From Pharmaceutical Substance to Product – An Industrial Perspective on Continuous Processing

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AstraZeneca

Overview of Presentation

- **Challenges of continuous processing in the pharmaceutical industry**
- **Continuous processing in AstraZeneca**
- **Drug substance**
  - Flow chemistry
  - Equipment
- **Continuous crystallisation**
- **Drug product**
  - Wet granulation
- **Conclusions**
- **Acknowledgements**

Continuous Processing in the Pharmaceutical Industry

A unique challenge?

- **Attrition**
  - Only a small percentage of what R&D work on is commercialised.
  - Capital Investment – existing facilities and supply chains, return on investment
  - Gaps in what we know; the science and traditional skills

- **Regulation**
  - The industry is highly regulated, risk averse and conservative.
  - Culture, ‘It’s not how we do things around here’

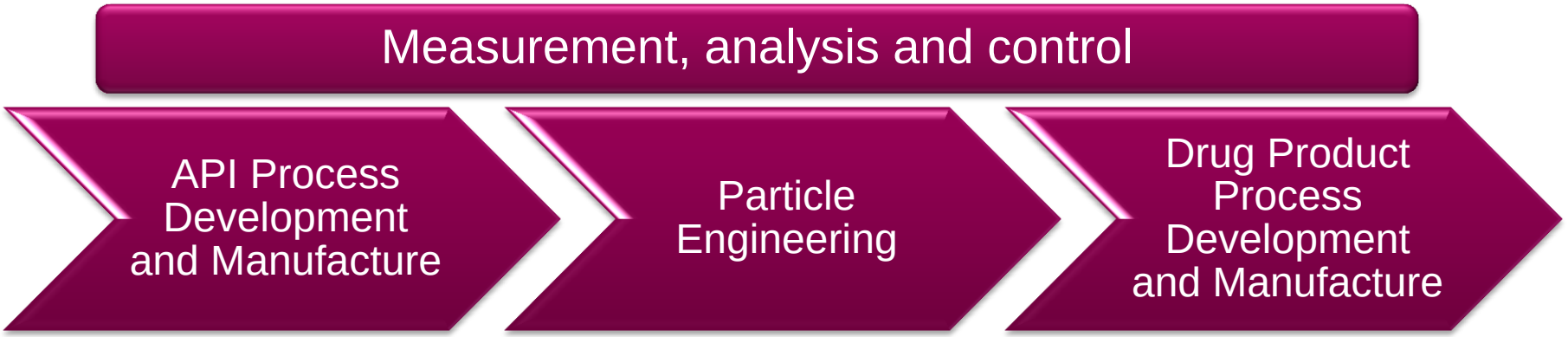
- **The Product**
  - A safe, efficacious, differentiated (and increasingly reimbursable) clinical outcome, not the medicine itself.
  - Focus of R&D investment

- These challenge the adoption of new manufacturing methodologies and technologies.

AZ Journey

- GOAL – to design and use continuous processes to generate value for the business throughout the lifecycle of the product.
- Different challenges in the different areas need different solutions
  - Outsourced API manufacture
  - Historically low investment in linking substance properties and product performance.
  - Internal, Global formulated product manufacture
- Winning hearts and minds
  - Overcoming techno-economic barriers
  - Addressing skills gaps
  - Changing culture

Continuous Processing in AZ
Built on collaboration



Identify, understand, implement and exploit continuous processing where it adds tangible benefits

Design and deliver the right API particles

Replace wet granulation with continuous dry granulation

COLLABORATION across industry and academia is an ESSENTIAL element of the AZ strategy.

- Academics more able to deliver fundamental science allowing industry to focus on application and methodologies. Key that real or good model compounds are used.
- Industrial collaboration in this precompetitive area supports knowledge sharing, leverages investment and strengthens internal and external influence.
- Key overcoming inertia and resistance to change.

Drug Substance

Benefits of Reactions in Flow

Why?

- Selectivity
- Safety
  - unstable/difficult to handle reagents
  - Reactive/explosive intermediates
- Critical mixing control
- Highly exothermic/endothermic reactions
- Excess temperatures
  - Cryogenic or high temperatures
- Unstable products/substrates
- Precise reaction times

Challenges

- Solids block flow reactors
- Work-up in batch may be a bottle-neck
  - Telescopes, liquid/liquid separations, continuous distillation, SMB chromatography

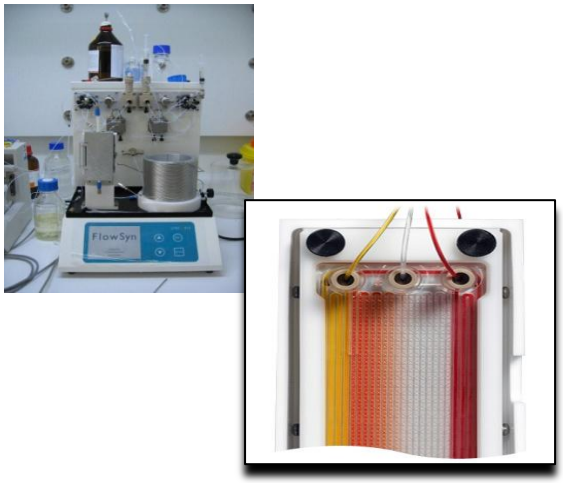
If the manufacture is not going well the process can be stopped and starting materials preserved – not possible in batch!

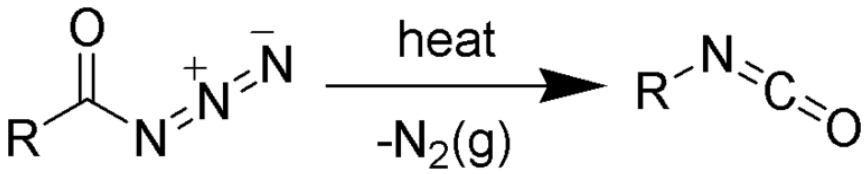
Example 1: Curtius reaction

A Safer More Efficient Process

- Delivered 700g at 85% yield
- Laboratory delivered (non GMP)
- Safer chemistry, enabling better control of hazardous reagents

Uniqsis Flowsyn Lab Reactor





Example 2: Nitration
Green chemistry example

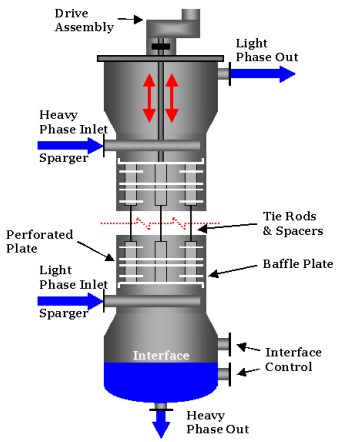
- Developed flow chemistry in <2 weeks
- Huge, process intensification
- Removed need for chlorinated solvent
- Solvent free reaction

Parameter	Batch	Flow
Rxn time	4 to 16 hours	30 to 60 seconds
Nitric Acid	Comparable equivalents	
Solvent	5.2 rel vols	None (neat acid)
Conversion	Comparable	

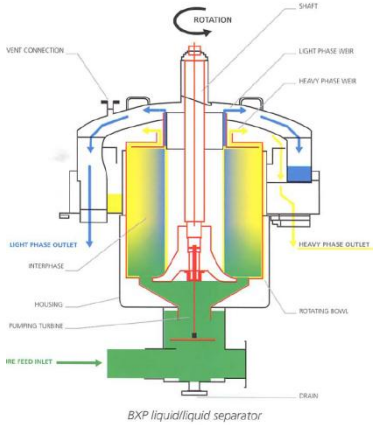
Equipment & Technology

New Lab Equipment

Karr Extraction Column

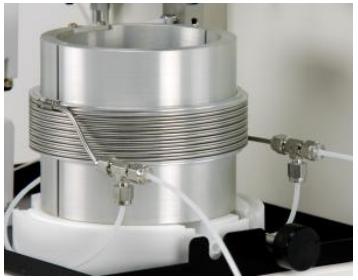


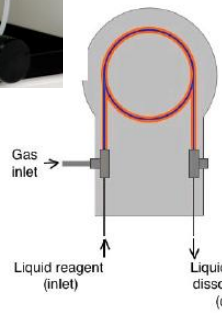
Centrifugal Extractor



BXP liquid/liquid separator

Gas Membrane Reactor





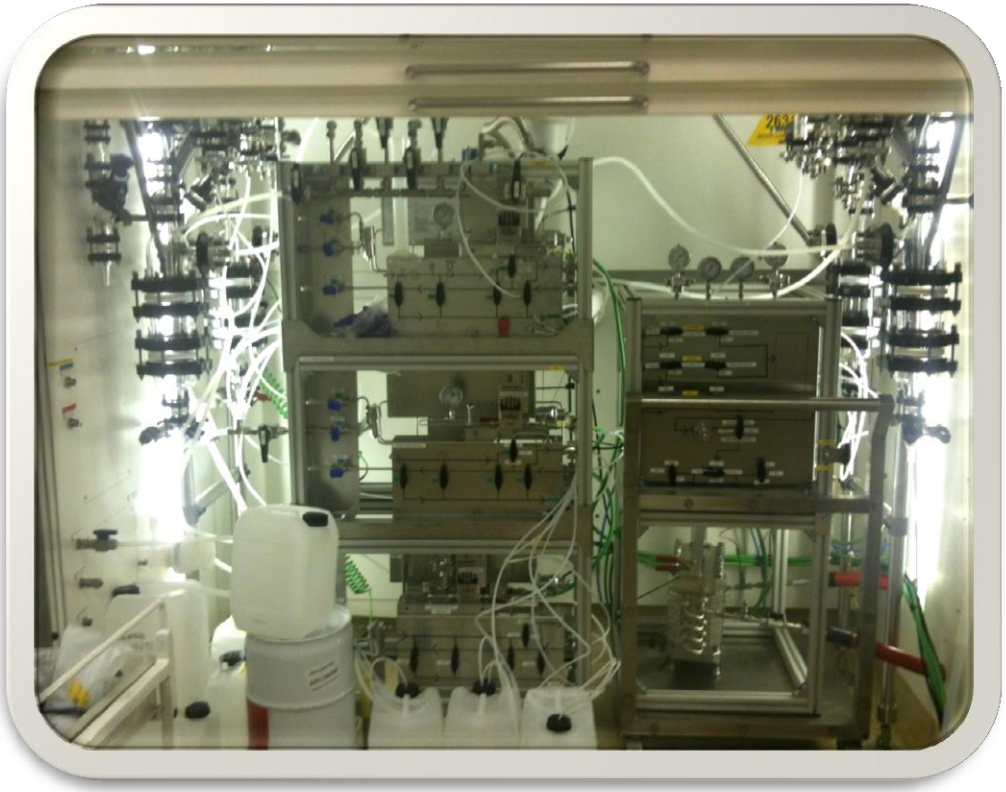
Work Up **Reaction**

Improving Laboratory Capability

Flow Chemistry Scale-Up

- GMP modular continuous processing equipment installed in LSL (Macc)

- Alfa Laval continuous flow reactor used to deliver early phase material: -
  - 1 kg processed in 7 hours
  - 74% yield (vs 60% batch)
  - Improved quality



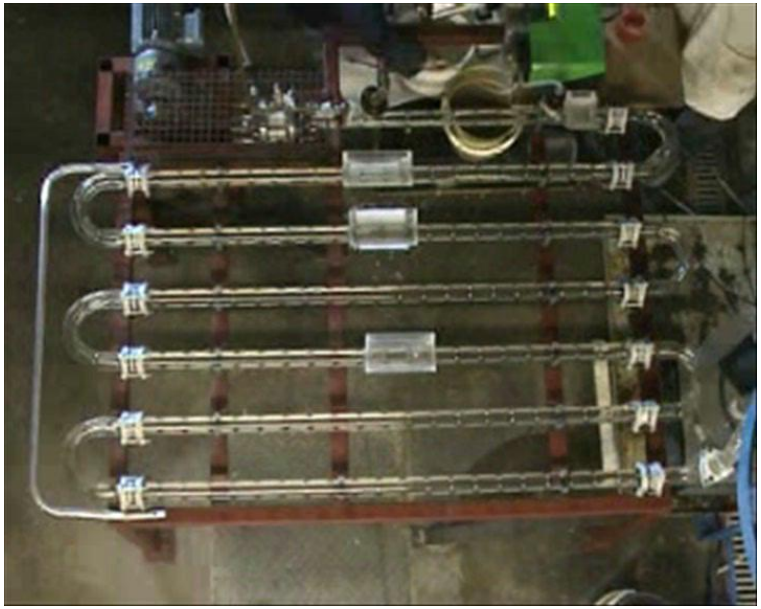
Continuous processing enables new operating conditions to be exploited

Crystallisation

Benefits of Crystallisation in Flow

- Batch to batch, campaign to campaign consistency in particle properties
  - *'same particles as last time'*
- Increased quality
- Variable 'batch size'
- Faster
- Leaner
- Avoid milling and micronising by achieving tighter control over particle size
- Control over particle size, shape and agglomeration

Crystallisation in a COBR



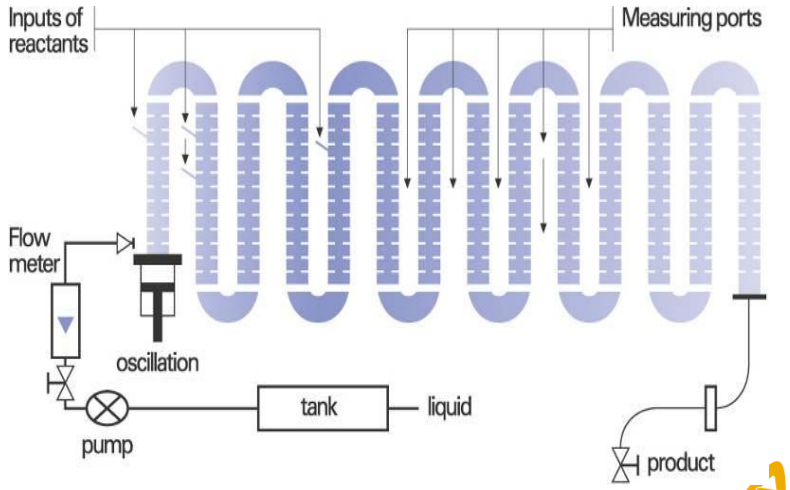
Continuous
- Material moves continually through the equipment

Oscillatory
- Although there is a net flow through the unit, the local flow moves back and forth

Baffled
- Small baffles are installed along the length to promote turbulence and hence mixing

Reactor
- Or crystalliser, or extractor, or…

• Mixing is controlled by oscillations, not the net flow as in the case of turbulent flows
• Plug flow characteristics are obtained in laminar flows
• This allows significantly shorter length of reactor and much compact reactor setup than conventional systems



Process Description

- Crude API is dissolved in solvent at reflux
- Heat to reflux and hold for dissolution
- Agitate and cool the flask contents by 20°C
- Hold
- Reduce the agitation speed and cool to 10°C
- Hold
- Total cycle time 9 hours 40 minutes
- Concentration of the order of 0.062kg/litre (or 6.2g/100ml)

Screening Trials

Batch

- Aim to identify key parameters for crystallisation of model API
  - dT/dt; Xo,f, C
- Carried out batch uni-variate experiments
  - Investigate key parameters
  - Would do FED in the future
    - More efficient use of resources

Screening Trials

Batch

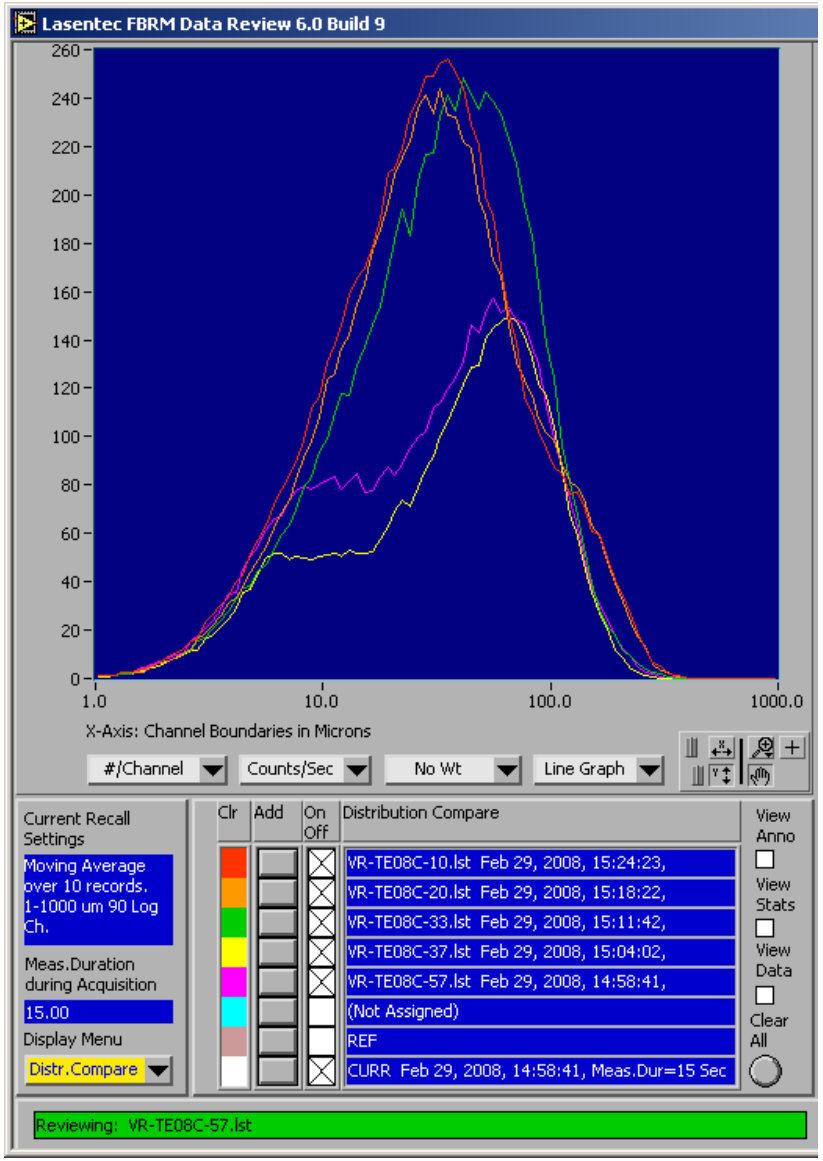
Oscillation displacement	Oscillation frequency	Baffle Spacing	Mixing
API Concentration	Use of Seed		Solution Chemistry
Cooling rate	Hold time for nucleation		Temperature

Screening Trials
Continuous Flow

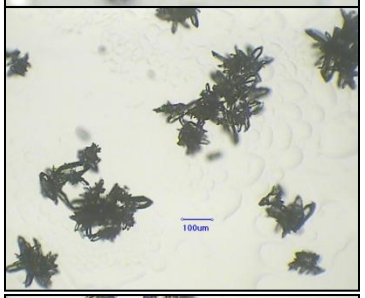
Aim to create particles of a defined size

Target	Cooling	Agitation	Concentration	Seeding
Small	Fast	High	High	None
Large rods	Slow 0.25ºC min^{-1}	Low	Std	None
Large Agglomerates	Fast	Low	Std	None
Mid size	1ºC min^{-1}	Std	High	None
Small	Fast	High	High	1%w/w @ 70ºC

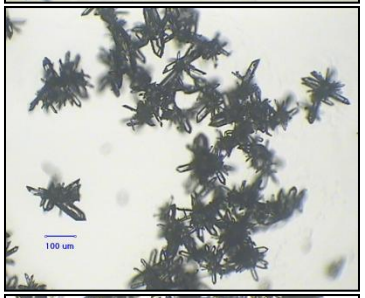
1°C/min



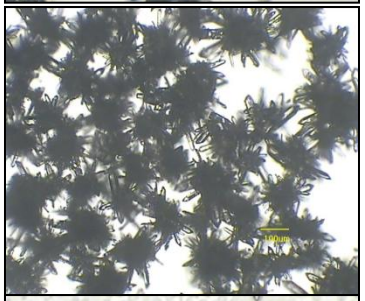
57°C



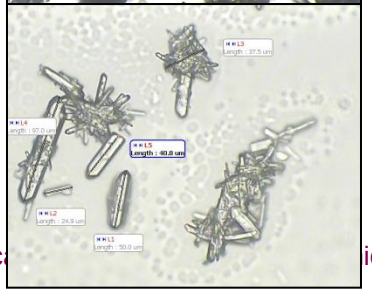
47°C



33°C

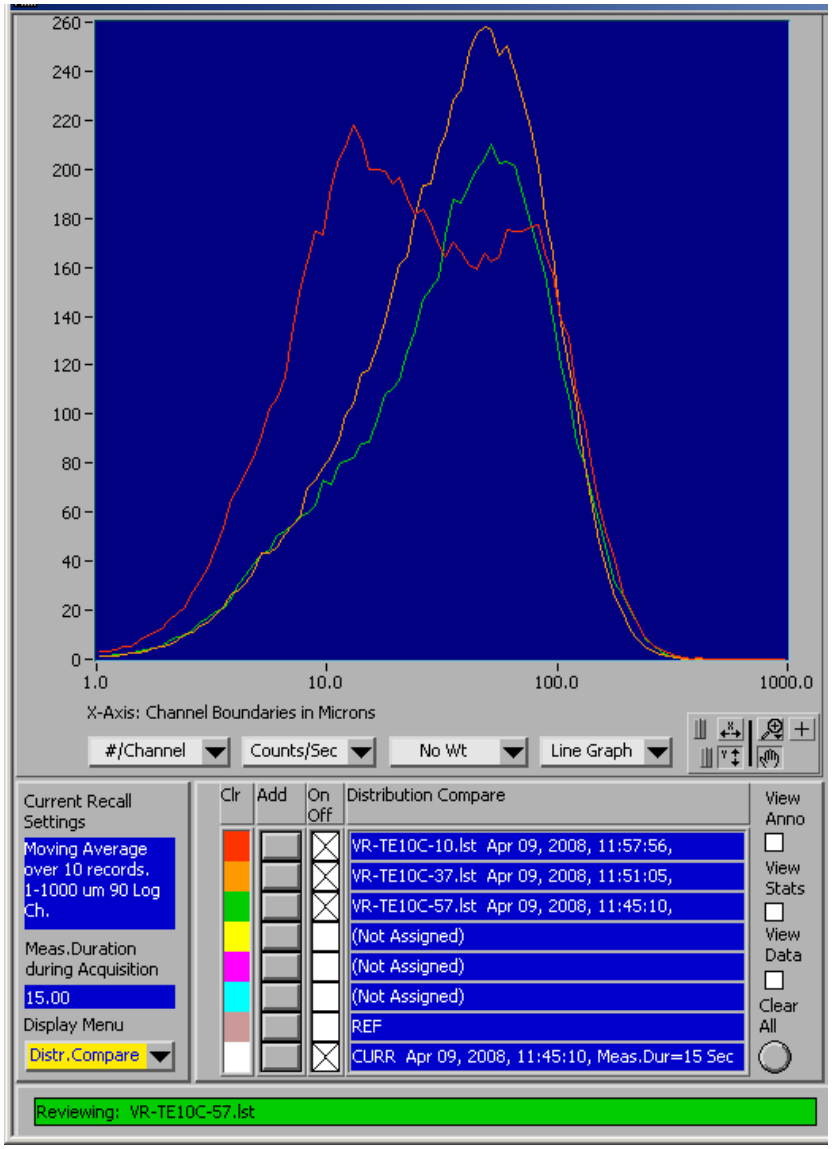


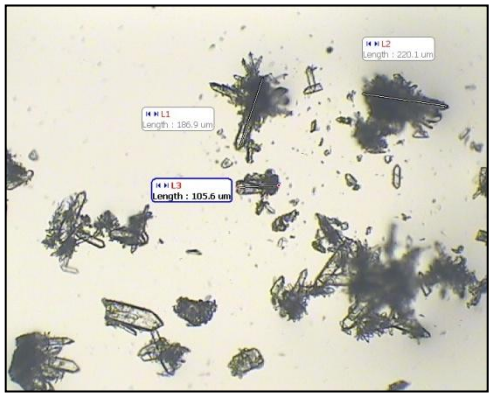
20°C



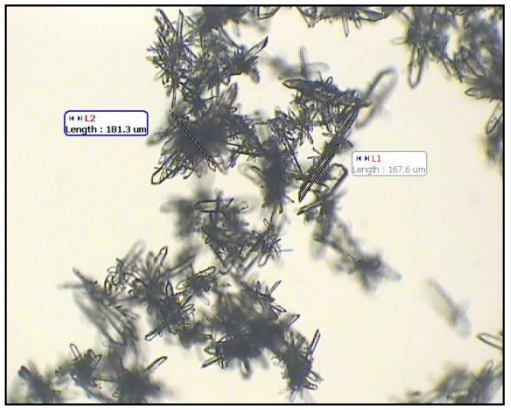
10°C

3°C/min seeded

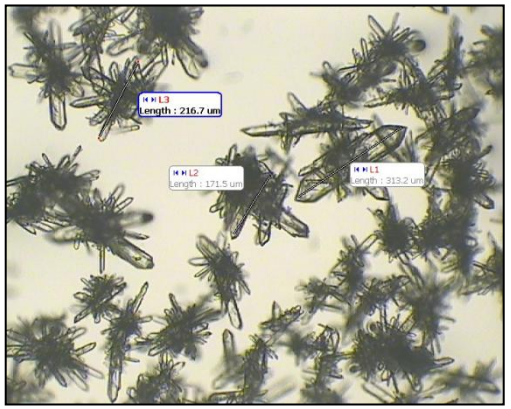




57°C

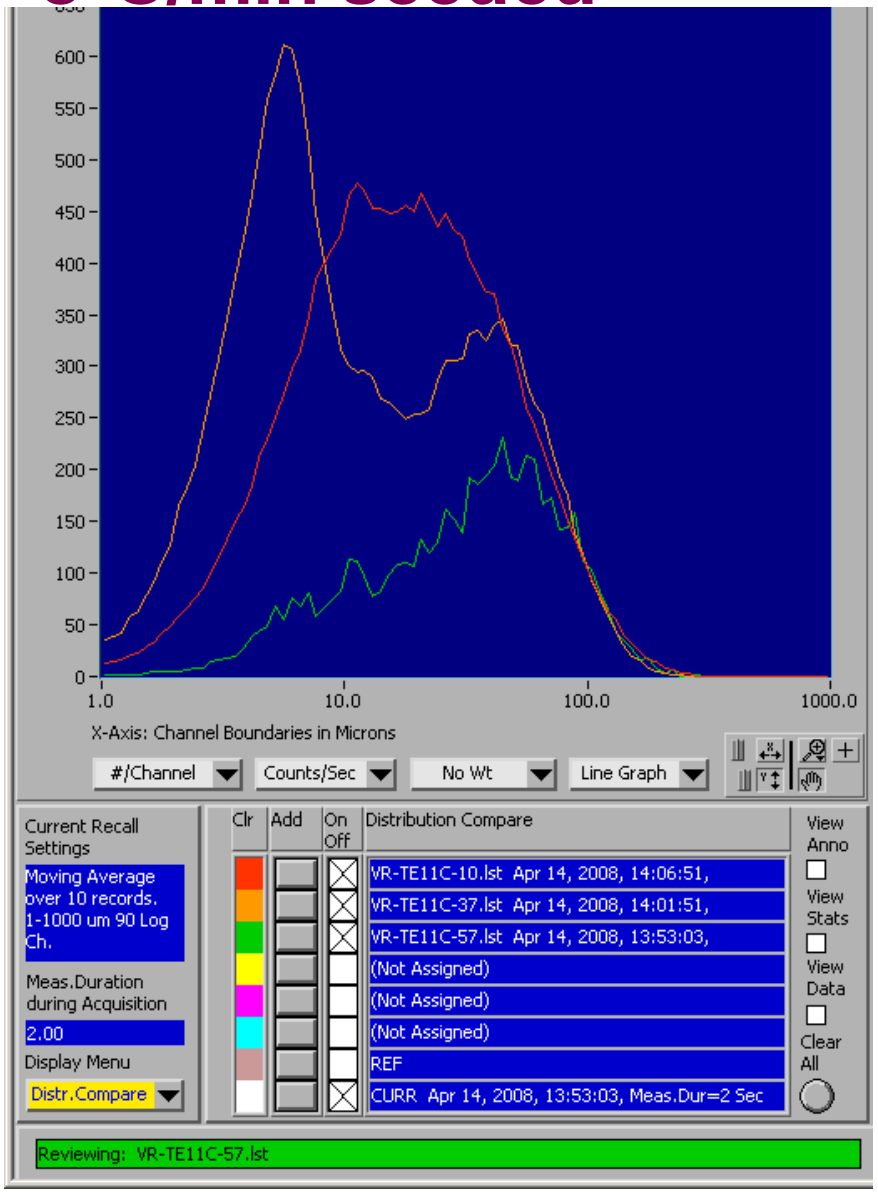


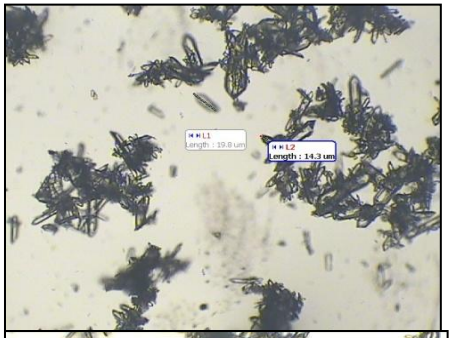
37°C



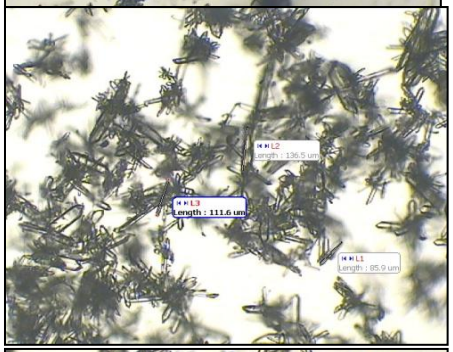
10°C after 5 mins

5°C/min seeded

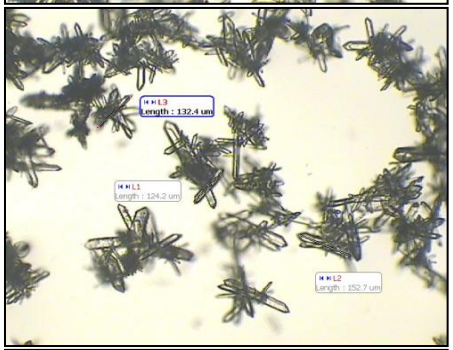




57°C



33°C



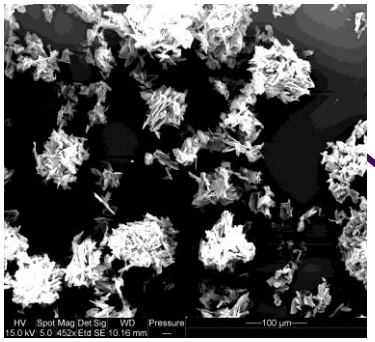
10°C no hold

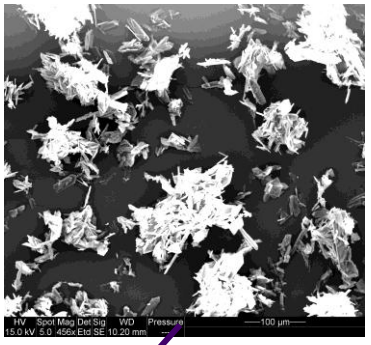
10°C 5 min hold

Aggregation or Agglomeration?

- Lasentec and microscopy data suggest that model API crystals form aggregates/agglomerates, even when seeded
- These aggregates/agglomerates appear to be broken down when a hold period is incorporated i.e. any crystalline bridges between the primary particles are not yet completely desolvated and cemented
- Any bonds that are formed can therefore be relatively easily broken by agitation

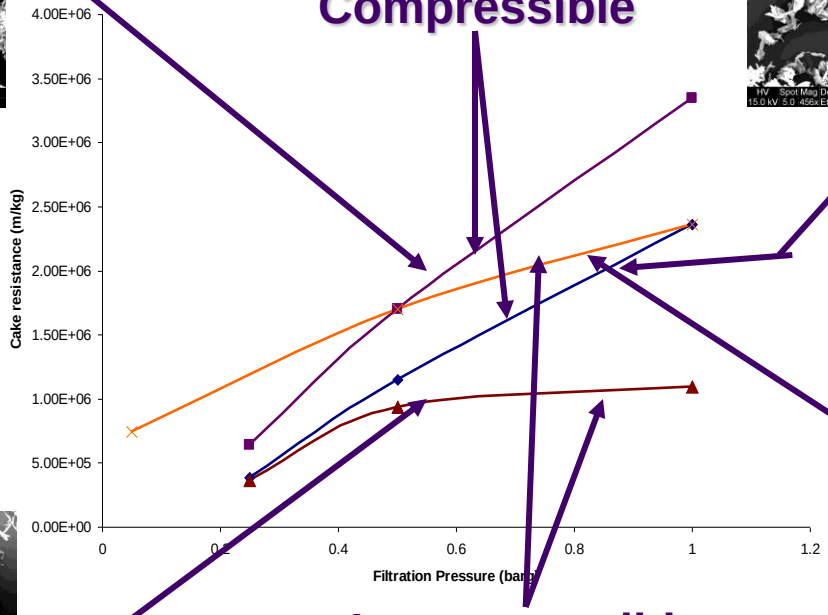
Product Performance





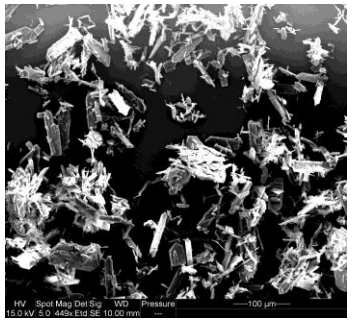
5°C/min

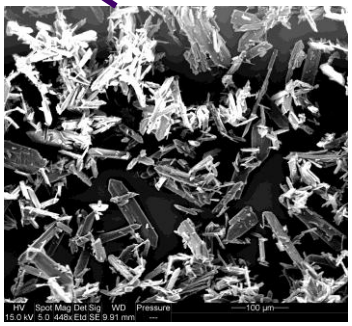
Compressible



Incompressible

1°C/min





Product Performance

- All continuously generated material filters very well
- Agglomerated/ aggregated material appears compressible
- Rods appear relatively uncompressible following cake consolidation

Drug Product

Benefits of Continuous Wet Granulation

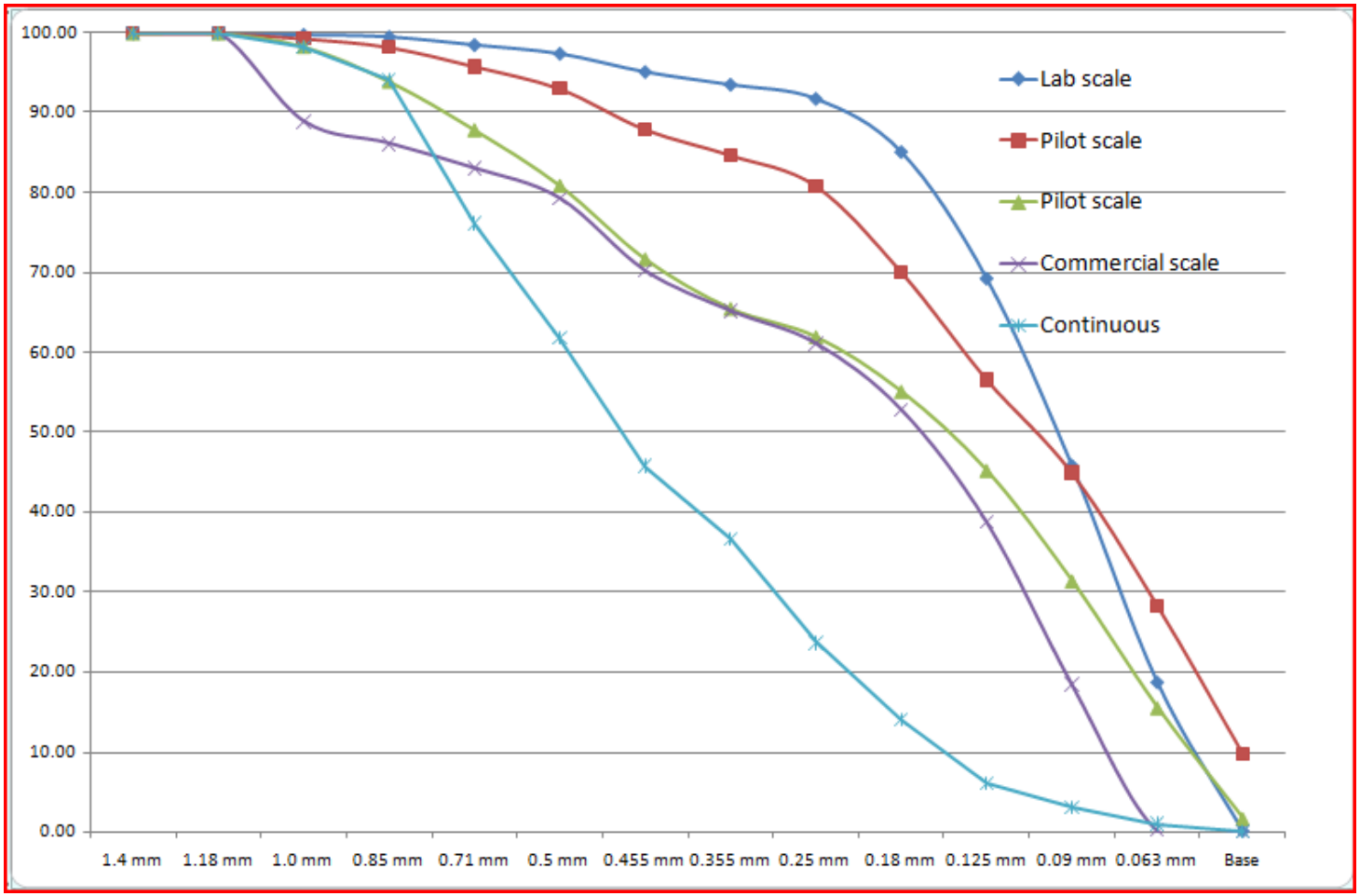
- Cost, time and material saving throughout the product life-cycle
  - More experiments in less time with less drug substance leading to greater accrual of knowledge and consequent increases in process control and robustness
  - Greater flexibility of batch size leading to reduced inventories and fewer issues of scale-up
  - Increased yield through fewer losses during processing
  - Smaller footprint with reduced infrastructure and energy costs
  - Potential for real-time release and reduced analytical costs

Early Observations

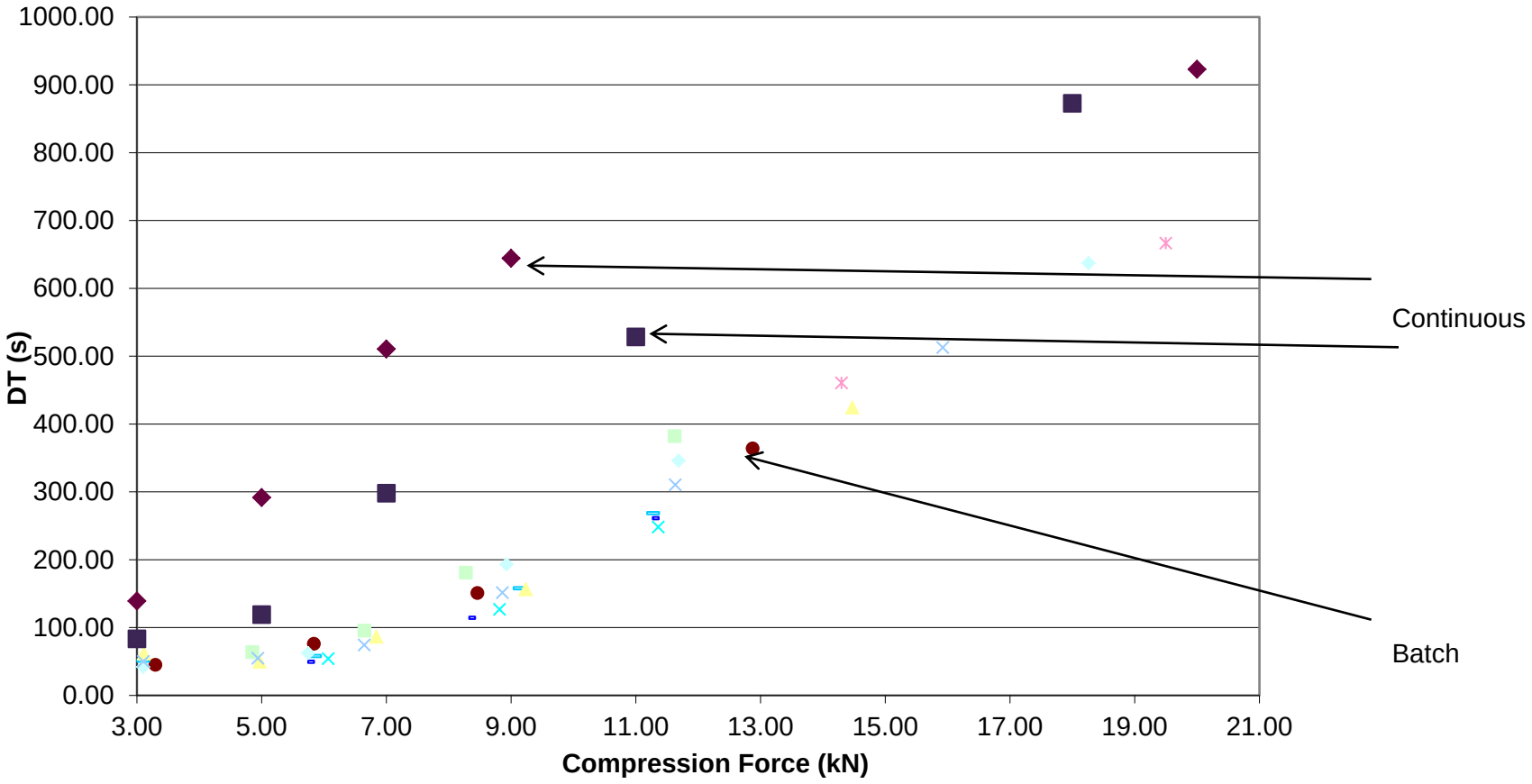
- Potential for rapid prototyping and process evaluation
- Partial process understanding
  - Impact of screw configuration and water quantity, throughput and screw speed
- Some differences in process and product attributes experienced between batch and continuous processes
- Rapid scale-up achievable by extending processing time
  - Stabilisation of the process critical to flexibility in batch size

Process Understanding: Continuous vs Batch

Granule analysis: Particle size analysis (sieve)

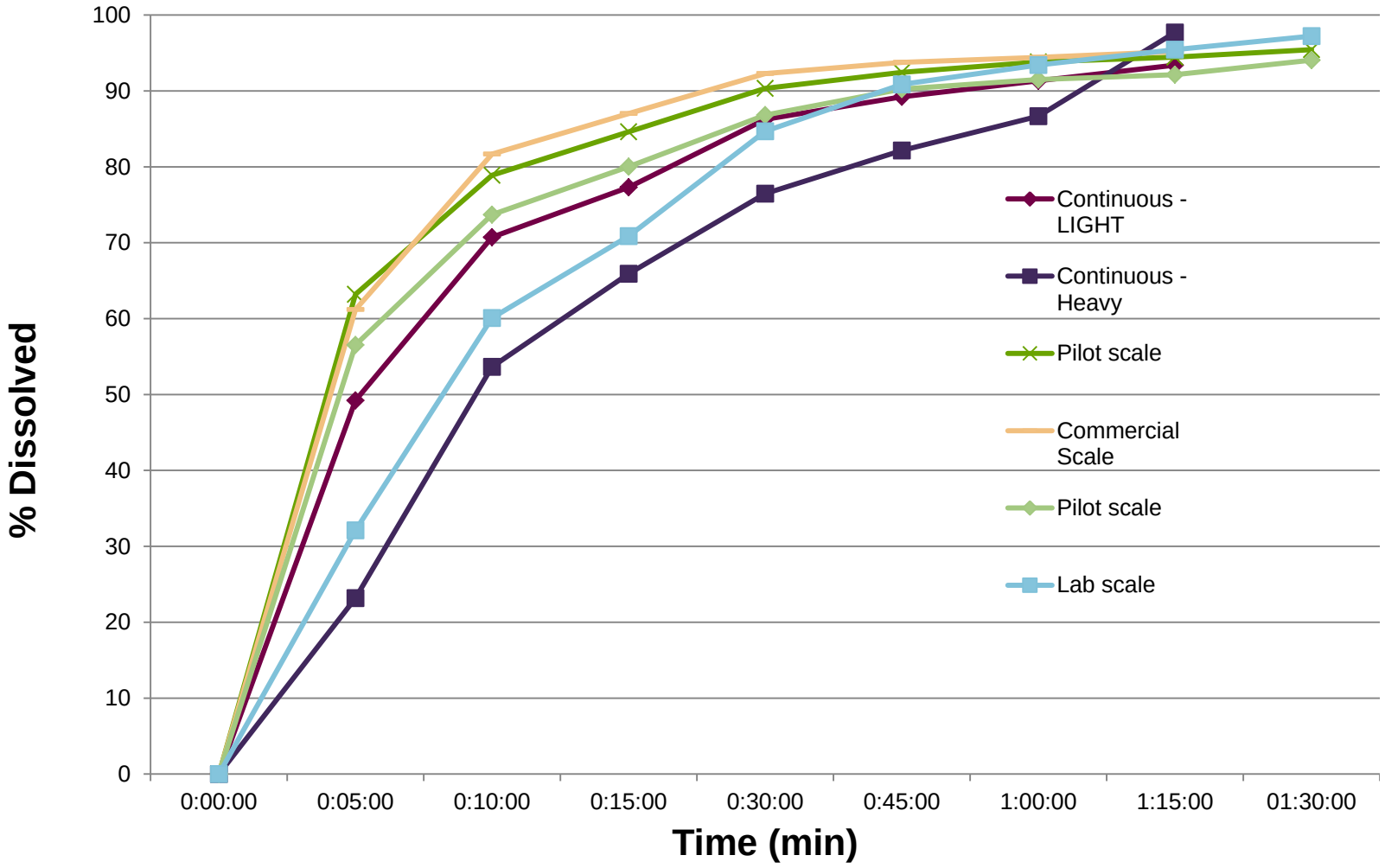


Force vs Disintegration Time

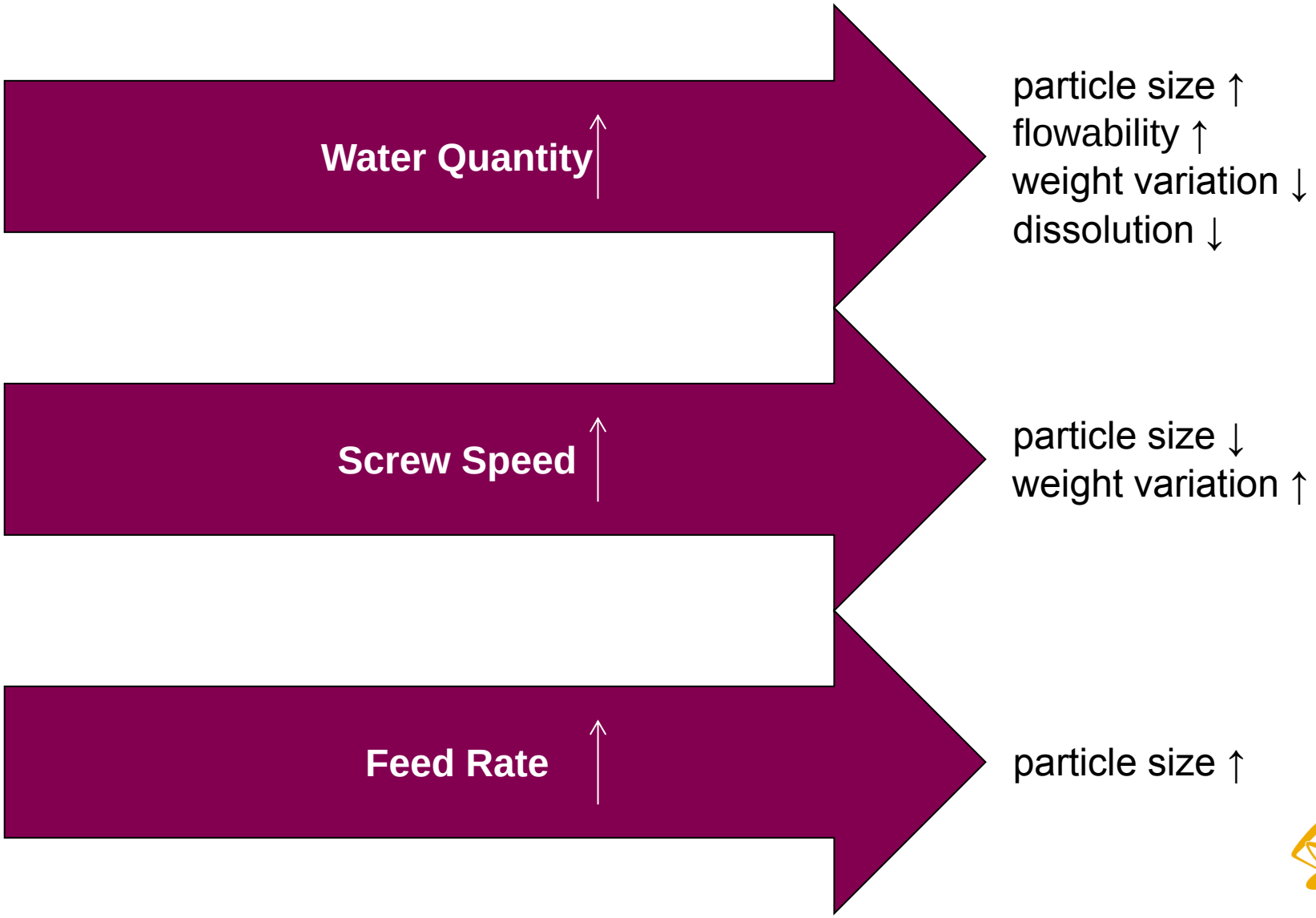


- **Long disintegration times**
- **Steep response → Denser granules?**

Dissolution



General process observations across products



Concluding Remarks

More than just a technical challenge ...

Substantial momentum gained and on the road to adoption of continuous processes in the Pharmaceutical industry

Understanding	Capability	Availability	
Delivery Risk	Existing Assets	Campaigns	Timelines
Regulators	Resources	Cost	
Culture of cross functional collaboration and innovation			

"A major cultural change is required on behalf of chemists, engineers and managers and it is this, rather than technical difficulty which represents the main obstacle to progress".

Prof. C Ramshaw

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