Developing Pharmaceutical Continuous Crystallization Processes - Knowledge & Gaps

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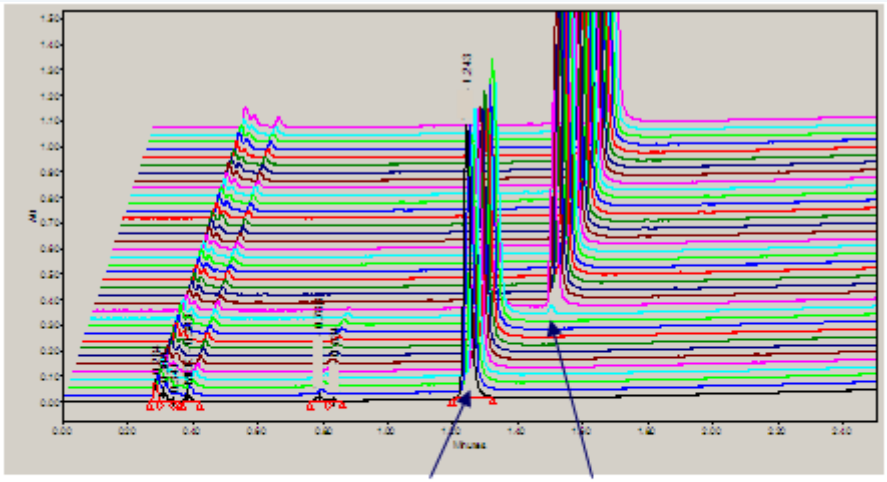
Product Development

Context - Innovative Manufacturing Initiative
Move from Batch, to End to End Continuous Processing

Reaction → Extraction →Reaction → Reaction → Reaction



The moment when the final reagent flow commences final intermediate is consumed and API product is formed

The power of PAT:
At line HPLC

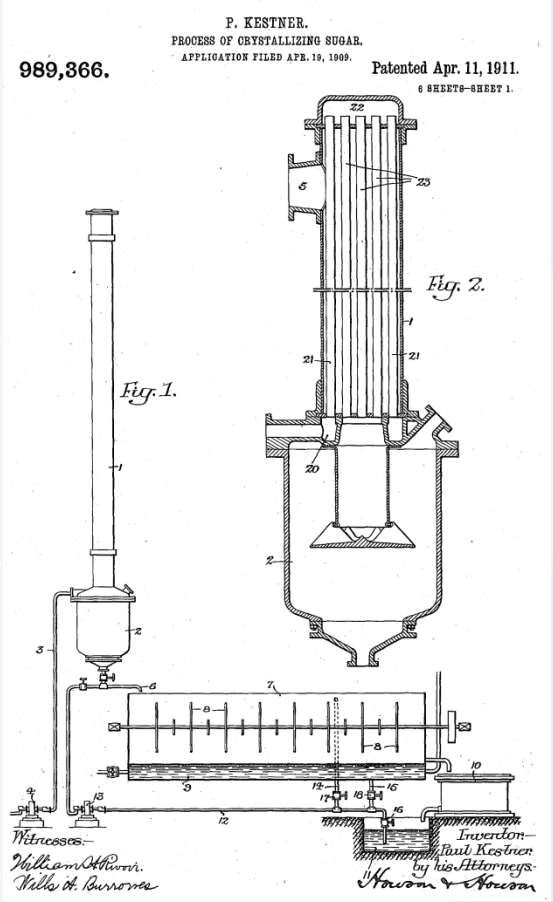
Extraction → Distillation → Crystallisation → Isolation

Task: Provide a multi-product, scalable, continuous particle formation & purification system delivering consistent API suitable for direct formulation.

Purity Chem & Phase	Batch produced NCE A is recrystallized for phase control & is very pure. NCE A forms many solvates
Particle Attributes	Particle size distribution, crystal habit, bulk properties suitable for direct formulation
Process Understanding	Suitable for a QbD filing using on / at line process monitoring & control
Consistency	Consistent attributes over extended process duration over a range of scales
Multi product	Applicable to most NCEs without major equipment redesign

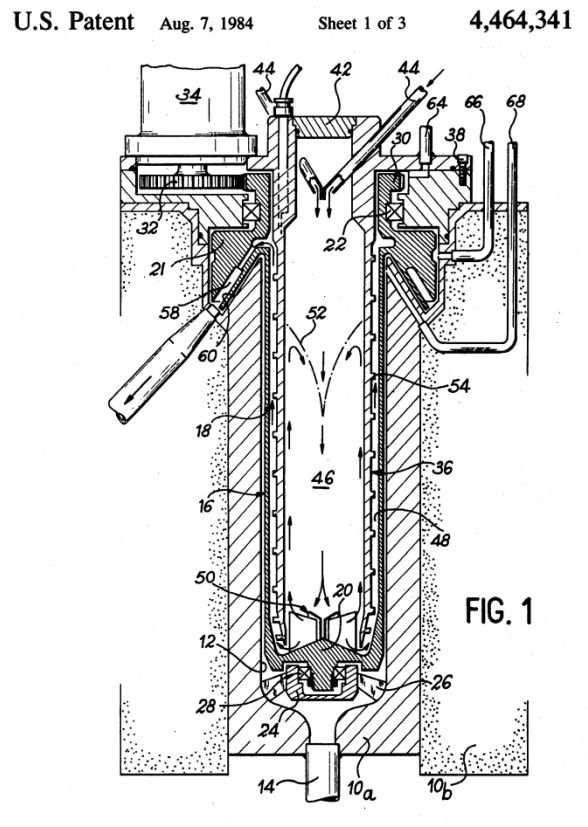
So what does 100 years of continuous crystallization teach us?

- To minimise encrustation operate at low supersaturation
- Slow growth delivers purification
- Suppress nucleation, to make large particles for easy separation
- Scale up / down is difficult
- Successful design requires an extensive data set collected at scale
- Operation at small scale is very challenging



How about continuous precipitation

- Potential to deliver fine particles
- Operate at high supersaturation to get high nucleation rates and minimal growth
- Delivers little purification
- Favours extreme crystal habits (needles / filaments)
- Large variations in special distribution of supersaturation make scale up difficult
- Risk of nucleating a meta-stable phase of polymorphic materials which then transforms during isolation



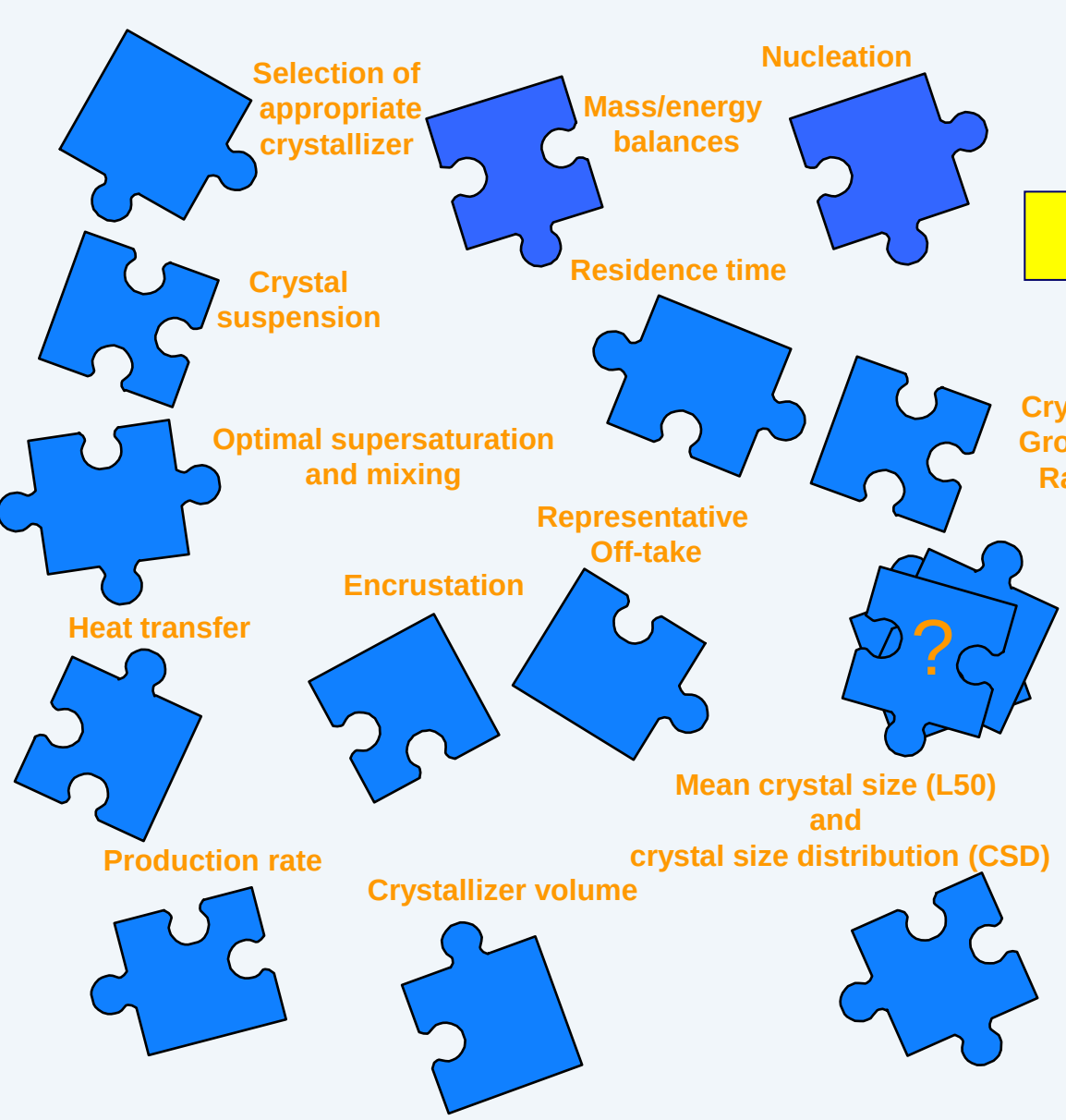
Ideas to take forwards

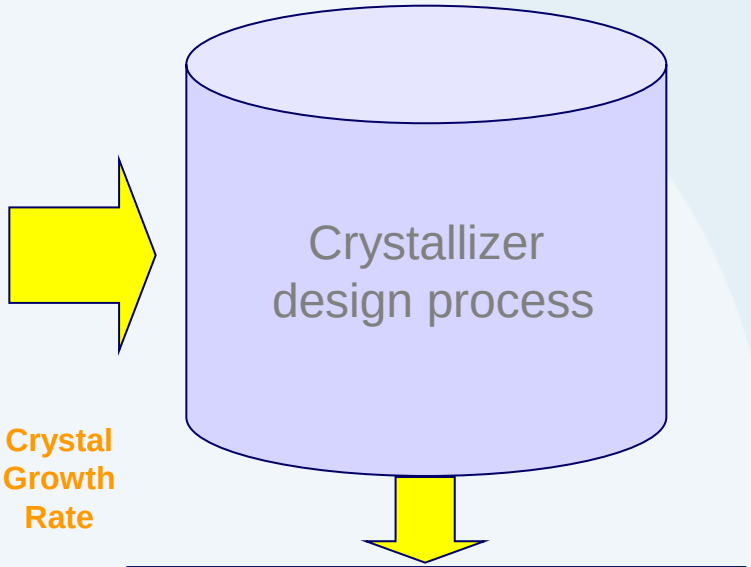
- Minimise encrustation by operating at low supersaturation
- Obtain purification by slow growth

Manipulate nucleation rate independently of supersaturation to achieve target size

How?

Technical design aspects to consider

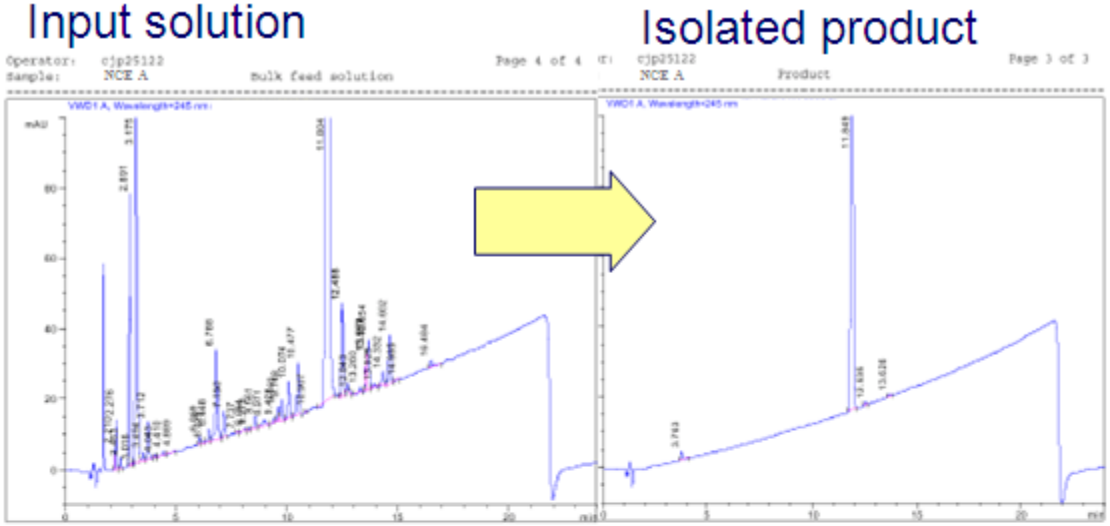


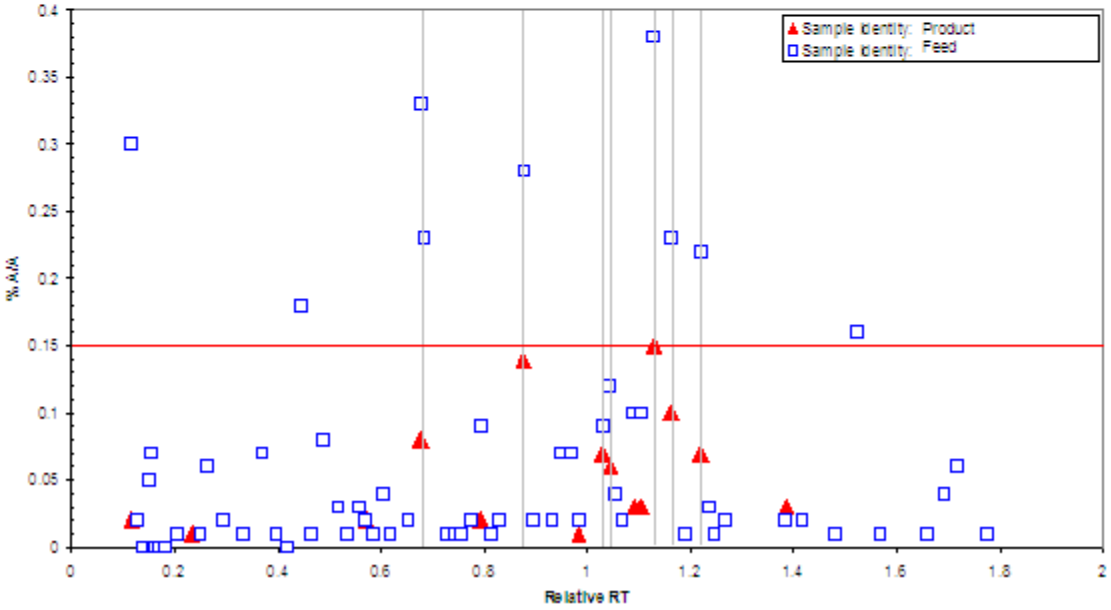


PRODUCT WITH CONTROLLED

Purity
Size distribution
Habit
Form
Consistency

NCE A Purification





Crystallization achieves significant purification but a few impurities need to be controlled.

Control strategy:

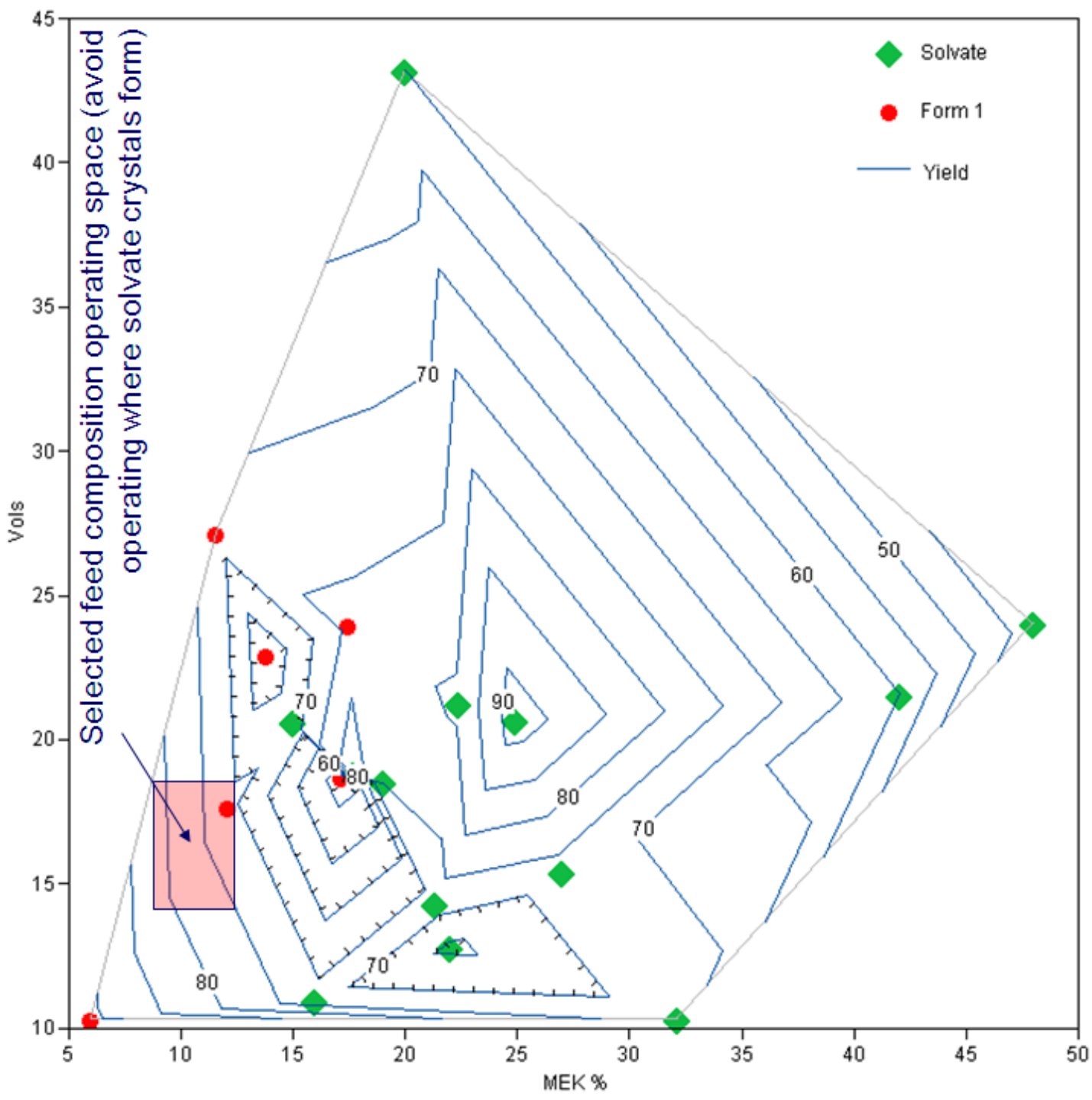
Control input quality

- Starting materials
- Reaction conditions

Monitor reactions by on-line assay

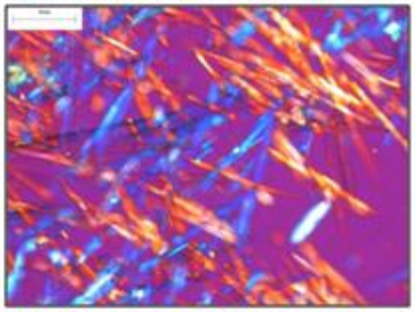
Control crystallization conditions.

Solvates concerns dominate NCE A crystallization development

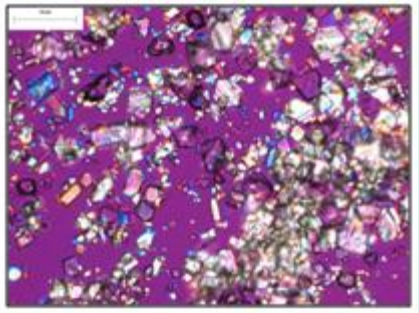


Batch DOE
To find level of MEK in MIBK to get yield & avoid MEK solvate

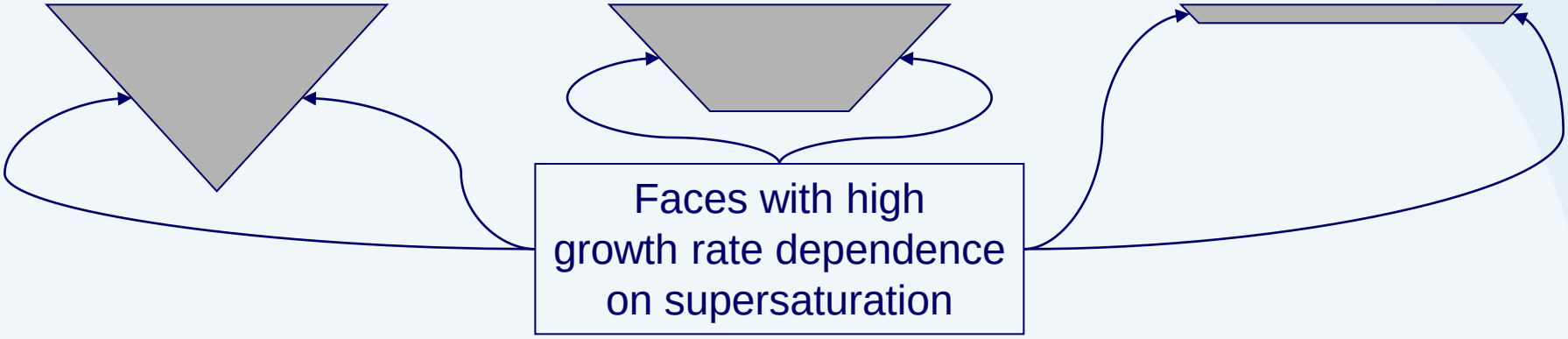
Low MEK concentration form unsolvated crystals

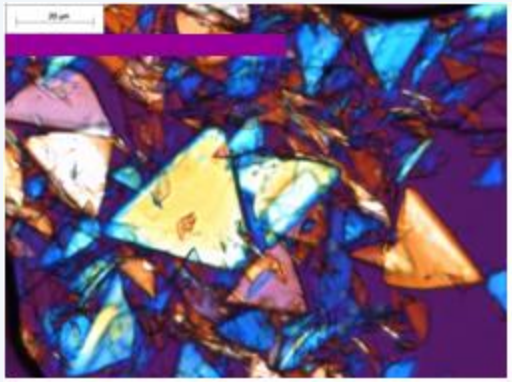


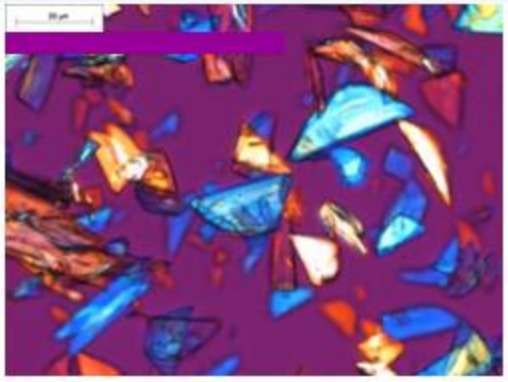
MEK > ca 15% tend to form MEK solvate

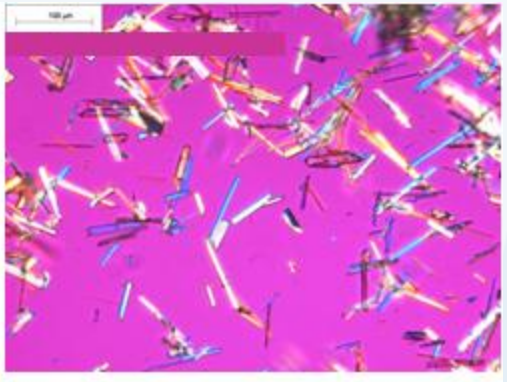


Impact of Supersaturation on Crystal habit



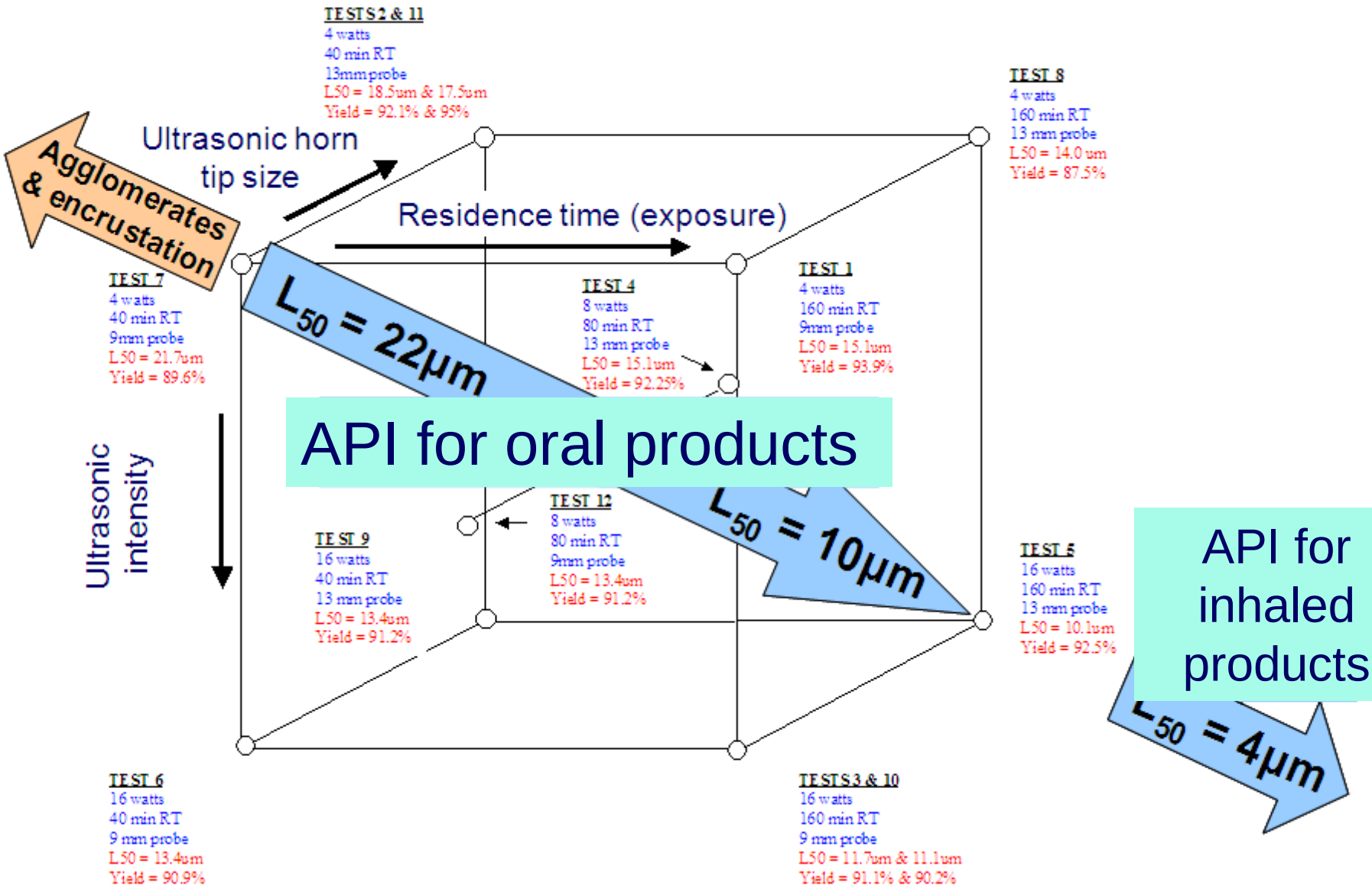






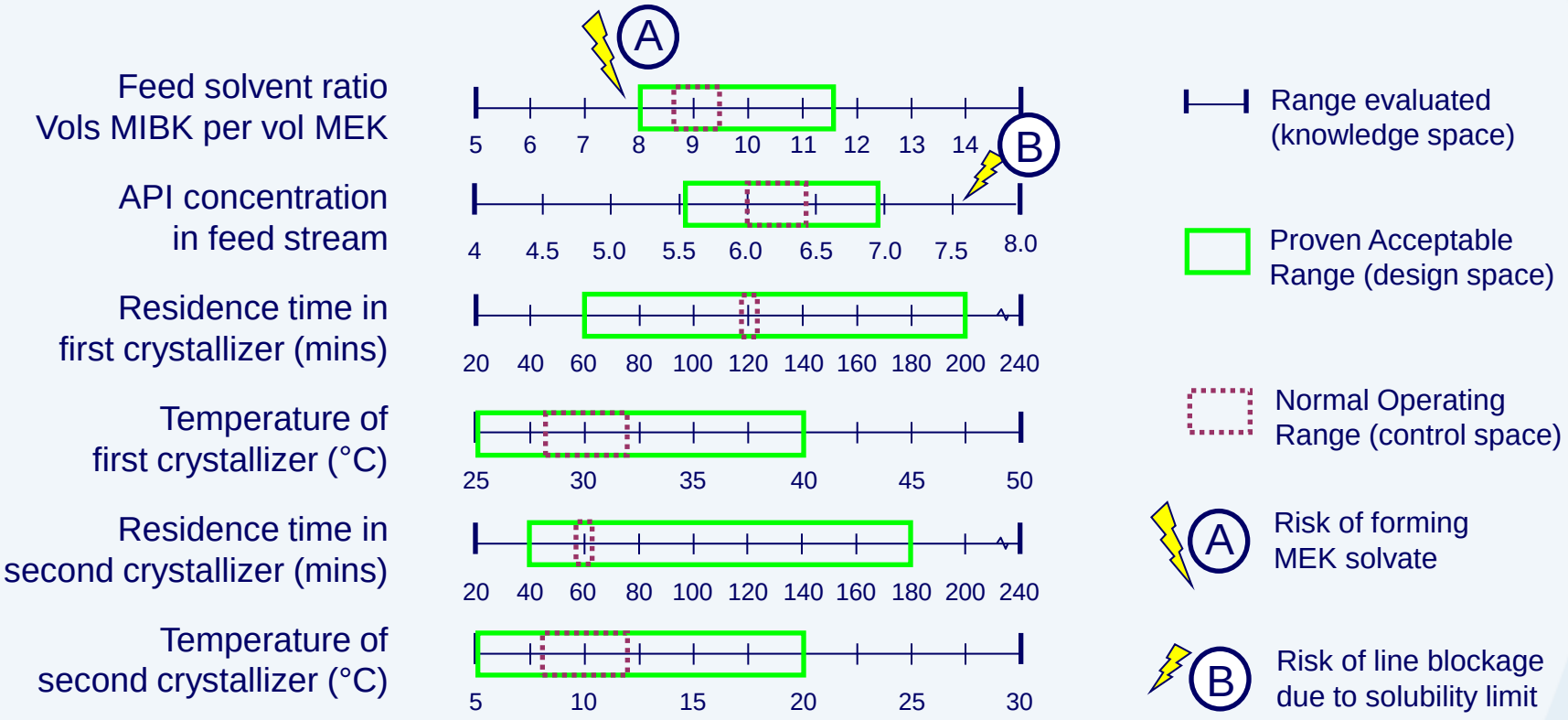
Decreasing Supersaturation

Particle Size Control - NCE A

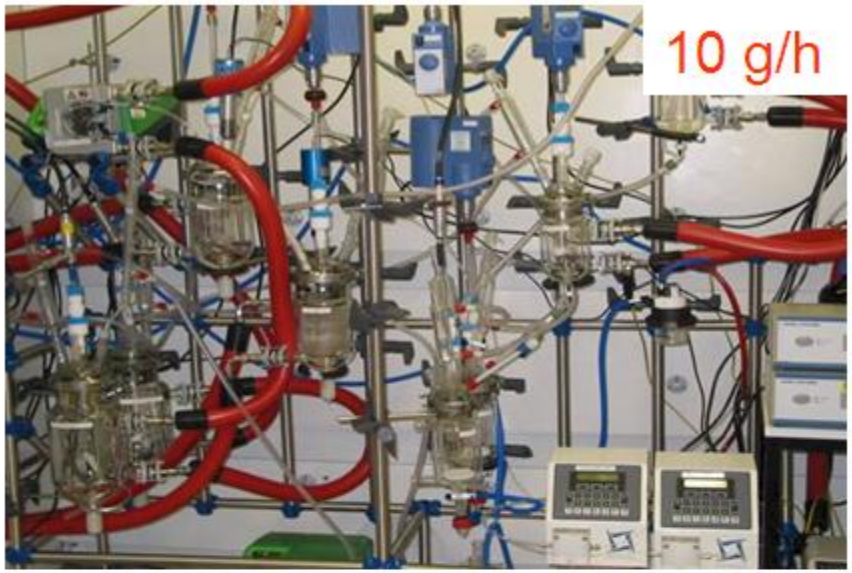


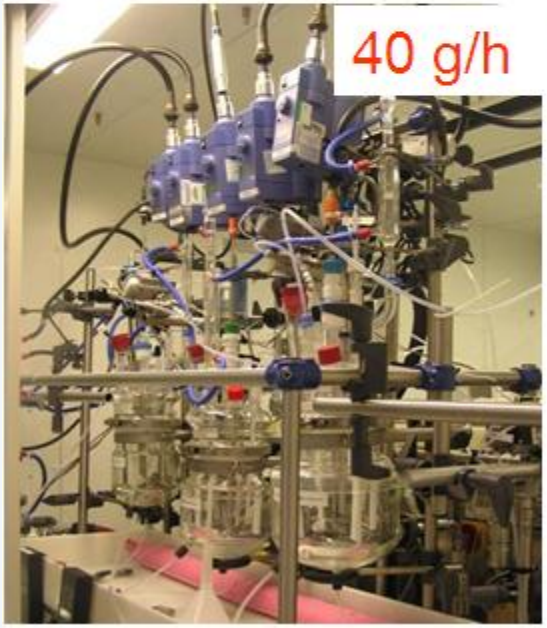
NCE A Crystallization Process Understanding

Strategy based on identification of process parameters and understanding their impact on process performance



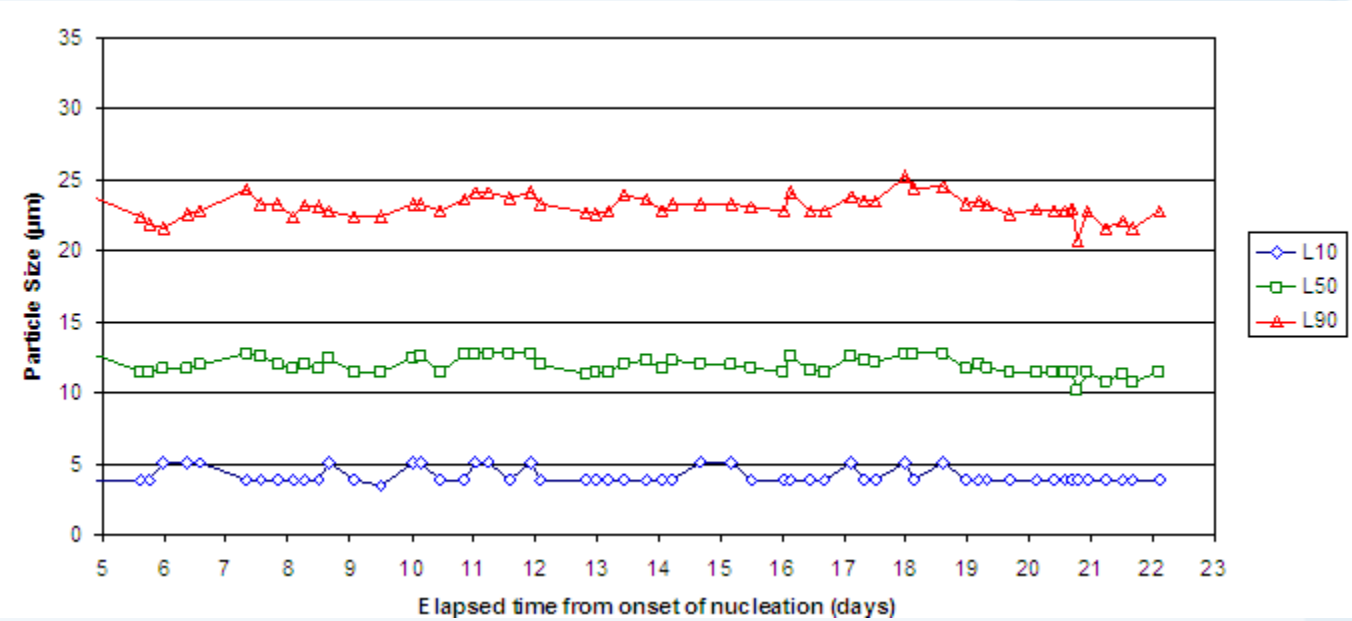
Scaling-up Continuous Crystallization



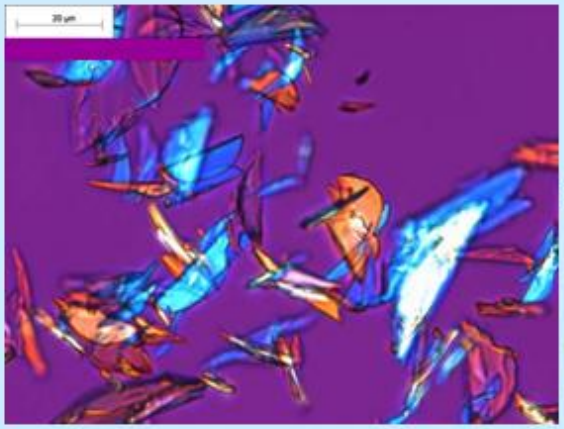


Delivering Consistent API

Consistency During a Manufacturing Scale Campaign

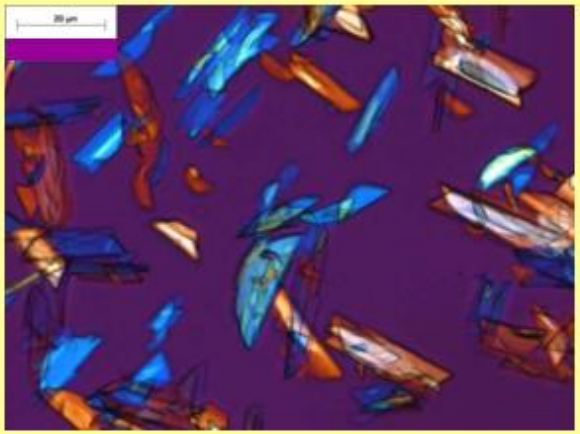


Consistency across scales – reliable scale-up

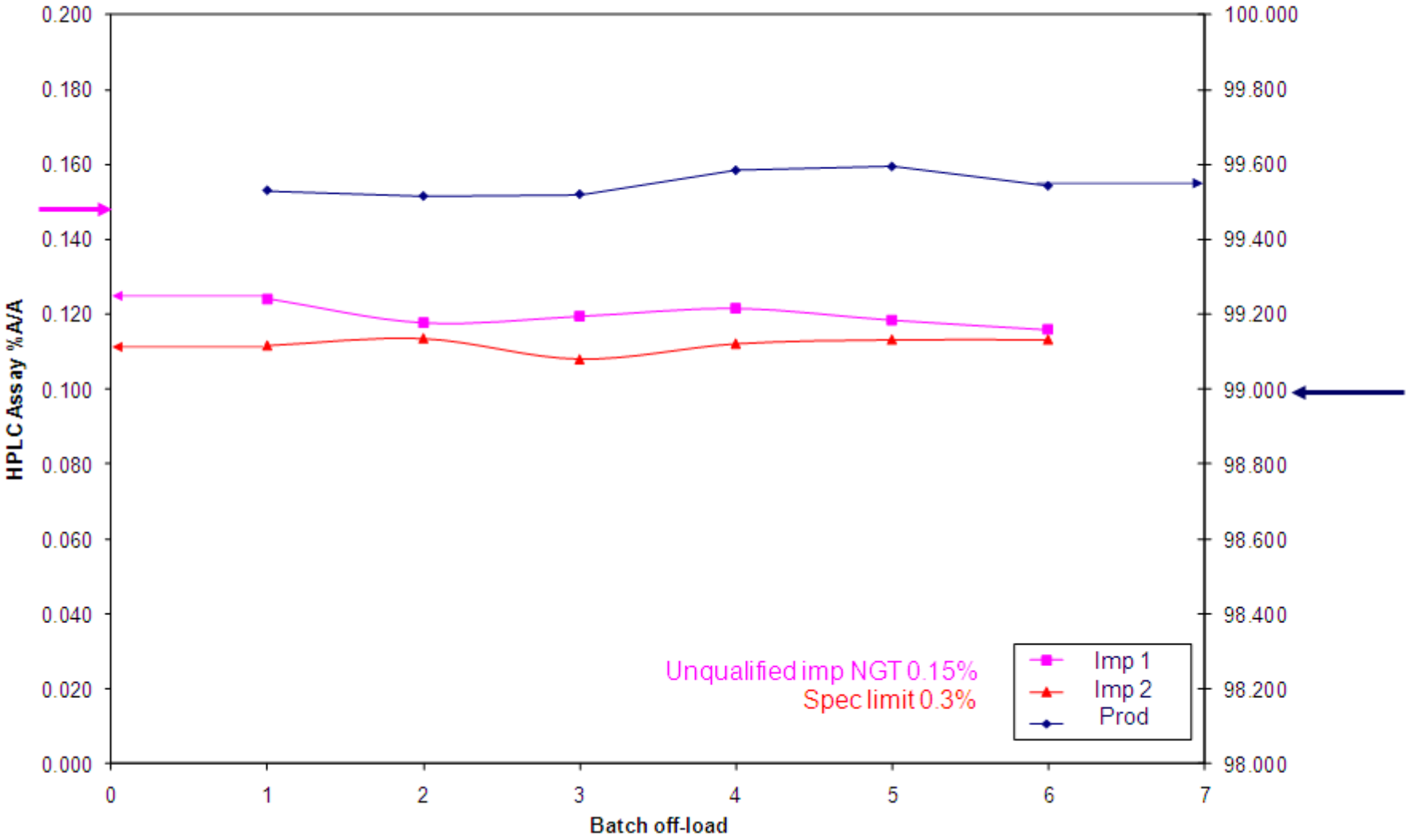


2005
Lab POC
L10 = 3.4 µm
L50 = 12 µm
L90 = 26 µm

2008
Plant Campaign
L10 = 3.8 µm
L50 = 12.7 µm
L90 = 24.3µm



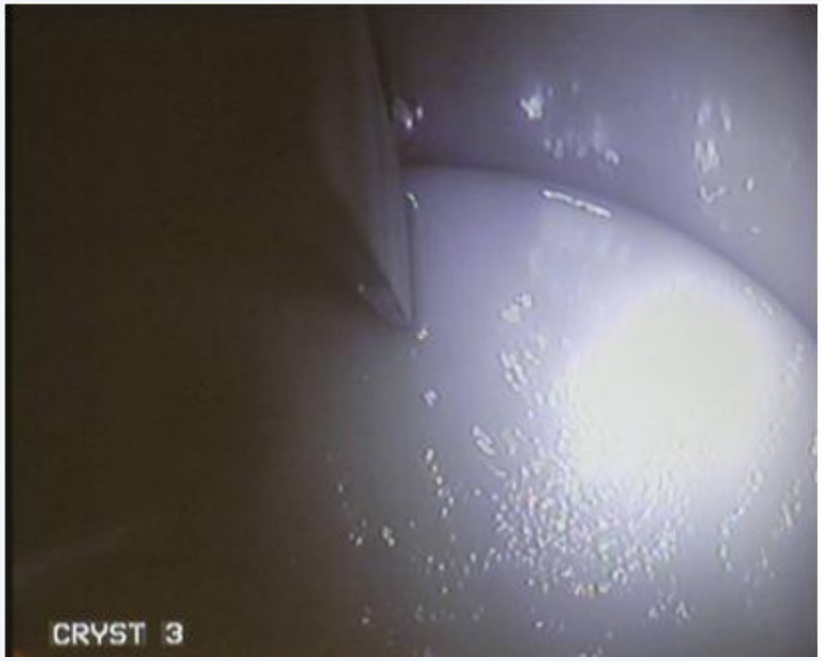
Consistency of purity and assay



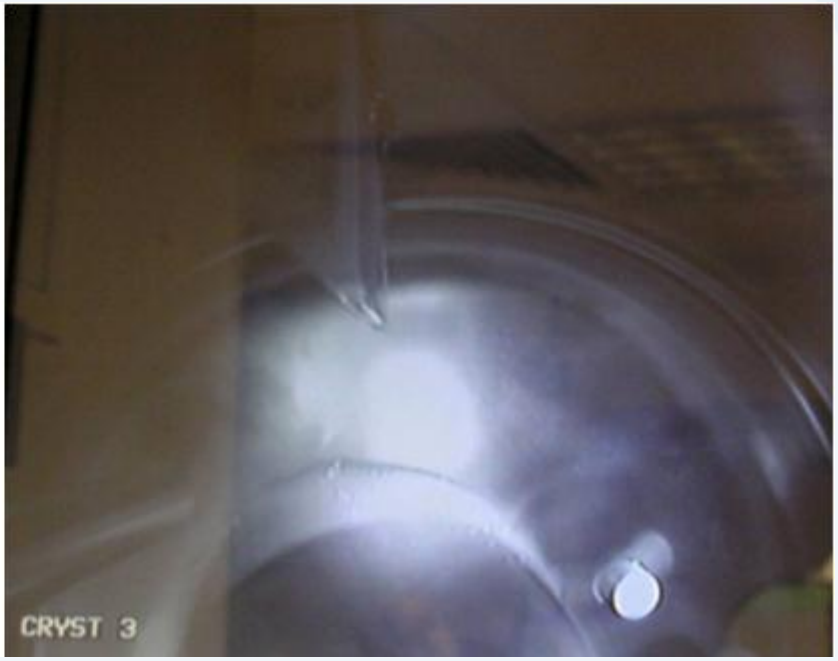
NCE A Plant Campaign Managing Encrustation

Crystallizer 3 operated in pilot plant for >20 days without cleaning:

Final minutes of operation



Crystallizer drained but not washed

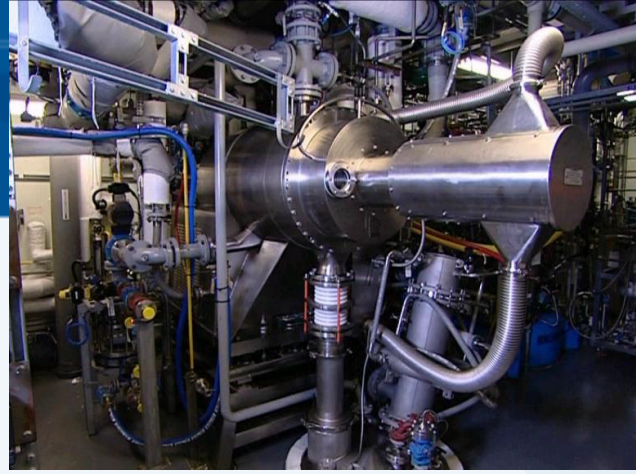


Encrustation was a significant issue during early stages of process development.
Operating at low supersaturation minimises the problem.
Building a cleaning procedure into the process has made long term operation possible

A Success ….
But is it applicable to other NCEs

- NCE A
  - Combined cooling & anti-solvent crystallization
- NCE B
  - Isothermal anti-solvent crystallization to produce a hemi-hydrate
- NCE C
  - Reactive & cooling crystallization
- NCE D
  - Cooling crystallization of material which tends to oil dreadfully
- NCE E
  - Combined cooling & anti-solvent crystallization
- A, C & D run at plant scale for extended periods > 12 days
- B & E run at lab POC scale for >30 hours

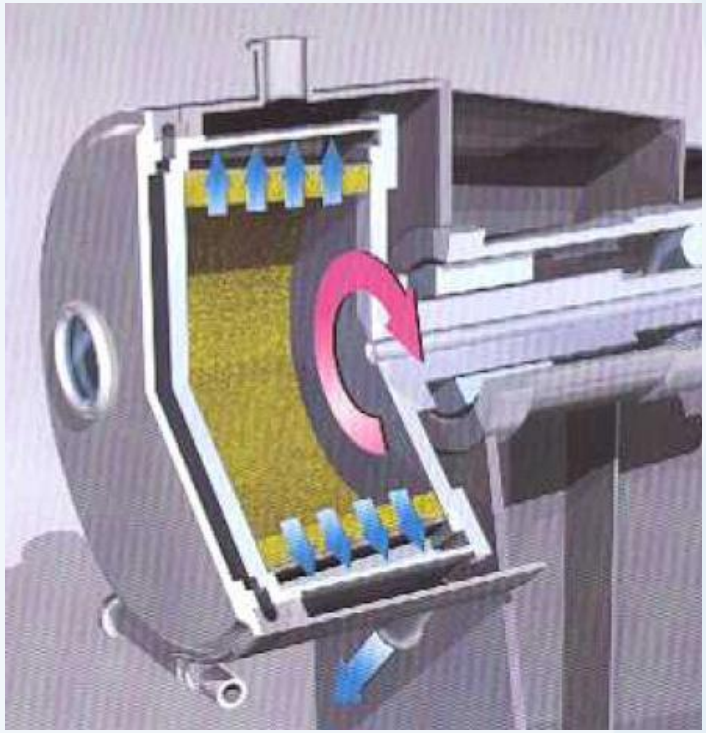
Isolation of API



- Filter & wash API to remove impurities and leave wet in a non-solvent to allow drying without agglomeration / granulation.

A semi batch approach has been demonstrated a pilot scale using the FIMA, a combined centrifuge and dryer.

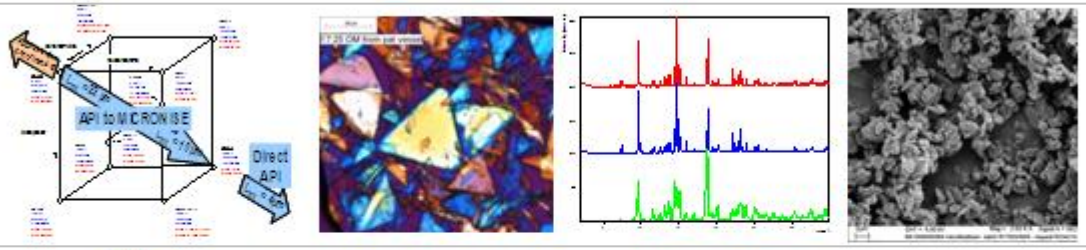
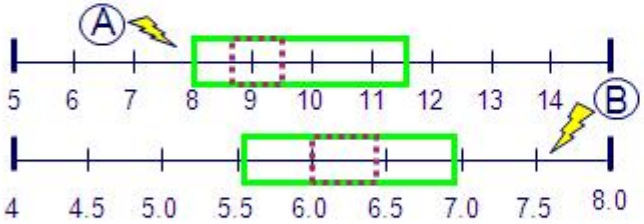
This necessitates the accumulation of a charge of product crystal slurry which is held for at least the duration of the isolation cycle.



A Continuous Crystallization Strategy for Pharma

- ***Manipulating nucleation rate independently of growth rate*** allows control of the product particle size, operating at low supersaturation minimises encrustation, delivers purity & less extreme crystal habits.
- ***Operation with a high crystal surface area of small crystals*** allows a high mass of API to be crystallized per unit volume of solution even at low supersaturation. Thus the equipment is small compared with the conventional continuous crystallizers.
- Making small organic crystals of similar density to their mother liquors avoids hydrodynamic constraints encountered in conventional continuous crystallizer design.
- ***Artificially enhancing rather than suppressing nucleation allows us to avoid compound specific crystallizer design***.
- Proven for cooling, anti-solvent and reactive crystallization
- Particle sizes are typical of APIs and are controlled.

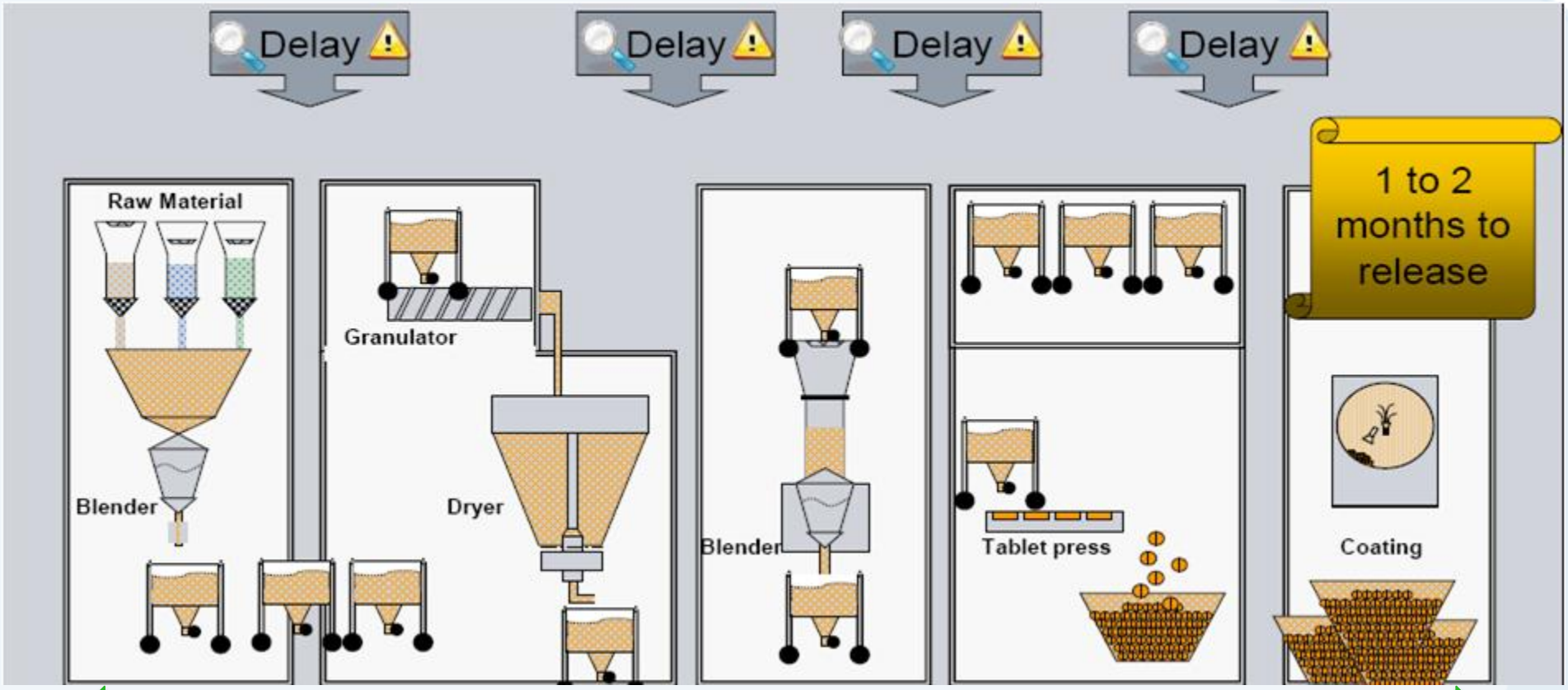
Success?

Purity Chem & Phase		✓
Particle Attributes		✓
Process Understanding		✓
Consistency		✓
Multi product	Cooling, anti-solvent & reactive crystallizations of 5 different NCEs each with their own challenges run at scale for meaningful duration	✓

So what about the gaps?

- Nucleation
  - This approach requires a high secondary nucleation rate at very low supersaturaion. There are several ways to do this well but our understanding is incomplete. There is more opportunity to improve the approach with a deeper understanding.
- Isolating the particles for direct formulation
  - Individual 2-20µm particles of API tend to have poor powder properties. Harvesting them as granules and incorporating “functional excipients” seems attractive.
- Linking continuous primary & secondary manufacture
  - An attractive future state

Secondary Processing
Benefits - Batch vs continuous approach- potential to streamline



Total processing + release + packing = 2days
Elapsed time 30-60 days

Continuous processing can help avoid this.
Possible to have raw materials to product in minutes/ hours
Online analysis/parametric release required but continuous facilitates this

Working Towards Fault-Tolerant Control

…*“fault handling* utilizes an integrated fault diagnosis system (MSPC) to allow fault-tolerant control”….

i.e. *only stop when there is a real risk to quality.*