



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.

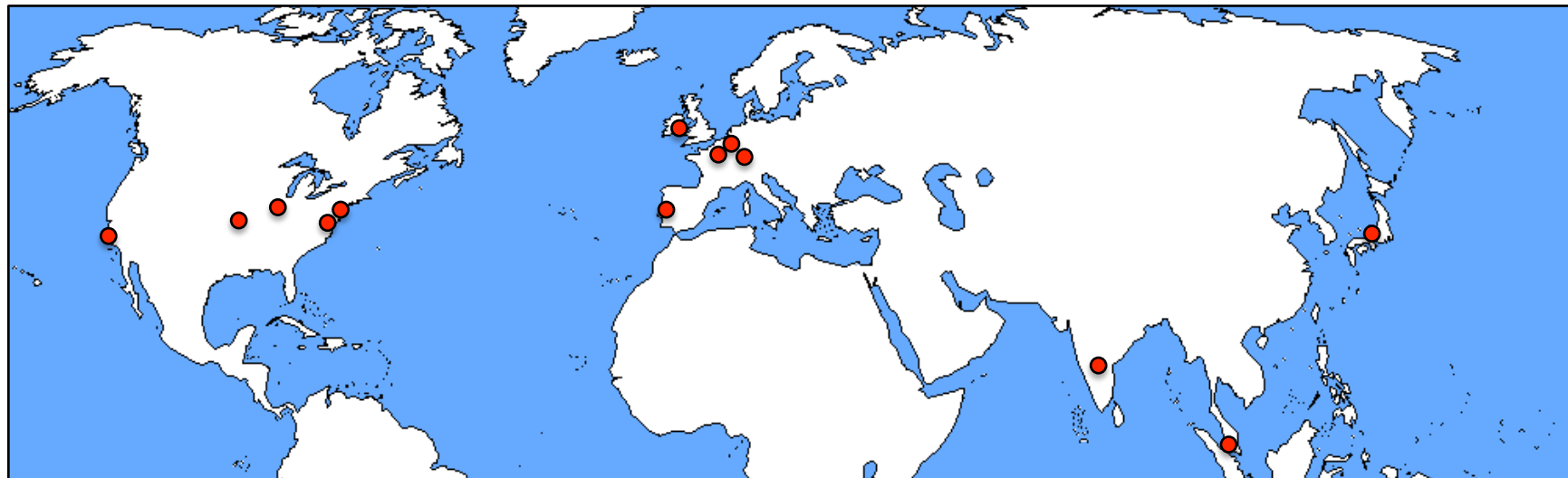


APC Introduction

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.

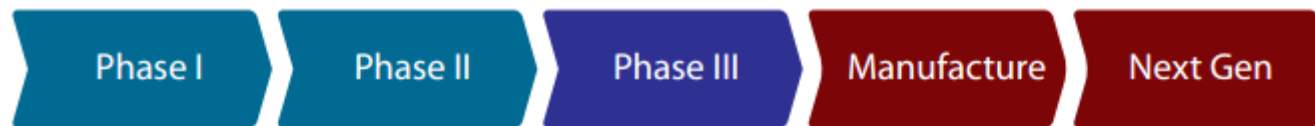
APC's highly experienced team consists of 25 chemical engineers, and process and analytical chemists. Team currently expanding to 30.



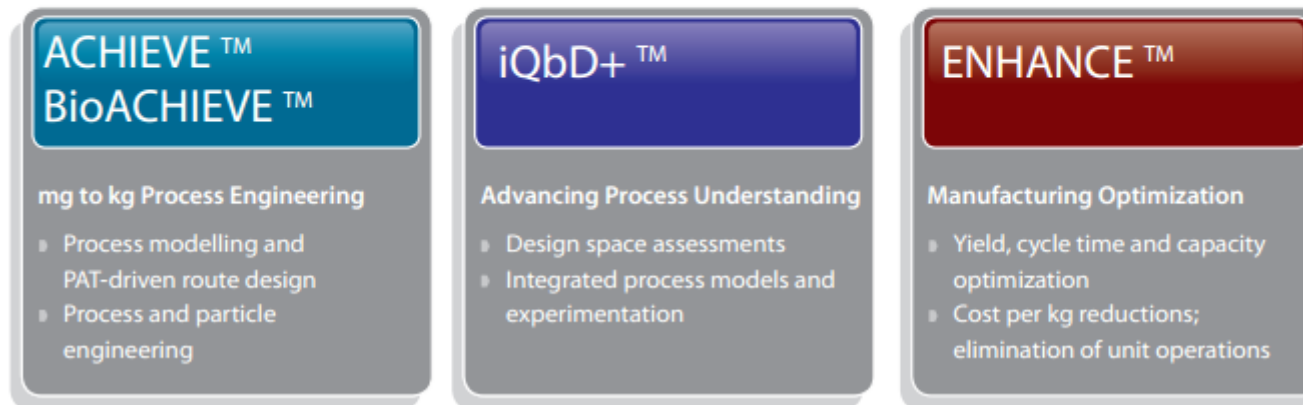


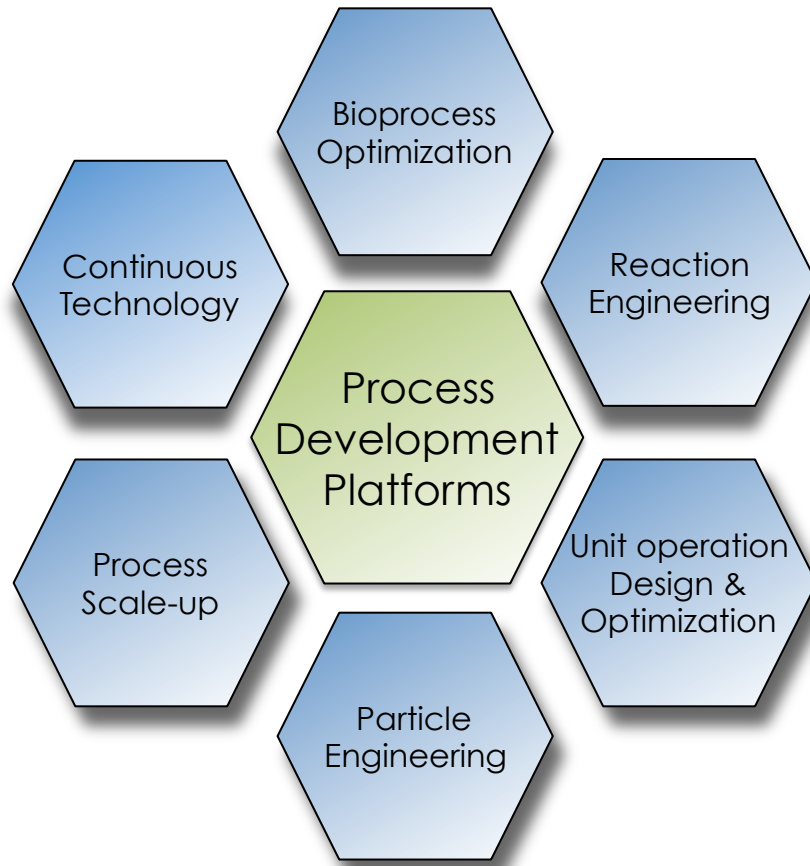
APC Introduction

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



Our Proprietary Technologies & Services





Objective:

Use Engineering tools (PAT, modelling, control etc) to provide

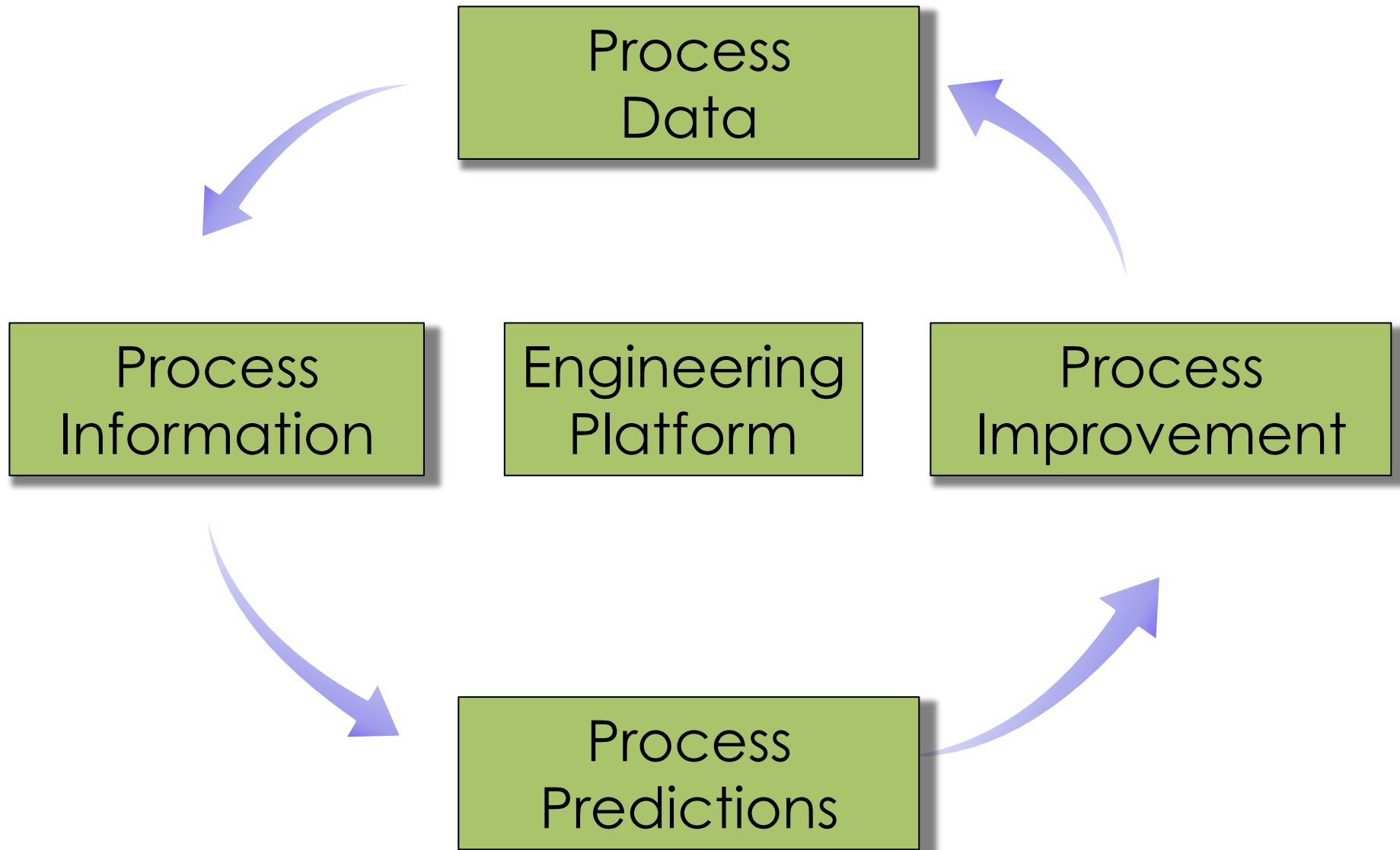
- better understanding
- more robust scale-up
- reliable risk analysis
- reliable identification of CPPs.

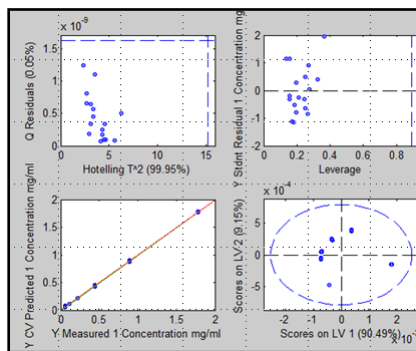
Focus on

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

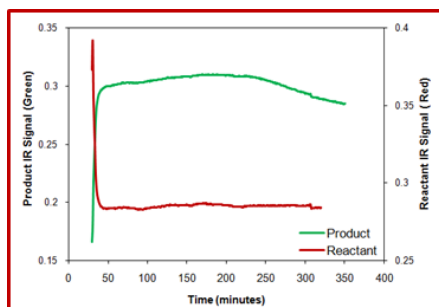


APC Platforms

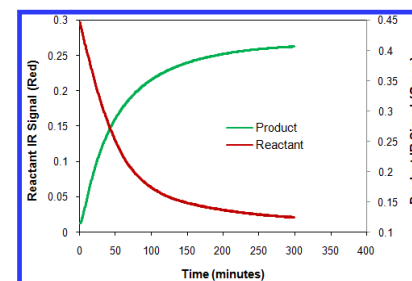




Chemometric method & model development



In Situ Process Monitoring



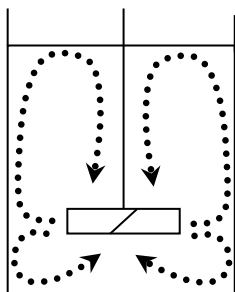
Model Inferred Reaction Optimization

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

Kinetic & Engineering Process Modelling

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

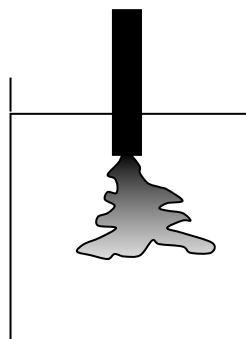
Macro-Mixing



Scale of tank, blend time

$$\tau_c = V/Q_c$$

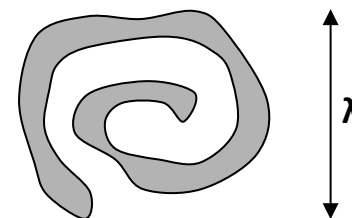
Meso-Mixing



Scale of feed pipe
- Reaction plume

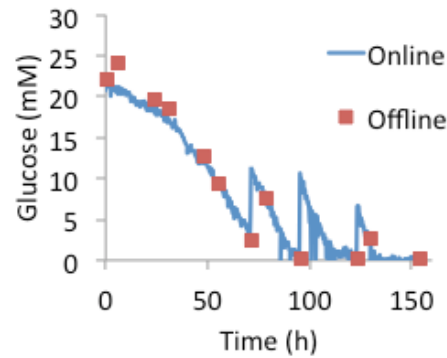
$$\tau_D = Q_{\text{FEED}} / u D_T$$

Micro-Mixing



Smallest scale of mixing
- Molecular diffusion

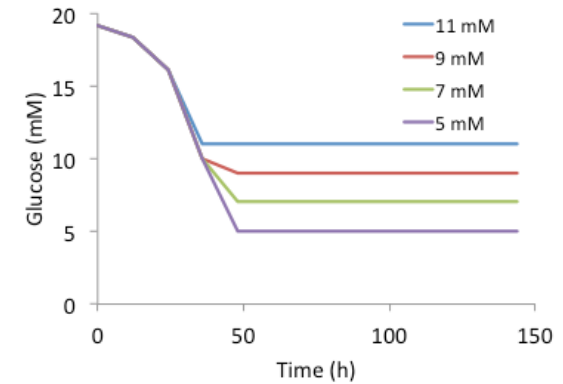
$$\tau_E = 17.24(v/\epsilon)^{0.5}$$



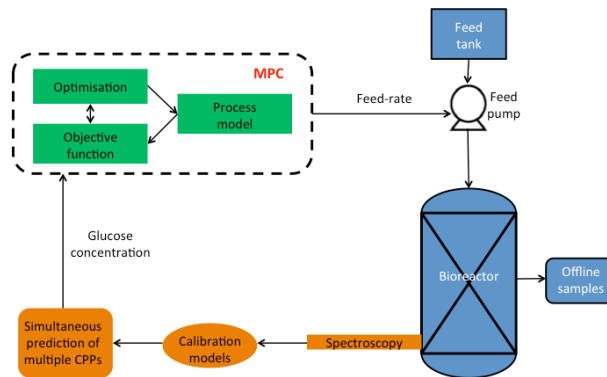
Advanced monitoring

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

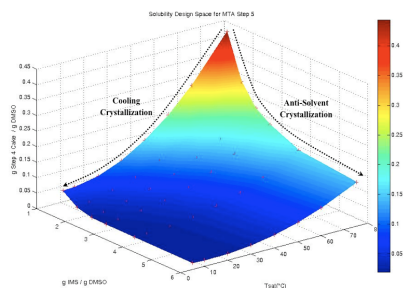
Process Monitoring



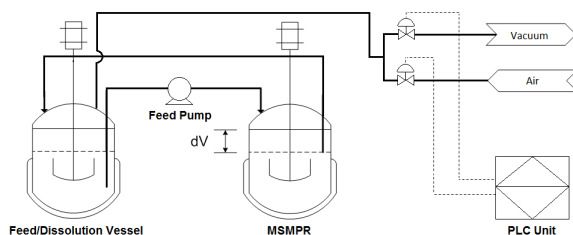
Bioprocess Optimization



Bioprocess Development Platform

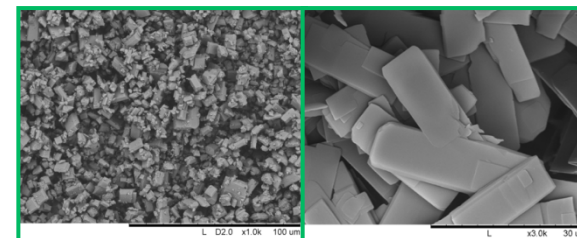


Solubility Design Space Assessment



APC Reactor Technology

ACHIEVE™



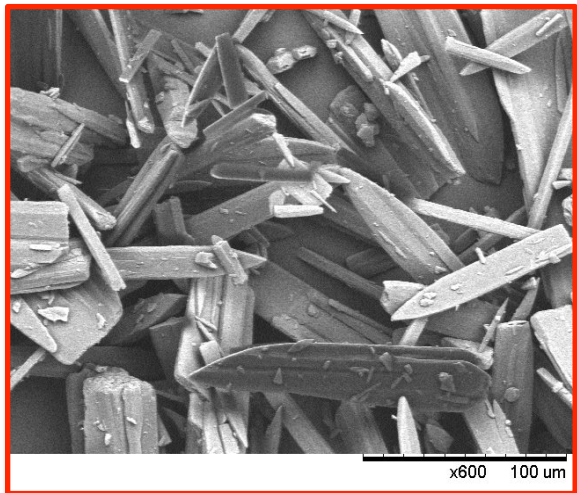
Engineered Particle Attributes

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

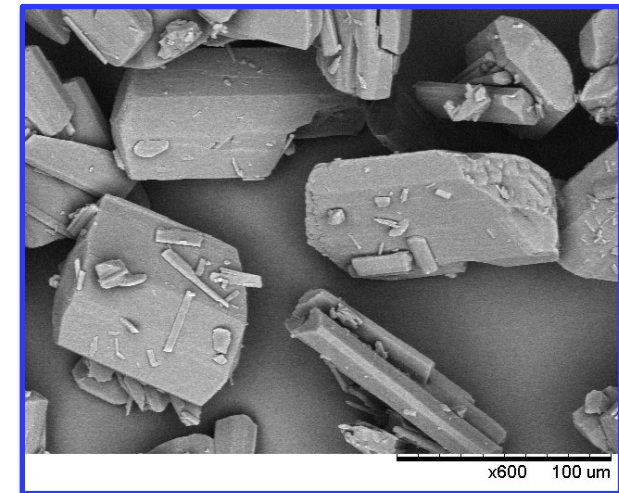
Transient and Kinetic Data Extraction

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

Current Process



New process

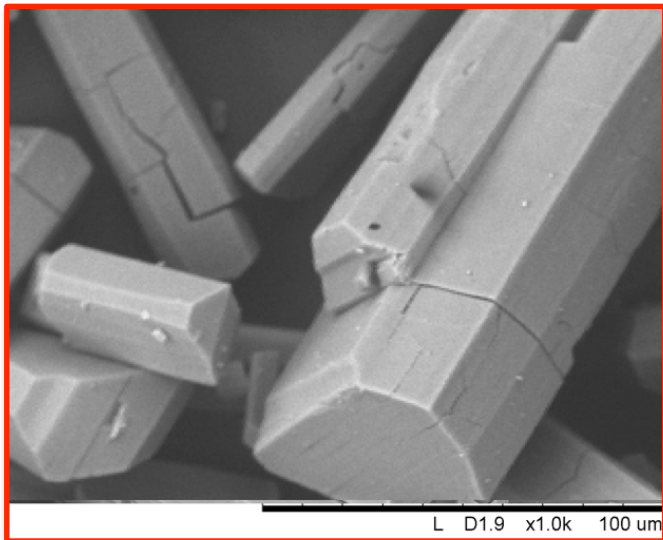


Outcome: Process improved to provide required crystal aspect ratio for milling.
Wet milling process successfully scaled-up to GMP manufacture.
Material characteristics for optimal formulation performance provided.

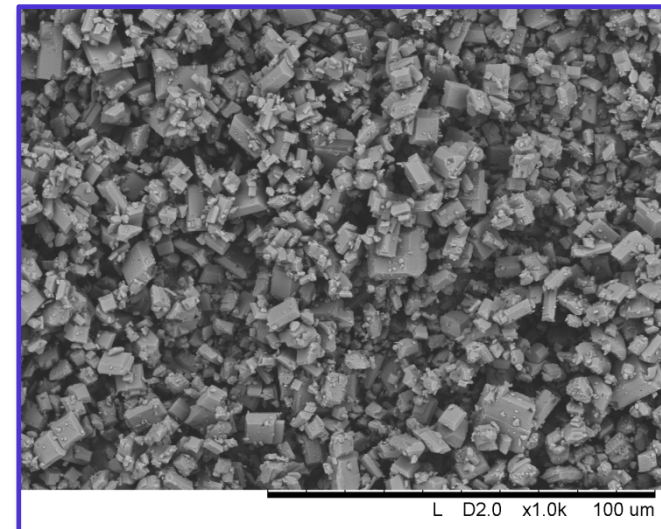
Duration: 12 weeks

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

Current Process



New Process

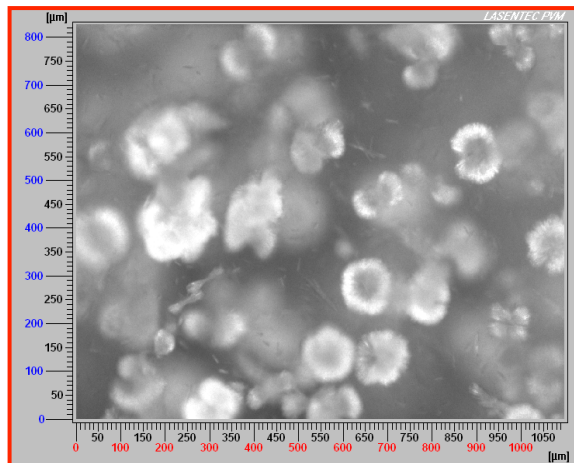


Outcome: Process modified within filing.
Micronisation eliminated.
Process scale-up enabled.

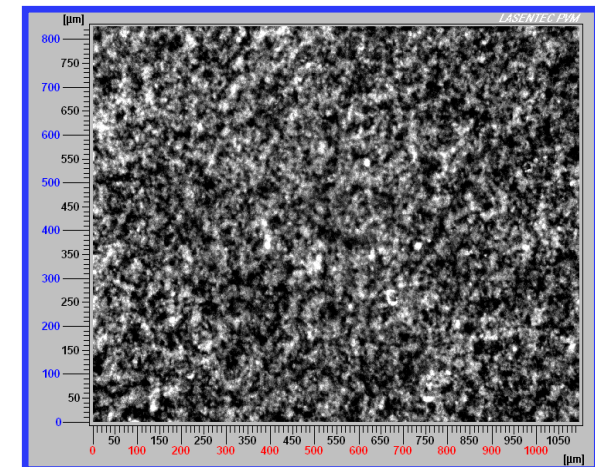
Duration: 14 weeks

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

Novel Calibration Free Technique

Based on single peak height.

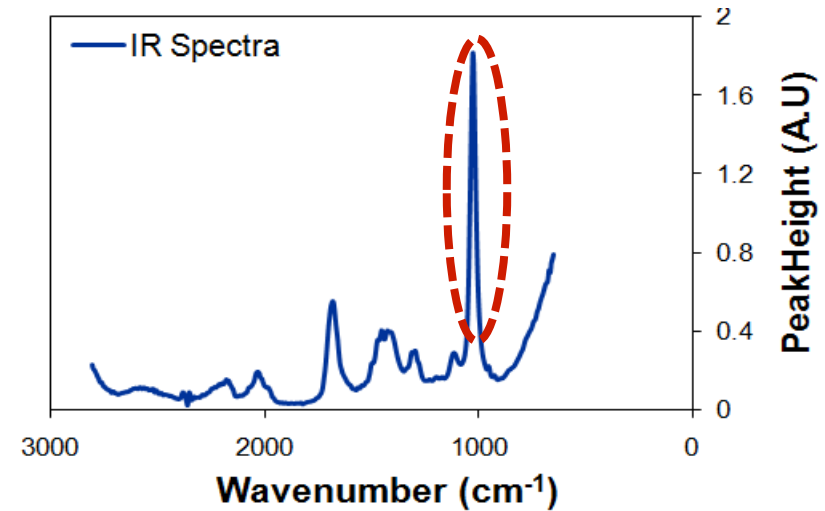
No empirical chemometric model required.

Solubility measurement integrated into method.

Independent of location in metastable region.

Temperature effects irrelevant.

Concentration expressed in terms of peak height.

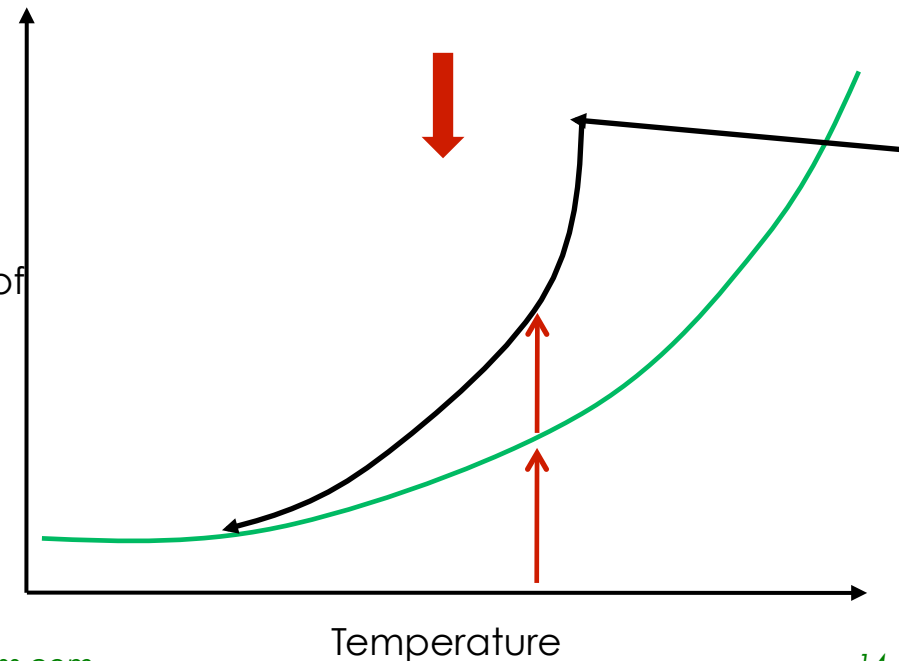


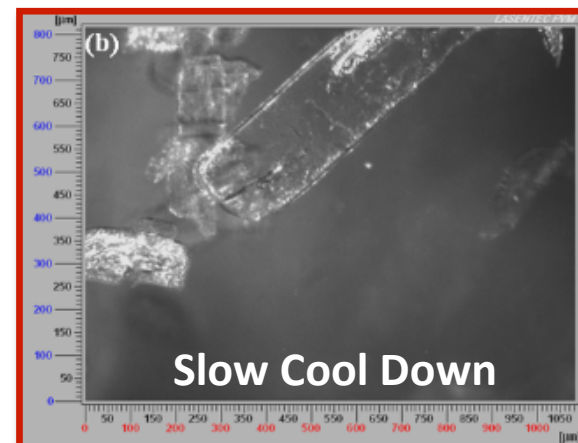
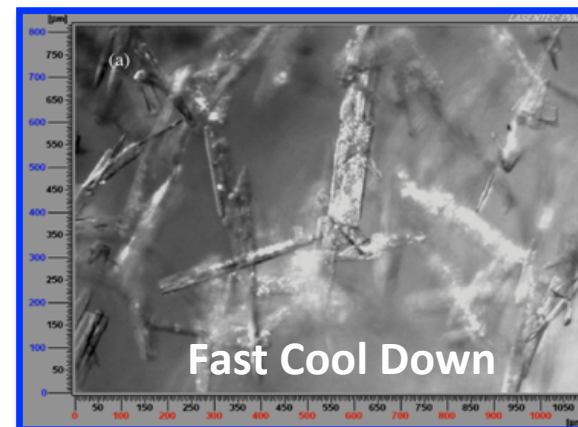
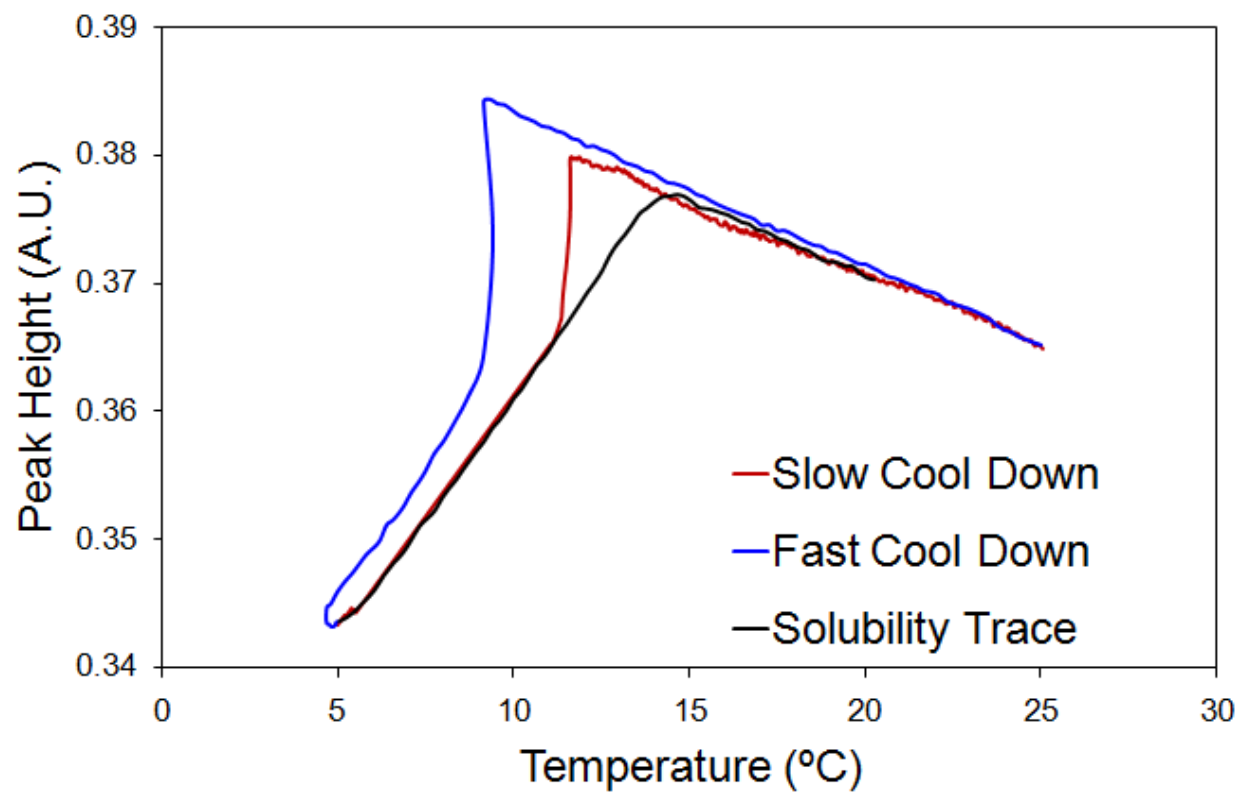
"Supersaturation tracking for the development, optimization and control of crystallization processes"

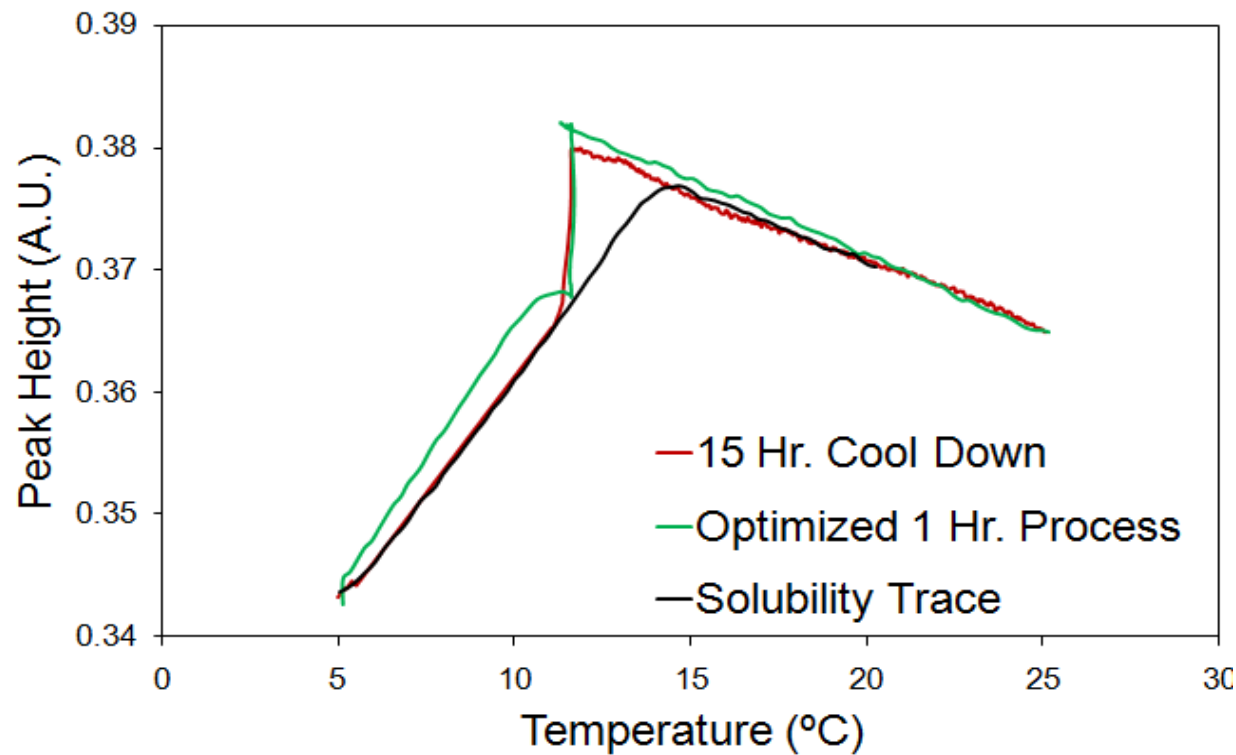
Barrett, M. et al.

Chem. Eng. Res. Des., **88**, 1108-1119, 2010.

Peak Height of
Solute (-)

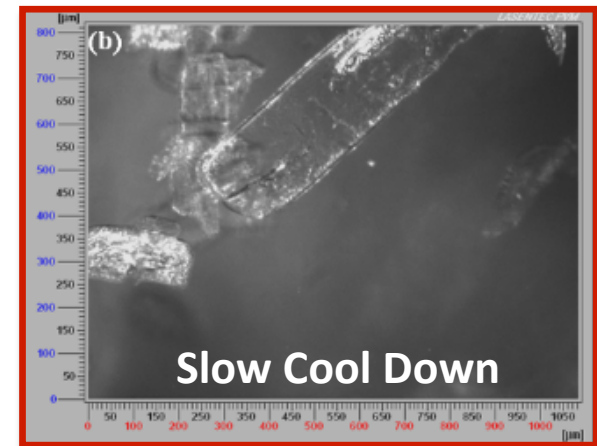




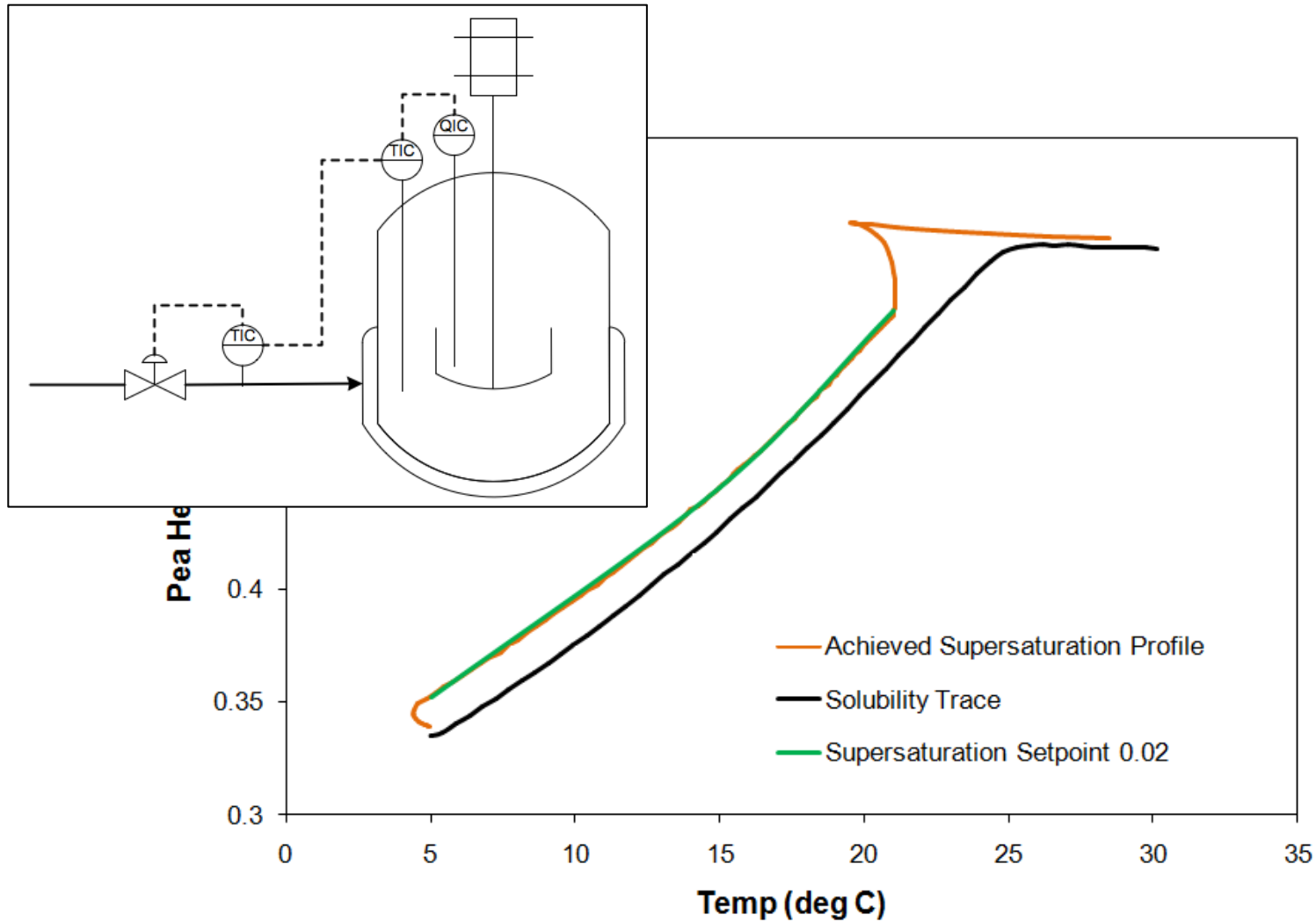


Rapid process evaluation & design method.

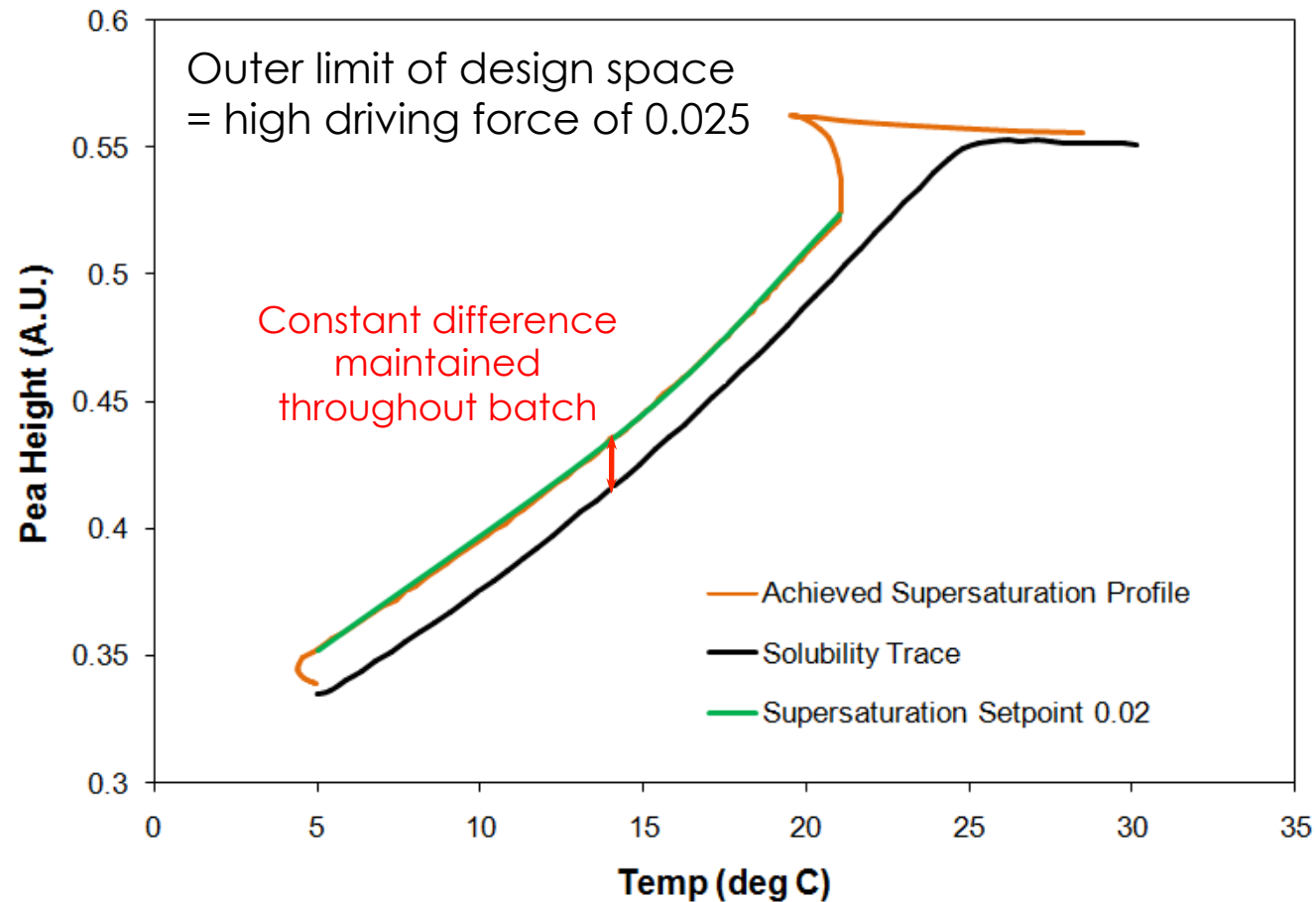
- days vs months



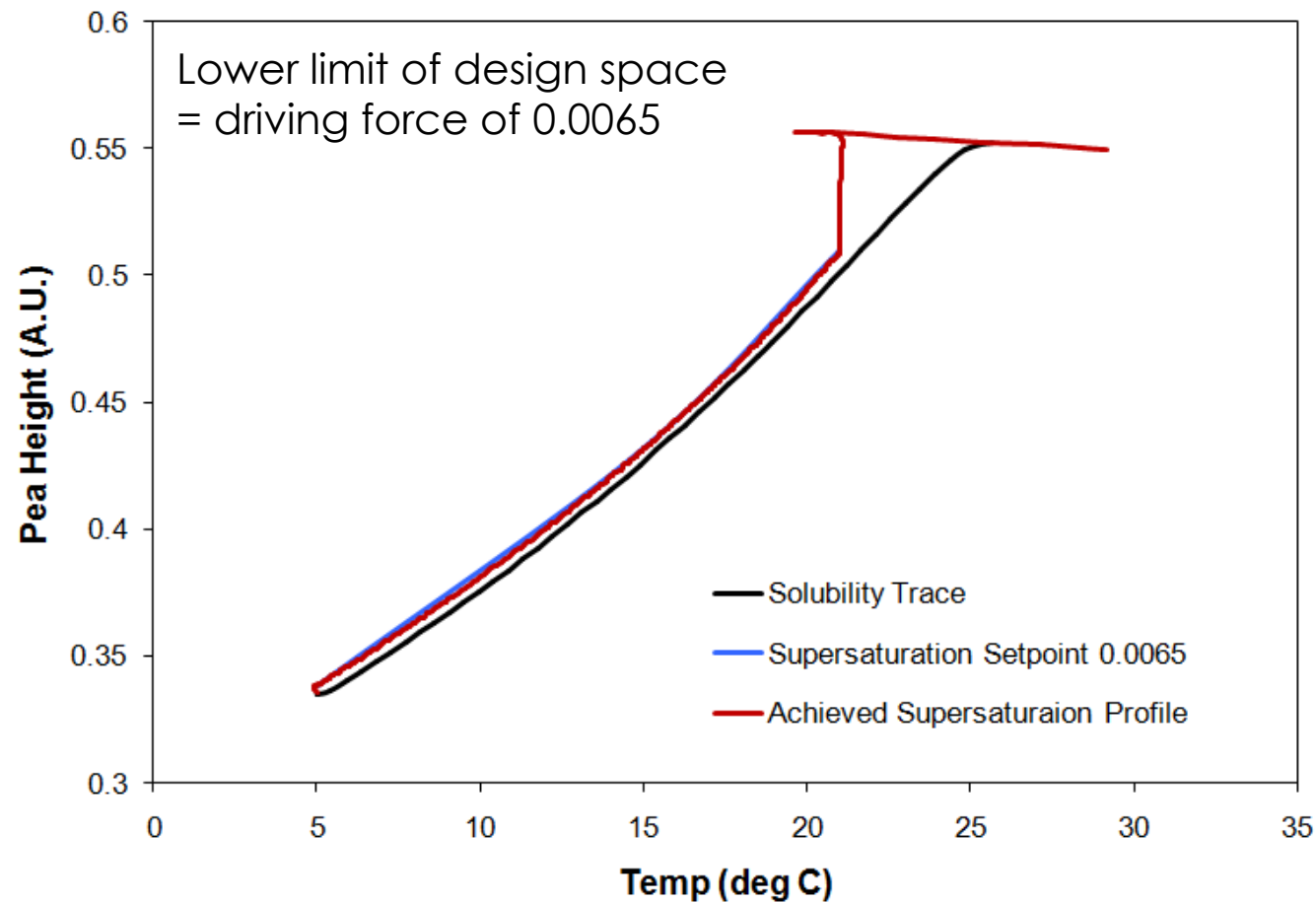
Problem statement: Develop lean process to deliver consistent PSD



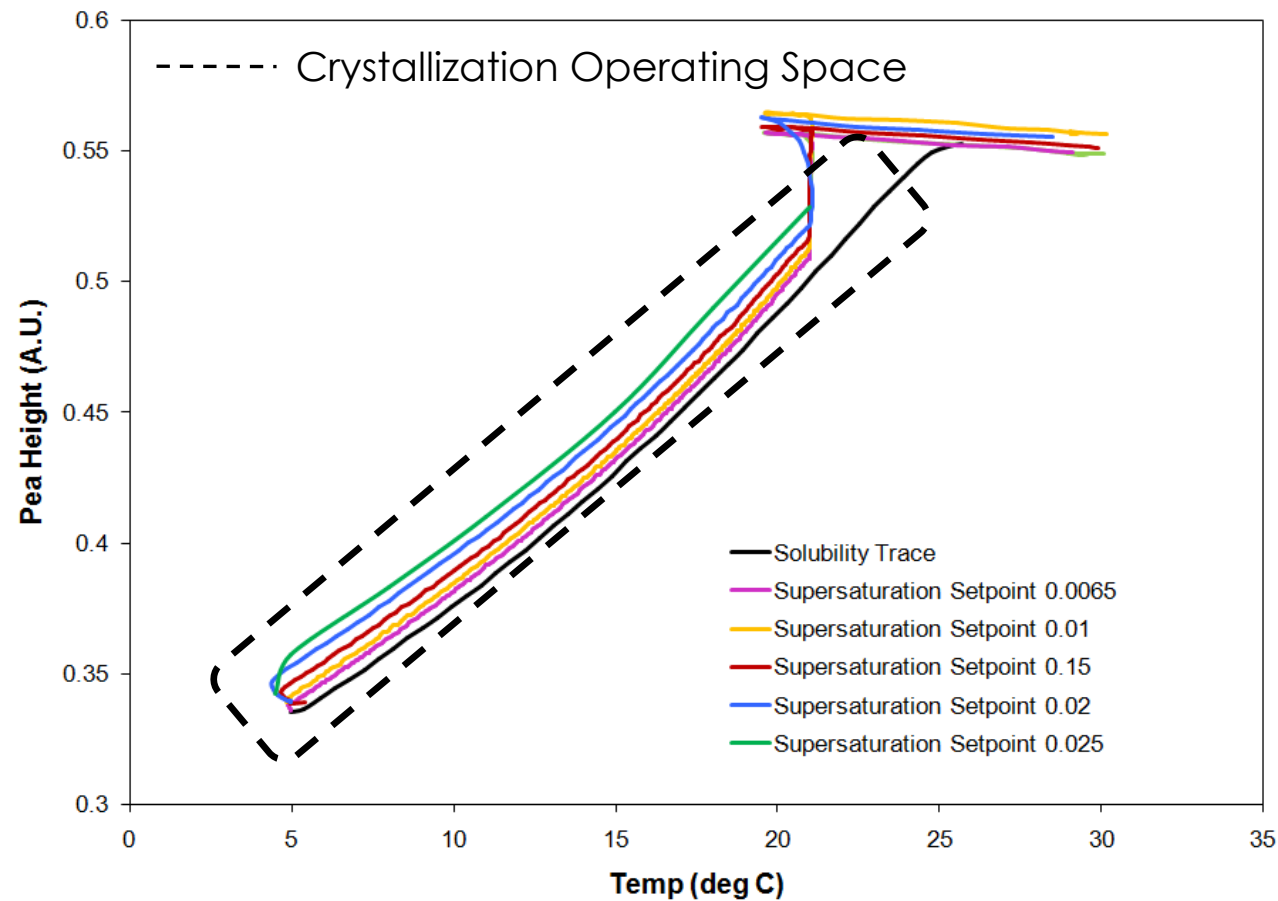
Problem statement: Develop lean process to deliver consistent PSD



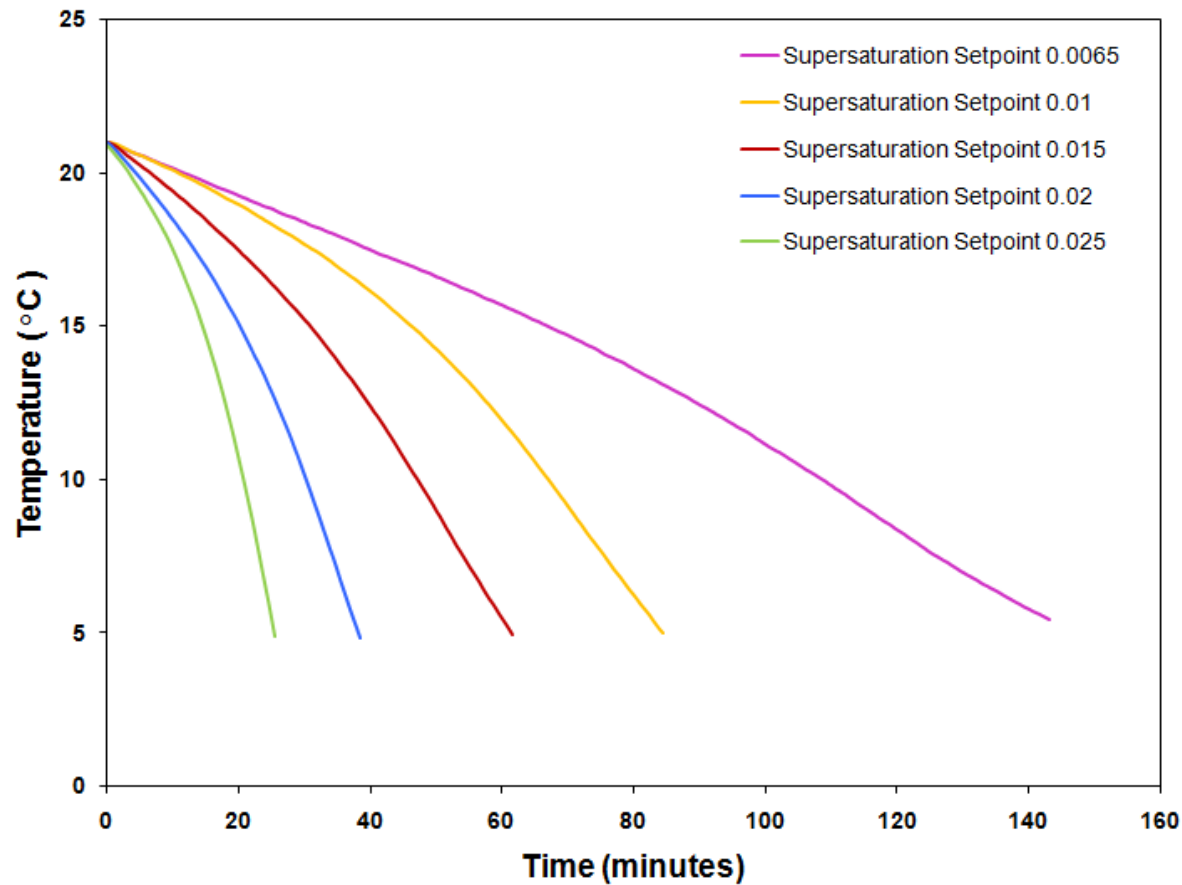
Interrogate various supersaturation trajectories using feedback control



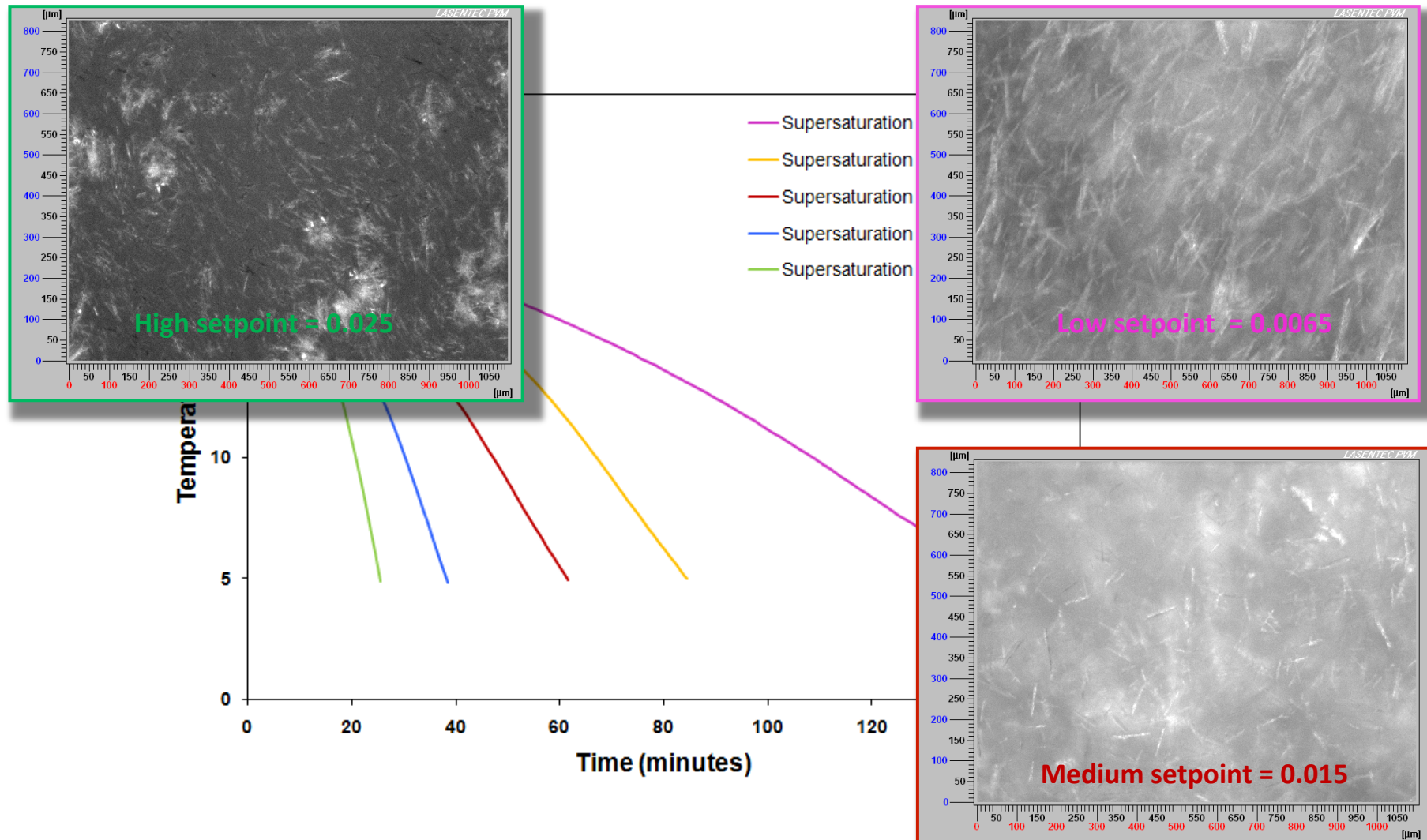
Rapidly establish operating space for crystallization process



Optimum cooling profile developed systematically



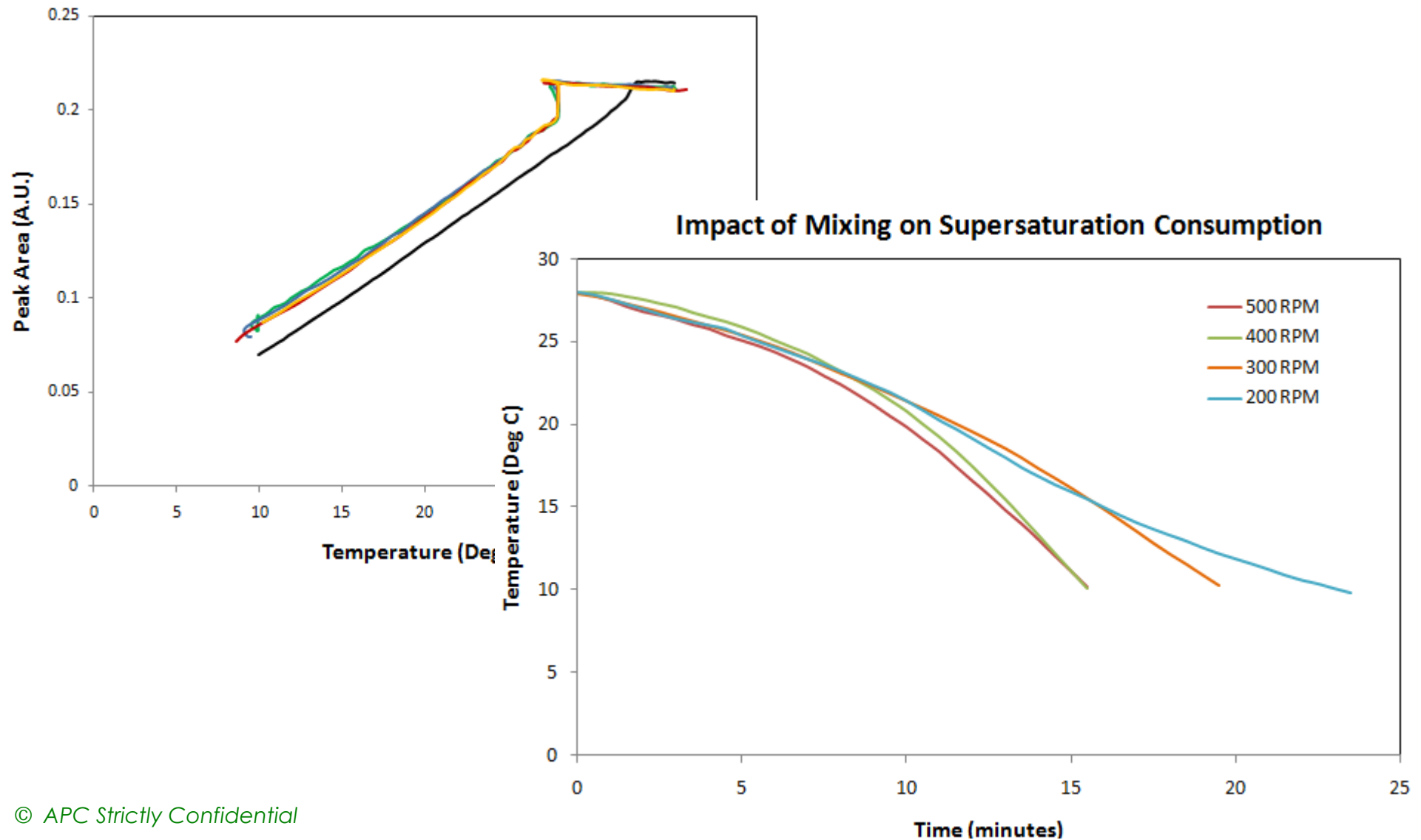
Optimum cooling profile developed systematically



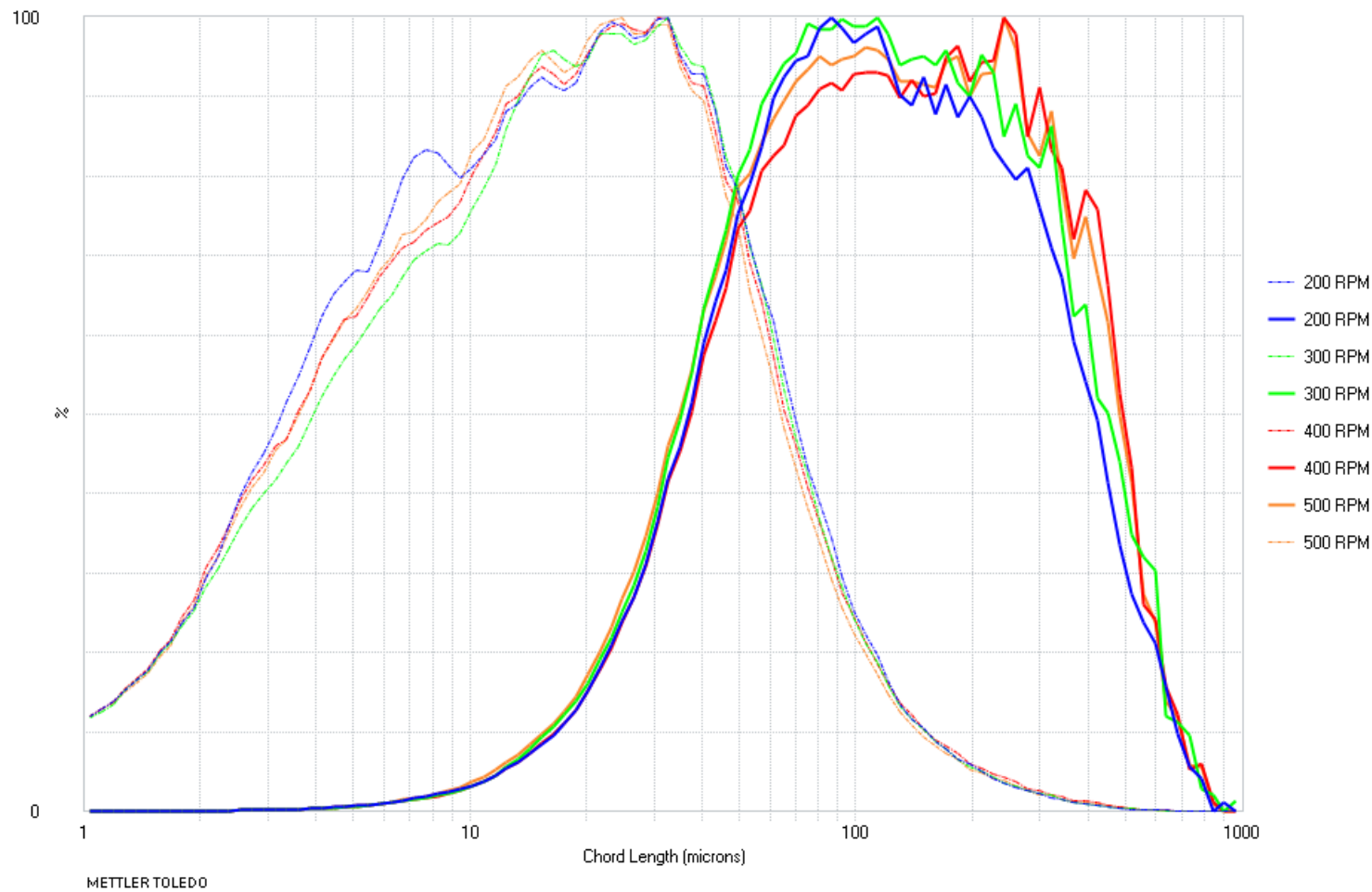


Case Study

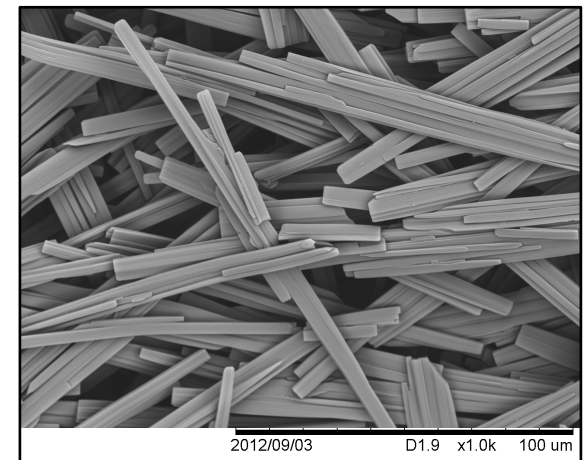
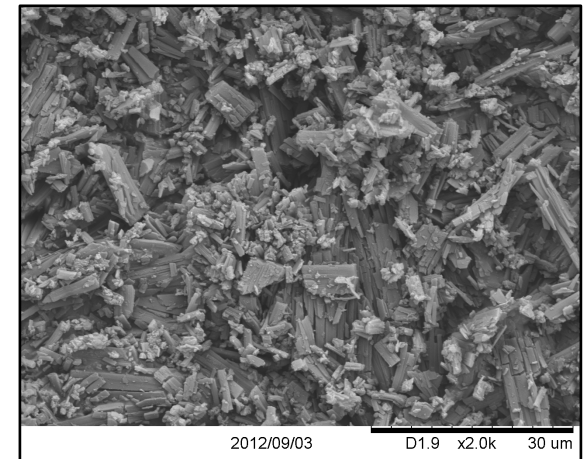
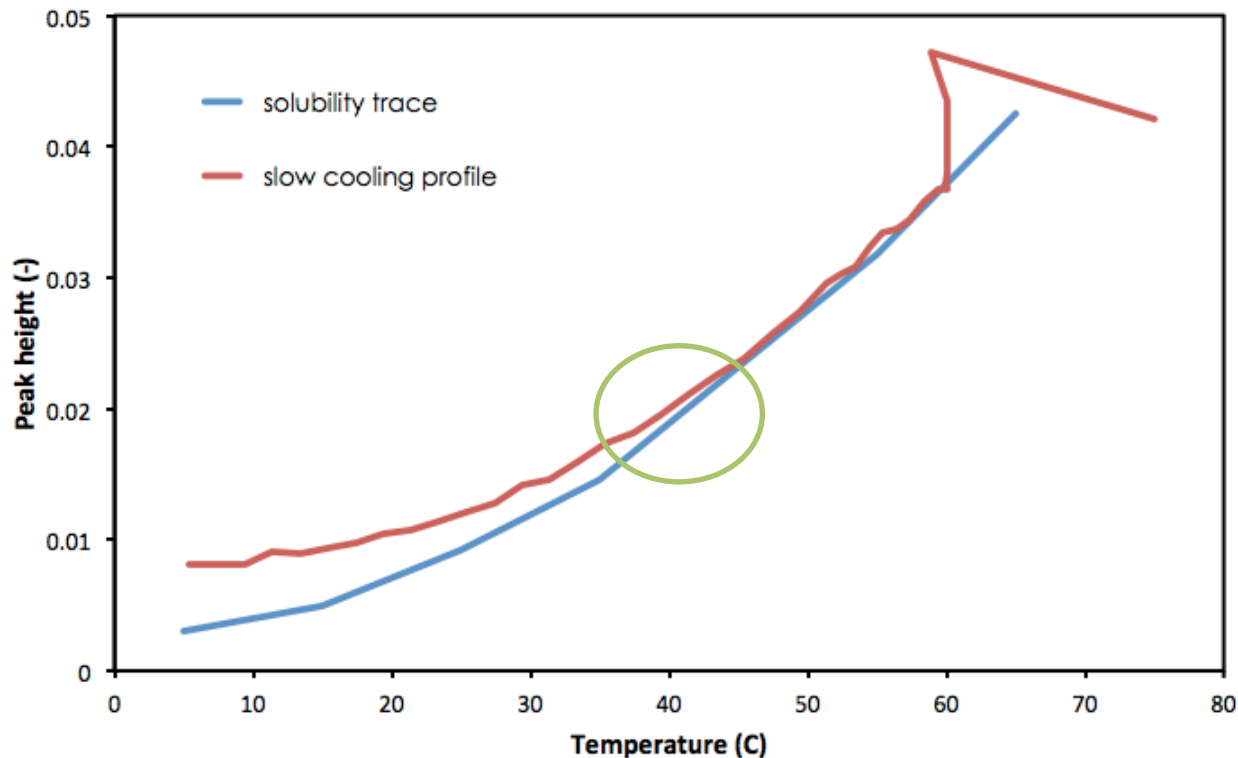
Develop of protocols to identify the scalability of crystallization process



Develop of protocols to identify the scalability of crystallization process



Problem statement: Develop robust batch process to deliver consistent product

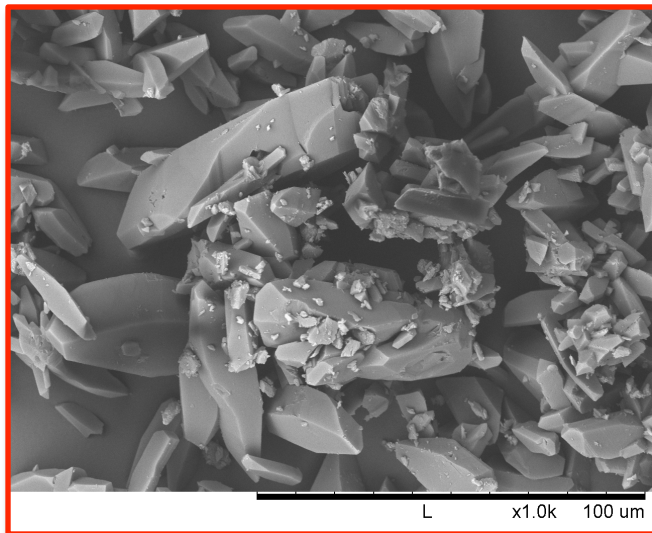


Outcome: Kinetic limitations identified using continuous operation.
Batch process redesigned to eliminate kinetic limitations.

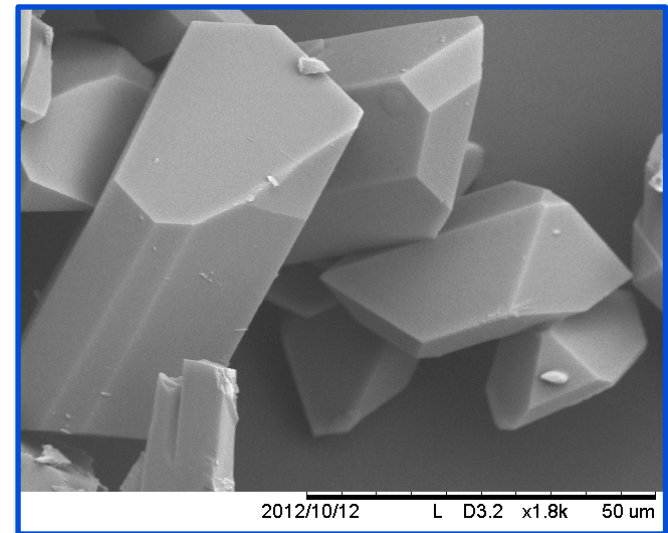
Duration: 20 weeks

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

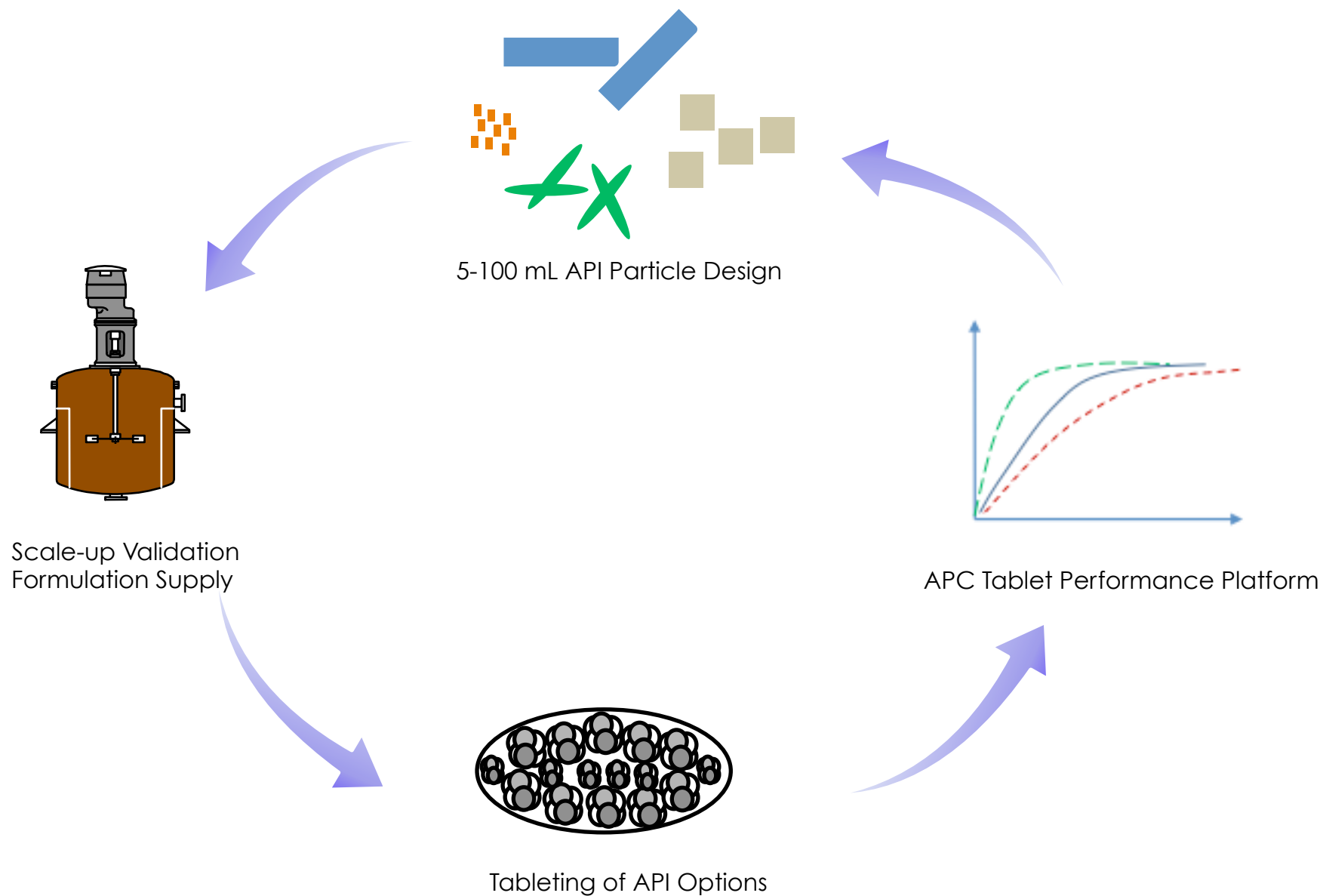


New Process



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

Duration: 16 weeks

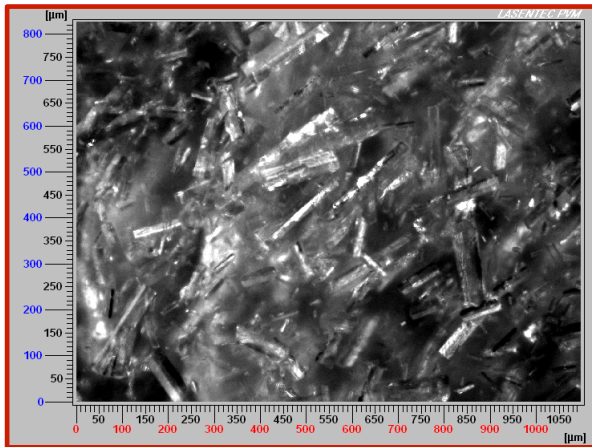




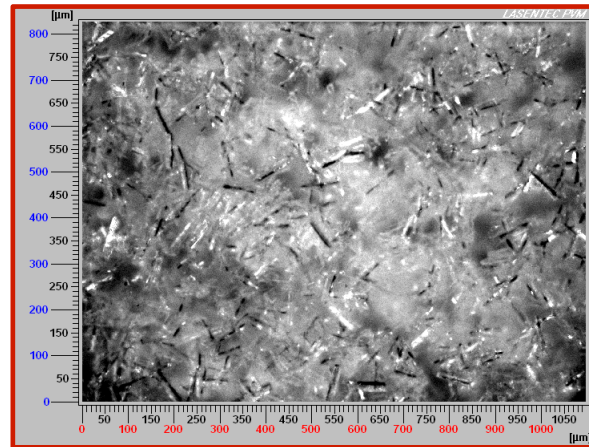
Case Study

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

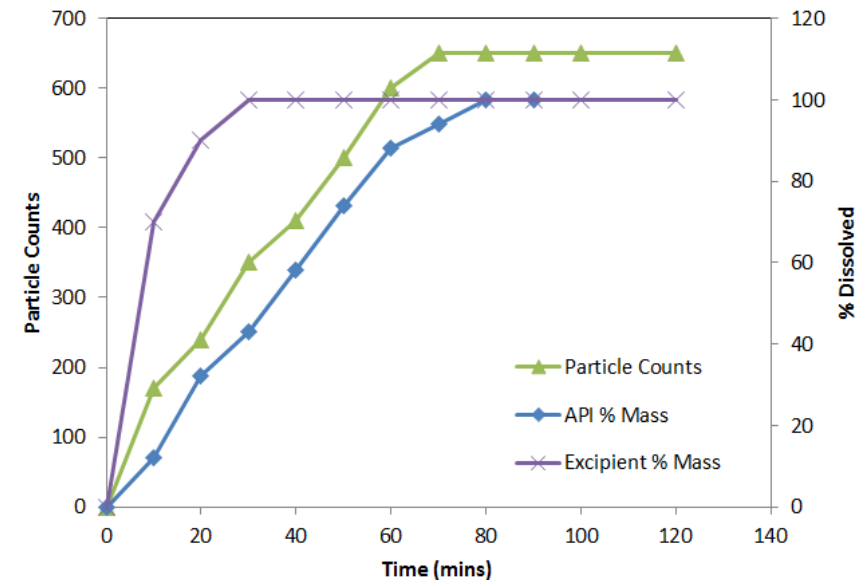
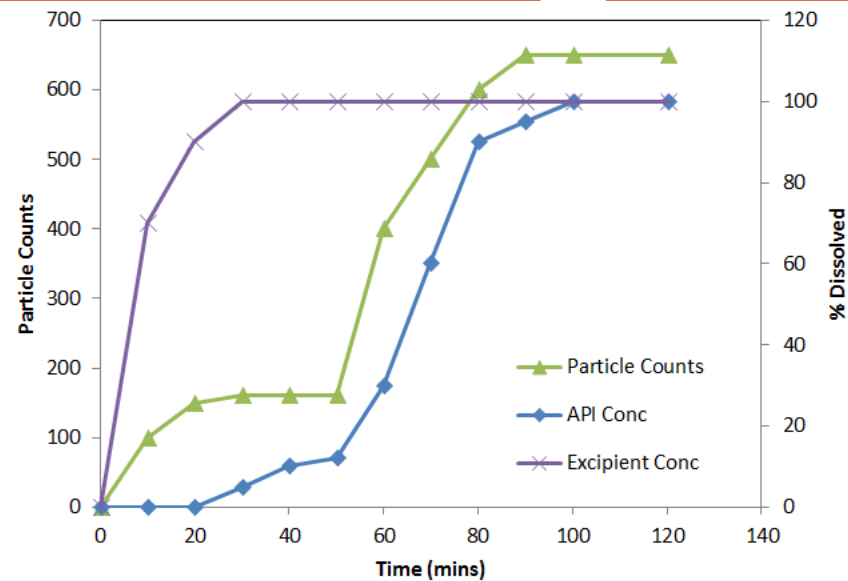
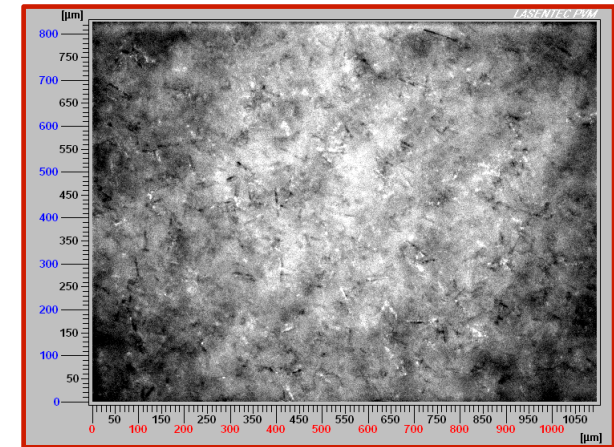
Option 1: $D_{90} = 250 \mu\text{m}$

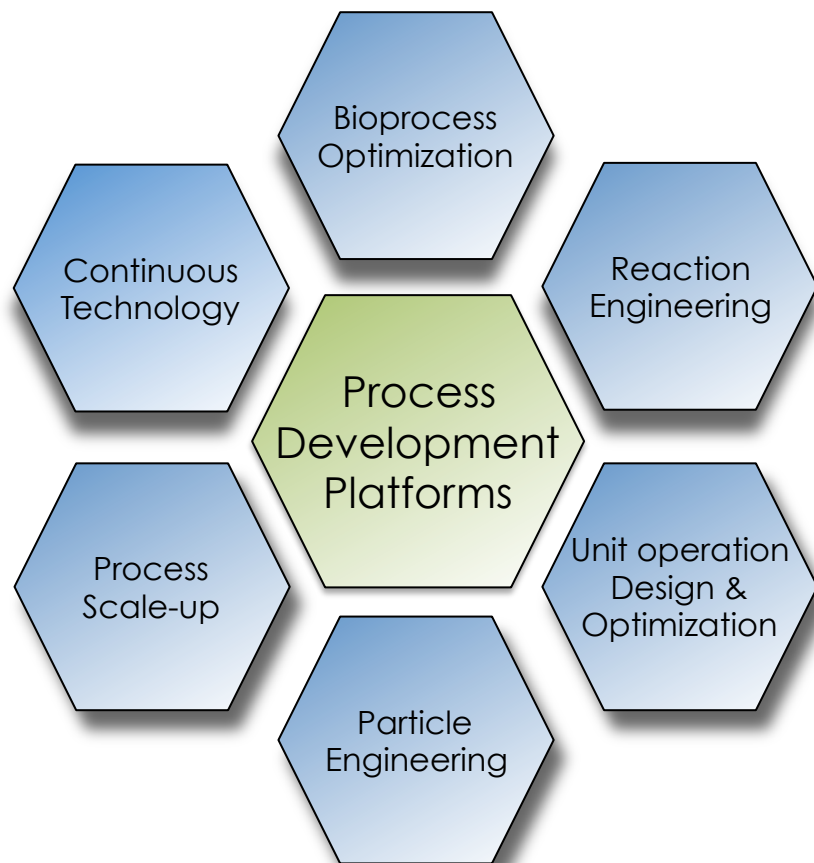


Option 2: $D_{90} = 30 \mu\text{m}$



Option 3: $D_{90} = 15 \mu\text{m}$





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.