AM Technology
Engineering Chemistry

ALMAC

Nordic-Irish Process Chemistry Forum 2023

Heterogeneous catalytic hydrogenations in flow – routes to scale-up

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Introduction

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AM Technology manufacture Coflore flow reactors

Founded in 2000

Mr Robert Ashe & Mr David Morris
Ashe Morris Ltd

UK Headquarters

Based in the North West, between Liverpool and Manchester

Multidisciplinary Team

Experienced team comprising of chemical, mechanical, electrical engineers and chemists.

R&D Facilities

Flow feasibility studies
Process development - lab to pilot
Engineering design

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Why Batch?

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Batch Reactors:

Simple:

Material is located in one place
Established 'one-pot' synthesis familiar to chemists

Multi Purpose:

Can be used with multiphase reactions
Various recipes with same equipment

Scalable:

Different sizes enable scale up to large volume manufacture
Well-established scaling parameters

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Where Are The Issues?

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Typical 1,000 L Batch Operation Steps

Charge Vessel
Addition of solvent/reagents and inertion cycles - can be slow

Temperature Control
Heat up or cool down of large reactor volumes - Large peak utility power requirements

Exotherm? Dropwise Addition...
Very time-inefficient

Reaction Time
What may take 5 minutes in a 10 mL flask could take 10 hours in a 1,000 L reactor

Equipment Cleaning
Required after every 1,000 L production

Reactor Downtime
Between each run

Capacity Utilisation: The % that plant capacity is used vs the theoretical maximum

Continuous manufacturing can reduce some or all of these process inefficiencies

Why Manufacture in Flow?

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THE WALL STREET JOURNAL.

| LEADER (U.S.)

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses On Manufacturing; FDA Acts as a Catalyst

By Leila Abboud and Scott Hensley Staff Reporters of The Wall Street Journal

Updated Sept. 3, 2003 12:01 a.m. ET

G.K. Raju, an expert in pharmaceutical manufacturing at Massachusetts Institute of Technology who advises drug makers and has visited many plants. Quality testing is done by hand. Computerized equipment and robots aren't as common as in other high-tech industries. One sign of inefficiency: Vats, blenders and presses in factories often sit idle.

Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Pharmaceutical CGMPs
September 2004

Facilitating continuous processing to improve efficiency and manage variability

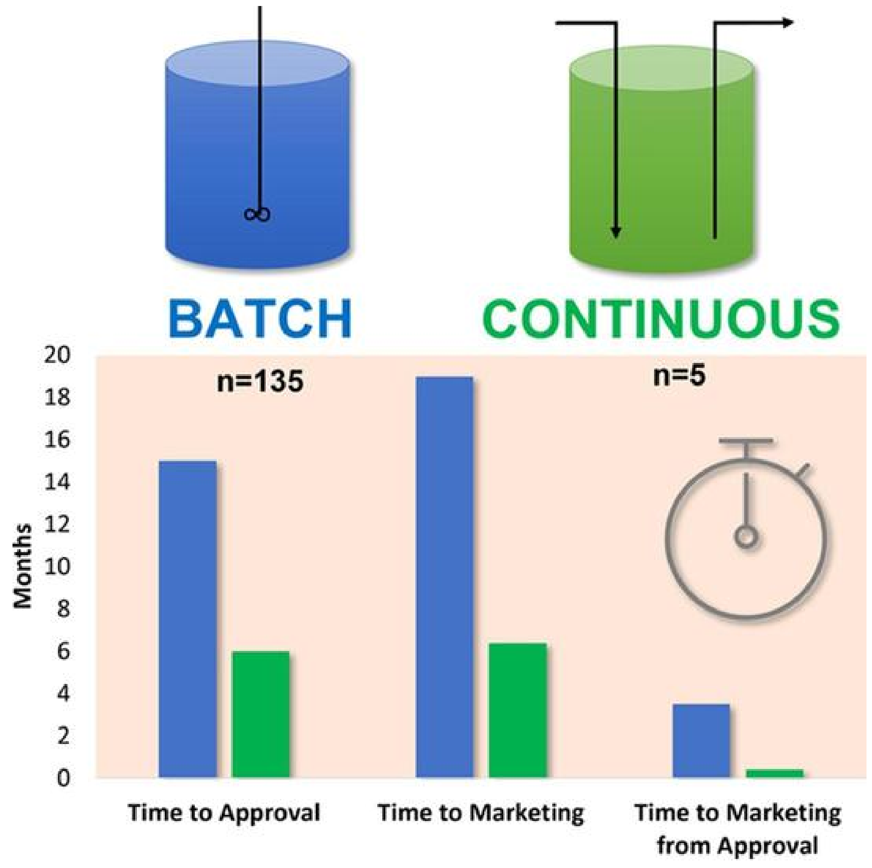
For example, use of dedicated small-scale equipment (to eliminate certain scale-up issues)

FDA U.S. FOOD & DRUG ADMINISTRATION

For Immediate Release: February 26, 2019

Statement From: Scott Gottlieb, M.D.

One of today's most important tools for modernizing the pharmaceutical industry is a process known as continuous manufacturing (CM). This approach transforms the



A.C. Fisher, W. Liu, A. Schick, M. Ramanadham, Sharmista Chatterjee, R. Brykman, S.L. Lee, S. Kozlowski, A.B. Boam, S.C. Tsinontides, M. Kopcha, *Int. J. Pharm.*, **2022**, *622*, 121778.

Challenges in Flow - Solids

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Avoidance

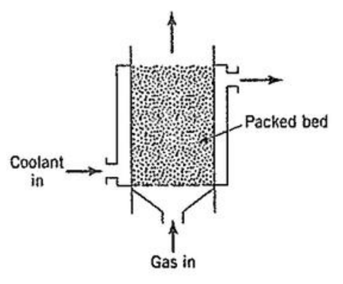
Solvent selection
Dilution
Homogeneous catalysis

Immobilisation

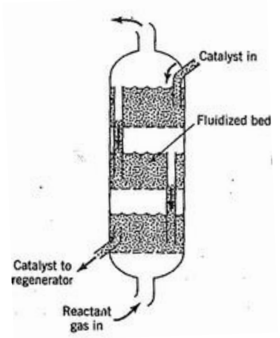
Packed bed, fluidised bed
Catalytic solids
Highly dedicated plant

Slurries

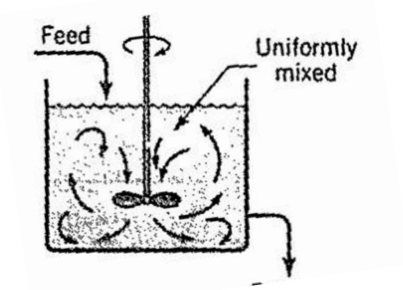
Static mixers, mechanical mixers
Dependent on flow regime and channel size
How to trial at lab-scale



Packed bed



Fluidised bed



Continuously Stirred Tank Reactor (CSTR)

O. Levenspiel, Chemical Reaction Engineering, Wiley, New Delhi, 3rd edn., 2016

Agitated Cell Reactor (ACR)

Agitated Tube Reactor (ATR)

H.P. Rice et al., *Chem. Eng. Process*, 2022, **179**, 109067.

Challenges in Flow - Solids

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Homogeneous catalysis

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Catalytic solids →
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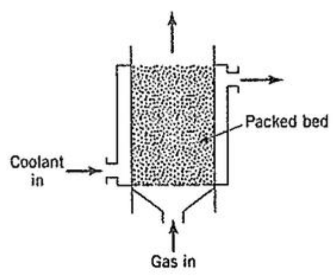
M. Irfan, T.N. Glasnov, and C.O. Kappe, ChemSusChem, **2011**, *4*, 300 – 316

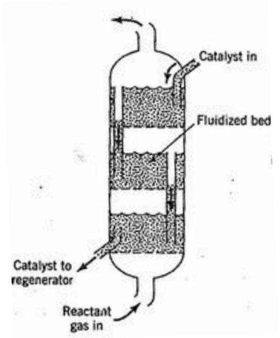
K. Masuda, T. Ichitsuka, N. Koumura, K. Sato, S. Kobayashi, *Tetrahedron*, **2018**, *74*, 1705-1730

Slurries

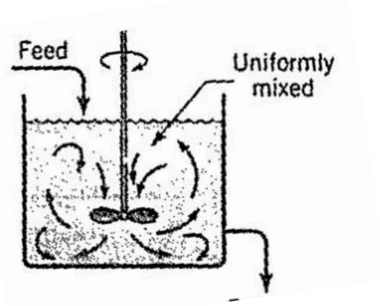
Static mixers, mechanical mixers
Dependent on flow regime and channel size
How to trial at lab-scale



Packed bed



Fluidised bed



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Challenges in Flow - Slurries

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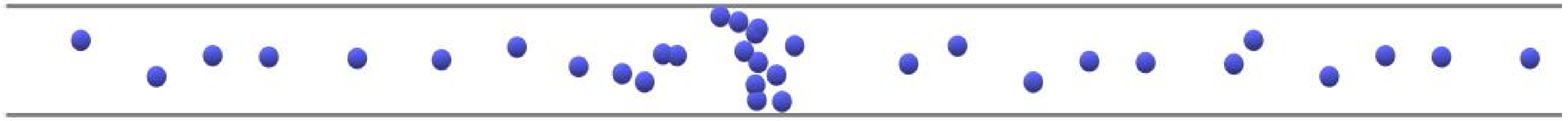
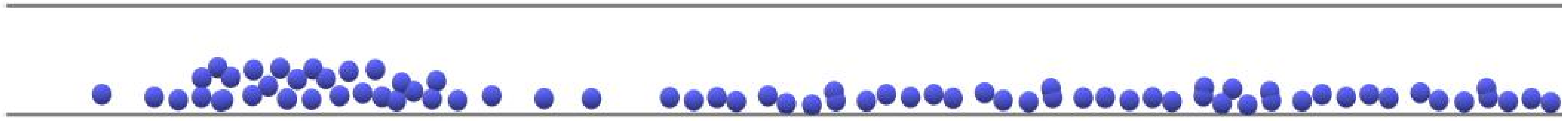
Issue | **Solution**

Bridging



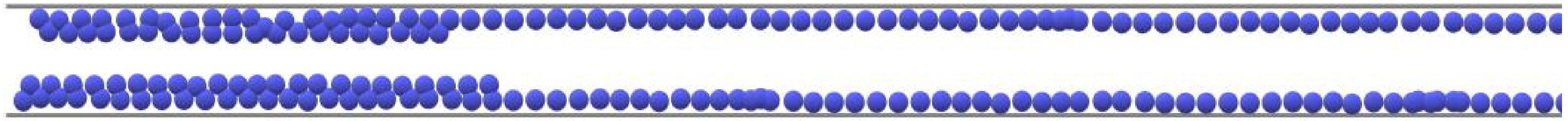
Increase Channel size

Settling



Increase Turbulence*

Fouling



Increase Wall Shear

***Through high fluid velocity or mechanical mixing**

Challenges in Flow - Immobilisation

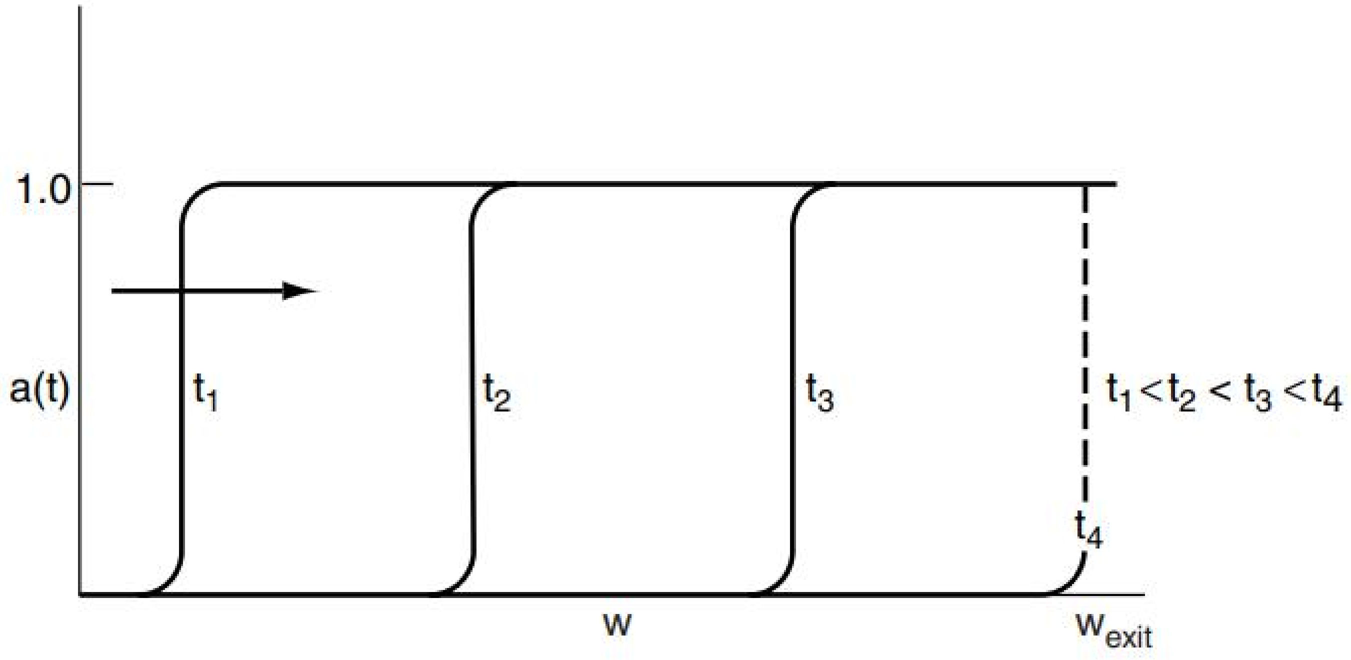
Packed Bed reactors are the most common form of Immobilised solids in flow.

Oversize to overcome drop in conversion:

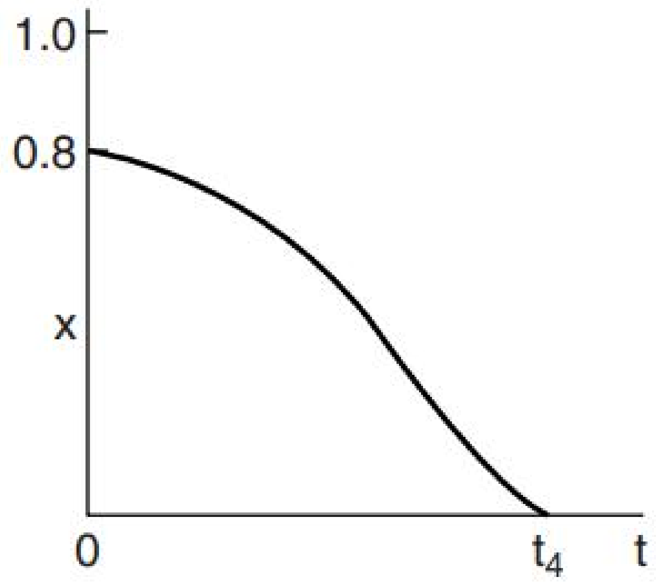
-Increase detrimental side reactions

-Increase pressure drop

-Cost impact on peripheral equipment

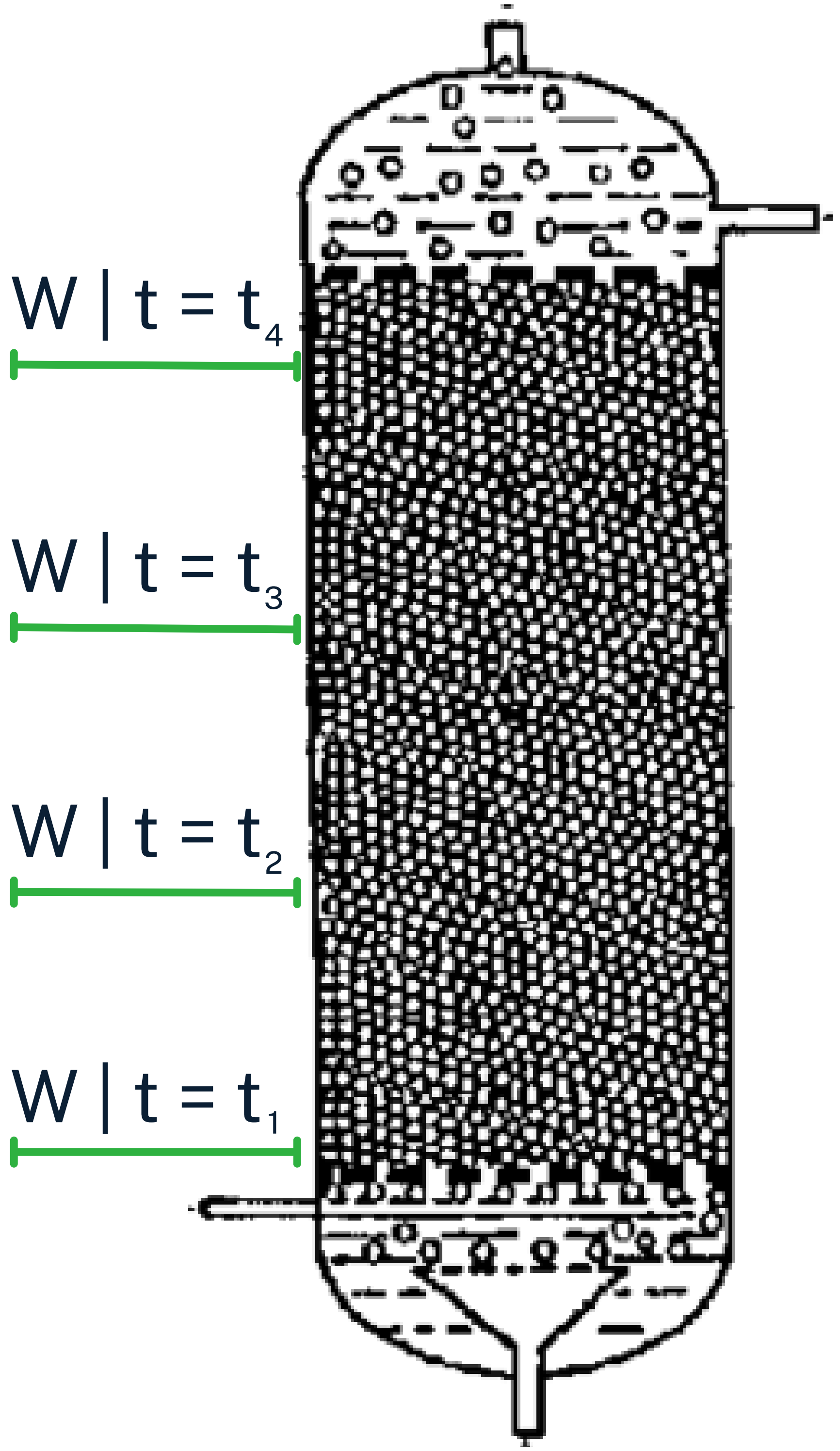


Movement of activity front in a packed bed



Exit Conversion as a function of time

H. Fogloer, Elements of Chemical Reaction Engineering, 4th edn, 2005



Dudukovic et. al, Multiphase Catalytic Reactors: A perspective on Current Knowledge and Future Trends, 2007.

Challenges in Flow - Comparison

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Slurry Fed Reactors		Packed Bed Reactors
Blockages always possible	**Reliability**	Low chance of blockages
Indefinite processing	**Run Length**	Shutdowns necessary
Large peripheral equipment	**Footprint**	Oversizing common
Only affected by conditions	**Product Consistency**	Conversion affected by run length
Catalytic and stoichiometric solids	**Versatility**	Limited to catalytic solids
High filtration requirements	**Downstream Processing**	Often only clarification

Case Study

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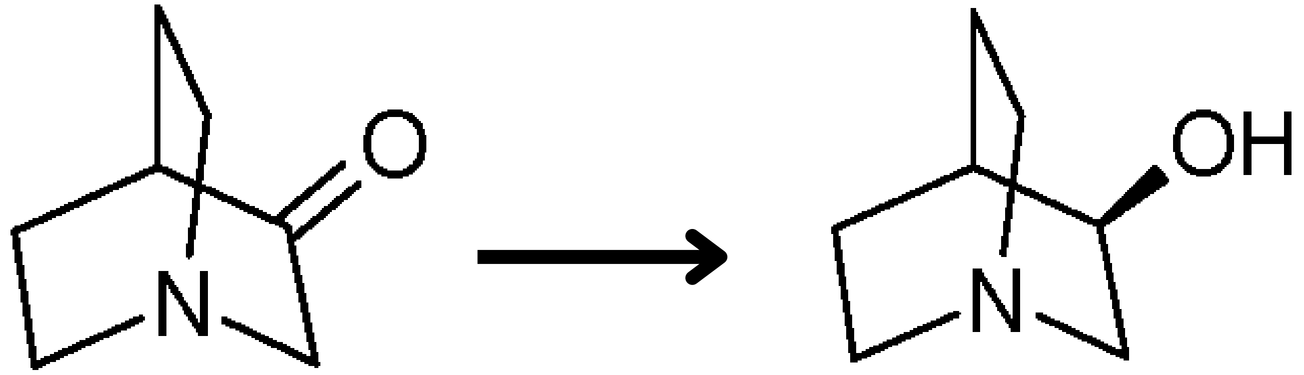
HydRegen

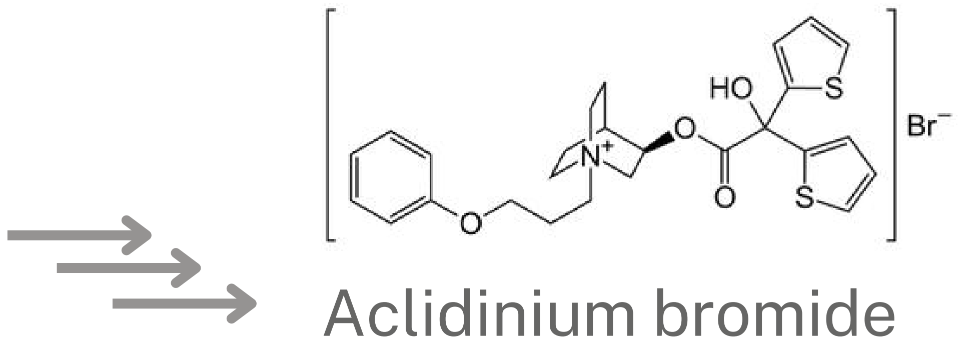
Reduction of Quinuclidinone in the Coflore ACR

ACR

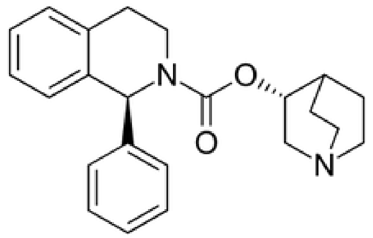


3-Quinuclidinone

3-Quinuclidinol

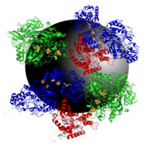


Aclidinium bromide



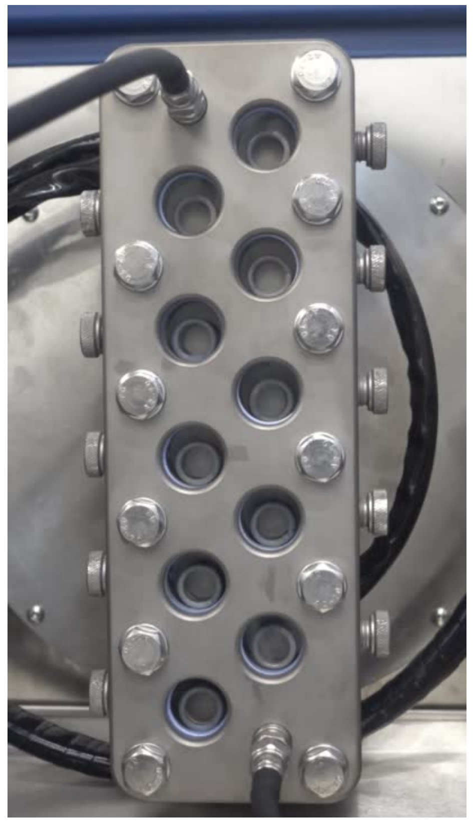
Solifenacin

Catalysis 3-ways

1) Slurry Feed - Biocatalyst 

2) Slurry Feed - Pd/C Paste 

3) Immobilised - Pd/C Pellets 



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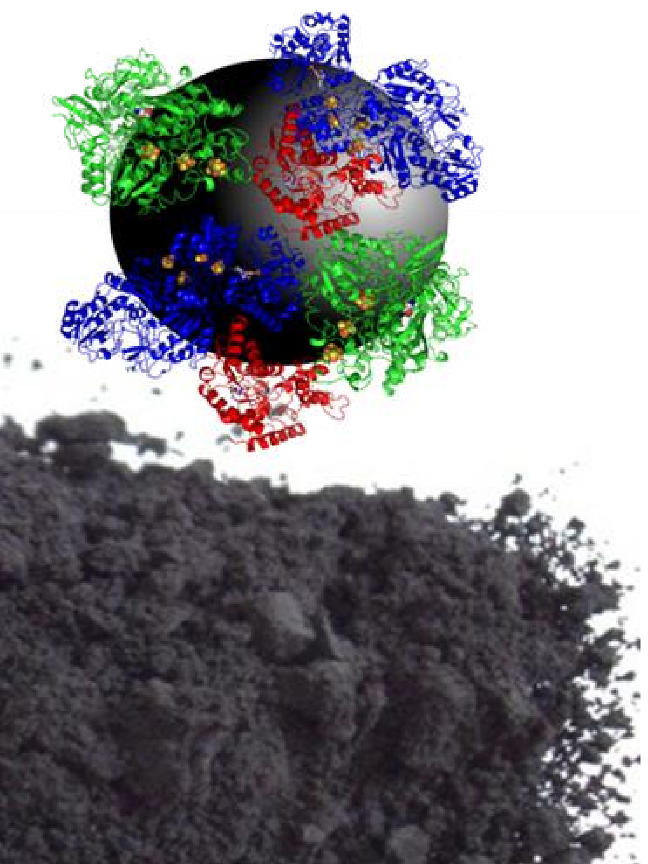
Biocatalytic Reductions

Black Powder Biocatalysts

Little to no experience with enzymes — ***Established experience with enzymes***

Complete solutions
'Slot in' alternatives to supported metal catalysts
(low barrier-to-entry, no new knowledge or infrastructure required)

New ways of working
Use your own proprietary enzymes
(less waste, less complicated, continuous manufacturing)



- Energy & resource efficiency
- Continuous manufacturing
- Circular / bio-based economies

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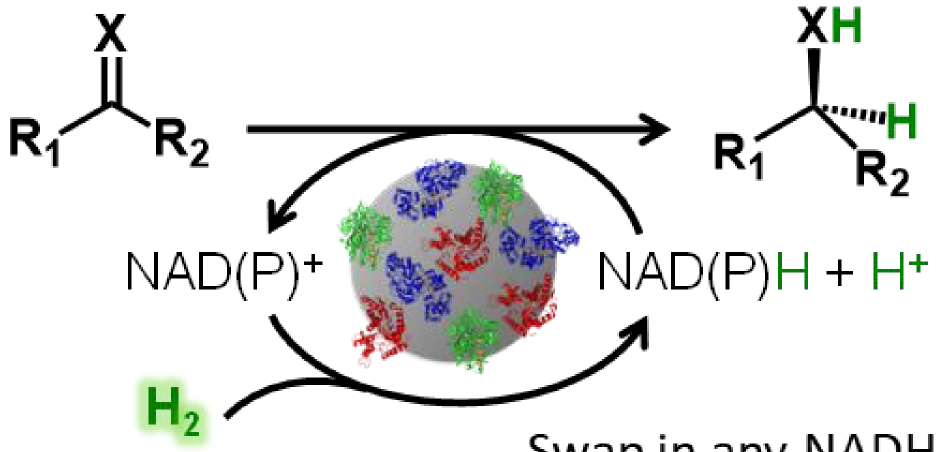
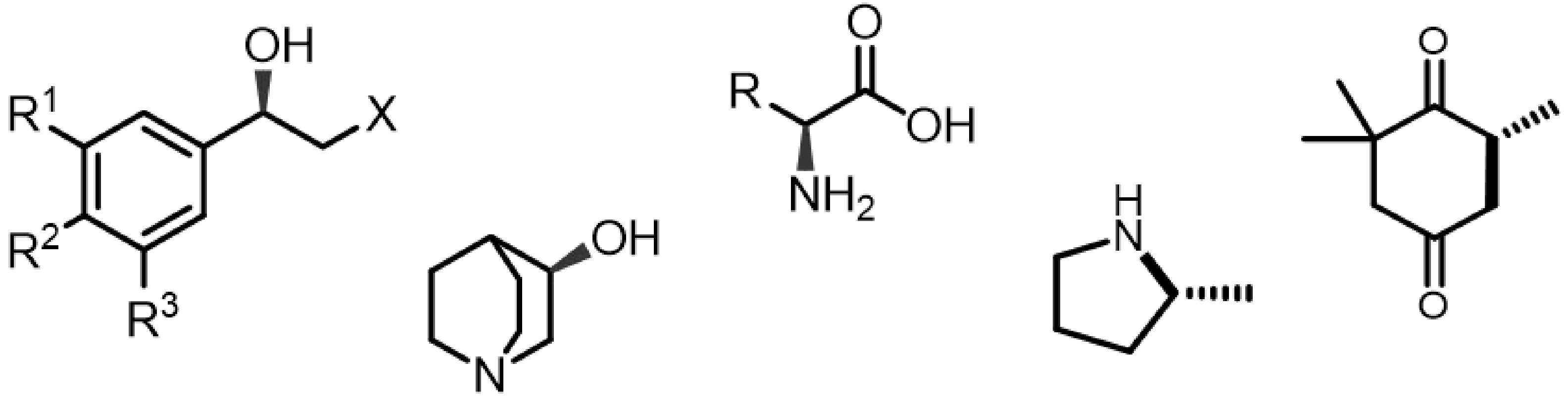
Biocatalytic Reductions Black Powder Biocatalysts

Asymmetric C=X hydrogenations



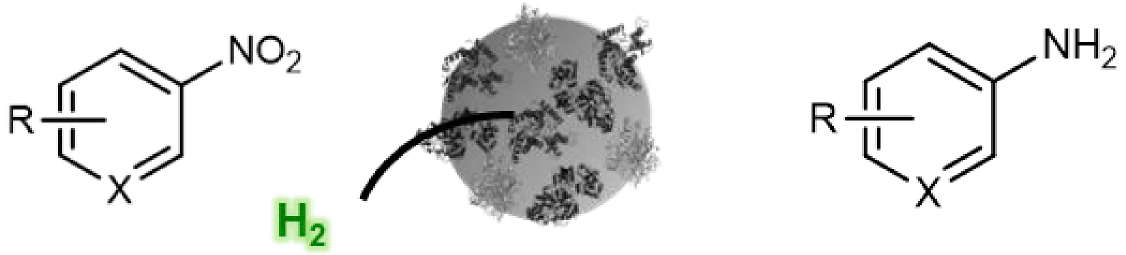
Swap in any NADH-dependent enzyme

Case examples:

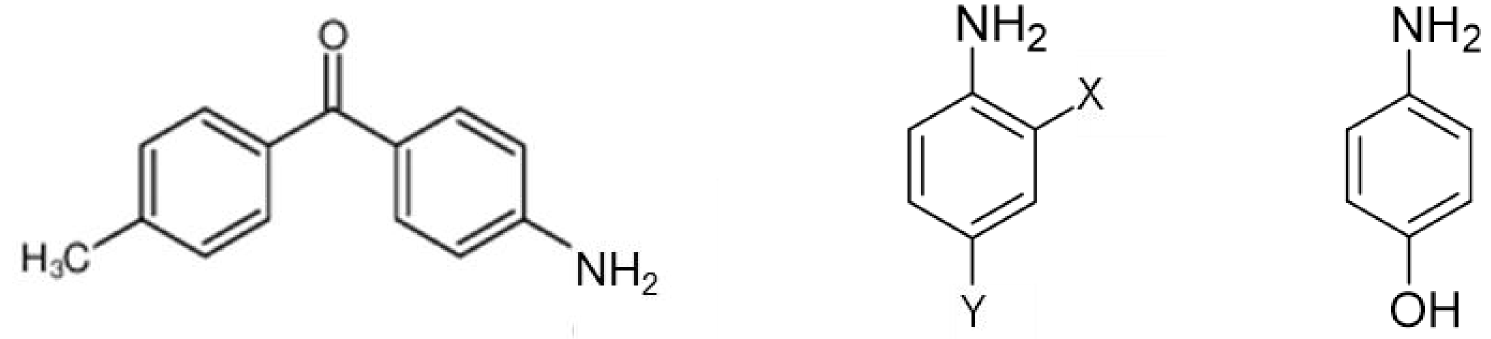


typically >99 % *ee*

Selective nitro to amine hydrogenation



Case examples:



- **Batch** and **continuous** reactors
- Simple catalyst removal/**reuse**
- **Scale-up** strategies
- Multi-day **stability**
- **Mild** conditions
- High yields, low waste
- Enzyme **selectivity** retained
- Functional group tolerance (halogen, sulphur, etc.)
- Replaces precious metals

Nitro or azide reductions: Manuscript in prep, get in touch for info!

Selective C=X reductions: H. A. Reeve *et al.*, *ChemCatChem* **2015**, *7*, 3480. | B. Poznansky *et al.*, *Front. Chem. Eng.* **2021**, *3*, 35. | S. E. Cleary *et al. Front. Catal.* **2023**, *3*, 1114536.

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Comparison of catalysts

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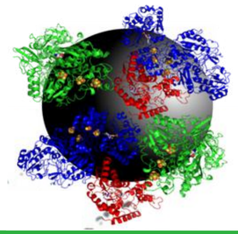
	Biocatalyst 	Pd/C Paste 	Pd/C Pellets 
Active Site Loading	~25% Enzyme	5% Pd/C	1% Pd/C
Catalyst Loading	0.15 mg / mL	0.15 mg / mL	0.96 g / 5.34 g
Particle size	20 - 50 nm	< 100 μm	1 - 3 mm
Specific surface area	1272 m^2/g	800-1000 m^2/g	941 m^2/g

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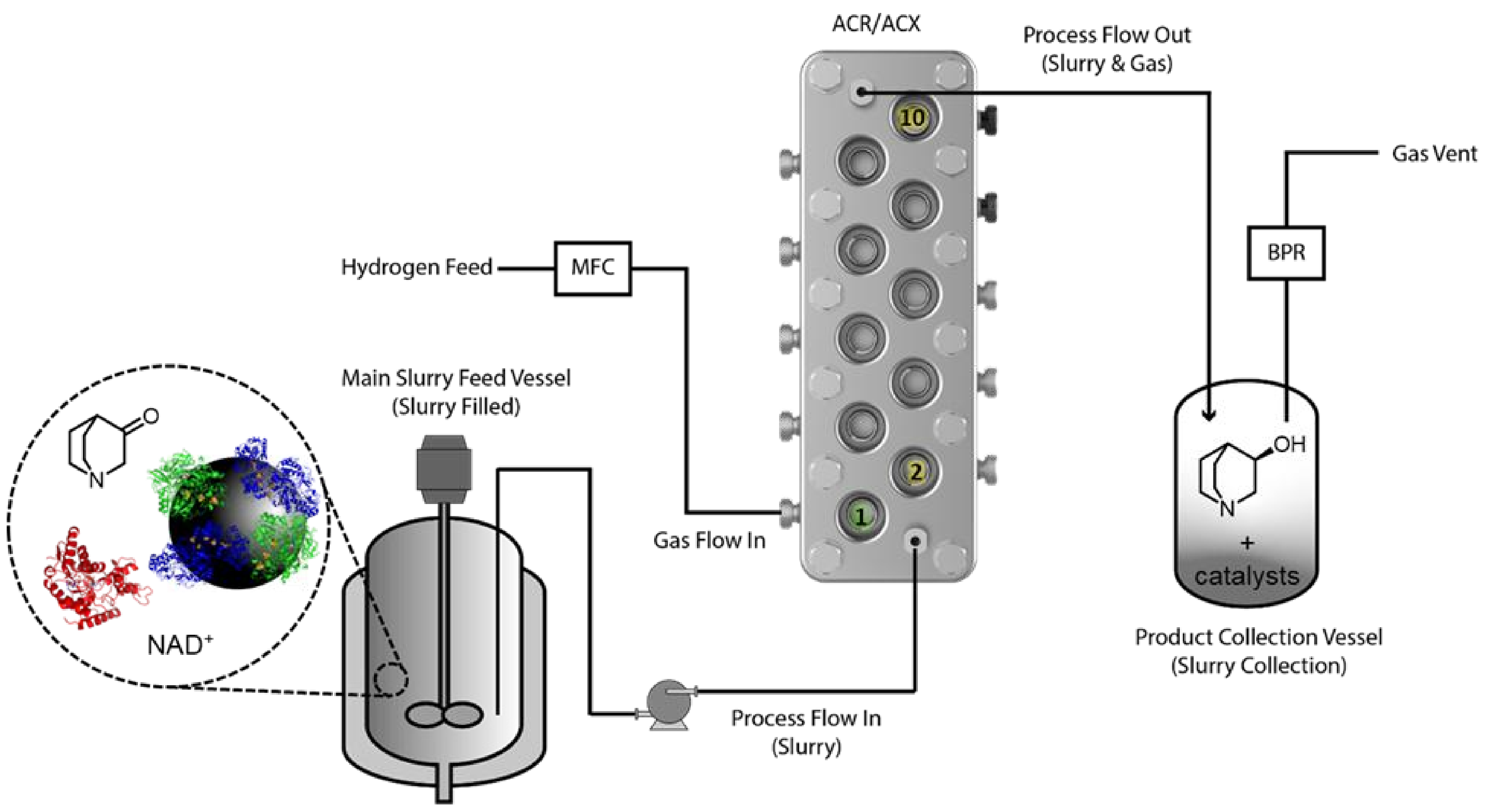
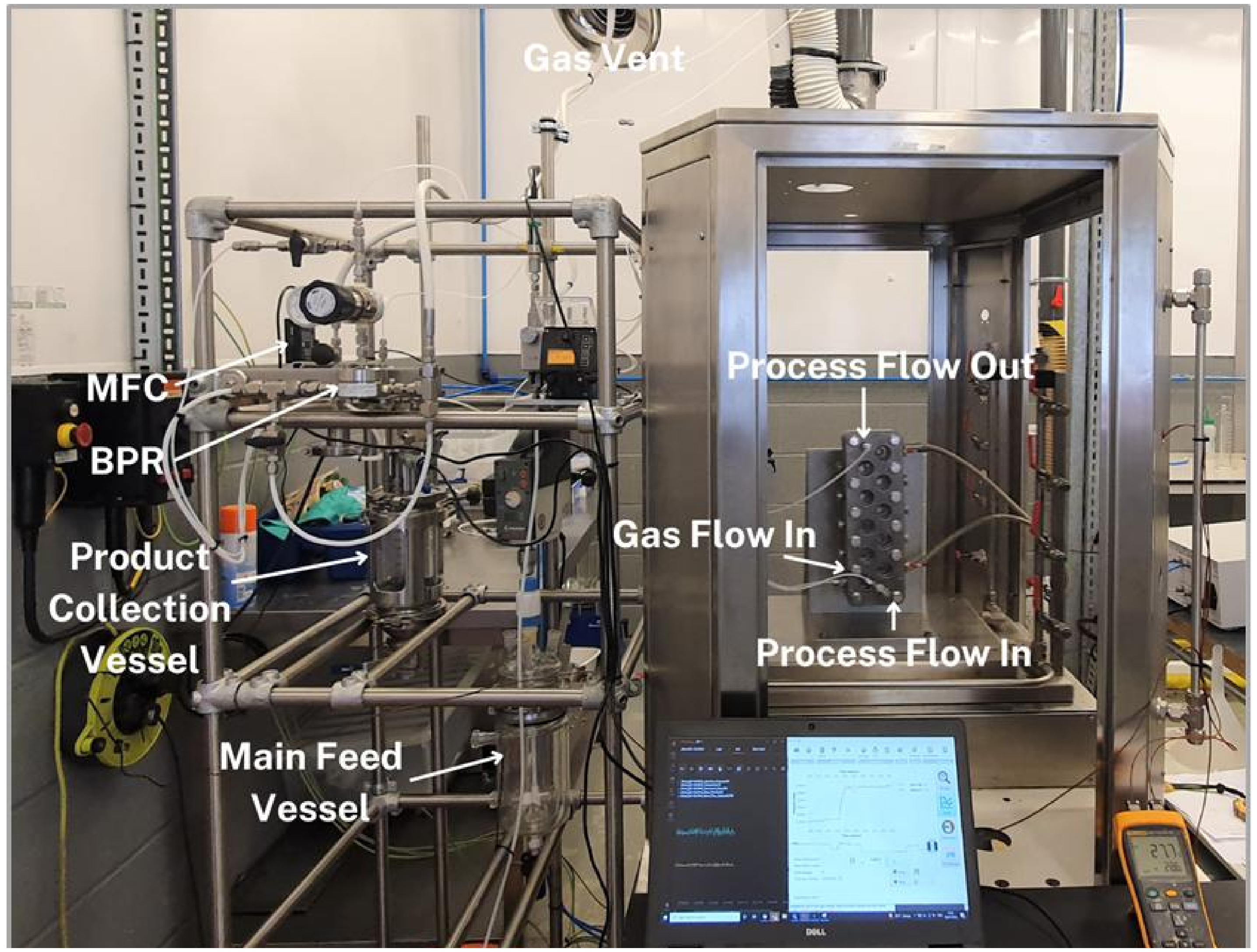
Setup Overview





All tests conducted in the same setup;

- 0.4 to 3 mL/min slurry feeding
- 15 to 108 minute liquid phase residence time

Setup Obstacles

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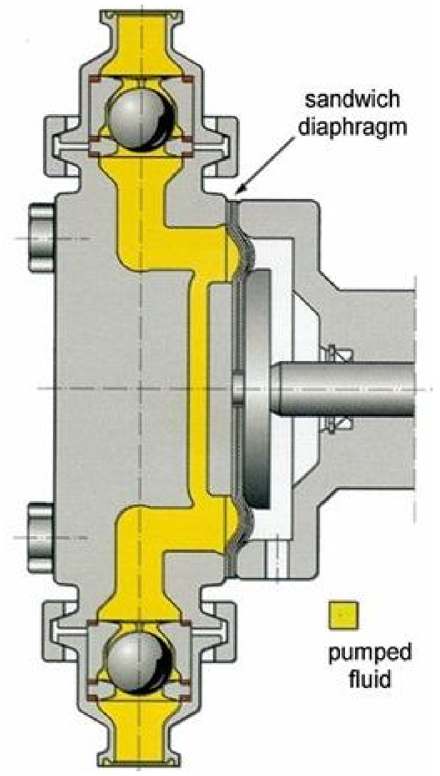
Diaphragm Pump



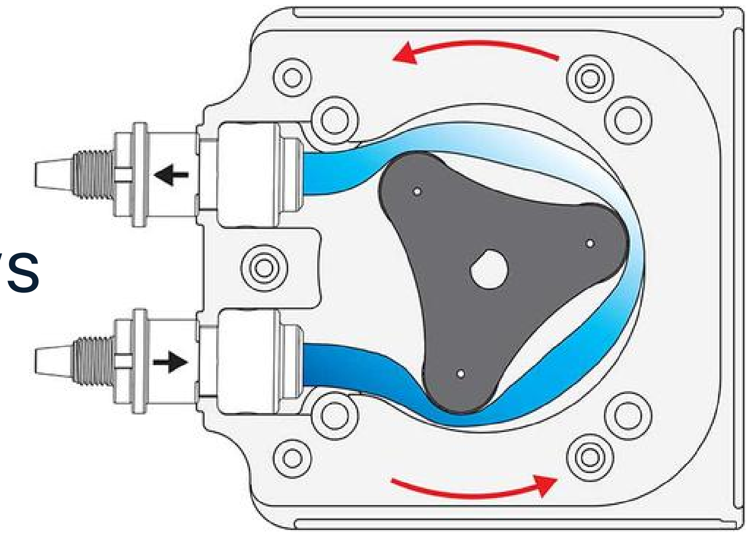
- High Pressure
- Scalable to higher Flows
- Integral Check valves

149 μm Activated Carbon ✓

20 - 50 nm Biocatalyst ✗

Peristaltic Pump

- Low - Mid Pressure
- High Turndown of low flows
- Material Compatibility



149 μm Activated Carbon ✓

20 - 50 nm Biocatalyst ✓

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Images Sourced from Flexachem, and Pumps and Systems.

Biocatalyst results

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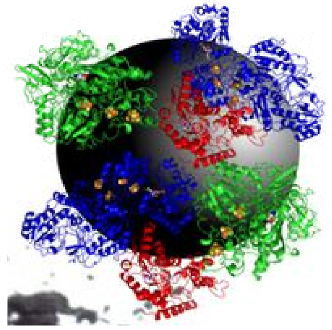
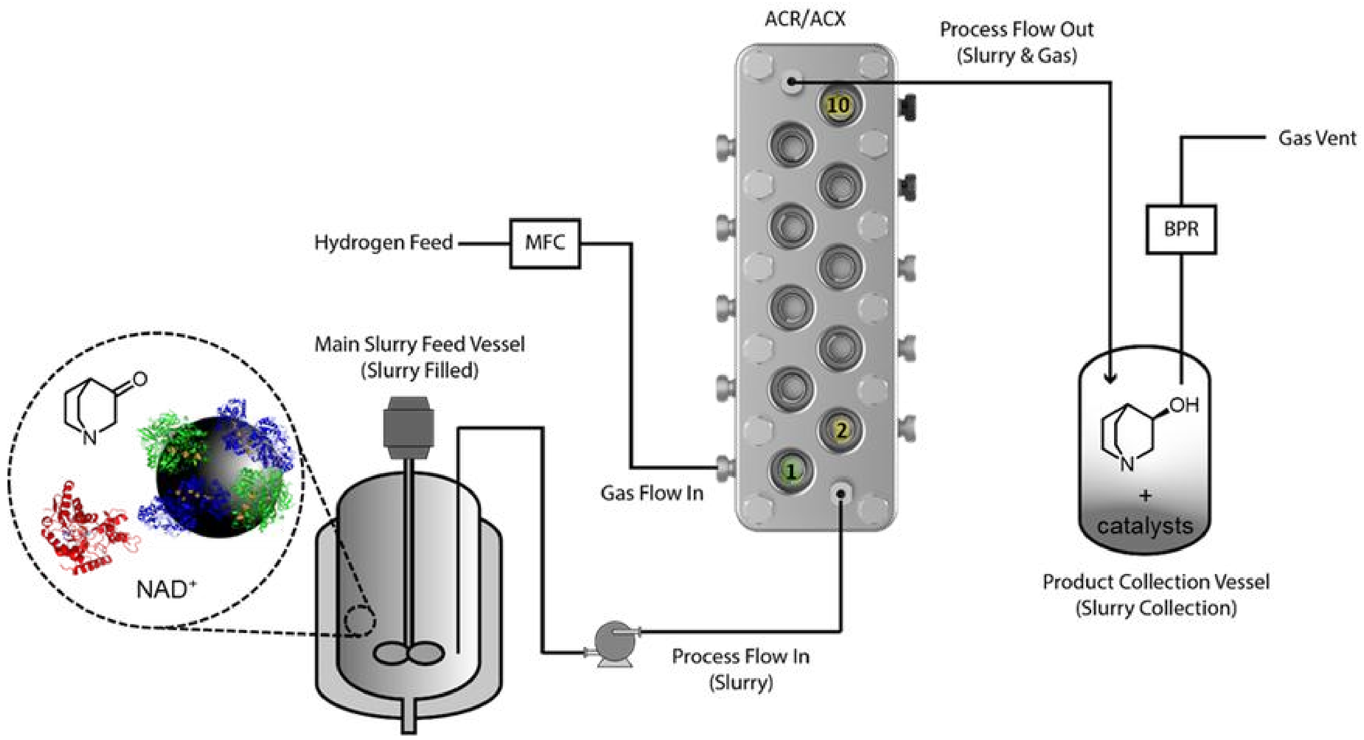
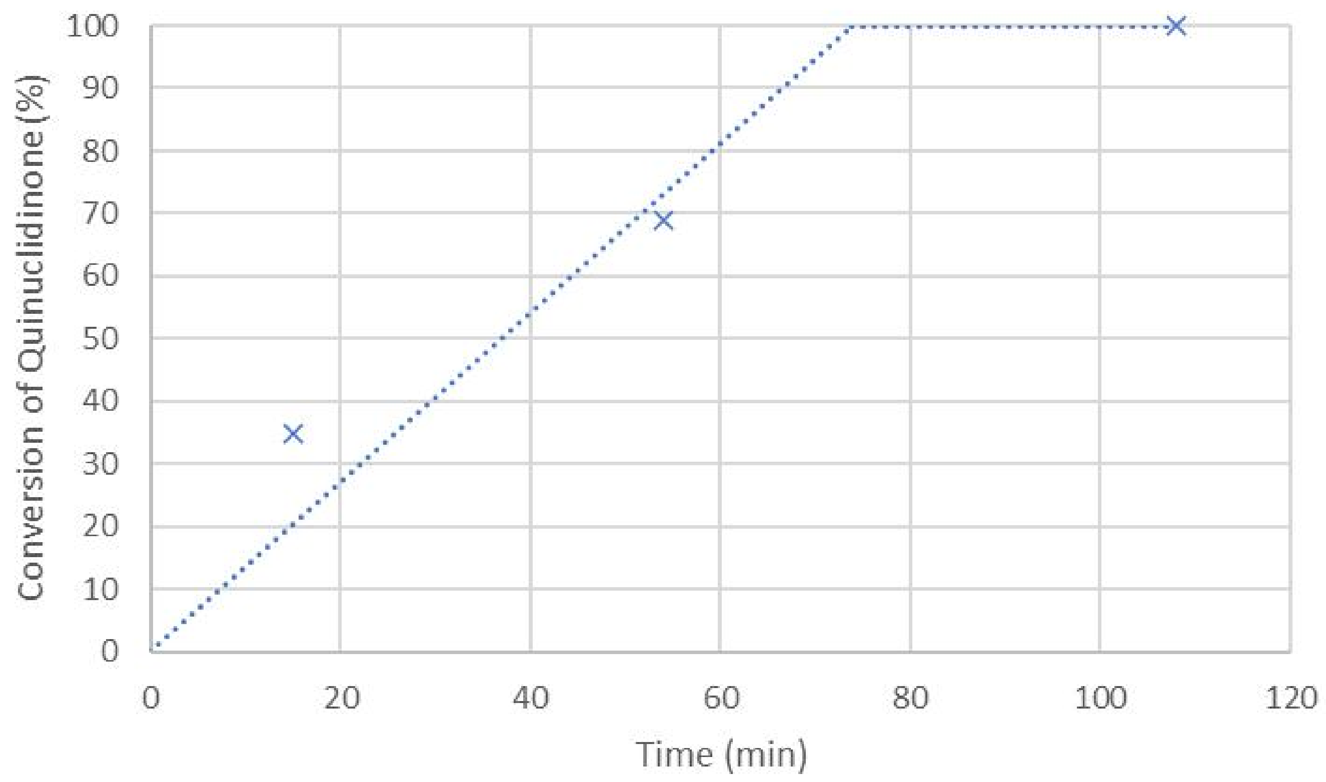


Assuming a 0^{th} order reaction,
full conversion in ~74 minutes
35 °C, **2 Bar**



System operated for >100 hours



TOF_{15} = 286 min^{-1} -15 minute Residence time

TOF_{54} = 161 min^{-1} -54 minute Residence time

TOF_{108} = ≥ 152 min^{-1} -108 minute Residence time

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Immobilised Catalyst results

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	Constant surface area scaled	Packed Catalyst Baskets
Catalyst Mass (g)	0.96	5.34
Reactor Volume (mL)	78	68
Residence time (min)	56	56
Conversion (%)	16 - 17	100
Pd TOF (min^{-1})	0.16	≥ 0.05
Pressure (bar)	**10**	**10**

ACR

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Comparison & Conclusion

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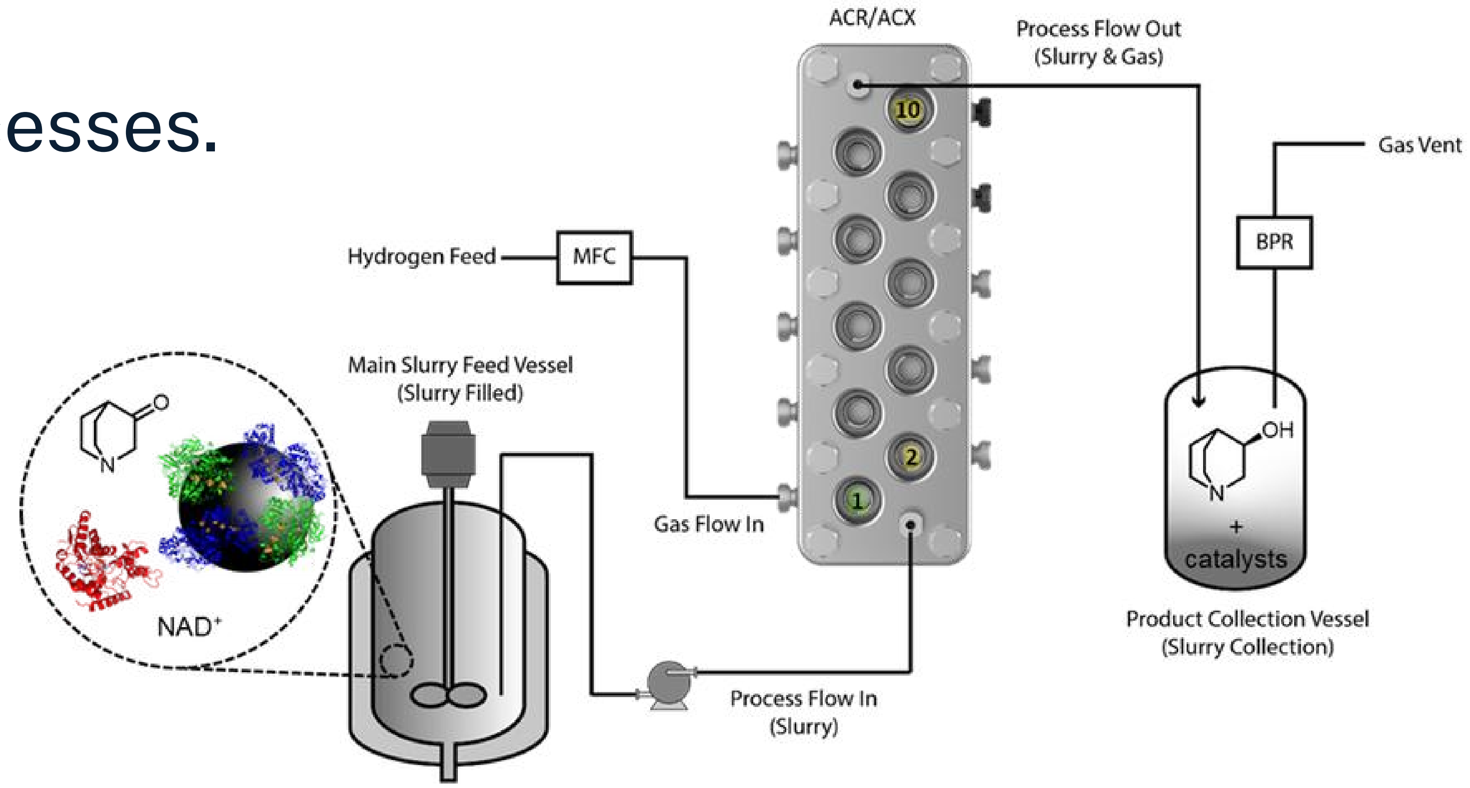
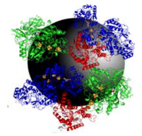
- Versatility is key. Same process design, different processes.
- Bio-catalyst offers a "Slot in alternative".
- Scale-down approach



	Highest observed TOF	Conditions used for TOF
 Slurry Biocatalyst	261 min^{-1}	35 °C, 2 Bar
 Slurry Pd/C Paste	<0.01 min^{-1}	35 °C, 2 Bar
 Immobilised Pd/C Pellets	0.16 min^{-1}	35 °C, 10 Bar

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Next Steps

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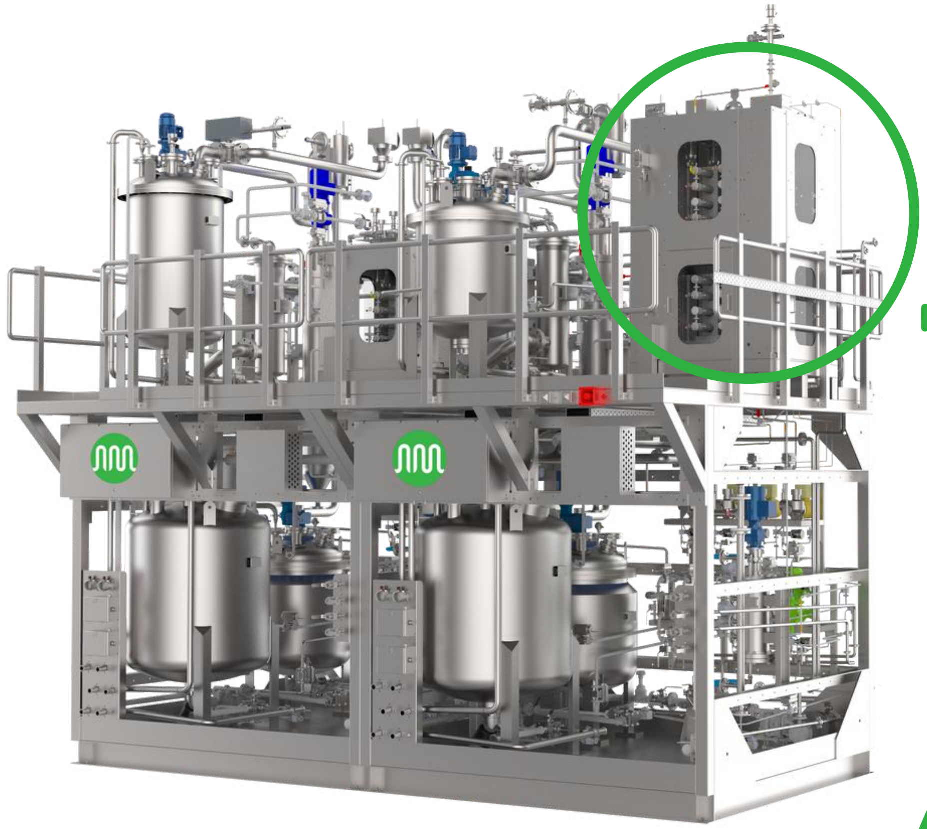
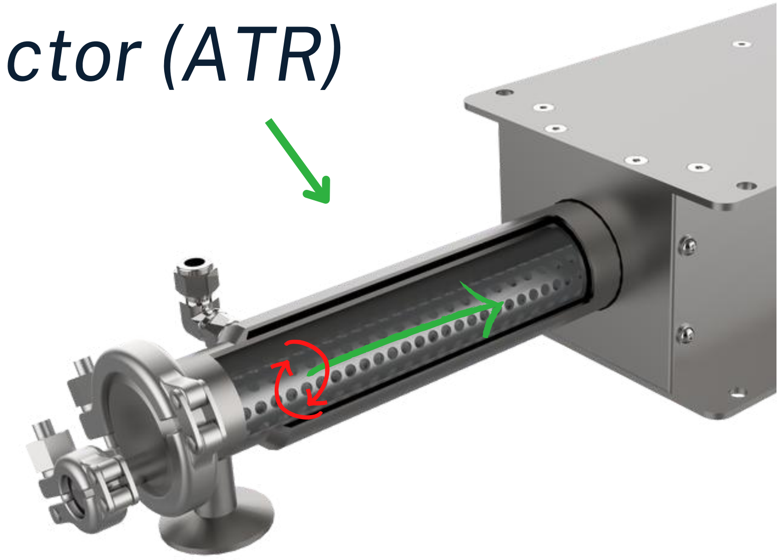
- Intensification of biocatalysis process
- Inline analytical development
- TOF vs. time for pellets vs. biocatalyst
- Scaleup - 10 L flow trials ongoing
- Downstream processing
- Final skid design

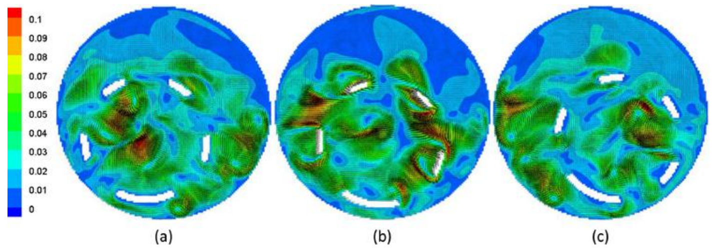


Agitated Tube Reactor (ATR)



Turbulent Radial Mixing

Axial Plug Flow



UNIVERSITY OF LEEDS | IbD Intensified by Design | AM Technology Engineering Chemistry

H.P. Rice et al., *Chem. Eng. Process*, 2022, **179**, 109067.

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Thank You

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Dr Mike Kenny
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ACR
30 - 90 mL

ATR
0.35 - 10 L

RTR
100 L

Dynamically-mixed flow reactors

HydRegen

Dr Sarah Cleary
sarah@hydregenoxford.com