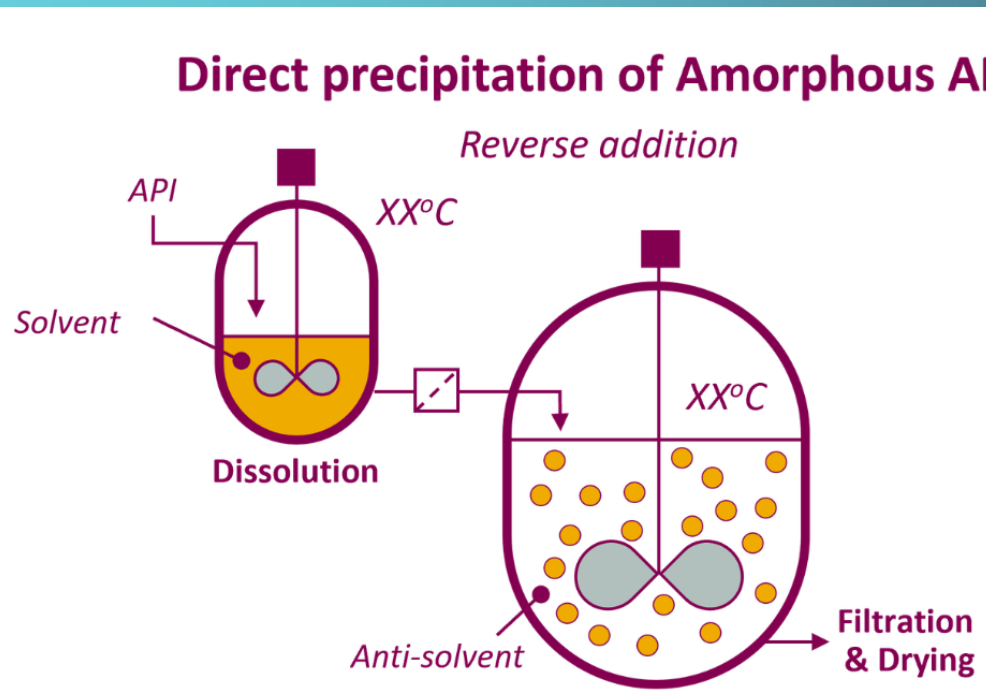


WEBINAR

Making Amorphous:
The challenges of Making Amorphous API in Early Phase Pharmaceutical Development

Presenter: Dr. Alex Cousen
Senior API Scientist, AstraZeneca, UK
MarketingTechnobis

Host: Dr. Carmen Guguta
Global Head BD &

Welcome

Webinar on:

Making Amorphous: The challenges of Making Amorphous API in Early Phase Pharmaceutical Development

A webinar open to researchers interested in amorphization, looking to solve day to day amorphous/crystallization challenges and optimize their best practices.

This webinar is being recorded and will be made available.

The audience is muted.

Please send your questions to info@crystallizationsystems.com.

This webinar will last 30-45 minutes.

Technobis

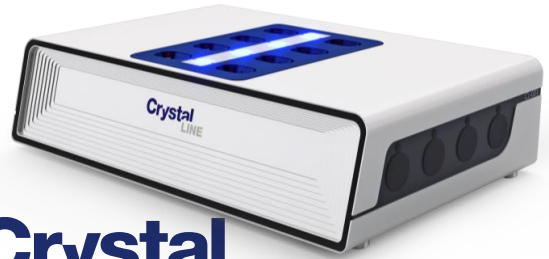
Technobis



Crystal BREEDER



Crystal 16

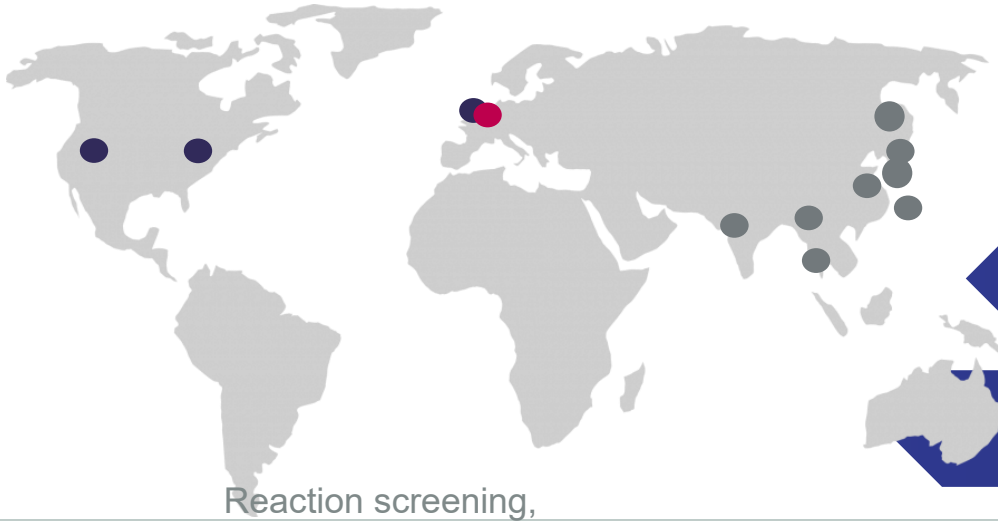


Crystal LINE



React ALL

MERCK, Lilly, UCB, Bayer, Amgen, Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, abbvie, sanofi aventis, Bristol-Myers Squibb, Eisai, BASF We create chemistry, TEVA, Johnson & Johnson, gsk GlaxoSmithKline



- In Business since 2005, 65+ employees on group level
- 800+ systems in the field, 3 product lines in our portfolio
- We have a global reach and presence, including a service organization
- Active in Pharmaceutical, Agrochemical, Food and Personal Care and Academia

Reaction screening,
Crystallization, Process development and Formulation

Technobis

Technobis portfolio

Crystal BREEDER | Crystal 16 | Crystal LINE





Product Line:
Crystallization Screening

2014 **CrystalBreeder**

2022 **Crystal16 V3**

2022 **Crystalline V2**

React ALL

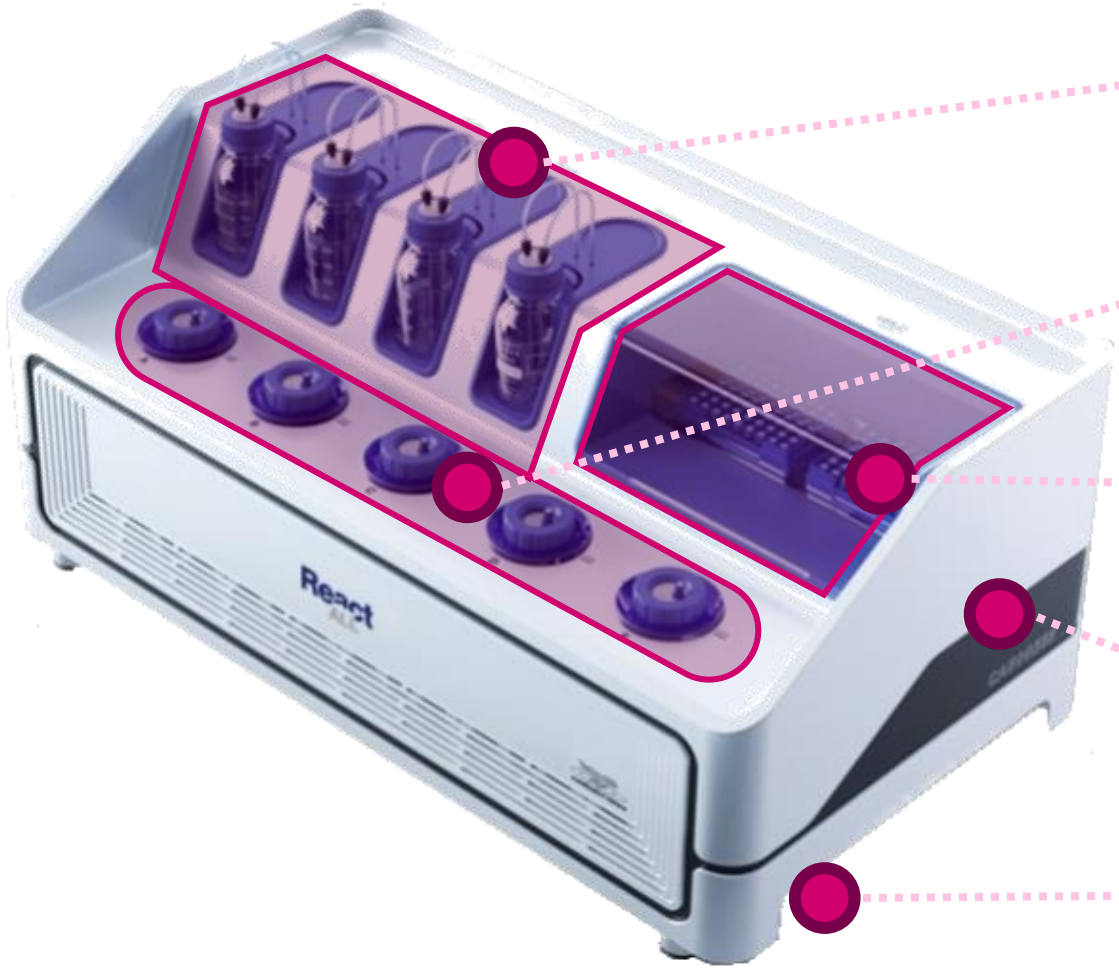
NEW!



Product Line:
Reaction Screening

More to come…

2024



Quench-Dilute-Rinse & Waste Station

4 solvent- and waste reservoirs for ***individualized choice of QDR-solvents***

Reactor Blocks

5 identical, independent reactor blocks with ***automated sampling***

Sample Preparation

Dispensing of samples to ***staandard HPLC vials***

Software User Interface

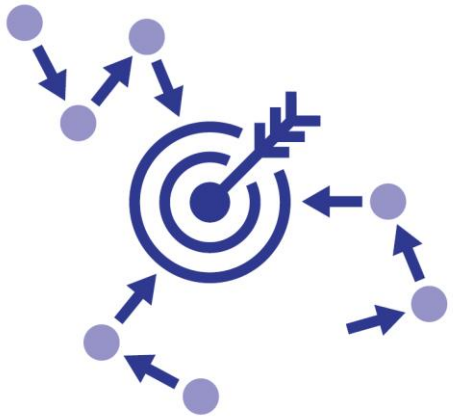
Intuitive, user-friendly, tile-based drag & drop-programming

Small Footprint

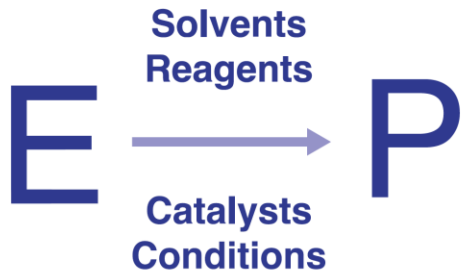
Designed to ***fit in standard fume hood***

ReactALL – Target Applications

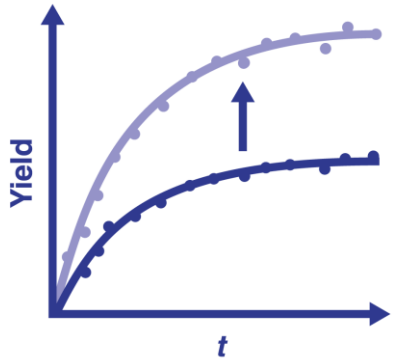
Route Scouting



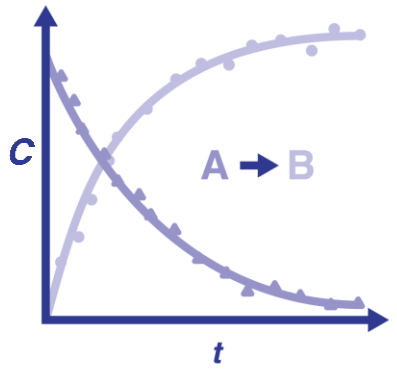
Reaction Screening



Reaction Optimization



Reaction Profiling & Kinetics



Crystallization Products Line

Crystal BREEDER



0.06 – 0,2 ml
32 reactors

Crystal 16



0.5 – 1 ml
16 reactors

Crystal LINE



2.5 – 5 ml
8 reactors

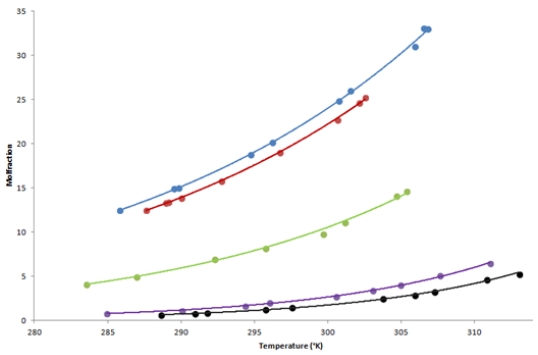
Discover

- Single crystals
- Solvent screening
- Solubility
- Solid state screening



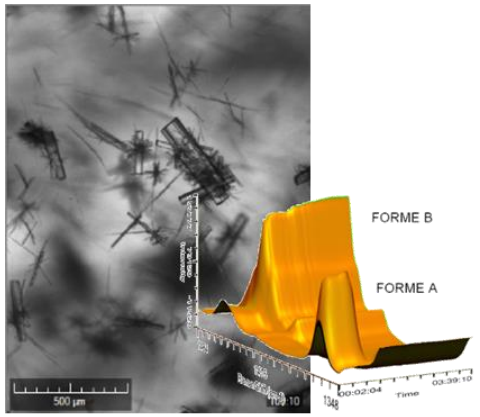
Screen

- Solubility, MSZW
- Nucleation rate
- Induction time measurements
- Phase diagrams
- Polymorphs, Salt and
- Co-crystals screening



Optimize

- Habit control
- Particle size
- Process optimization
- Formulation



Technobis

Your Speaker – Dr. Alex Cousen



Senior API Scientist, AstraZeneca, UK

Alexander earned an MChem in Chemistry from the University of Bath, UK, in 2014, followed by a PhD in Crystallization Science and Crystallography in 2018 under the supervision of Professor Chick Wilson. He is part of the EPSRC Future Manufacturing Hub in Continuous Manufacturing and Advanced Crystallization (CMAC). His research focused on screening materials for chiral crystallization processes and developing continuous crystallization platforms for co-crystal systems. In 2018, he completed a placement with Bayer, Germany, as part of the Early Solid-State team.

Since joining AstraZeneca in 2018, Alexander has worked as a Senior API Scientist, focusing on crystallization and precipitation process development for active pharmaceutical ingredients (APIs) supporting preclinical programs and Phase I and II clinical trials.

Technobis

Thank you! Hope to see you back at our next webinar!

Dr Alex Cousen (he/him)
Senior API Scientist, AstraZeneca, UK





- MChem in Chemistry → University of Bath, UK (2010-14)
- PhD in Crystallisation Science & Crystallography → University of Bath, UK (2014-18)
  - Part of EPSRC Future Manufacturing Hub in Continuous Manufacturing & Advanced Crystallisation (CMAC)
  - Focussed on screening materials for Chiral Crystallisation processes and developing continuous crystallisation platforms for co-crystalline systems
  - Placement at Bayer, Germany in Early Solid-State team (2018)
- Senior API scientist → AstraZeneca, UK (2018 to present)
  - API stage crystallisation & precipitation development for pre-clinical and Ph 1 & 2 trials

- Love the great outdoors; hiking, camping
- Love my coffee!!!!
- Lots of Outreach & Volunteering
- Big rugby fan – Sale Sharks rugby
- Enjoy cooking and socialising with friends – especially love board games
- Recently became a Dad to beautiful twin boys!!

Making Amorphous:

The challenges of making amorphous API in early phase pharmaceutical development

Technobis webinar 2026

Dr. Alex Cousen

Early Chemical Development, Pharmaceutical Sciences, R&D, AstraZeneca, Macclesfield, United Kingdom

22/10/2026

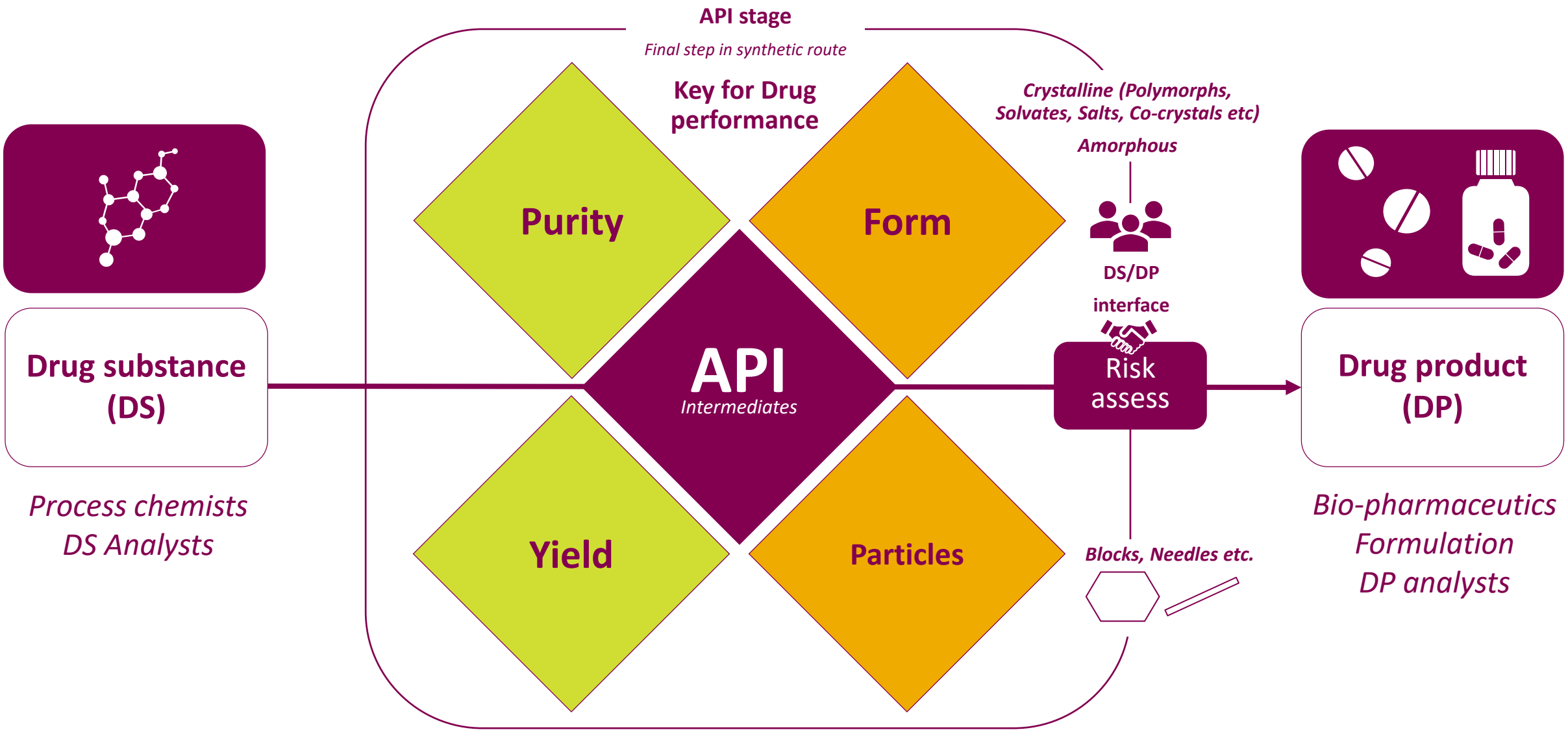


Agenda

1. Early Phase Pharmaceutical Chemical Development
2. Amorphous materials
3. Making amorphous – Direct Precipitation
4. Case studies

Crystallisation (API) Scientist – What do we do?

API = Active Pharmaceutical Ingredient



Solid-State, Predictive & Material Science, Process Engineering, Kilo-Lab, Pilot Plant, Downstream Processing, Process Safety…

Pharmaceutical development – API development

Development stage:

Discovery → Earl-stage Development → Ph1 → Ph2

Key timepoints:

Lead Generation (LG) → Lead Optimisation and Identification (LOI) → Ph1 → Ph2

Drug molecule candidates:

100-1000 candidates

10 candidates

1 candidate

The challenges:



Quantity needed:

mg

g

10-

Develop and deliver Drug Substance API for preclinical and early clinical studies (Phase 1 & 2)

Focus on first 'Fit for purpose' manufacture campaigns

Multiple on-going projects

Tight delivery timelines

Multiple consecutive/ parallel campaigns

Limited material & knowledge

Challenging impurity profiles

Increasingly complex portfolio

Sustainability objectives

Amorphous API

Amorphous materials

What are amorphous materials?

Why would we want to target them?

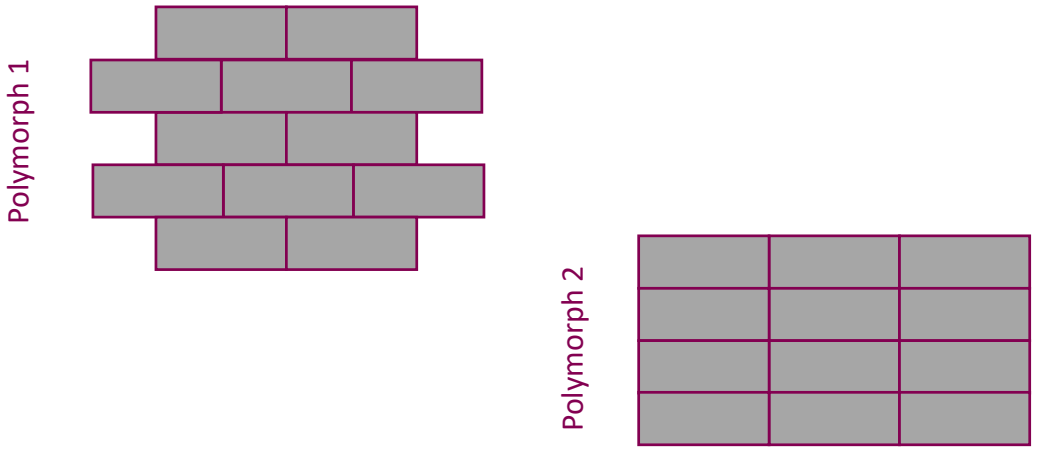
How can we go about making them?

Amorphous materials – Comparison to crystalline materials

Molecule

Crystalline

Regular & repeating arrangement of atoms, molecules or ions in a 3D structure
Long & short-range order

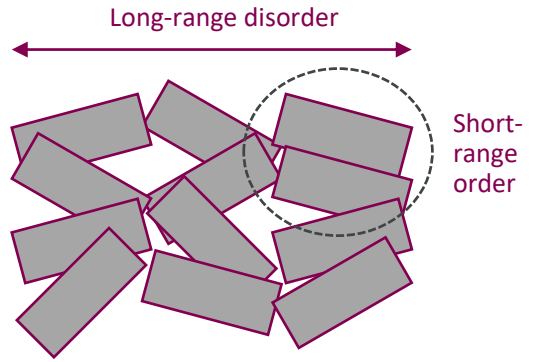


Coherent structures

Lower energy state

Amorphous

Lack of long-range order of atoms, molecules or ions in a 3D structure
Can exhibit short-range order



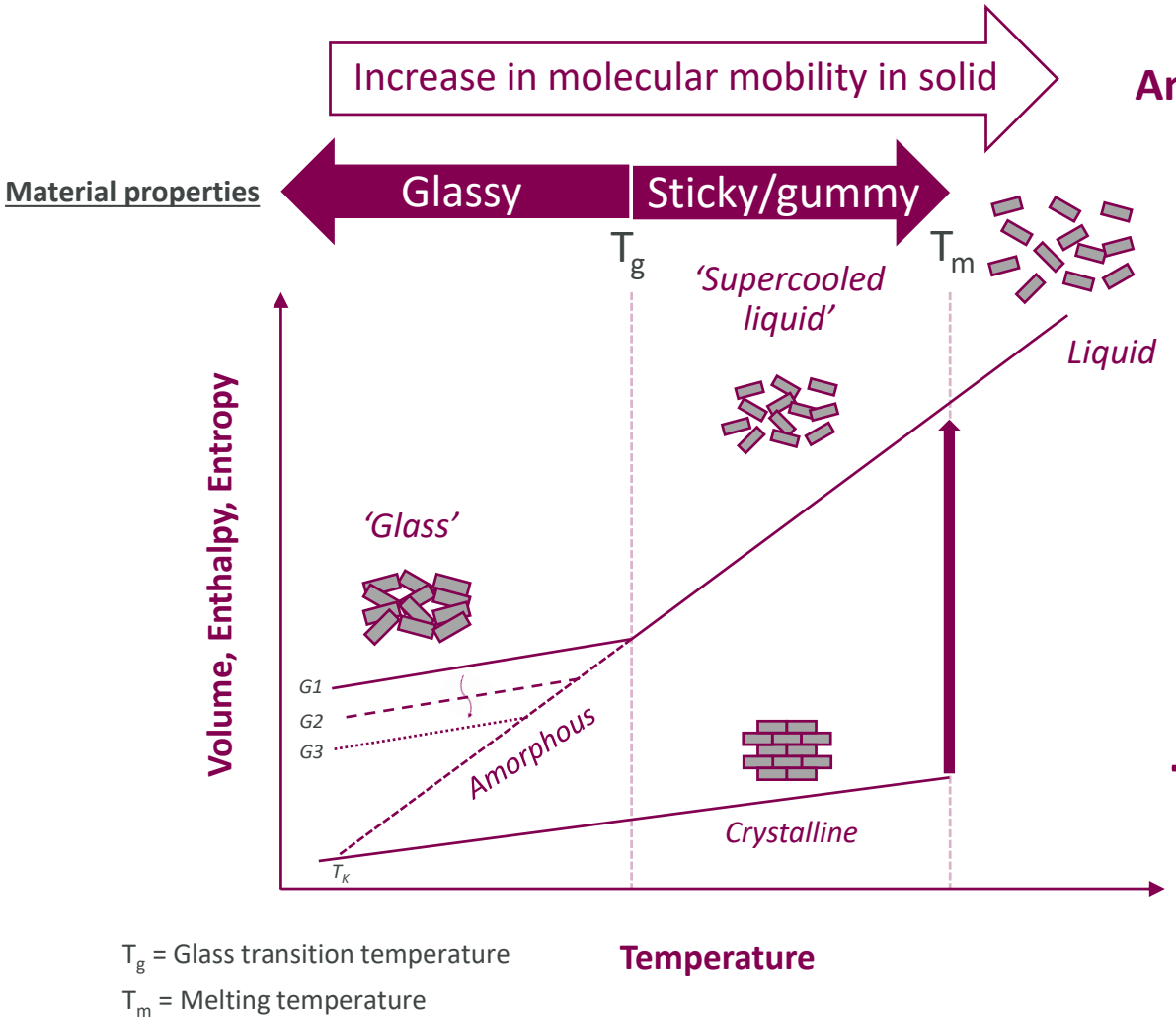
Incoherent (variable) structure

Higher energy state

'Meta-stable'

Amorphous materials – Physical properties

Molecule



T_g = Glass transition temperature

T_m = Melting temperature

Amorphous materials = high degree of molecular mobility (MM)

Glass transition temperature (T_g) = inflection point in MM

Degree of molecular mobility dependent on/impacted by:

- Temperature
- Pressure
- Solvents
- Impurities

} Impact on position T_g

Typically, higher the T_g → greater stability

How close are you operating to your T_g?

Hancock, B.C. and Zografi, G. (1997), Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci., 86: 1-12. https://doi.org/10.1021/js9601896

Amorphous materials – Challenges and rewards

Challenges

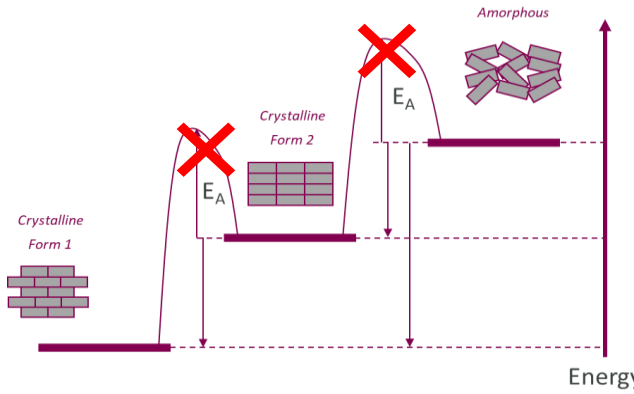
Given ‘meta-stability’, molecular mobility and inherently variable structure…

- Physical & chemical degradation risk
- No impurity purging
- Inherent material variability (batch to batch)
- Challenging material properties



So why choose amorphous for API?

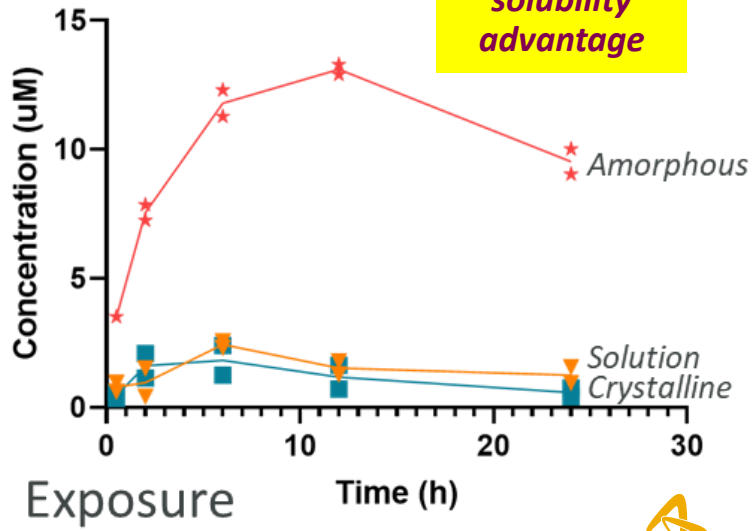
Challenging API crystallisation



Reward

Biopharmaceutics

Can have a x10 fold solubility advantage



Stability: Amorphous < Crystalline

Amorphous → Higher solubility &/or faster dissolution rates

Improved bioavailability

Amorphous materials – Challenges and rewards

An aside…

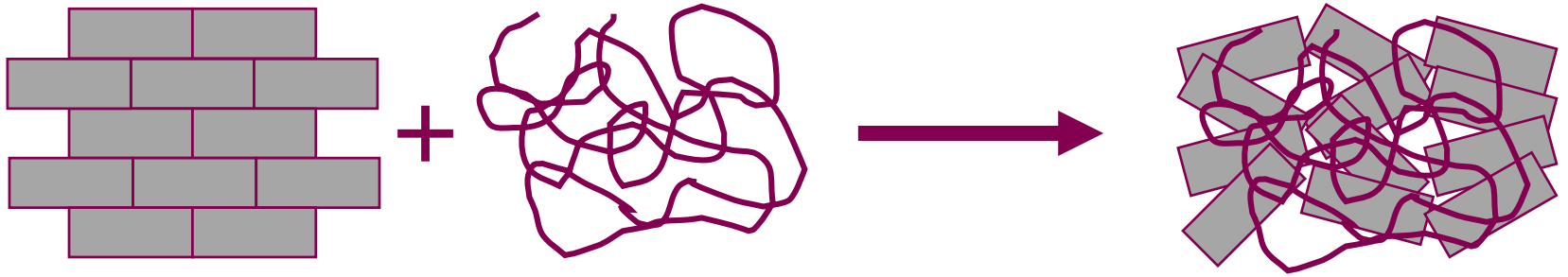
Not the focus today

Molecule

Increased risk of physical degradation (re-crystallisation)

Amorphous Solid Dispersion (ASDs)

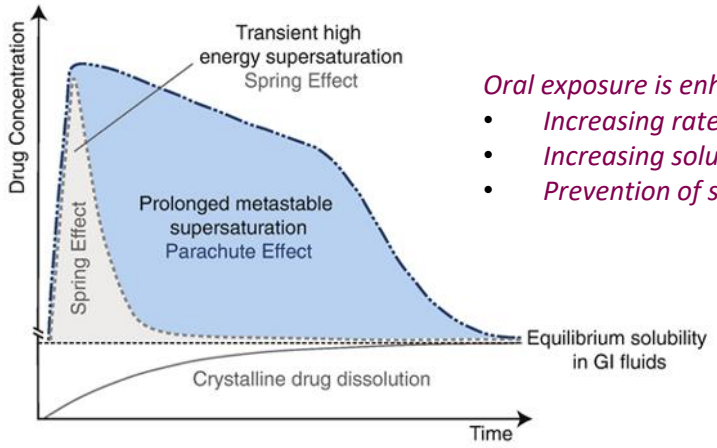
Drug molecularly dispersed in a polymer matrix



API + Co-polymer → ASD

Stabilising amorphous phase

In-vivo performance



Oral exposure is enhanced by:

- *Increasing rate and extent of drug dissolution*
- *Increasing solubility in GI tract (supersaturation)*
- *Prevention of subsequent drug precipitation*

However:

- Increased bulk of Drug Product
- Further development and manufacturing steps

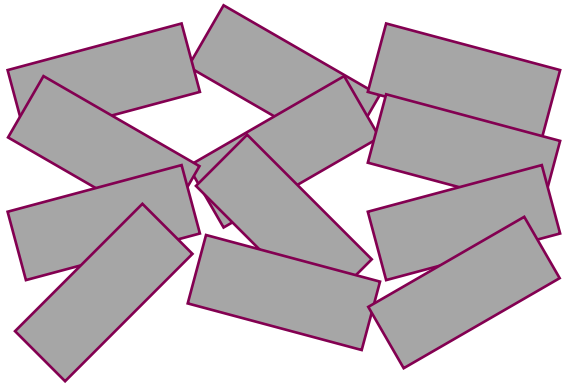
Therefore:

- If amorphous free form has sufficient stability, can be used directly in Drug Product

O.M. Feeney et al. / Advanced Drug Delivery Reviews 101 (2016) 167–194

Amorphous materials – Developing Amorphous

Characterisation and classification



Initial assessment: **Taylor Classification System**

Baird et al. J PharmSci. ***2010****, 99, 3787-3806*

Understanding of Tg

Assessment via DSC

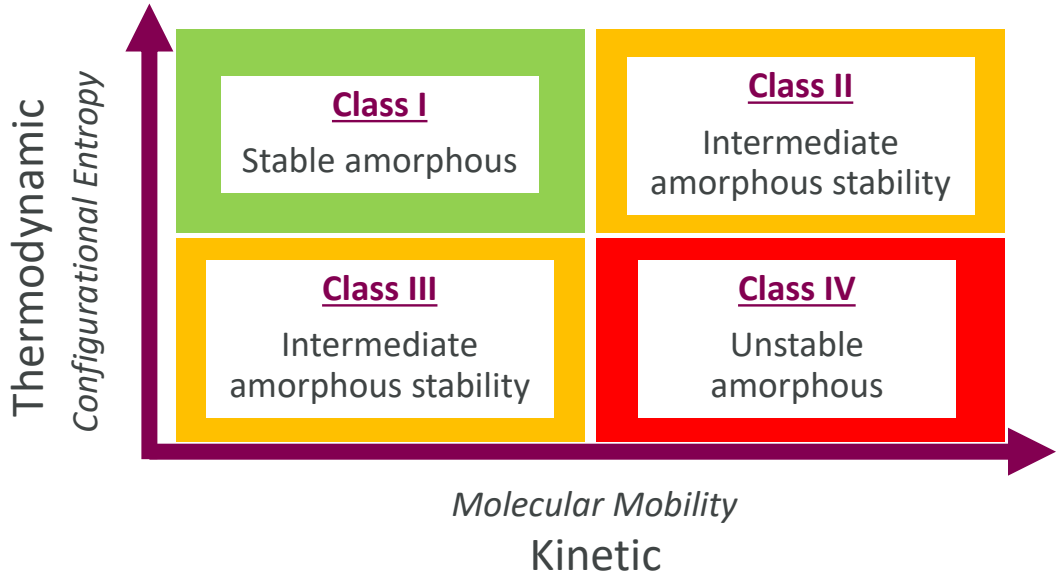
- Class I – High crystallisation tendency, low glass forming ability
- Class II – Intermediate crystallisation tendency
- Class III – Low crystallisation tendency, high glass forming ability

Advanced assessment: **Amorphous Classification System (ACS)**

Zhou, D., et al., Mol. Pharmaceutics ***2019****, 16, 2742–2754*

Measurement:

- Glass Transition Temperature (Dry T_g): High? (> 80°C)
- Hygroscopicity: Low? (< 2 wt%)
- Solubility advantage (or predicted): > x2 increase?
- Assessment of structure: PDF, ssNMR etc.



Amorphous materials – Developing Amorphous

Isolating amorphous

Precipitation = amorphous
Crystallisation = crystalline



Crystallisation

'Slow & steady'

More stable phases

Precipitation

'Fast & aggressive'

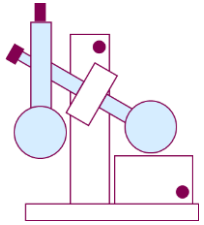
Less stable phases

Lots of ways of isolating amorphous (cryo-milling, cooling from melt, etc.) but to be scalable need to look to solution-based processes…

Aggressive conditions ⇨ High supersaturation ⇨ More nucleation events ⇨ **Meta-stable solid i.e. Amorphous**

Evaporation

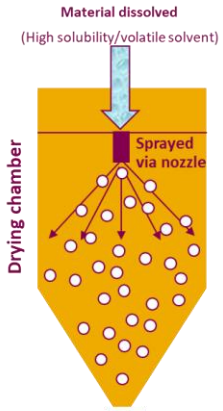
Rotary evaporator



High yield, simple

Not scalable, little control

Spray drying

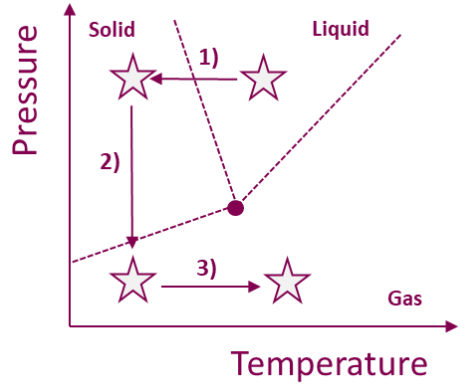


Scalable, control

Variable yield, capacity

Sublimation

Freeze drying

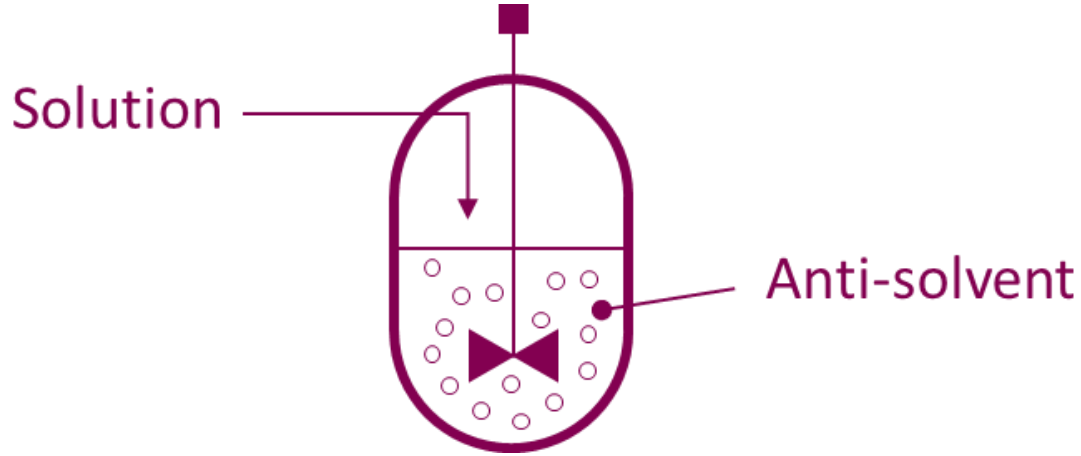


High yield, scalable

Control, capacity

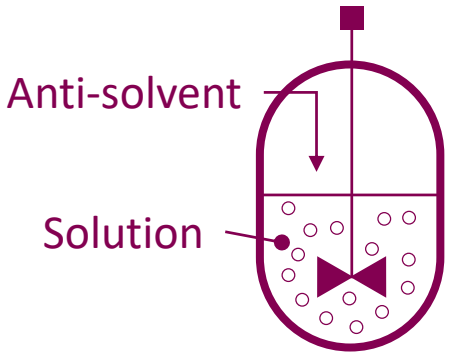
Can we leverage traditional Drug Substance manufacturing facilities to deliver amorphous material at scale?

Direct precipitation



Direct precipitation – Reverse addition

Precipitation = amorphous
Crystallisation = crystalline



Crystallisation

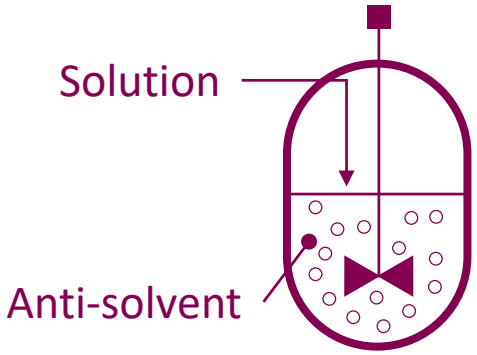
'Slow & steady'

More stable phases

Precipitation

'Fast & aggressive'

Less stable phases



Advantages:

- Fast processing
- Utilise conventional assets

Challenges:

Solvent 'rich' environment

- Lower Tg
- Increased crystallisation risk
- Potentially challenging material properties (i.e. stickiness)
- Limited particle control
- Limited solvent or impurity rejection

Direct precipitation – Why?

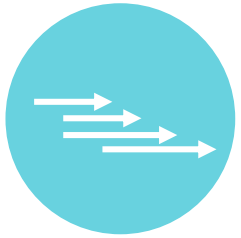
Early phase: **‘Fit for Purpose’**

Multiple on-going projects

Tight delivery timelines



Multiple consecutive/ parallel campaigns



Increasingly complex portfolio



Limited material and knowledge



Impurity challenges from chemistry



Sustainability objectives



Given speed and complexity, strong desire to keep early campaigns in-house

Amorphous API

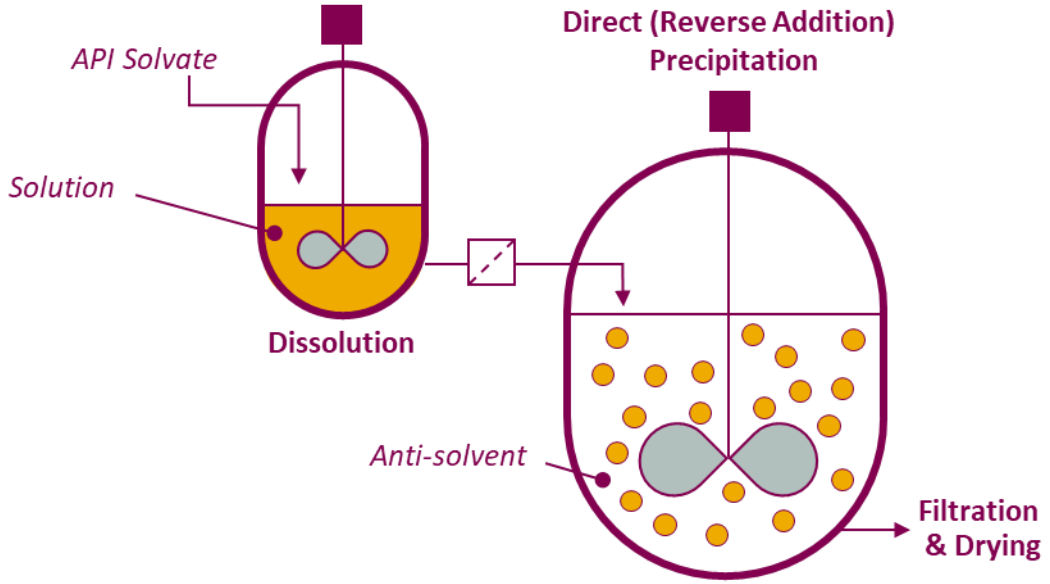
Direct precipitation – AZ case studies

Case study 1 – Directly precipitating a ‘challenging’ amorphous system

Case study 2 – Directly precipitating a ‘well-behaved’ amorphous system

Moving to Continuous Direct Precipitation

Direct precipitation case study 1



Case study 1 – Direct Precipitation

Limited material → Early material (amorphous), later material (semi-crystalline solvate)
Limited assessment of scale-up.

Project context:

- Small organic molecule
- No crystalline forms identified (freeform, salts, co-crystals)
- Material needed urgently – very tight timelines
- Amorphous deemed was suitable
  - *ACS Class II/IV*
  - *High Tg (> 160°C)*
  - *Moderate hygroscopicity*
  - *Challenging chemical stability*

Step 1

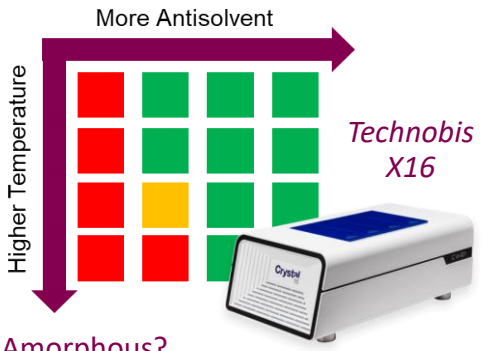
Solvent selection

Solvents - Freely soluble
2-MeTHF

Anti-solvents - Insoluble
n-Heptane

Step 2

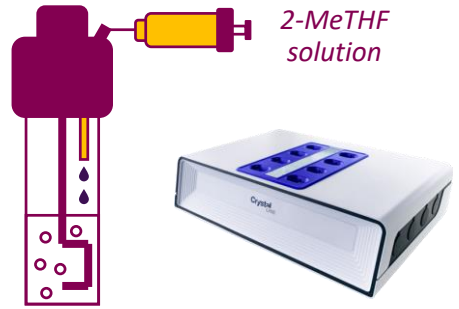
Understanding the operating space



- Amorphous?
- Stickiness in process (processibility)?
- Isolated material properties?

Step 3

Proof of Concept



- Solution (5 RV) → Anti-solvent (25 RV)
- Temp. = 15°C

Step 4

Scale-up

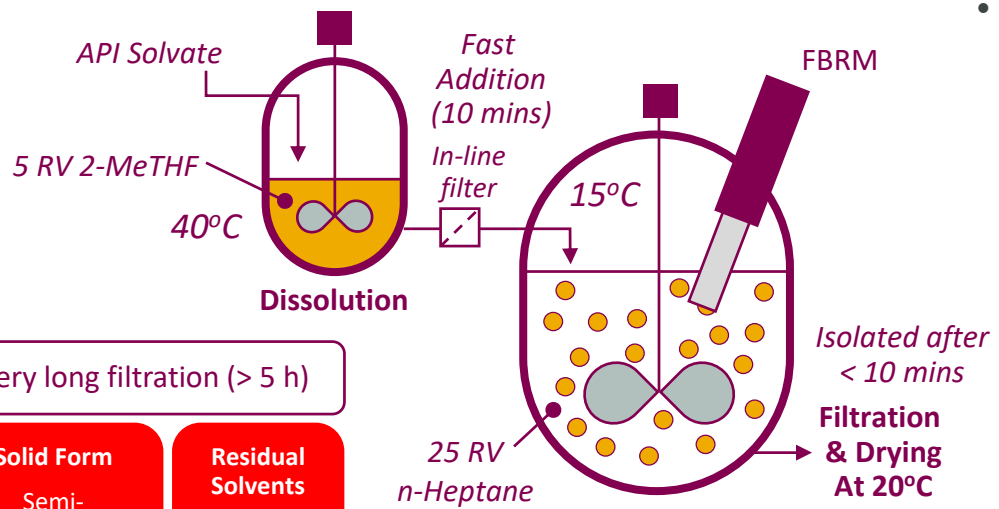
Mettler Toledo EasyMax



Solid Form
Amorphous

Residual Solvents
~2.5%ww

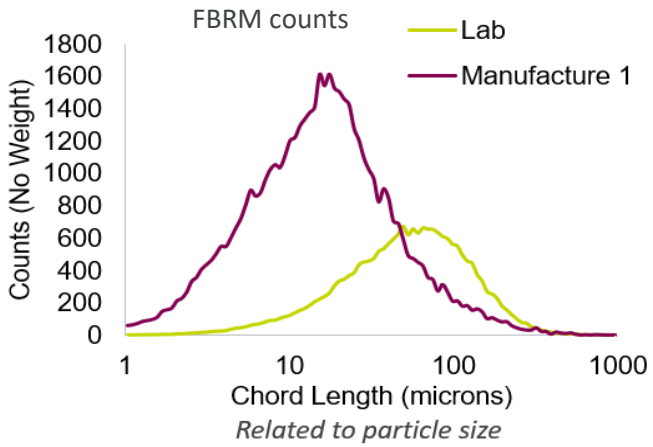
1st kilo manufacture



Very long filtration (> 5 h)

Solid Form
Semi-crystalline solvate

Residual Solvents
Total: ~6%ww



- Smaller particles generated in manufacture
- Higher agitation applied in manufacture
- Crystallisation was found to occur during filtration/washing

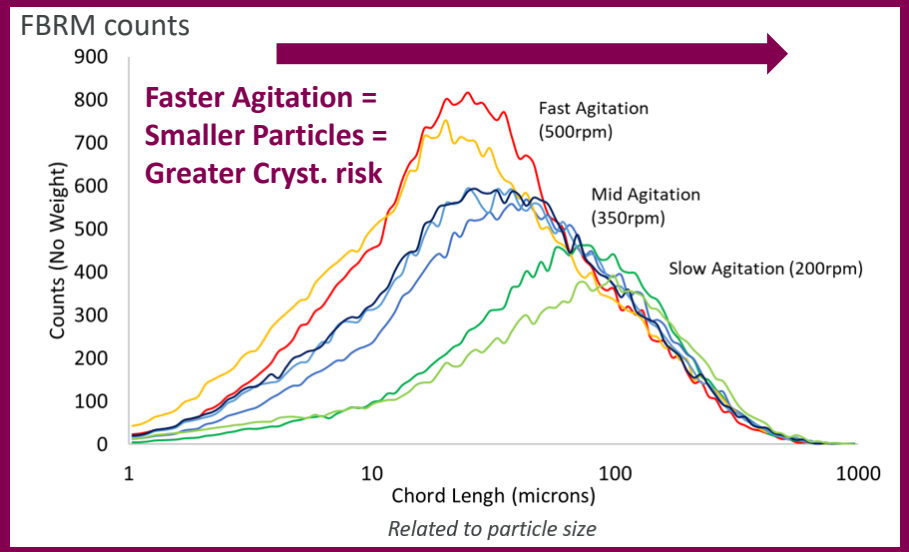
FBRM = Focussed Beam Reflectance Measurement

Case study 1 – Direct Precipitation

Back to the Laboratory

Initial considerations: Agitation → Particles → Filtration

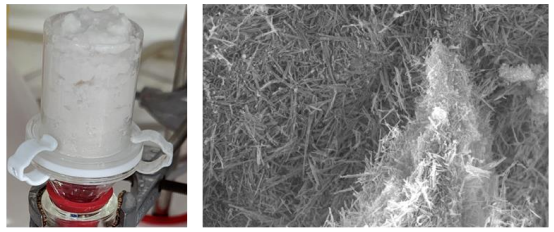
DoE: Agitation v Addition rate



Addition → Not deemed significant

Fastest agitation → Rapid re-crystallisation in cake

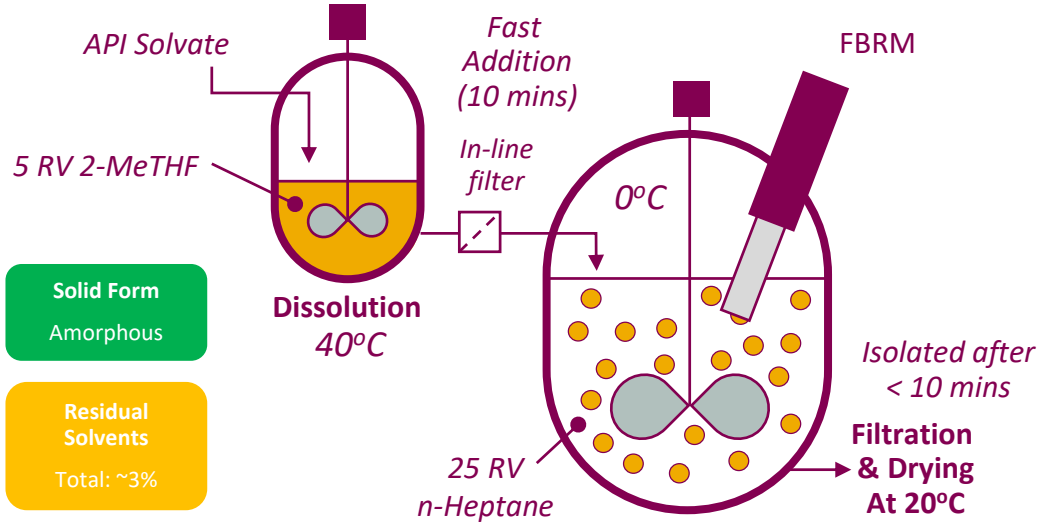
Worst case example

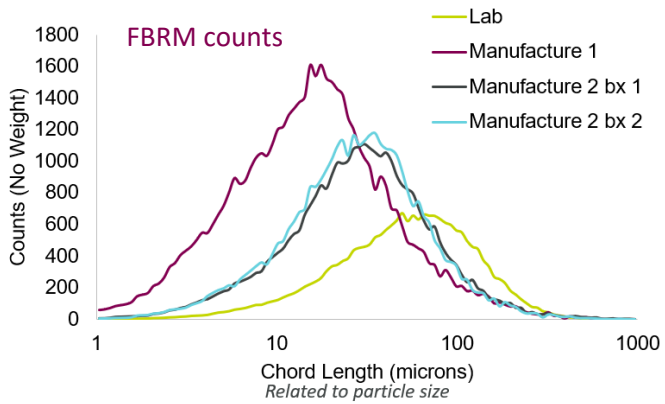


Mitigations for next manufacture:

- **Slower agitation rate**
- **Temperature to 0°C**
- **Minimise hold times**

2nd/3rd kilo manufactures → 2 x 3 kg



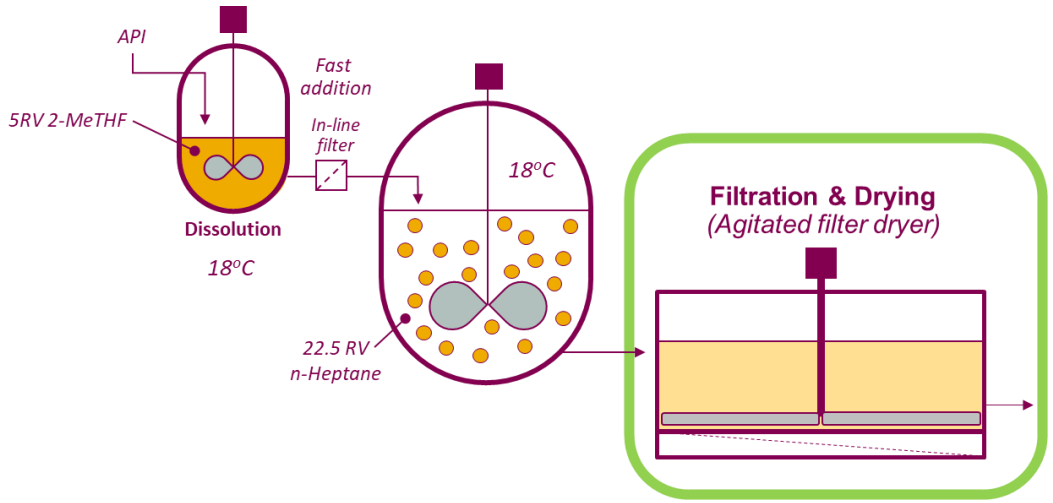


- Much slower agitation
- Large particles
- Better filtration (< 1 h)

Key points:

- **Appreciation of 'in-process' crystallisation propensity key (wet Tg)**
  - **Agitation impact on particle size**
  - **Impact on filtration**

Direct precipitation case study 2



Case study 2 – Direct Precipitation

Project context:

- Small organic molecule
- No suitable crystalline forms identified (freeform, salts, co-crystals)
- Amorphous deemed was suitable
  - *ACS Class I*
  - *High Tg (> 160°C)*
  - *Moderate hygroscopicity*
  - *Amorphised via a range of methods*
- Manufacture in kilo-lab

Step 1

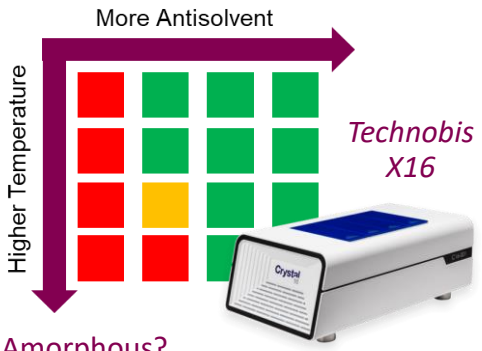
Solvent selection

Solvents - Freely soluble
2-MeTHF

Anti-solvents - Insoluble
n-Heptane

Step 2

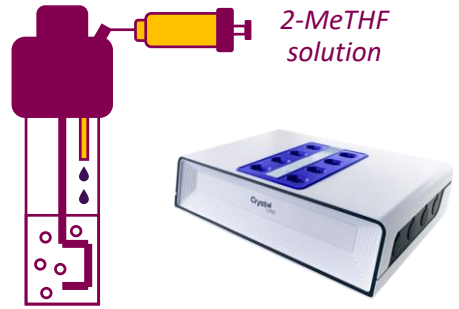
Understanding the operating space



- Amorphous?
- Stickiness in process (processibility)?
- Isolated material properties?

Step 3

Proof of Concept



- Solution (5 RV) → Anti-solvent (22.5 RV)
- Temp. = 18°C

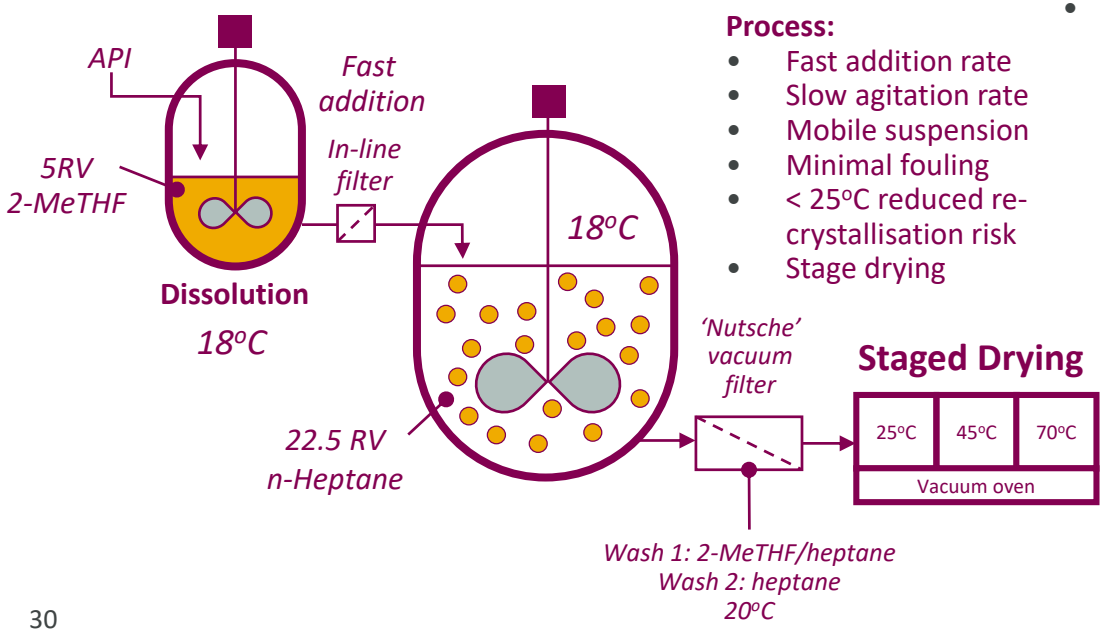
Step 4

Scale-up

3L RX-10



8 x kilo manufacture (1.5-3 kg)



Process:

- Fast addition rate
- Slow agitation rate
- Mobile suspension
- Minimal fouling
- < 25°C reduced re-crystallisation risk
- Stage drying

Solid Form
Amorphous

Residual Solvents
Total: < 1 %

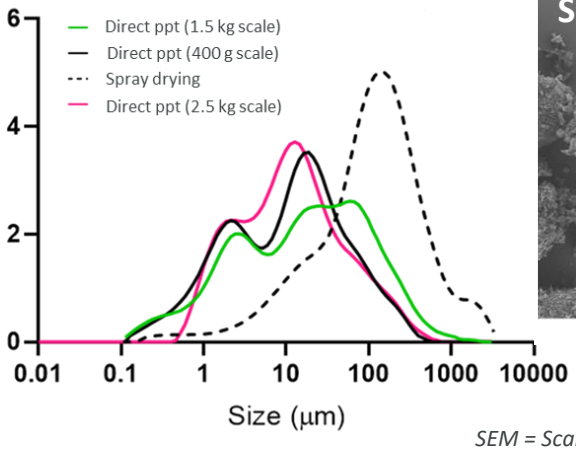
> 95 % yield

Manageable powder properties for DP development

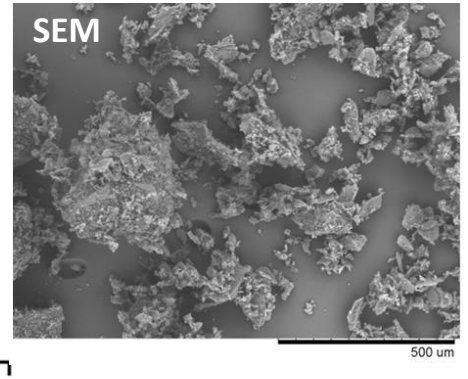
Solid Form
Amorphous

Residual Solvents
<2%ww

PSD



SEM



SEM = Scanning Electron Microscope

PSD = Particle Size Distribution

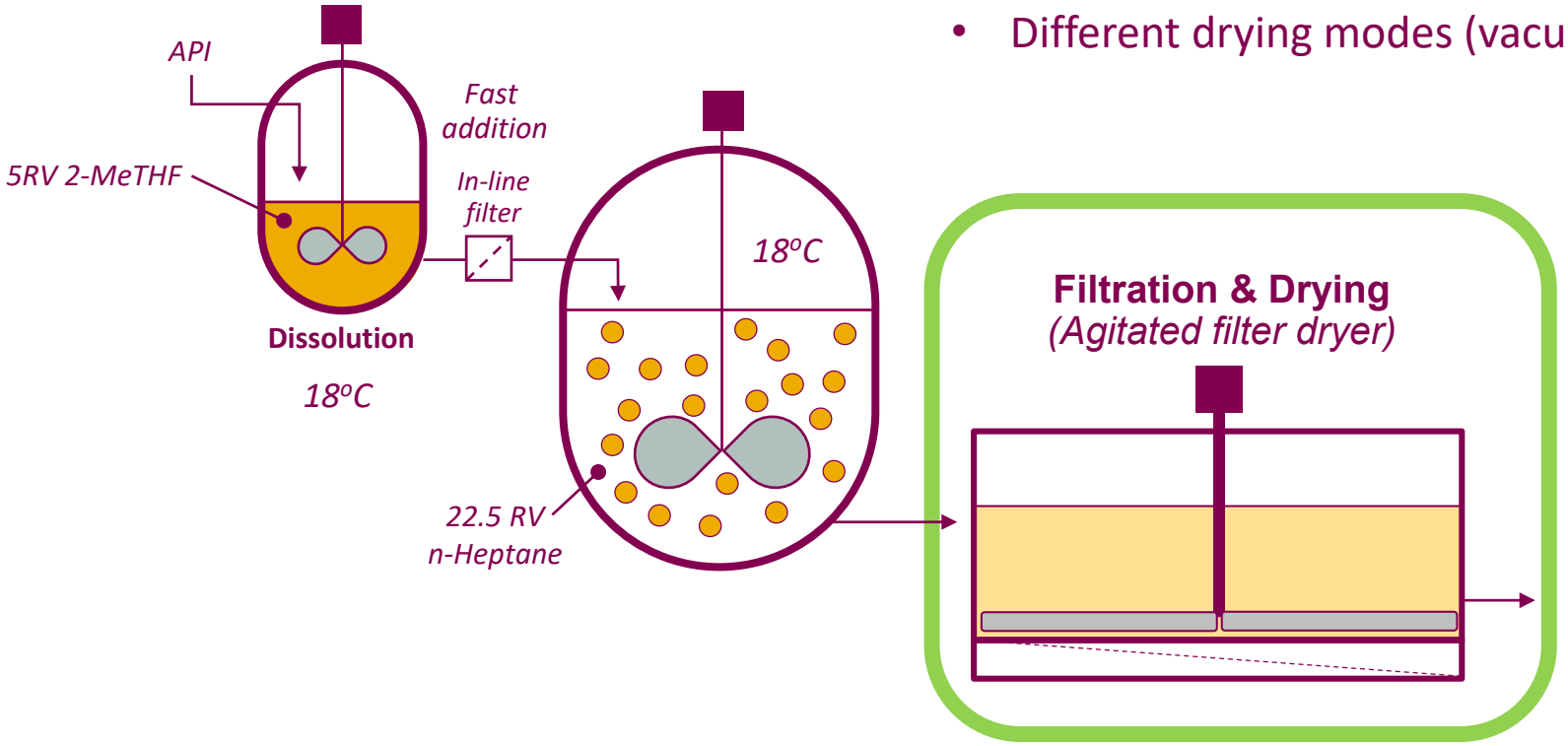
Case study 2 – Direct Precipitation

Kilo-lab (100 L) to Pilot Plant Manufacture (1000 L)

Key difference: Isolation/drying technology

Key differences:

- Agitation during isolation/drying
- Different drying modes (vacuum, N_2 pressure etc.)



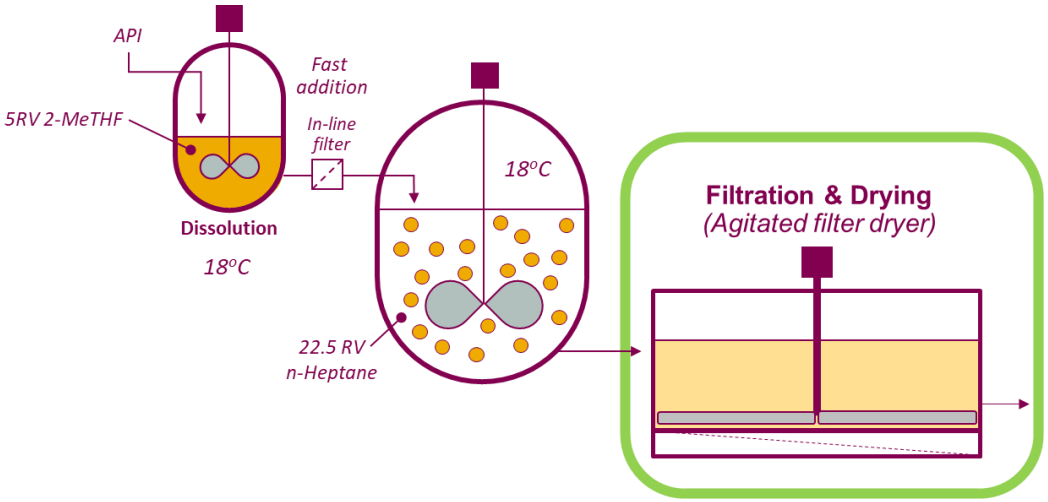


Case Study 2: Better case for Technology Transfer and Scale-up

Case study 2 – Direct Precipitation

Kilo-lab (100 L) to Pilot Plant Manufacture (1000 L) – Isolation & drying

Lab Development



Paste strength assessment: Suitable solvent prior to agitation of cake

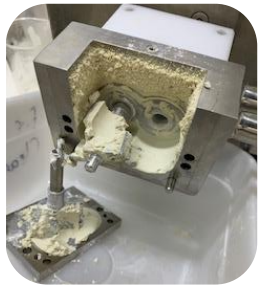
Consideration of 'wet' T_g & material properties (balling)

Pressure filter assessment: Cake compressibility

Highly compressible cake, lower pressures suitable to achieve filtration rate

Agitated drying assessment: *agitation, staged drying, drying modes (vacuum, hot N_2)*

Mixer Torque Rheometer (MTR)



Pocket filter



Glass Filter Dryer (GFD)



Pressure Filter Dryer (PFD)



Proposed procedure:

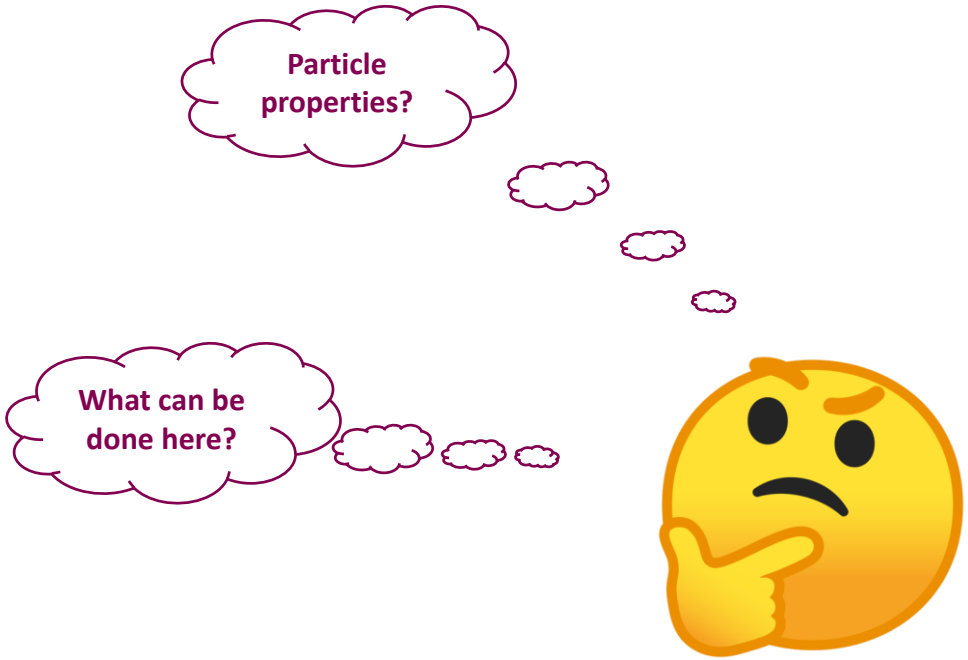
- **Filter to > 77 % paste strength**
- **Agitation**
- **Filter under vacuum**
  - **20°C**
  - **30°C**
  - **55°C**
- **Further option**
  - **Flow through hot N_2 at 70°C**

- Amorphous maintained
- Suitable filtration rate
- Solvent content within spec

Just before manufacture:

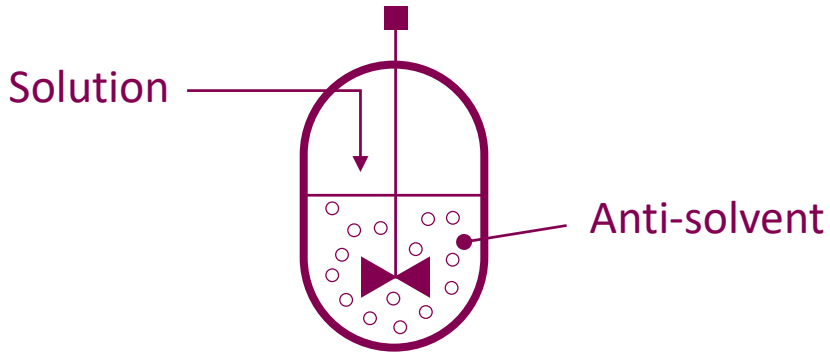
Project Halted prior to Pilot Plant!!!

Direct precipitation - Continuous



Direct precipitation – Continuous

Batch direct (reverse addition) precipitation



- Utilises conventional batch assets
- By understanding material dynamics & process development, can access '**fit for purpose**' amorphous material for DP development

However, for batch:

- Amorphous material experiences constantly changing solvent environment (Solution → Anti-solvent)
- Challenges with scale-up & batch-to-batch variation
- **Minimal particle control (challenging for amorphous)**



Continuous direct precipitation

	Batch	Continuous
Scale- up	Non-linear scale up	Linear scale up
Mixing	Unpredictable temp and concentration gradient	More uniform temp gradient and more uniform product
Energy	High energy requirement for heat and cool crystallisation cycle	Small mass, more energy efficient
Throughput	Low efficiency	High productivity
Footprint	High cost of production site	Production cost reduced, smaller scale
Technology	Well established	Developing technology, high capital required

Collaboration with

CMAC

Case study 2

Focus on two technologies:

- Static mixer (cross piece)
- Taylor Couette Reactor

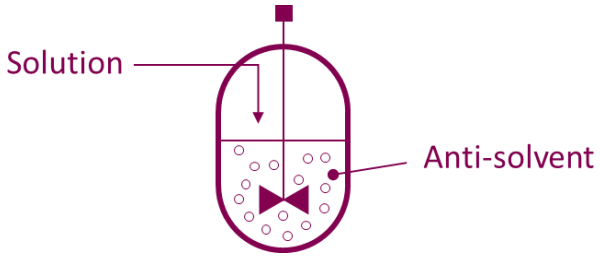
Direct precipitation – Continuous

Case Study 2
Small molecule
AZ compound

CMAC

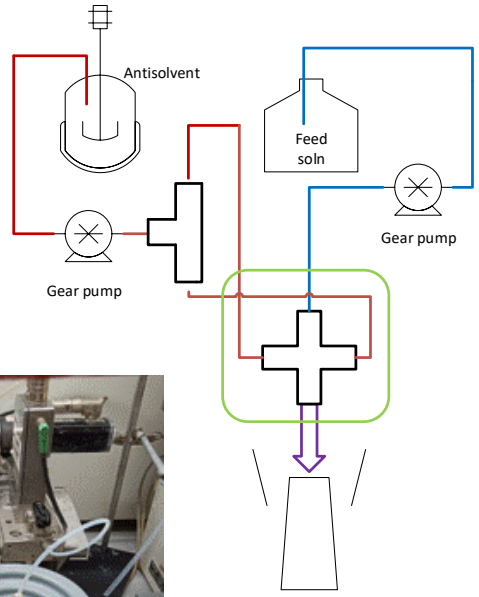
Batch showed the importance of:

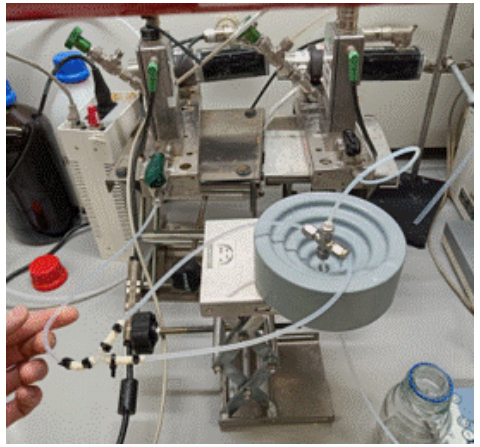
- Temperature (18°C)
- Solution to Anti-solvent ratio (1:5 vol)
- Mixing (slow)



Static mixer

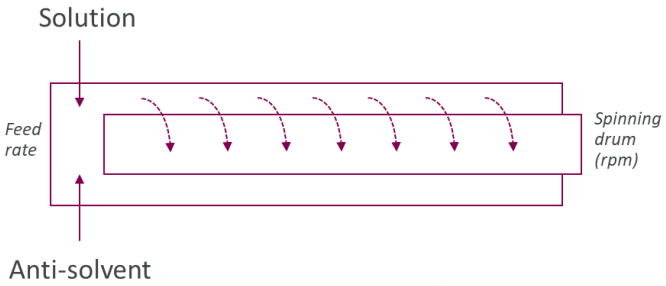
Higher ends of laminar flow mixing



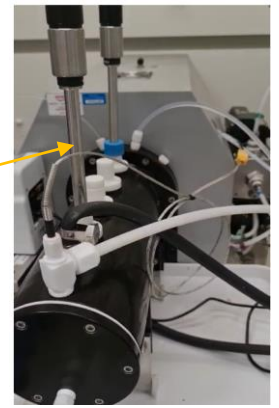


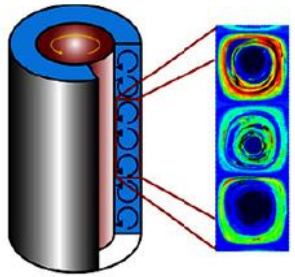
Taylor Couette Flow Reactor

High mixing and shear force



PAT





Laminar™ Reactor

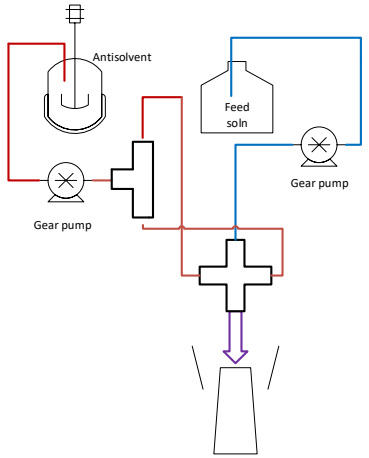
0-50rpm → laminar single periodic vortex
50-300rpm → laminar double periodic vortex
300-900rpm → turbulent vortex flow
>900rpm → turbulent flow without any vortex

PAT = Process Analytical Technology

Direct precipitation – Static mixer

SEM = Scanning Electron Microscope

PSD = Particle Size Distribution



Proof of concept:

x4 runs – varying flow rates

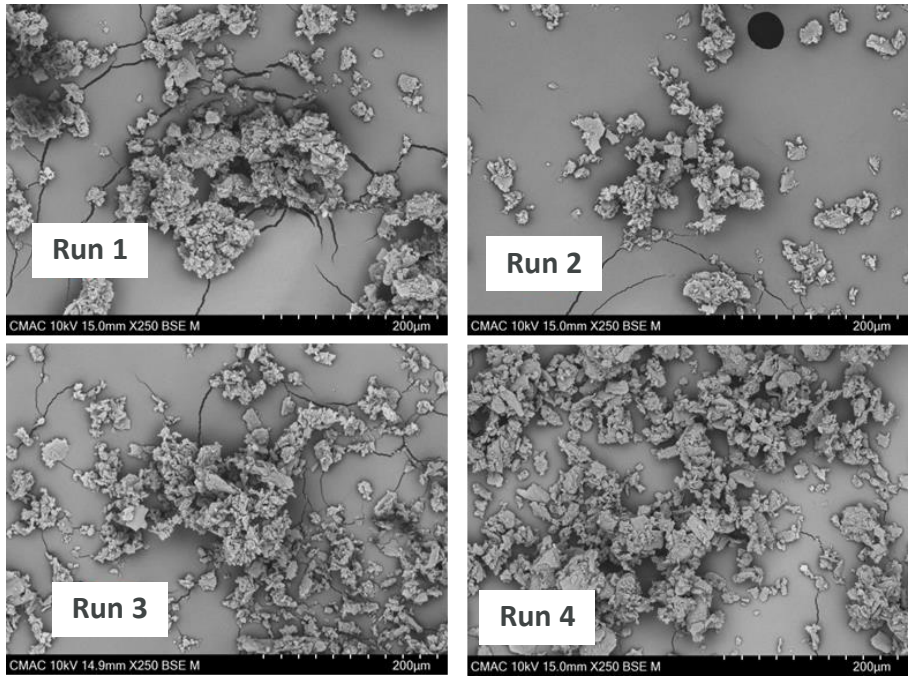
- Set solution concentration
- Each run approx. 200ml slurry

20°C

2-MeTHF/heptane (1:2 vol.)

Exp	Velocity (m^2/s)	Pressure drop (Pa)	Shear rate (1/s)	Residence time (s)	Reynold's no	Mean size (µm)
Run 1	0.17	139	694	0.58	279	--
Run 2						14
Run 3						19
Run 4*	0.87	694	3471	0.12	1396	26

**Pressure due to blockages observed → impact on operational effectiveness*



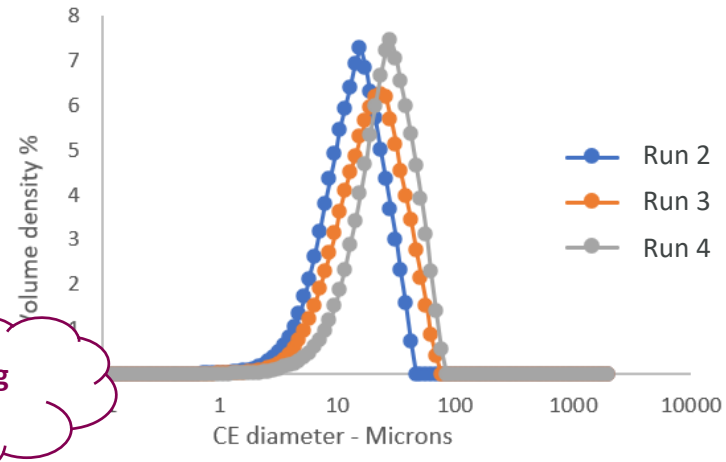
SEM

Solid Form
Amorphous

Increased shear rate → **Increased particle size** → **Potentially more agglomeration**

Particles





PSD

PSD = Particle Size Distribution

Direct precipitation – Taylor Couette Flow Reactor

Design of Experiments (DoE):

x8 runs – varying flow rates, flow ratios, RPM

- Set solution concentration

20°C

2-MeTHF/heptane

Exp no	Flow rate (mL/min)	RPM	Flow Ratio	Residence time (s)	Mean size (µm)	Span
Run 5	60	1300	1:4	16.6	34	1.6
Run 8	150	800	1:4	6	39	1.2
Run 4	60	700	1:2	16.6	45	
Run 6	120	400	1:2	8.3	46	
Run 7	150	800	1:4	6	49	1.3
Run 3	60	500	1:2	16.6	55	1.3
Run 2	60	500	1:2	16.6	58	1.5
Run 1	60	600	1:4	16.6	70	1.6

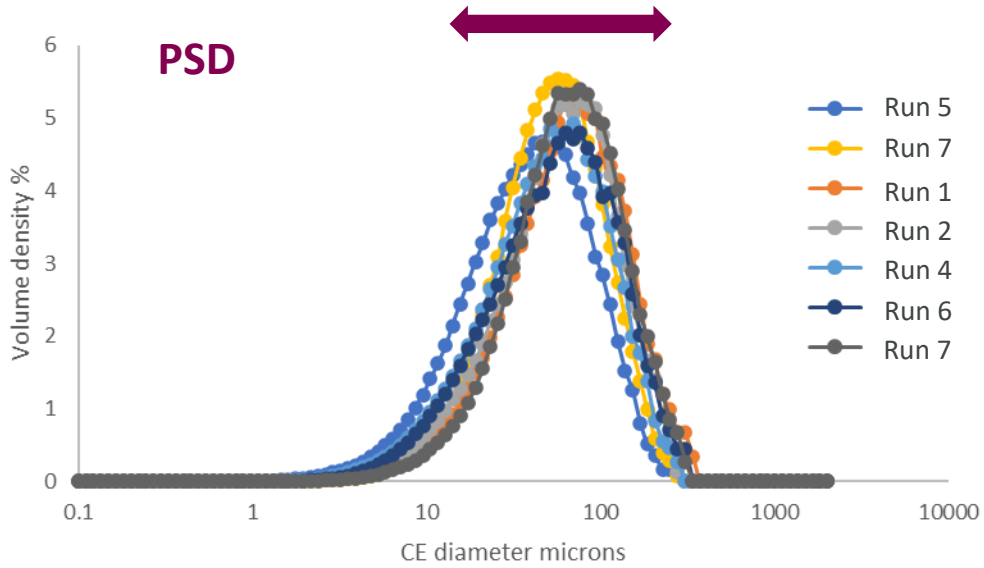
Solid Form
Amorphous

Particles:

Flow rate + **RPM** + **Flow ratio**

No blockages

Towards being able to tune the PSD



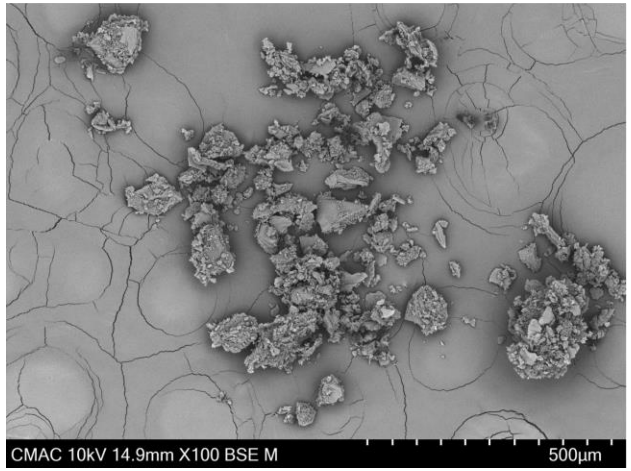
Repeat runs (Runs 1 & 5):

PSD results were reproducible!

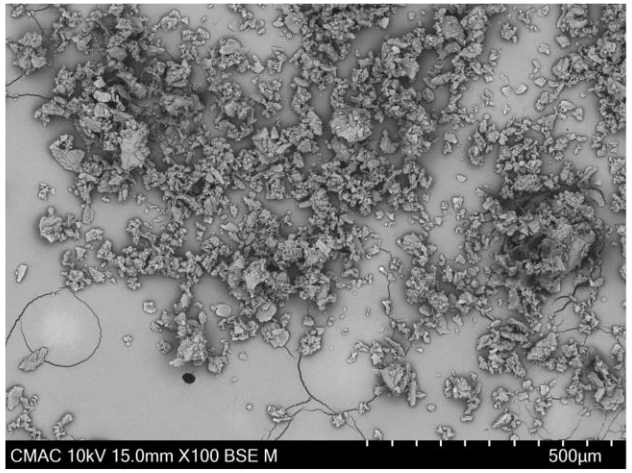
Direct precipitation – Batch v Continuous Material properties

Batch

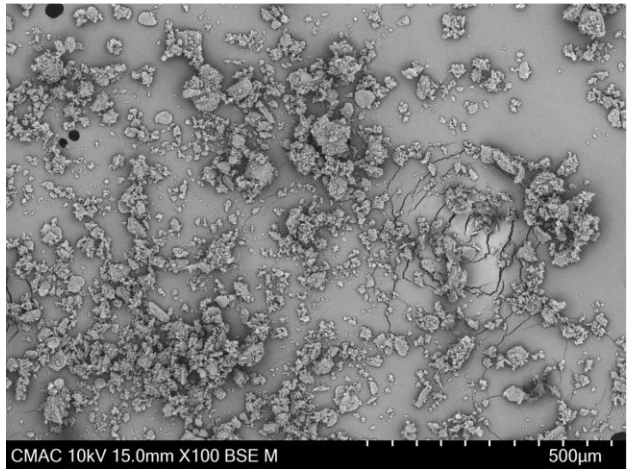
Amorphous reference material



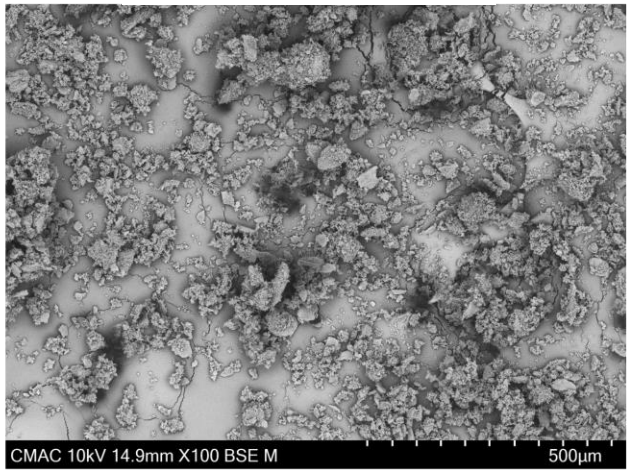
Static Mixer



T-C Reactor - Run 5



T-C Reactor - Run 1



- Smaller particles → More agglomerates (lumps)
- Smaller particles → more static

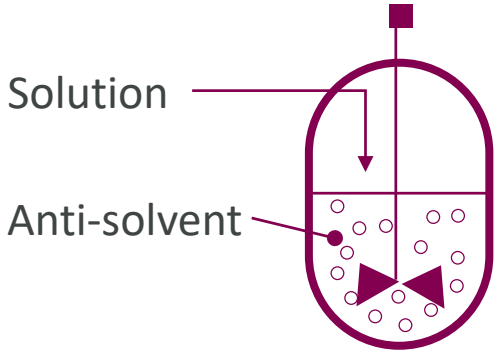
Bulk density and flow properties

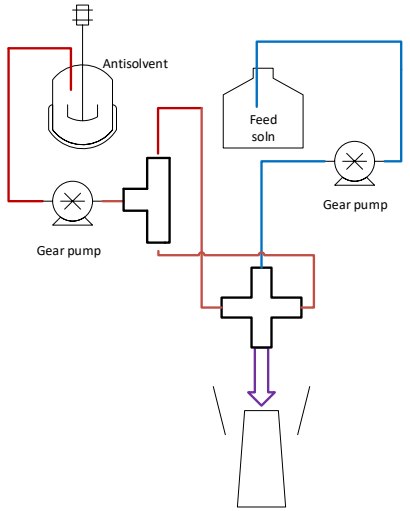
		Bulk Density	Flow Function Coefficient (FFC)
Batch process	Reference		<4
Cross mixer	Run 4	0.128	8.68
Taylor Couette reactor	Run 1	0.137	8.11
	Run 5	0.188	7.60
	Run 3	0.123	8.15

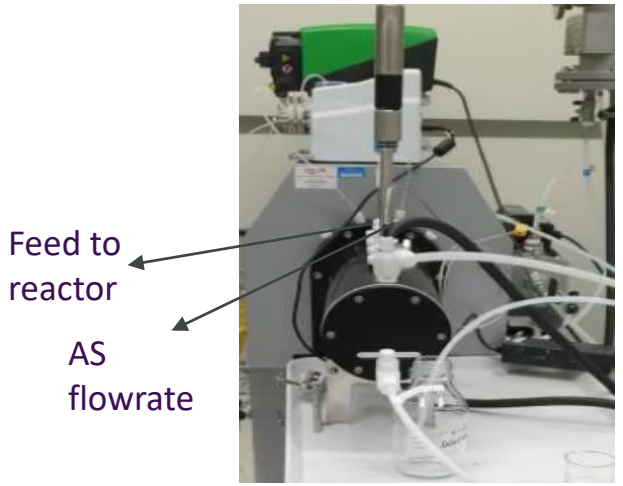


- Comparative bulk densities across continuous runs
- Significantly improved Powder Flow

Direct precipitation – Batch v Continuous







Measure	Batch	Static mixer	Taylor Couette
Mode of operation	Batch	Continuous (stable by 2nd RT)	Continuous (stable by 2nd RT)
Volumes	100ml-100L (tested)	As small as 3ml to 100ml	330 mL to 1000 L (commercial)
Flowrates ml/min	Dependent	20-150	20-300
Solution/Anti-solvent ratio	1:5	1:2	1:2
AS addition	Reverse addition to vessel	Continuous addition at mixing	Continuous addition at mixing
Sheer rate S^{-1}	Low	Medium	Medium-High
Particle size	Wide distribution of particles & agglomerates (50-100 µm)	Smaller particles & agglomerates (20-40 µm)	Potential for tunable particles (10-50 µm)

Still in the process of understanding the continuous space but promising signs for the future.

Summary

- **Amorphous compounds are becoming more common** and, despite being *meta-stable*, can unlock **improved bioavailability**.
- **Fit-for-purpose precipitation strategies** are key to supporting **early phase development** in a demanding portfolio.
- **Success depends on targeting the biggest risks**: processability, isolation and drying, stability, residual solvents, and material properties.
- **Continuous processing can add value** by reducing **re-crystallisation risk** and improving **particle control**.

Acknowledgements

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Martin Sims

Many more from AZ

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Thanks to everyone

Thank you for listening
Any questions?



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