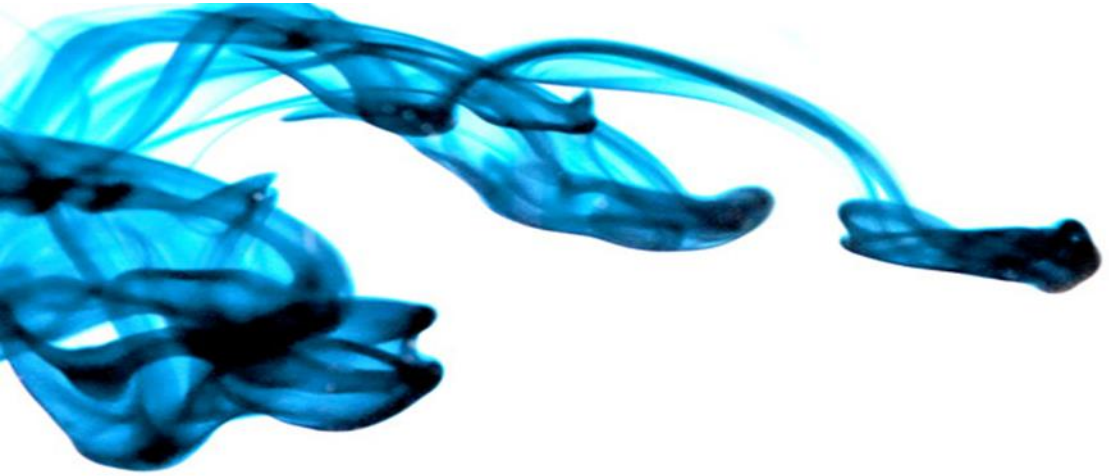

Innovative flow processing solutions
From Laboratory to Plant

High Performance Fixed Bed Flow Hydrogenation

Expanding the Commercial Manufacturing Envelope

Chemspec Europe 2017

Oliver Tames

IntensiChem

Summary

1) Current Hydrogenation technology review
    - Trickle bed
    - Batch
    - CSTR
2) Fixed bed flow hydrogenation
    - Approach
    - Basic principles
    - Safety and Risk
    - advantages
3) The path to plant

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Background

Increased interest in continuous flow approach

- Increased yields
- Reduced impurities
- Reduced footprint
- Automated efficient manufacturing

Hydrogenation technology drivers:

- Economical use of PGM catalysts
- Exploration of new synthetic methodology
- Supporting continuous manufacturing strategies

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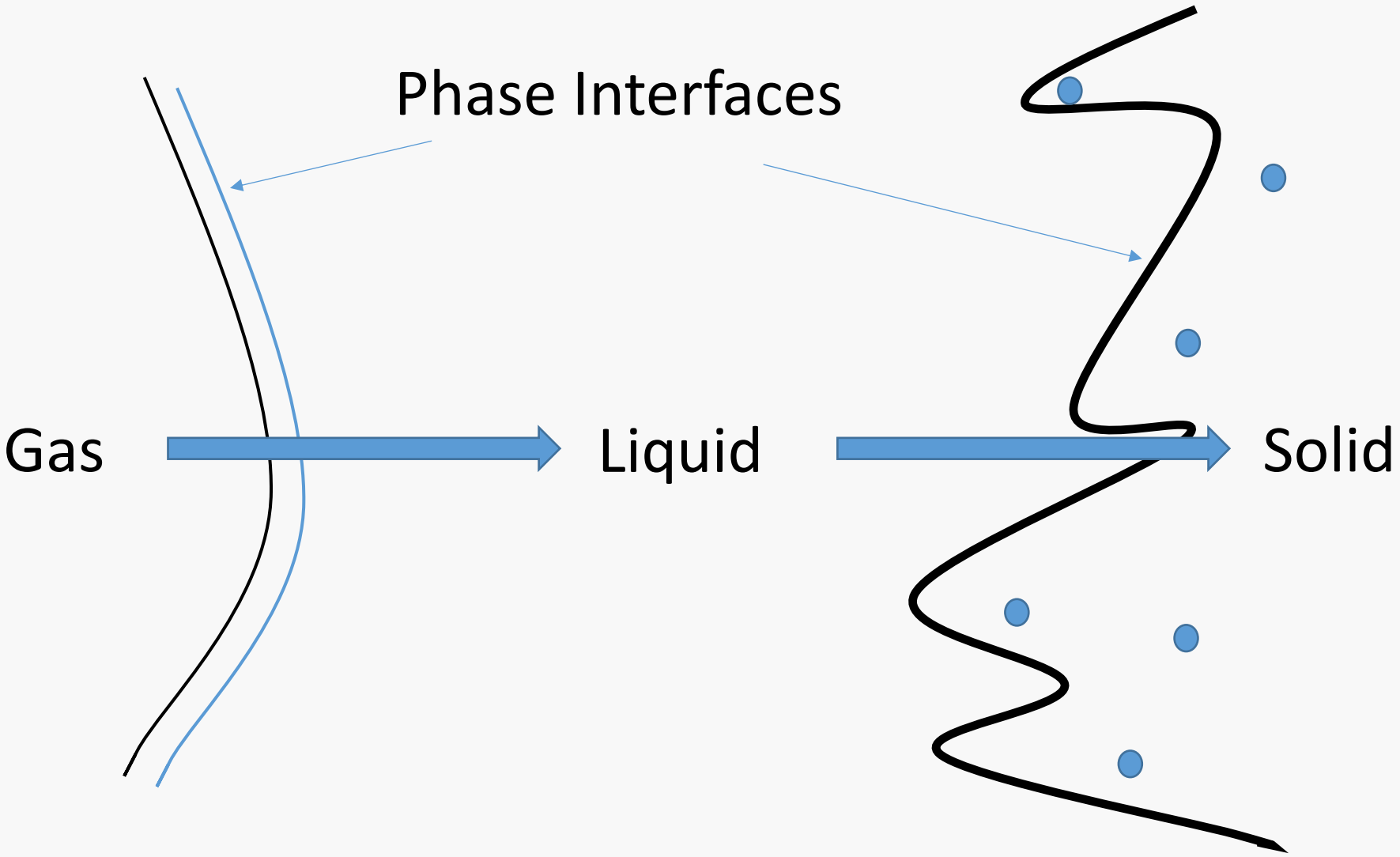
Heterogeneous Hydrogenation



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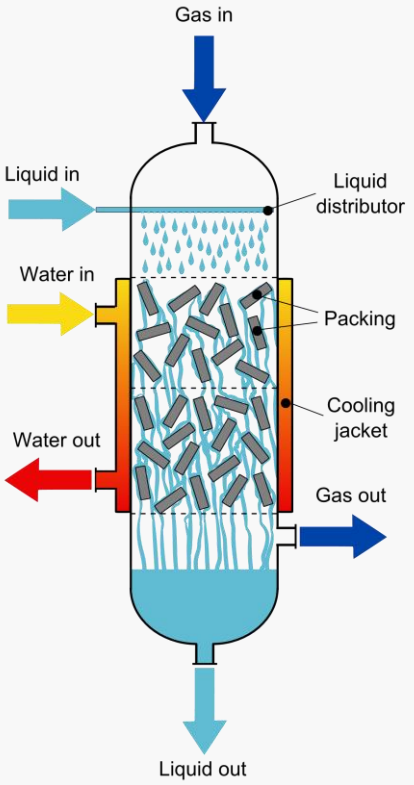
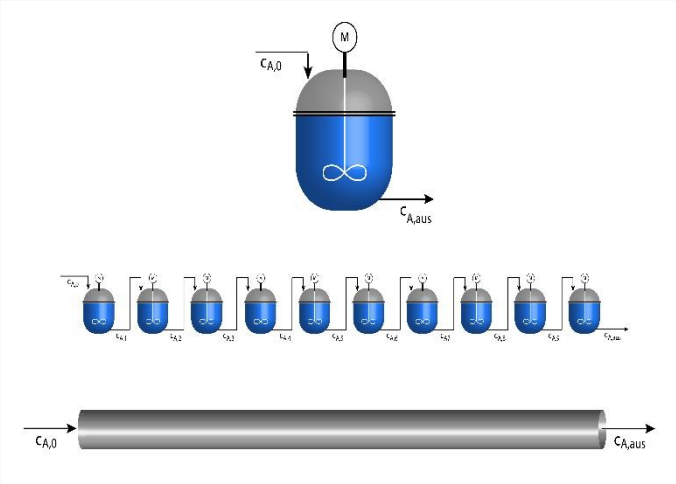
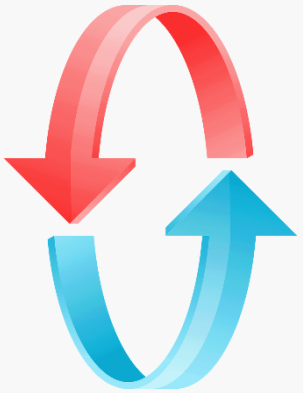
Hydrogenation Technology Review

- Batch
- CSTR
- Fixed bed
- Loop
- Trickle Bed







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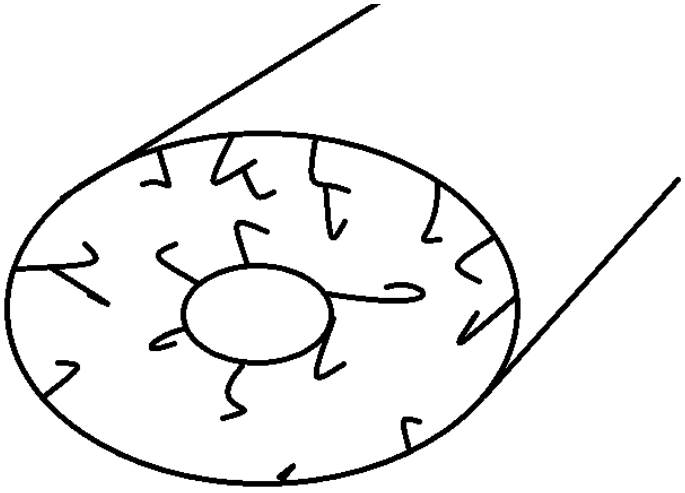
Trickle Bed – Extruded Catalyst

- Catalyst presented in pellet form
- Catalyst pellet has small surface area
- Catalyst can come in a number of different extruded cross sections
- Material can flow over
- Material can flow through
- Reaction path difference



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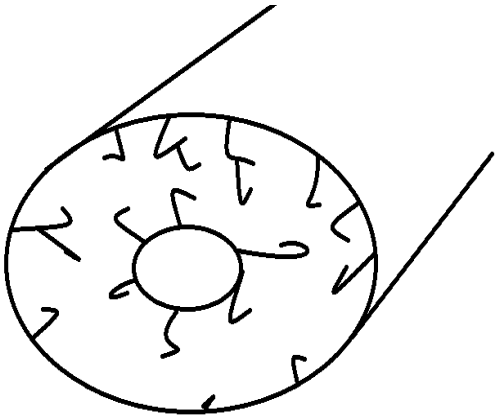
Extruded catalyst - Cont

- Gas is at surface of pellet
- Long gas diffusion path
- Surface high gas concentration
- Inside particle – low concentration
- Different reaction conditions



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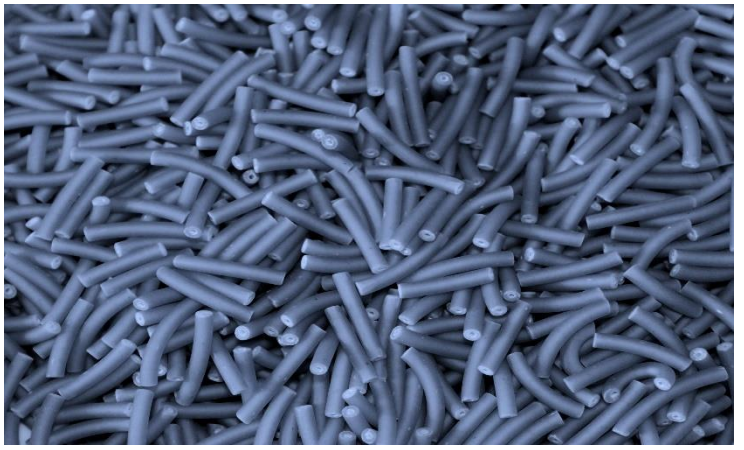
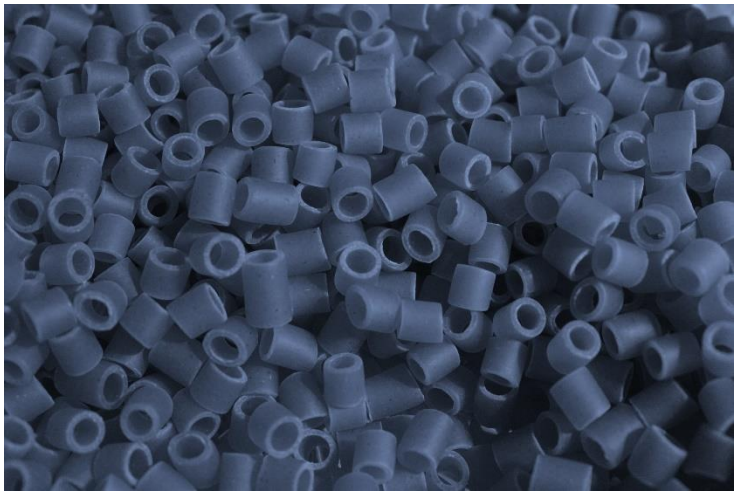
Trickle Bed - Thermal Control

- Liquid phase passes down through bed under gravity
- Catalyst pellets connected by liquid film
- Heat generation results in vaporisation of solvent
- ‘Hot Spots’ can form as areas loose more liquid
- Poor control of reaction temperature





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Trickle Bed - Summary

- Poor control of reaction
- Poor control of gas concentration
- Poor thermal control
- Sensitive compounds can suffer thermal degradation and impurity formation from over reduction.
- May be possible, but control remains a significant challenge

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Batch - General

- The batch reactor is the tool of choice for current fine chemical and pharmaceutical manufacturing
- Excellent thermal control
- While hydrogen is easily controlled in a semi-batch protocol, it is mass transfer limited.
- Extensive catalyst screening is normally performed during development – an essential optimisation tool.

Batch - Safety

- Batch reactors are large, and filled with explosive gas
- Expensive protocols are required to ensure safety – blast walls, bunkers, up not out
- Explosion risks are low – but essential to reduce to an absolute minimum due to severity of potential incident
- Essentially safe – at a cost

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Batch limitations

- Reaction time limited by mass transfer
- Batch optimisation precludes fast reactions – can take hours just to reach temperature
- Normally low pressure (~10 bar) for heterogeneous catalysis – large high pressure vessels are extremely expensive
- Does not interface well with other continuous processes

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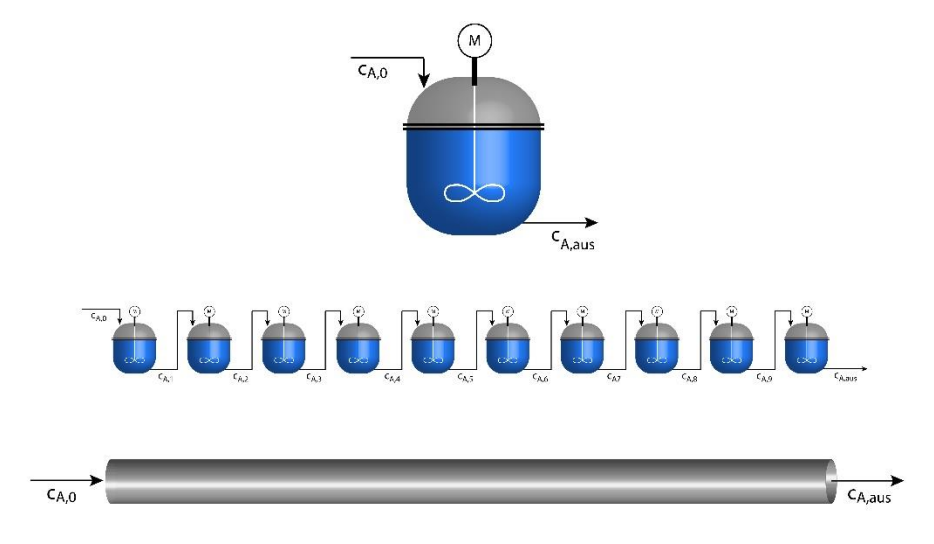
CSTR

- Continuous
- Batch conditions
- Catalyst management
- Good slurry option
- *Slightly* more enabling than batch



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Hydrogenation Overview

	Reaction Time Control	Gas Mass Transfer	Reaction Speed	Safety Risk	Continuous	Slurry Phase Reactions
Batch	Excellent	Poor	hours	High	No	Yes
Trickle	bad	Good	minutes	High	Yes	No
CSTR	good	Poor	hours	Medium	Yes	Yes
Loop	bad	Good	hours	High	No	Yes
HPFB?	Excellent	**Excellent**	**seconds**	**Low**	Yes	**No**!

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High Performance Fixed Bed - *Trickle Bed Without the Trickle*

- Fixed bed with catalyst particles typically less than 100um
- Use of high pressure pumps – not gravity
- Control of hydrogen injection rate
- Tight residence time distribution
- Suitable for complex pharmaceutical products
- However - *Traditionally challenging scale up.*

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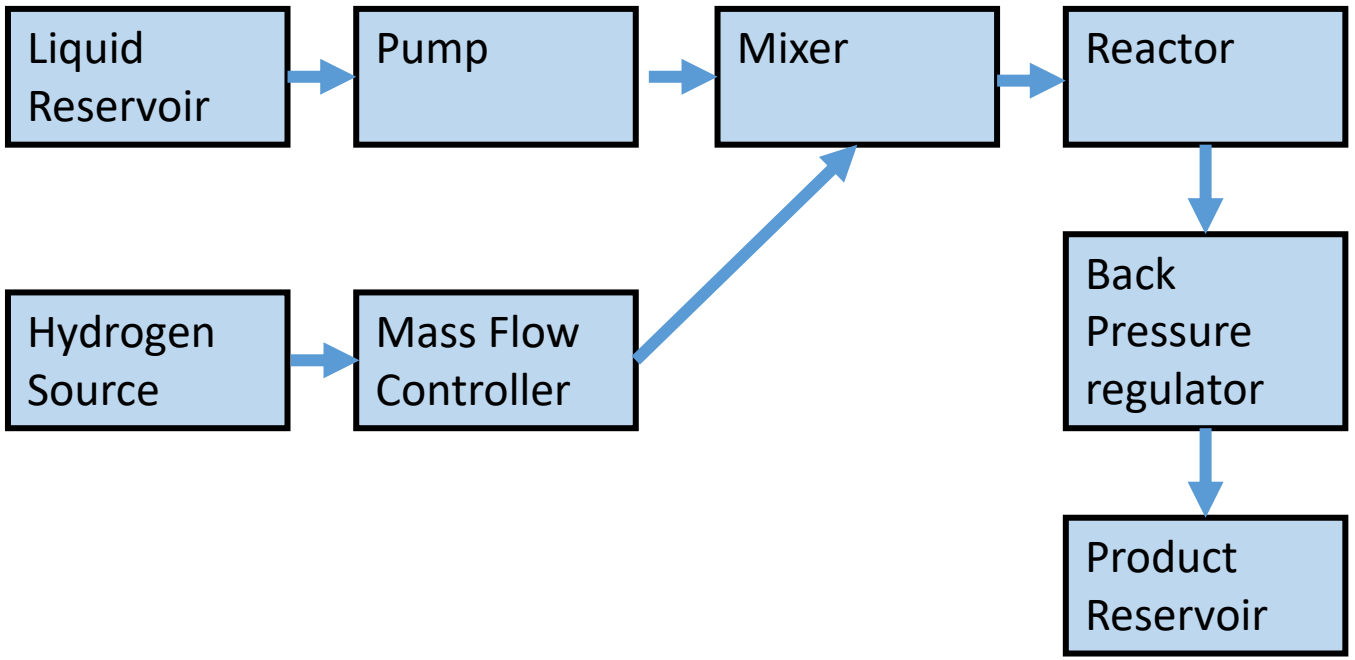
Simple Flow Diagram



The Devil is in the Detail!

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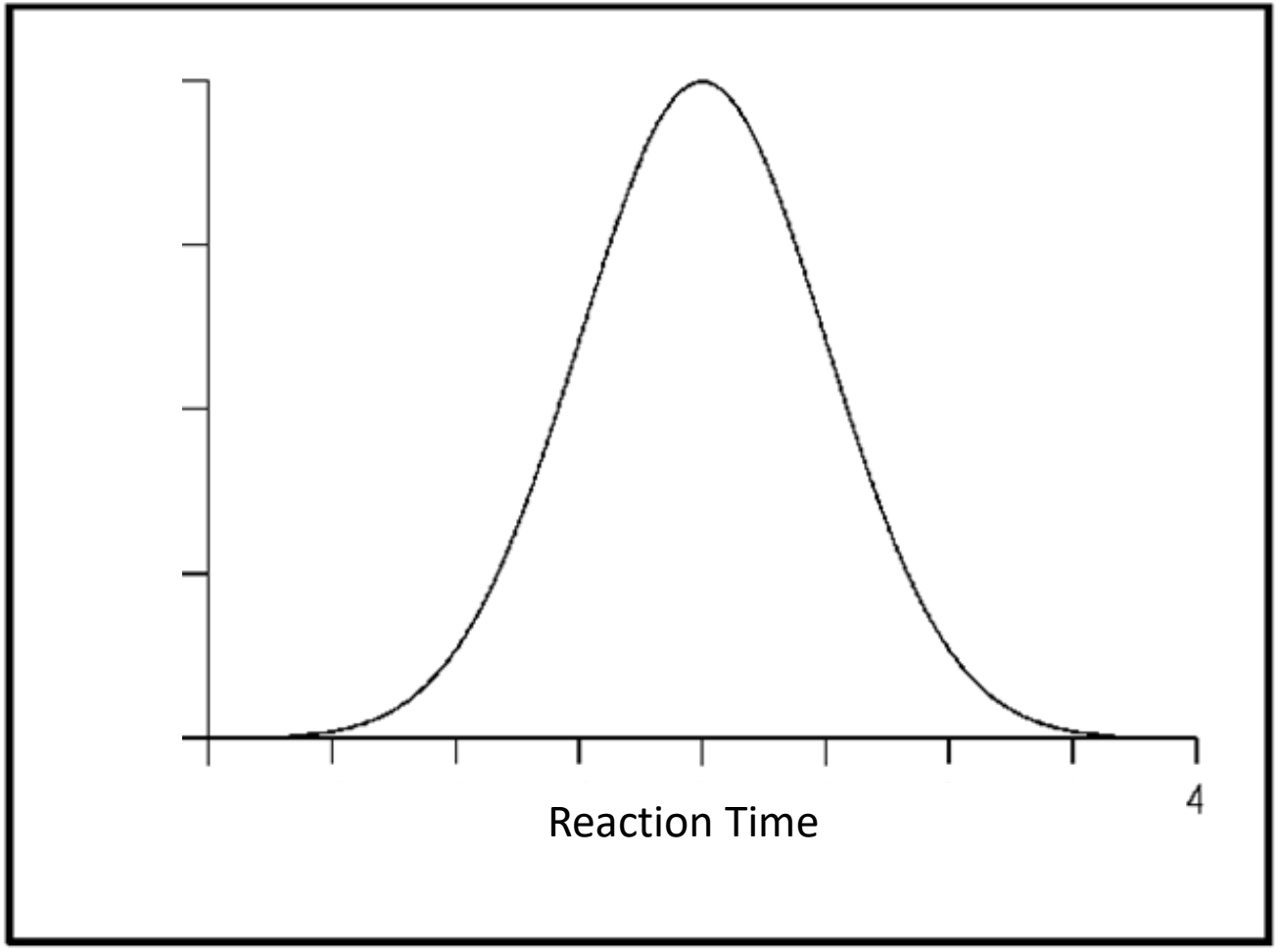
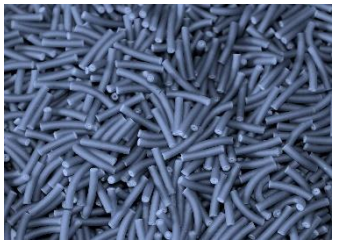
Reaction Time Distribution and Path Length



Wide



Tight

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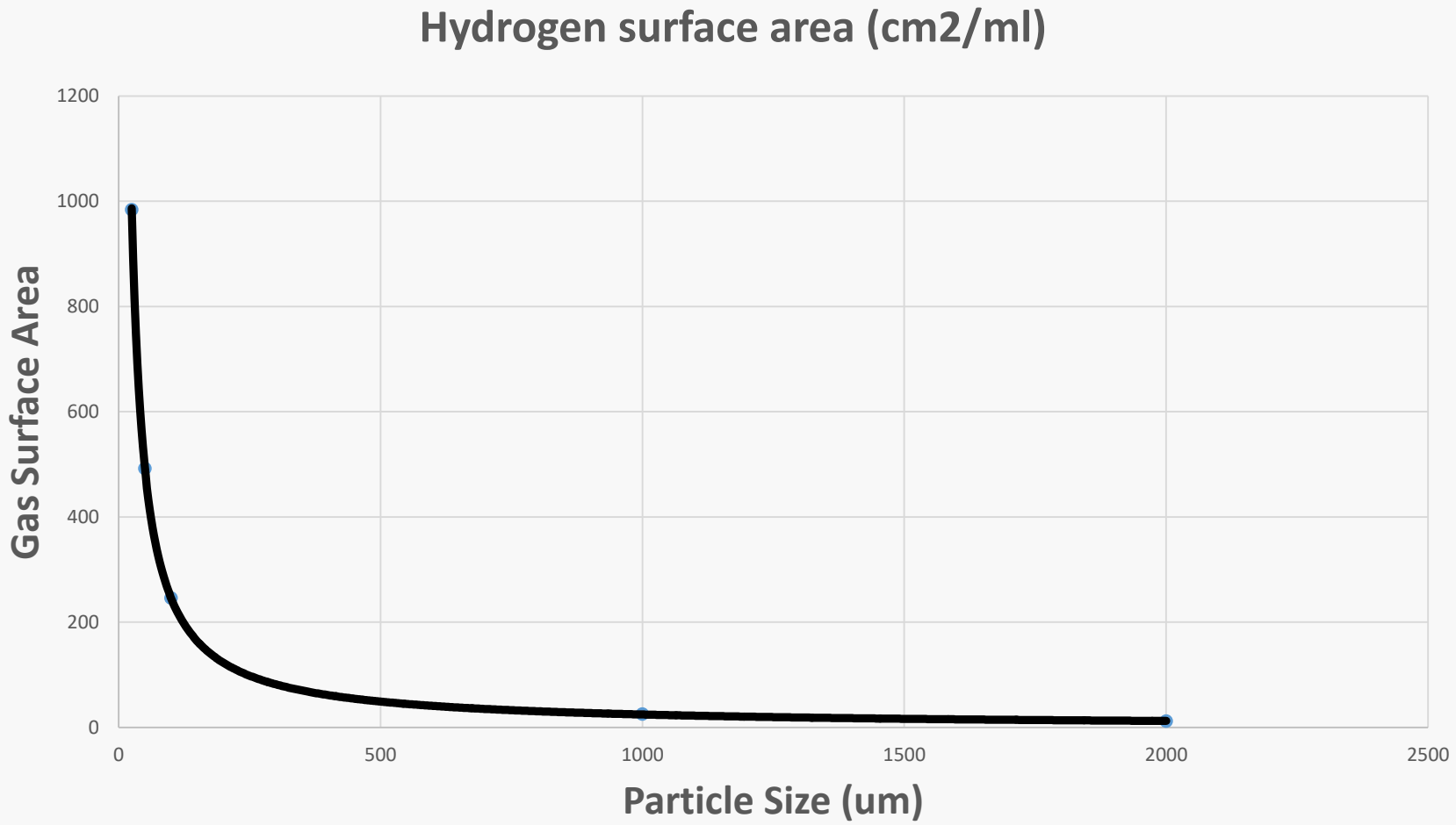
The effect of bed particle size on gas surface area



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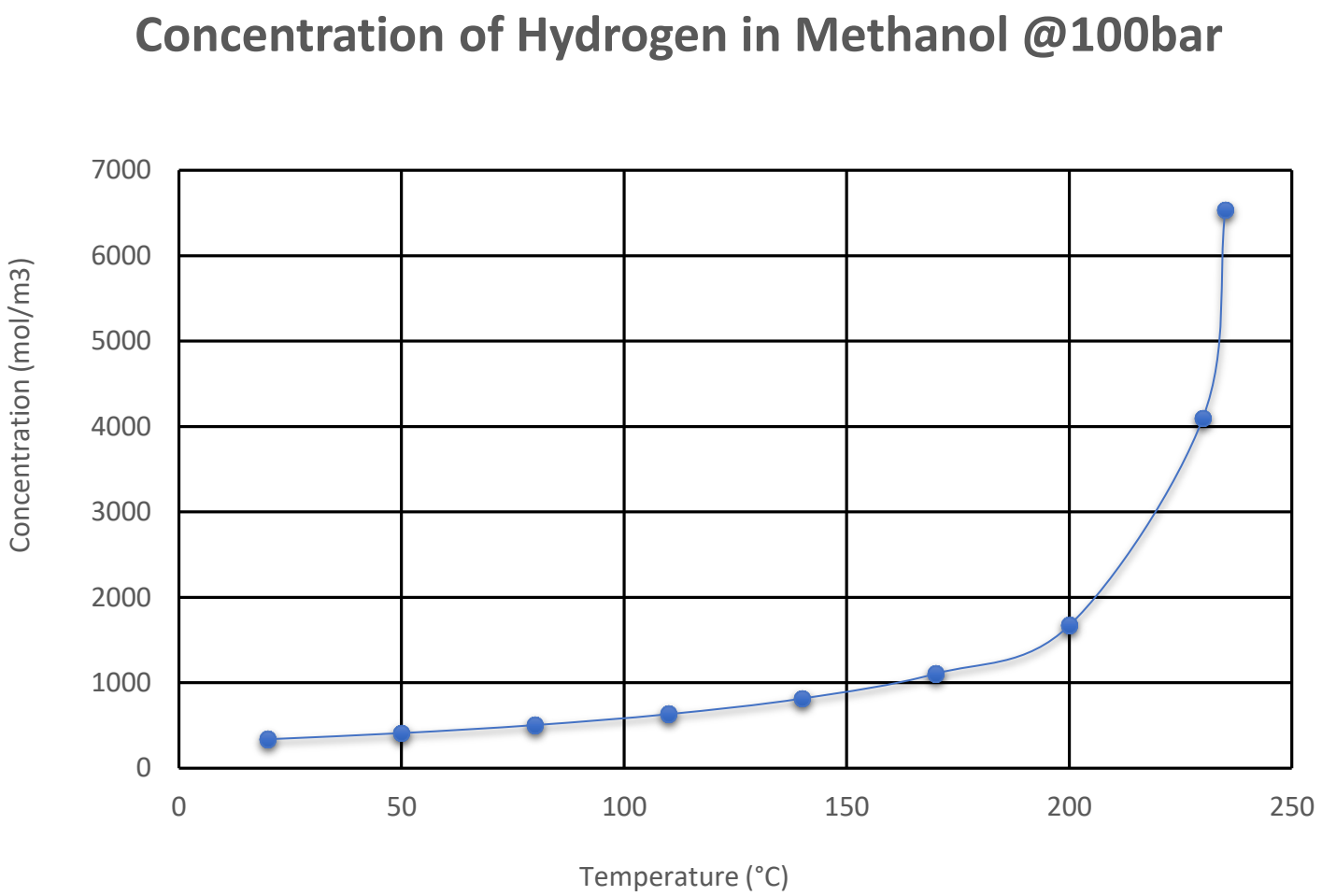
Gas Solubility vs Temperature



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Calculated By
Dynochem

Pressure

- High performance fixed bed hydrogenation can easily be configured for high pressure
- Using off the shelf components, IntensiChem is assembling a 700bar (10,000psi) system
- Hydrogen concentration is proportional to pressure
- Processes sensitive to hydrogen concentration can be optimised by using higher pressures

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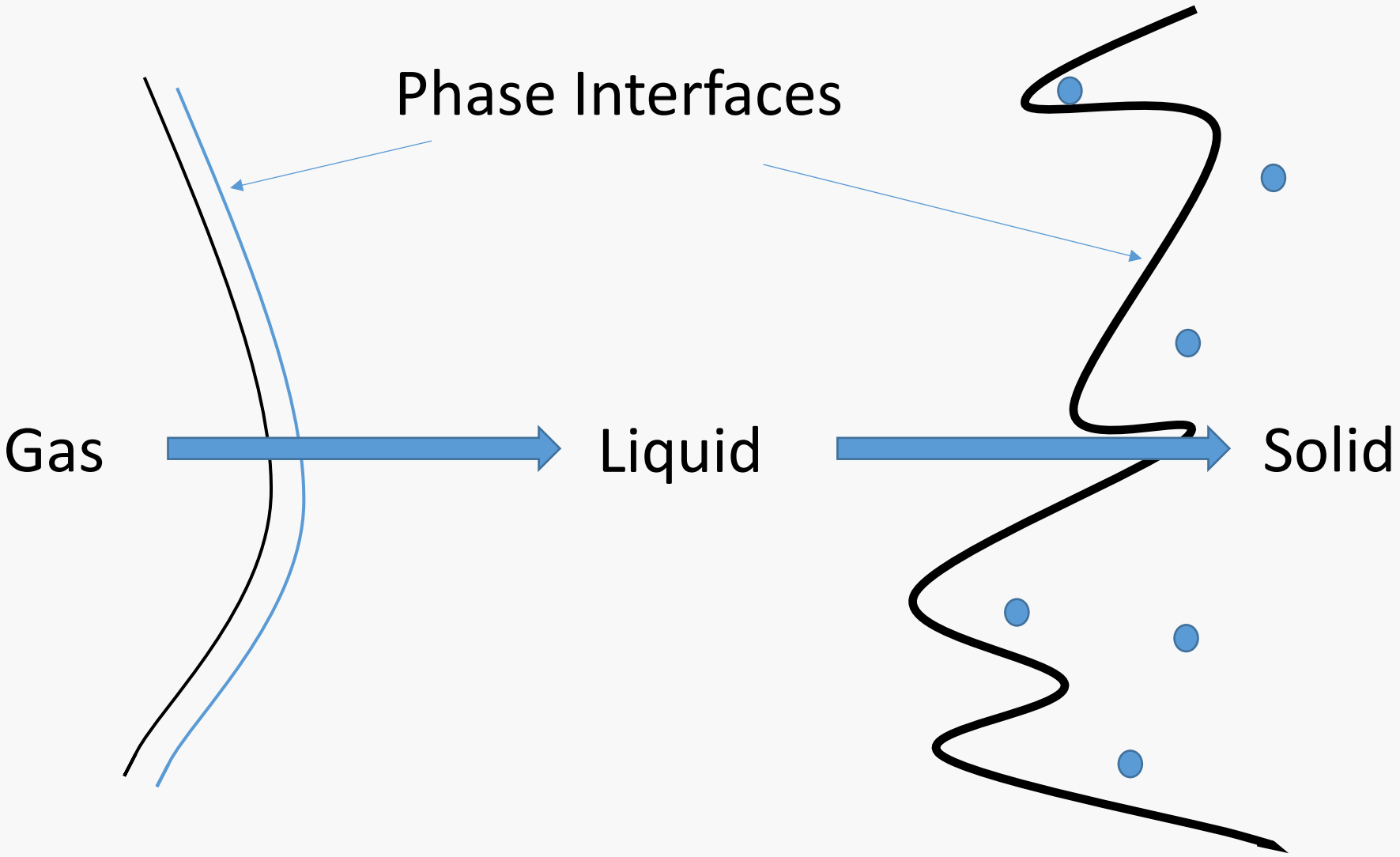
Heterogeneous Hydrogenation



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Summary of driving principles

- High pressure – gas concentration proportional to pressure
- Small particles – High gas surface area
- High temperature – Gas concentration increases with temperature
- Effective control of mass transfer
- *Enabling commercial scalability*

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Note on Case Studies

- All current project work is commercially sensitive.
- The only limitation is solids. Solids cannot be present in the feed and solids cannot be formed during the reaction.
- As long as this criterion is met, we can adapt the approach to any commercial hydrogenation challenge.
- We have achieved good conversion on every project attempted – unless solids present.
- All existing chemistry is in scope – google for flow examples.

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Safety and Risk

Very small reactors

- 250ml – 1tonne per month
- Can be enclosed in economical explosion proof container

Steady state quality

- Only waste small amount of material when reaching steady state
- Parameter failure would cease flow – limiting losses

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Process Advantages

- Optimisation of the process chemistry without limitation
- Fast reactions, but also high yielding with reduced impurity formation
- Can carry out processes that are not commercial in batch
- Can easily interface with other continuous manufacturing systems

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The Path to Plant

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Lab Development Tool

- Manual parameter setup
- Maximum pressure – 100bar
- 250°C Maximum temperature
- Maximum flow rate – 15ml/min
- Automated sampling
- Focus on flexibility and reaction understanding

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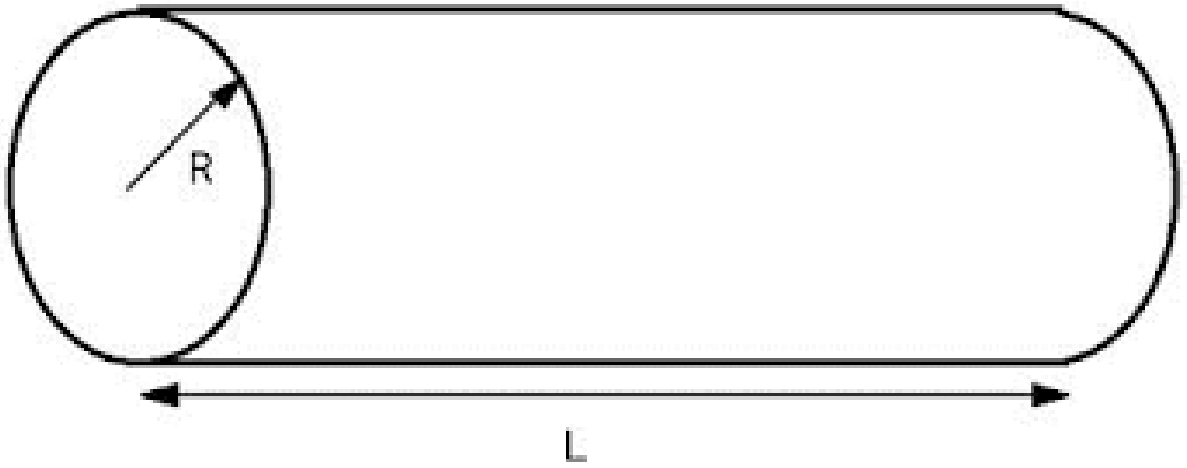
Scale up basis

- Scale up is proportional to cross sectional area and bed length – due to effective elimination of mass transfer at scale



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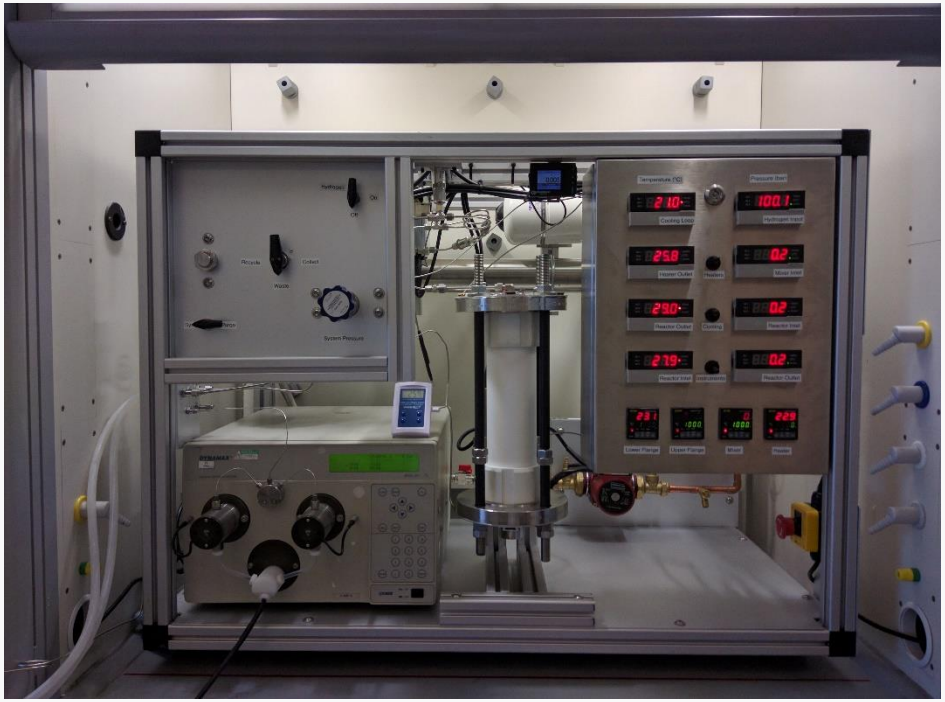
Scale Up System

- Maximum pressure 200bar (120bar current)
- Maximum flow rate – 200ml/min
- Maximum temperature – 200°C+ (engineered for production chemistry)
- Re-configured to the specifics of the clients chemistry



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Delivering the Solution

- IntensiChem is working with Manrochem to deliver manufacturing plant
- First plant has just completed commissioning
- Pharmaceutical ‘GMP’ grade
- Delivers better yields than batch technology
- Laboratory scale up system was shown to be an excellent process model!

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The Plant Solution

manrochem
making it possible
www.manrochem.co.uk

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Summary

- Optimisation of temperature, pressure and surface area using a fixed bed has delivered seamless scale up to plant manufacturing
- Cheaper, safer, more efficient and cleaner than other current manufacturing technologies
- Efficient integration with other continuous manufacturing technology

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Questions?