Making Amorphous:

The challenges of making amorphous API in early phase pharmaceutical development

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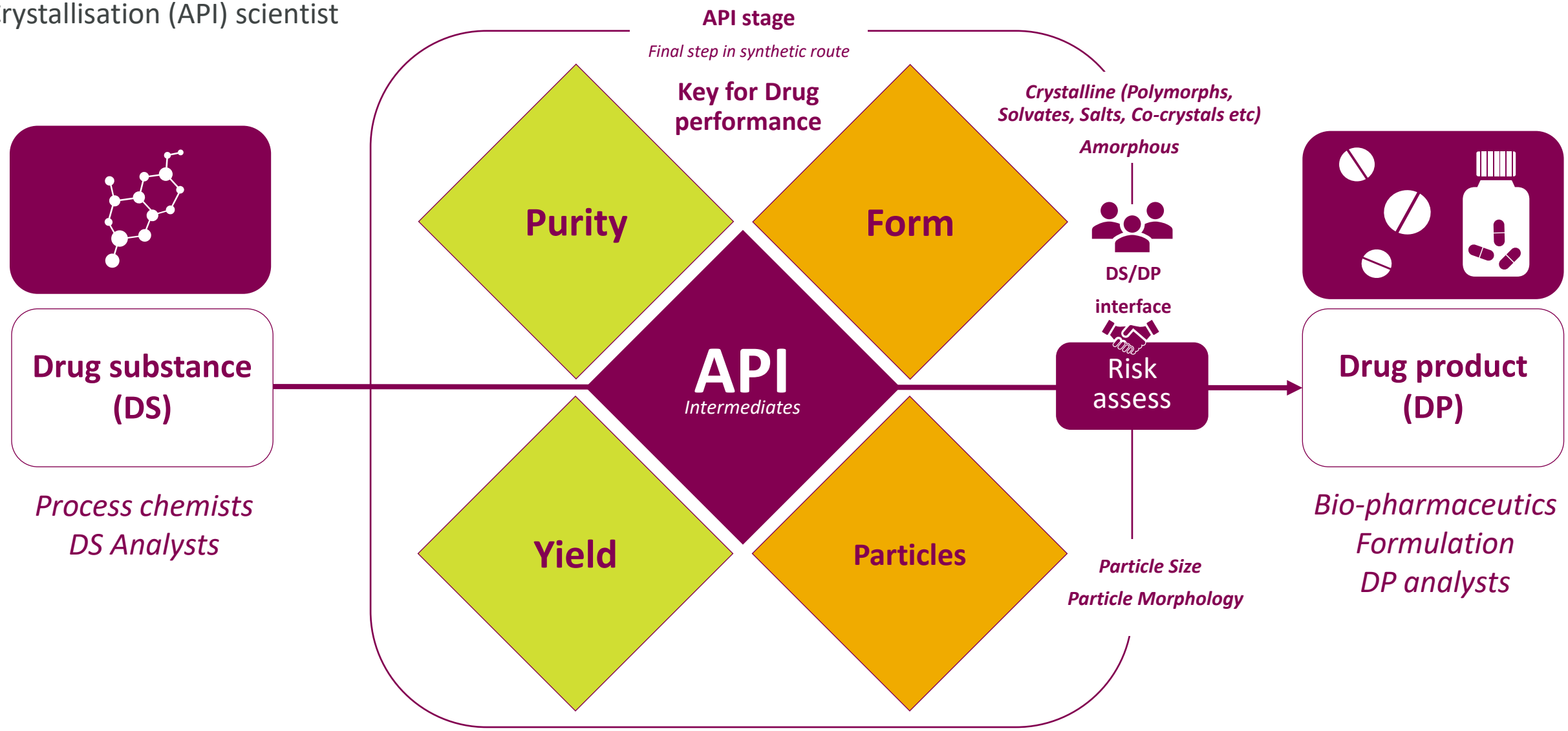
Agenda

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

API = Active Pharmaceutical Ingredient

Pharmaceutical development – API development

Crystallisation (API) scientist



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?

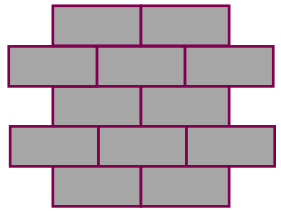
Amorphous materials

Molecule

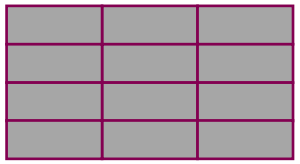
Crystalline

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

Polymorph 1



Polymorph 2

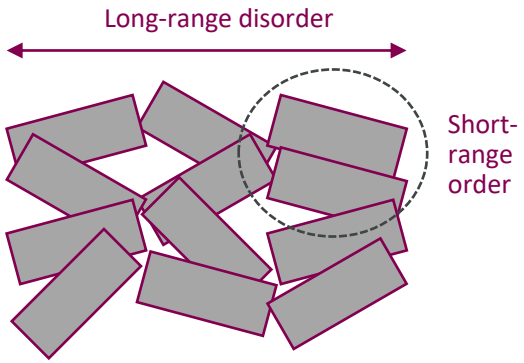


Coherent structures

Lower energy state

Amorphous

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

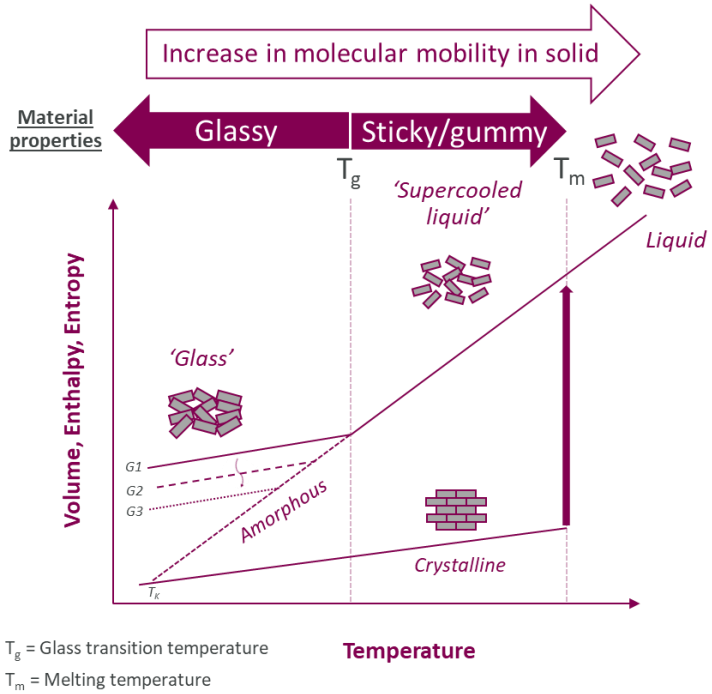


Incoherent (variable) structure

Higher energy state
'Meta-stable'

Can stabilise with polymers – Amorphous Solid Dispersions (ASDs)

Not todays focus



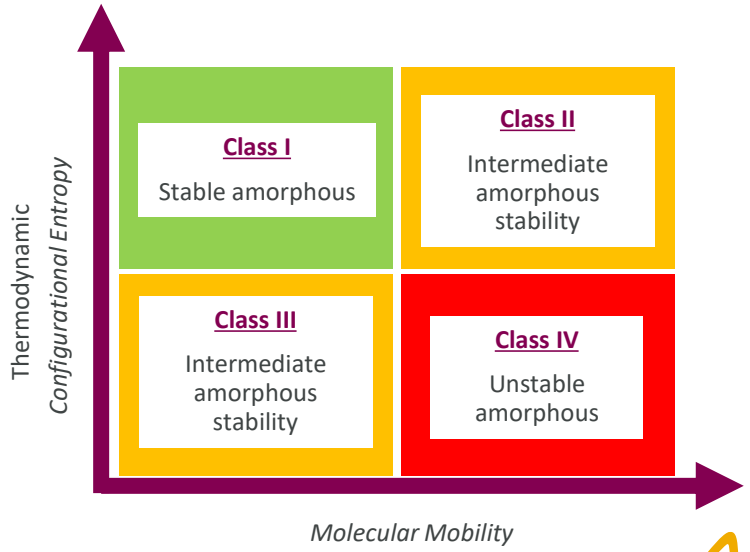
T_g = Glass transition temperature
T_m = Melting temperature

Amorphous materials = high degree of molecular mobility (MM)

Glass transition temperature (T_g) = inflection point in MM

Molecular mobility can be impacted by solvent, temperature, impurities etc.

Amorphous Classification System (ACS)



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

Amorphous materials – Challenges and rewards

Challenges

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

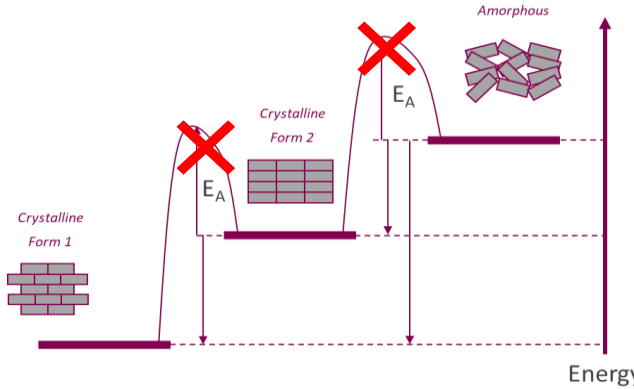
- Physical & chemical degradation risk
- No impurity purging
- Inherent material variability (batch to batch)
- Challenging material properties

So why choose amorphous for API?

No suitable crystalline Form

or

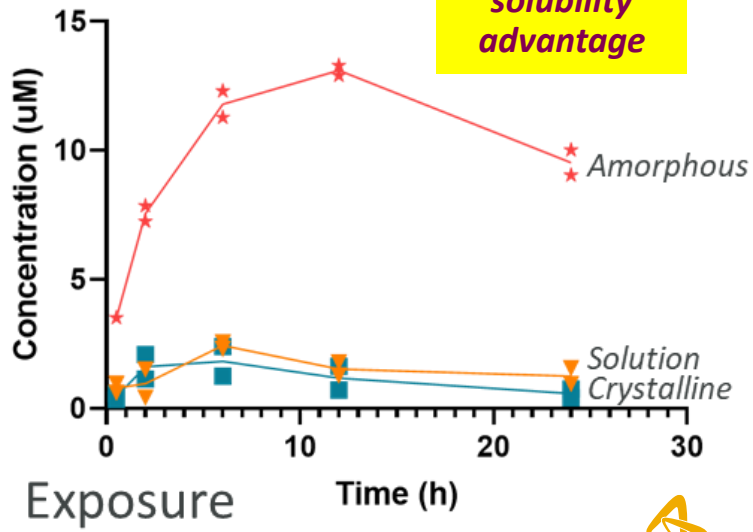
Form challenging to crystallise



Reward

Biopharmaceutics

Can have a x10 fold solubility advantage



Stability: Amorphous < Crystalline

Amorphous → Higher solubility &/or faster dissolution rates

Improved bioavailability

Amorphous materials – Making Amorphous

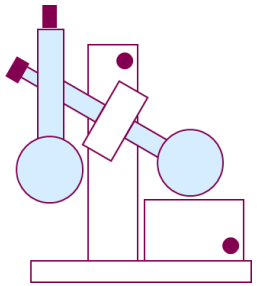
Lots of ways to make amorphous (not limited to…)

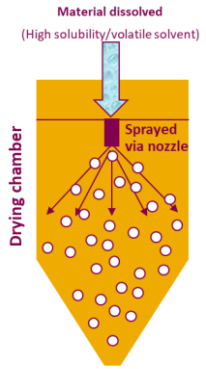
Aggressive conditions ⇨ High supersaturation ⇨ More nucleation events ⇨ **Meta-stable solid i.e. Amorphous**

Quench-cooling *Holt melt extrusion*

Milling *Ball milling* *Cryo-milling*

Evaporation *Rotary evaporator*

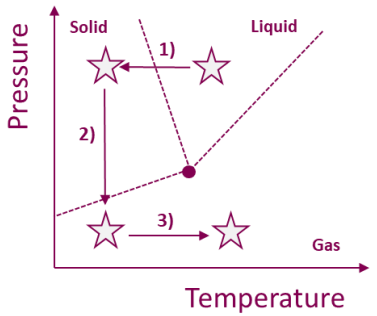




Spray drying

Lyophilisation

Freeze drying



All have advantages & disadvantages…

- Stage of development
- Scale of manufacture
- Capacity for production
- Yield

Etc.

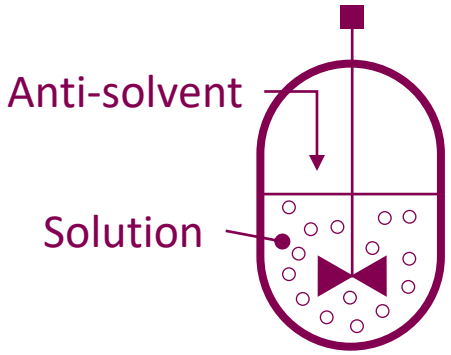
Manufacturing strategy

- **Can we avoid additional 'Drug Product intermediate' processing?**
- **How can we leverage Drug Substance assets for amorphous delivery?**

Direct Precipitation

Direct precipitation – Reverse addition

Precipitation = amorphous
Crystallisation = crystalline



Crystallisation

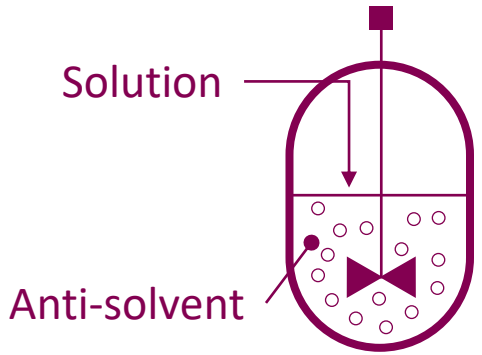
'Slow & steady'

More stable phases

Precipitation

'Fast & aggressive'

Less stable phases



Advantages:

- Fast processing
- Utilise conventional assets

Challenges:

Solvent 'rich' environment

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

Direct precipitation – AZ case studies

Batch mode

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

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

Moving to Continuous Direct Precipitation

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 T_g (> 160°C)*
  - *Moderate hygroscopicity*
  - *Challenging chemical stability*

Step 1

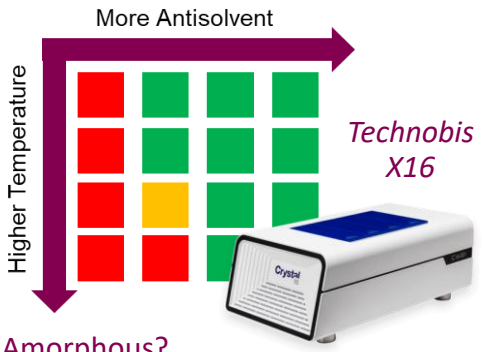
Solvent selection

Solvents - Freely soluble
2-MeTHF

Anti-solvents - Insoluble
n-Heptane

Step 2

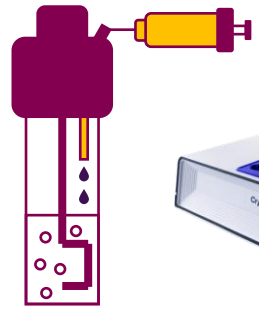
Understanding the operating space

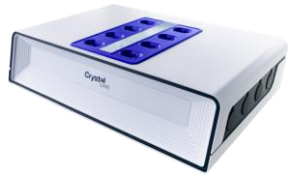


- Amorphous?
- Stickiness in process (processibility)?
- Isolated material properties?

Step 3

Proof of Concept





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

Step 4

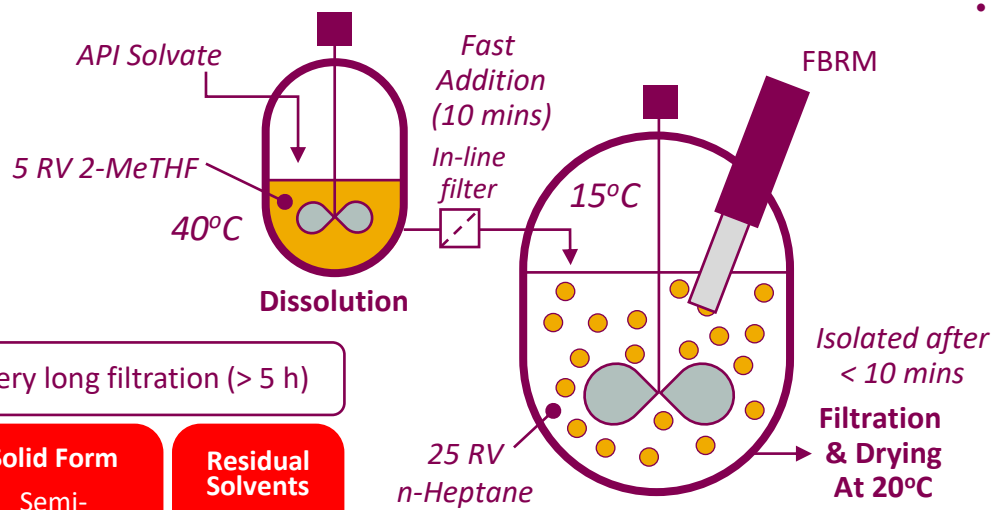
Scale-up

Mettler Toledo EasyMax

Solid Form
Amorphous

Residual Solvents
~2.5%ww

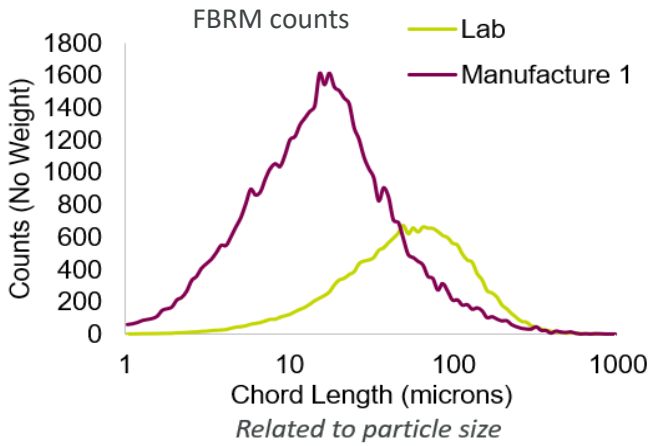
1st kilo manufacture



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

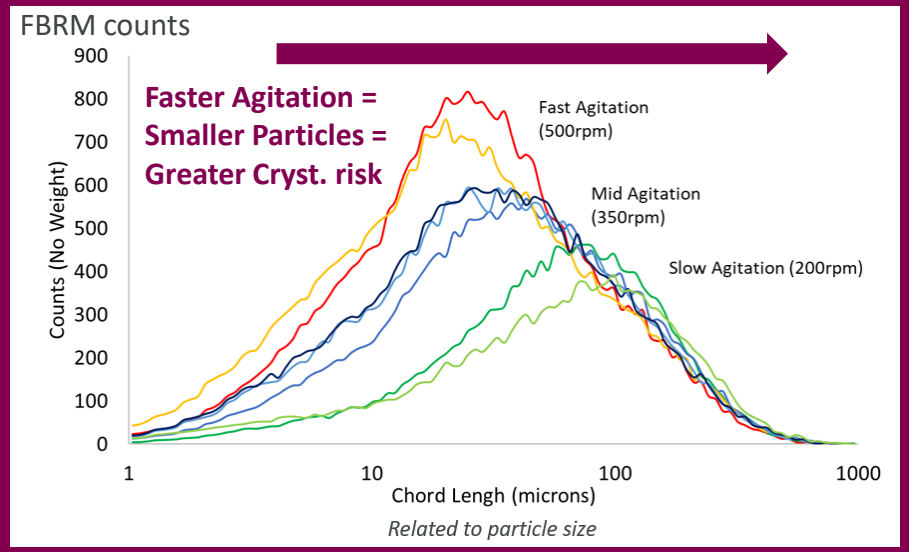
FBRM = Focussed Beam Reflectance Measurement

Case study 1 – Direct Precipitation

Back to the Laboratory

Initial considerations: Agitation → Particles → Filtration

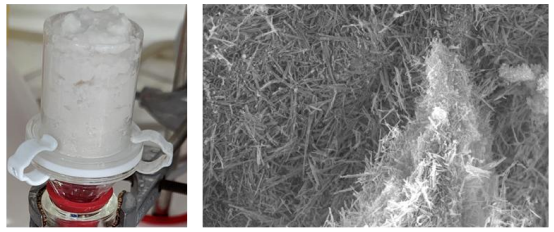
DoE: Agitation v Addition rate



Addition → Not deemed significant

Fastest agitation → Rapid re-crystallisation in cake

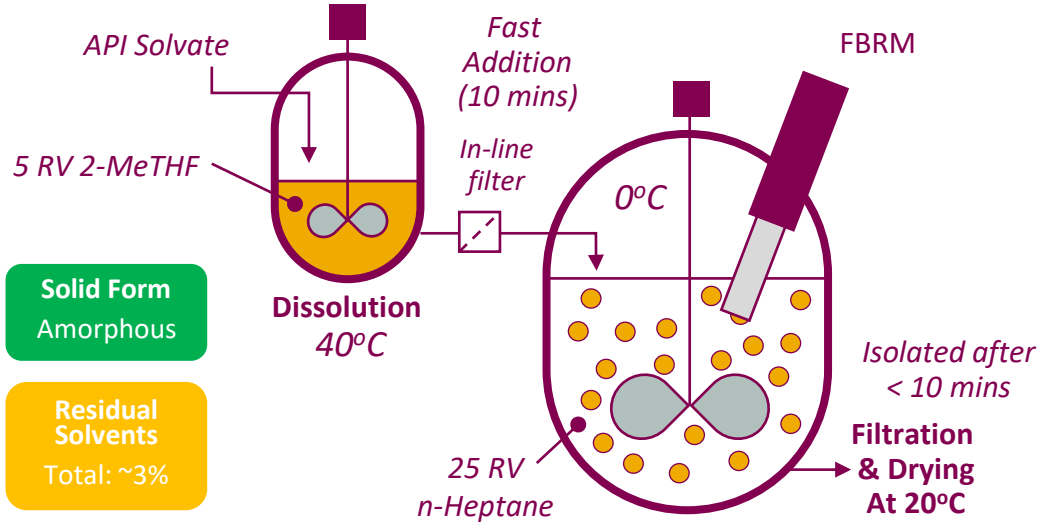
Worst case example

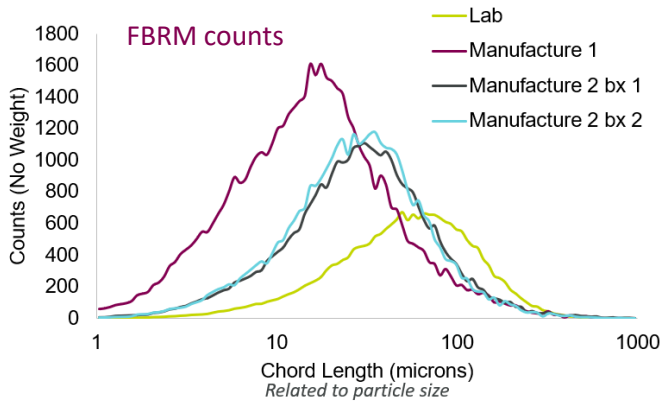


Mitigations for next manufacture:

- **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 T_g)**
  - **Agitation impact on particle size**
  - **Impact on filtration**

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 T_g (> 160°C)*
  - *Moderate hygroscopicity*
  - *Amorphised via a range of methods*
- Manufacture in kilo-lab

Step 1

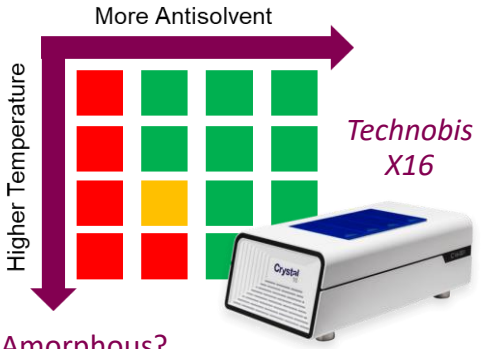
Solvent selection

Solvents - Freely soluble
2-MeTHF

Anti-solvents - Insoluble
n-Heptane

Step 2

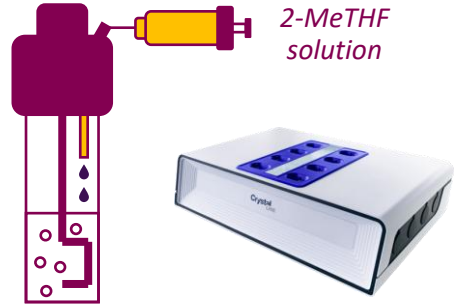
Understanding the operating space



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

Step 3

Proof of Concept



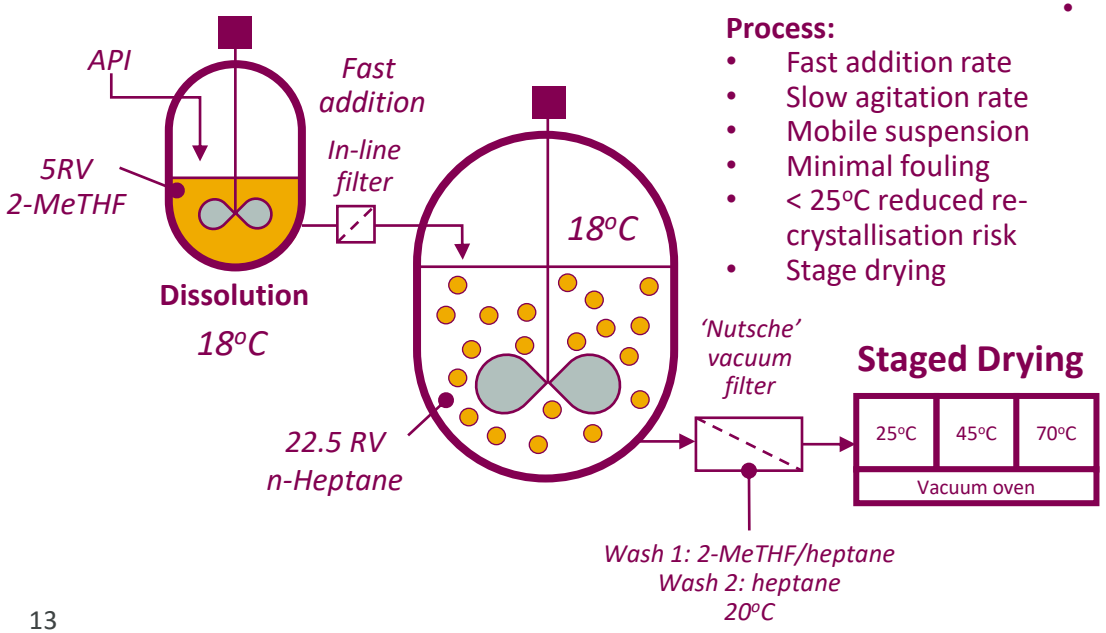
- Solution (5 RV) → Anti-solvent (22.5 RV)
- Temp. = 18°C

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 %

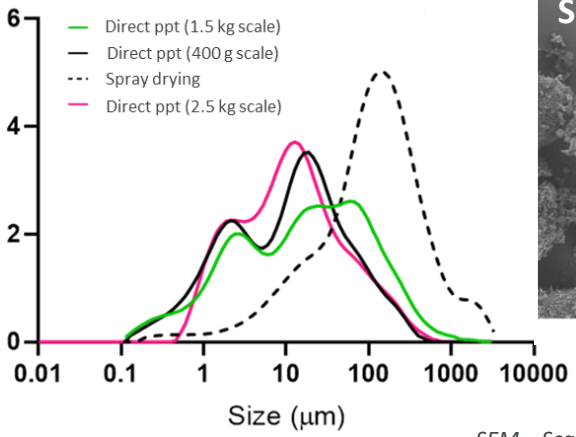
> 95 % yield

Manageable powder properties for DP development

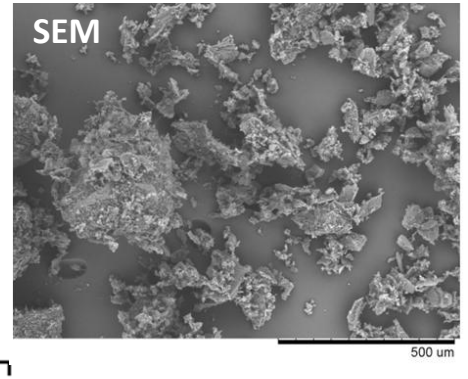
Solid Form
Amorphous

Residual Solvents
<2%ww

PSD



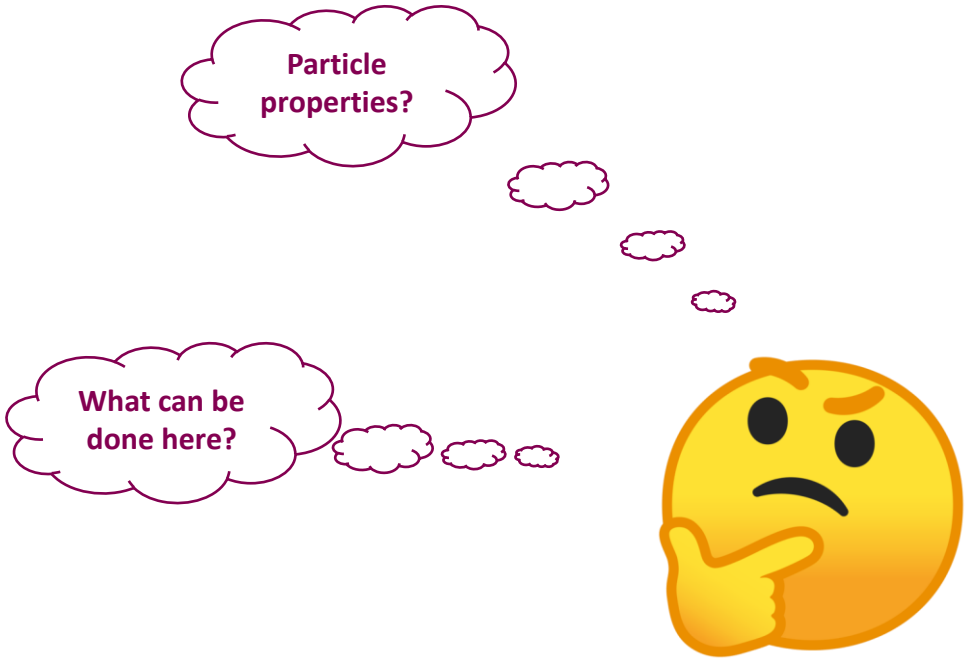
SEM



SEM = Scanning Electron Microscope

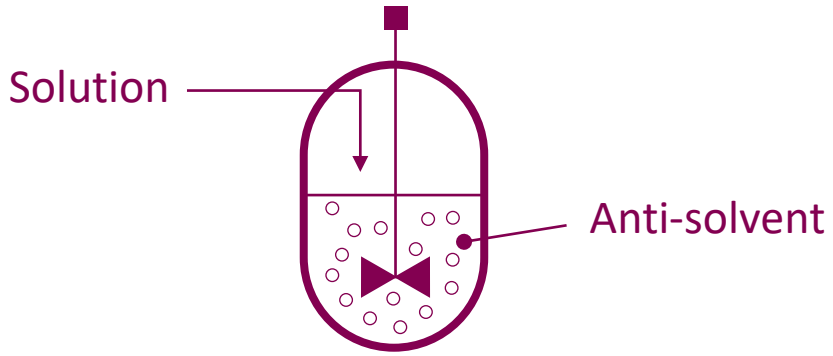
PSD = Particle Size Distribution

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

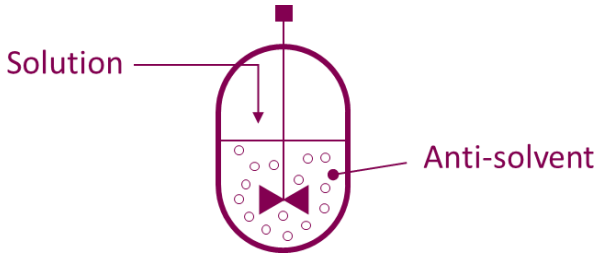
Direct precipitation – Continuous

Case Study 2
Small molecule
AZ compound

CMAC

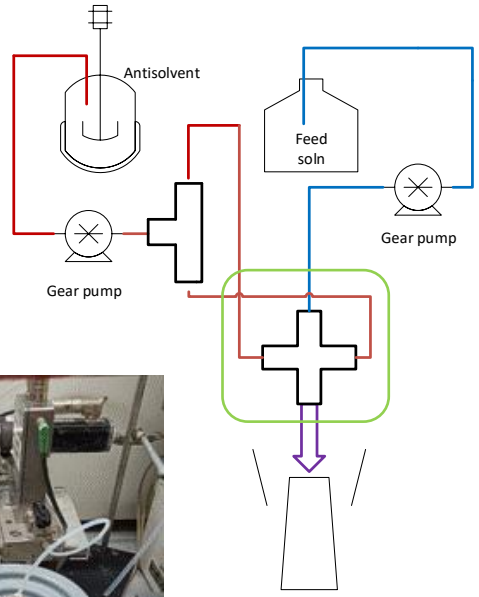
Batch showed the importance of:

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



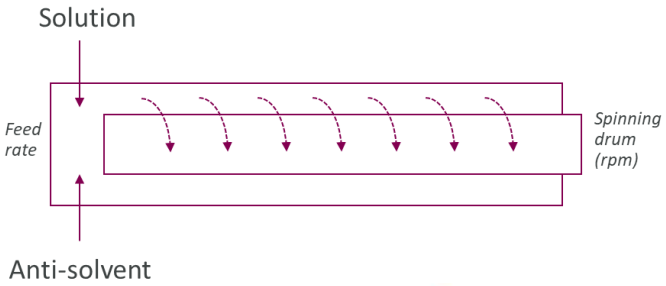
Static mixer

Higher ends of laminar flow mixing

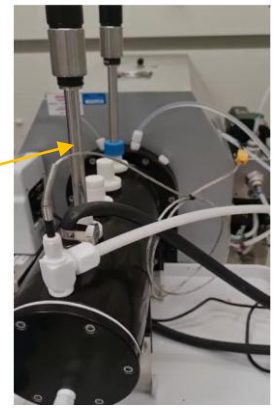


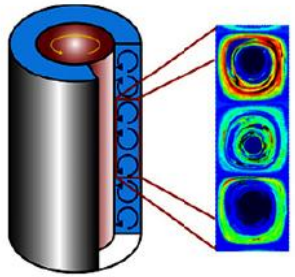
Taylor Couette Flow Reactor

High mixing and shear force



PAT





Laminar™ Reactor

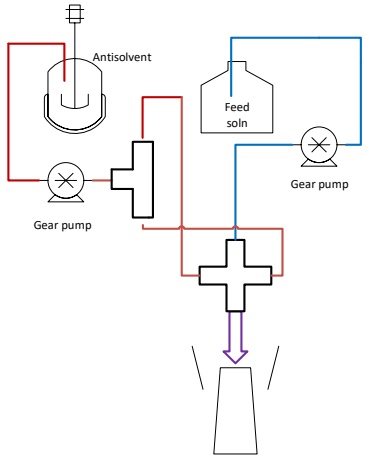
0-50rpm → laminar single periodic vortex
50-300rpm → laminar double periodic vortex
300-900rpm → turbulent vortex flow
>900rpm → turbulent flow without any vortex

PAT = Process Analytical Technology

Direct precipitation – Static mixer

SEM = Scanning Electron Microscope

PSD = Particle Size Distribution



Proof of concept:

x4 runs – varying flow rates

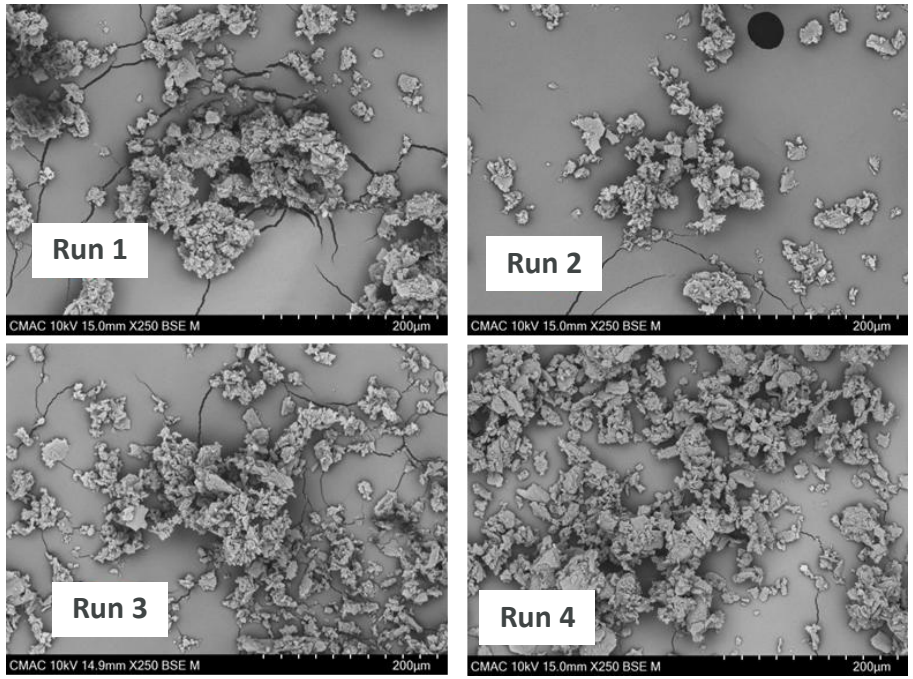
- Set solution concentration
- Each run approx. 200ml slurry

20°C

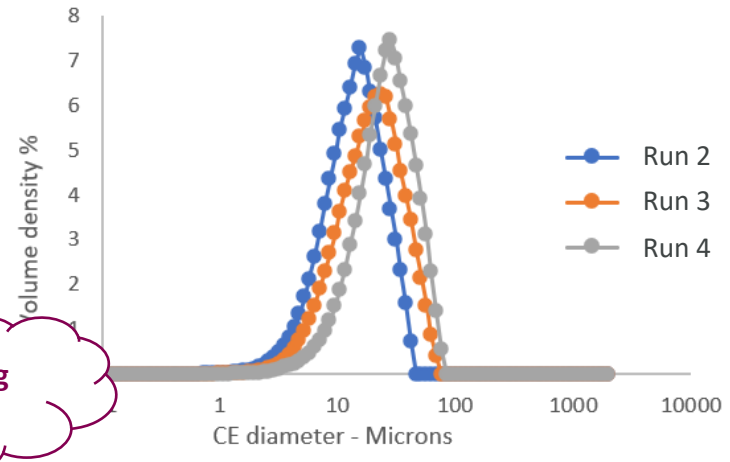
2-MeTHF/heptane (1:2 vol.)

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



PSD

Solid Form
Amorphous

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

Particles

Something better?

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

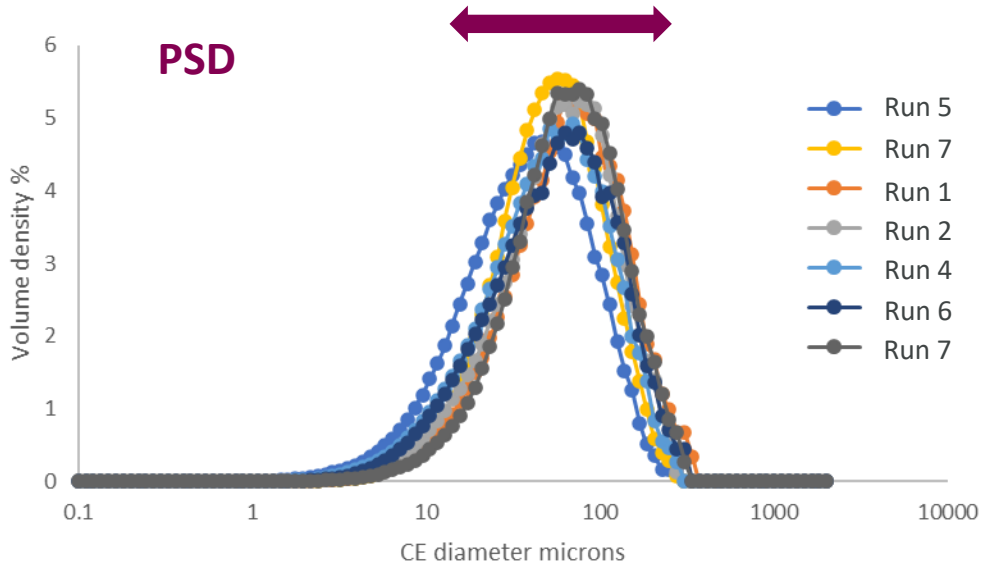
Solid Form
Amorphous

Particles:

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

No blockages

Towards being able to tune the PSD



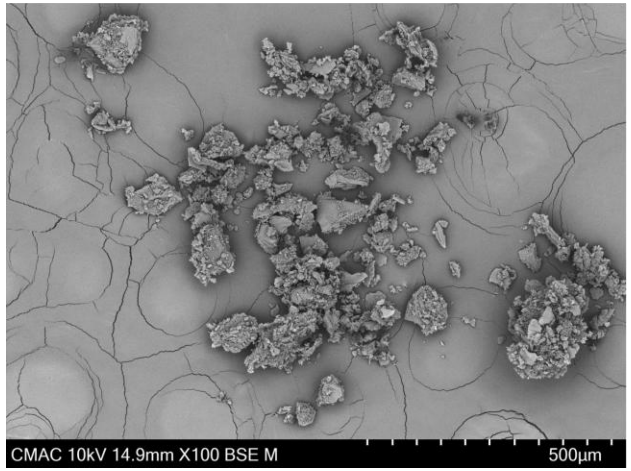
Repeat runs (Runs 1 & 5):

PSD results were reproducible!

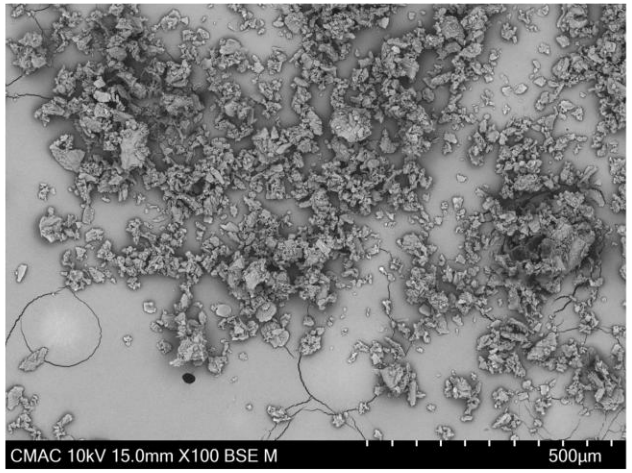
Direct precipitation – Batch v Continuous Material properties

Batch

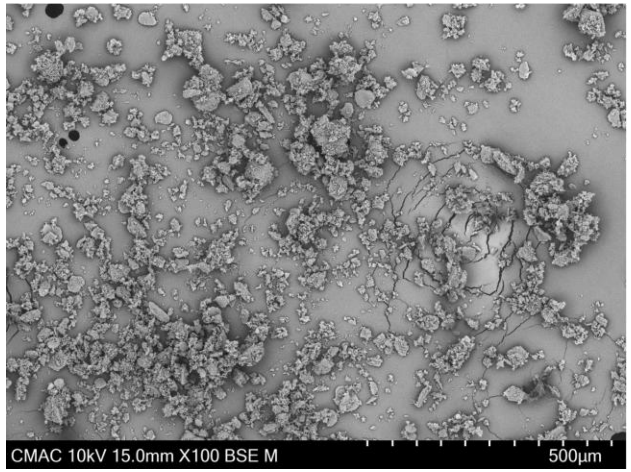
Amorphous reference material



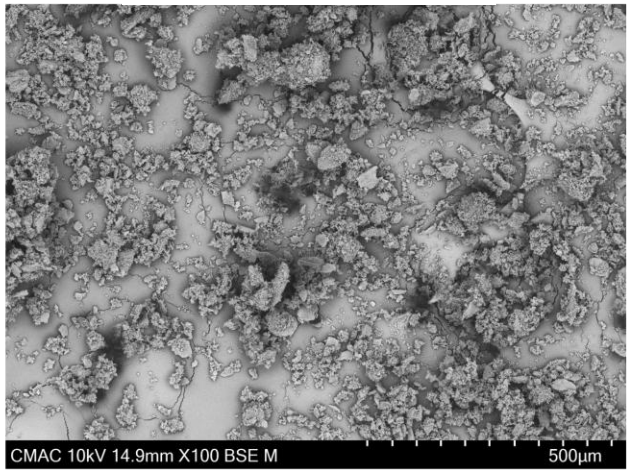
Static Mixer



T-C Reactor - Run 5



T-C Reactor - Run 1



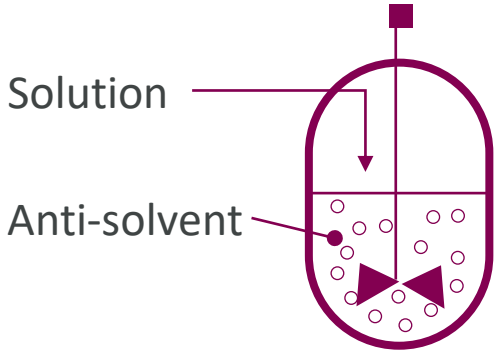
- Smaller particles → More agglomerates (lumps)
- Smaller particles → more static

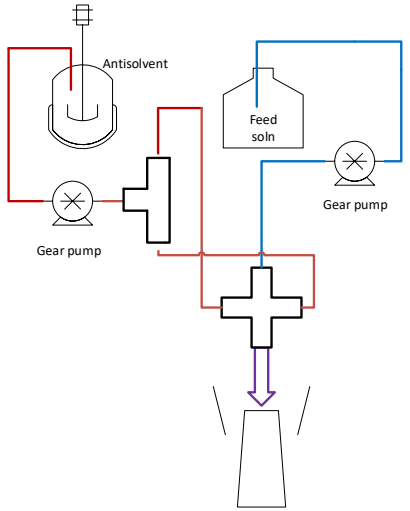
Bulk density and flow properties

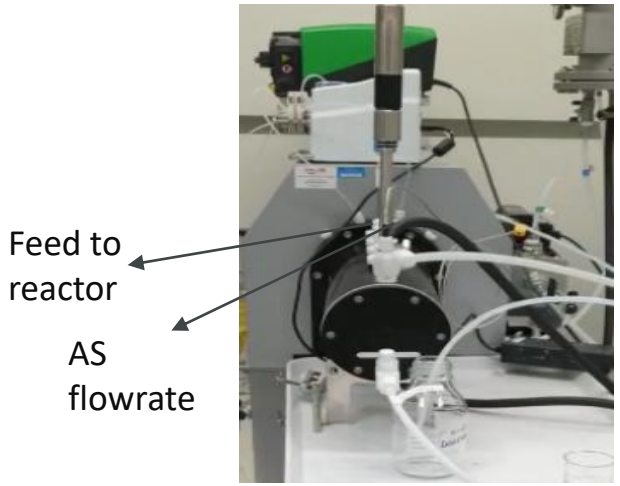
		Bulk Density	Flow Function Coefficient (FFC)
Batch process	Reference		<4
Cross mixer	Run 4	0.128	8.68
Taylor Couette reactor	Run 1	0.137	8.11
	Run 5	0.188	7.60
	Run 3	0.123	8.15

- 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**.

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AZ Team

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Thank you for listening
Any questions?