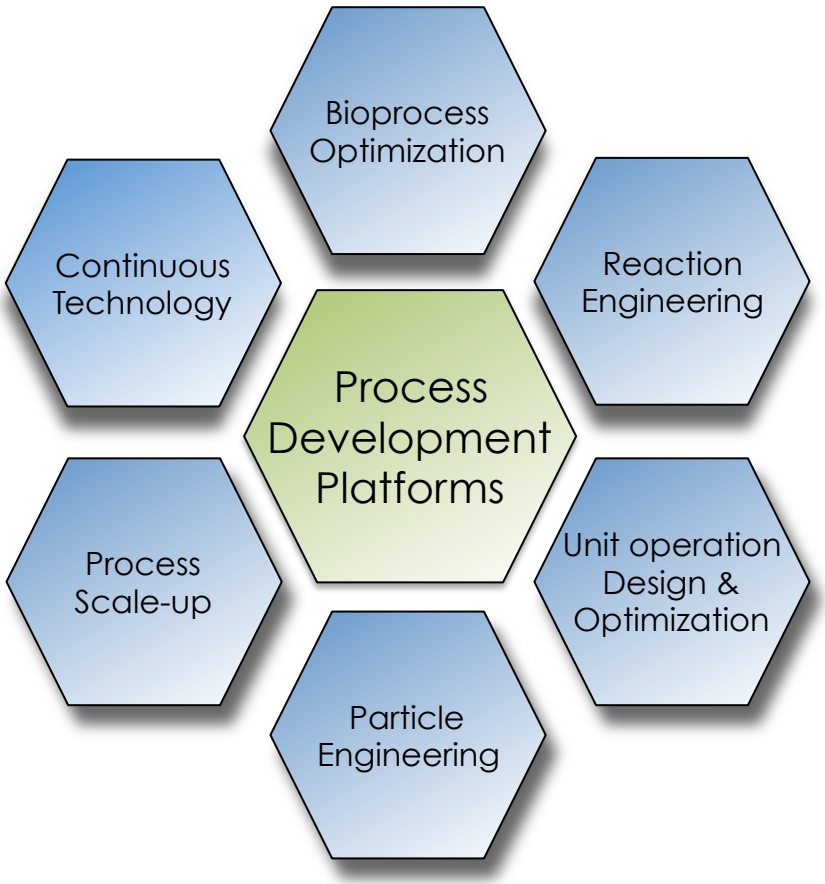
Option 3: D_{90} = 15 µm







Engineering Process Performance



Research to Manufacturing Connectivity
Connectivity and integration between research and internal / external manufacturing organisations

GMP Research Focus
Introduction of GMP experience and scalability concepts to early phase R&D

Innovation
Integration of innovative new engineering practise and technologies to early stage support and manufacturing support

Expansion of Chemical Engineering Focus
Expansion of chemical engineering applications and assessments across early, late, commercial and next generation stage products.