Reaction Optimisation and Scale-Up in Continuous Flow Reactors

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CPAC Summer Institute, Seattle, 19-21 July 2011
Benefits of Micro Reactor Technology

• Increased reaction control
  – Efficient mixing
  – Accurate control of reaction time, temperature and pressure
  – Improved atom efficiency, product selectivity, yield and purity
  – Increased run-to-run and reactor-to-reactor reproducibility
  – Increased catalyst turnover and lifetimes

• Increased process safety
  – Due to rapid dissipation of heat of reaction
  – Low reactant hold-up
  – Real-time *in-situ* analytical evaluation of reactions

• Lower cost and shorter development cycles
  – Higher chemical selectivity leading to higher yield
  – Reducing the amount of reagents and catalyst
  – Reducing the size of the plant
  – Faster scale-up from lab to plant scale
Better definition of a ‘Micro’ Reactor

• ‘Micro’ reactors
  – Defined as a series of interconnecting channels formed in a planar surface
  – Channel dimensions of 10-300 μm
  – Very small dimensions result in very fast diffusive mixing
  – Rapid heat transfer
  – High throughput experimentation
• ‘Flow’ (or meso) reactors
  – Dimensions > 300 μm (up to 5 mm)
  – Mixing much slower
    – Incorporate mixers
  – Throughput higher
• Reactors fabricated from polymers, metals, quartz, silicon or glass
• Why glass?
  – Mechanically strong
  – Chemically resistant
  – Optically transparent
Where is MRT being used?

• Industry generally introduces MRT where safety is a major concern
  – Xian Chemicals (China) - 30 tonne/annum nitroglycerine manufacture
  – DSM - Ritter reaction (1700 tonnes manufactured to date)
  – DSM - Nitration to form Naproxen intermediate (190 tonnes conc. HNO₃ in 7 weeks)

• Case studies published showing financial savings of using MRT in production

• Drug discovery
Continuous Flow Concept: Facile Up-Scaling

• Rapid scale-up is a ‘strategic competitive advantage’
  – Process chemists require methodology that increases reactor throughput without lengthy re-optimisation steps

– Furthermore ideally want to optimise the process:
  • Fast
  • Using minimal material
Labtrix

- Reaction optimisation

Features
- Syringe pumps
- Automated sample collection and control
- Tests at pressures of 25 bar and temperatures of -15 to 195°C
- Standard interchangeable reactors:
  - Catalyst reactor:
Rapid Reaction Evaluation

Optimal conditions:
- Micro reactor: 180 sec, 125 °C, 100% conversion
- Batch stirred reactor 1 h, 125 °C cf. 93.6 % conversion

Investigation:
- Number of reactions: 200
- Time taken to generate samples: 27 h
- Volume of reactants employed: 5.97 ml (94.3 mg 1,3-diketone)
Azide Synthesis

• Synthetically useful route to primary amines, triazoles and isocyanates

\[
\begin{array}{c}
\text{R} - \text{SO}_{2} - \text{O} - \text{SO} \\
\text{NaN}_{3} \\
aq. \text{EtOH} \\
\rightarrow \\
\text{R} - \text{SO}_{2} - \text{O} - \text{SO} - \text{N}_3
\end{array}
\]

Disadvantages:
• Exothermic reaction
• Products are often hazardous substrates
• Generation/build-up of explosive intermediates
  • Diazidomethane and hydrazoic acid

Why investigate under continuous flow?
• Increase reactor safety
  – No headspace therefore reduced risk of HN\textsubscript{3} build-up
  – Efficient dissipation of heat generated
• Increase productivity as a function of wider operating temperatures
• Increase economic feasibility
• Provide a generic method for the production of these versatile intermediates
Azide Synthesis

Operating Conditions:
- Pressure-driven flow
- 0.66 M reagents
- 25 to 195 °C
- 25 Bar pressure
- Optimised conditions
- 30 sec residence time
- 99 % conversion
Azide Synthesis

- Employing 0.66 M (EtOH) alkyl precursor and 0.66 M (50:50 aq. EtOH) NaN$_3$

- Order of reactivity was observed to be OMs > Br >> Cl
- Using OMs derivative, the azide obtained at a throughput of 79 mg h$^{-1}$ @195 °C
  - Analytically pure after an aqueous extraction
- Cl derivative gave 70% conversion under these conditions
  - Potentially offers economic advantages overall
Paal-Knorr reaction:
- Second order reaction
- Rate constant @ 75 °C = 5.4 x 10⁻³ L mol⁻¹ s⁻¹

Optimal conditions: 2.5 M reagents, 37 s @ 150 °C affords the pyrrole 3 at a throughput of 418 mg h⁻¹
Hydrolysis of \( p \)-Nitrophenyl Acetate

Reaction manifold:

\[
\begin{align*}
\text{aq. \text{NaOH}} & \quad \text{aq. HCl} \\
\text{Organic Phase} & \quad \text{Aqueous Phase}
\end{align*}
\]

Reaction Conditions:
- \( p \)-Nitrophenyl acetate in toluene (0.05 M) and NaOH in DI H\(_2\)O (0.5 M)
- Total flow rate = 2 to 20 \( \mu \text{l min}^{-1} \), Temperatures = 25 to 150 °C

Biphasic System:
- Immiscibility of reactants affords segmented flow
Hydrolysis of $p$-Nitrophenyl Acetate

Optimal conditions:
- 60 sec, 125 ºC affording 100% conversion

Extraction of kinetic information:
- Performing flow experiments at several reaction times enables the $k_{\text{obs}}$ to be readily extracted from the data generated
  - i.e. @ 75 ºC, $k_{\text{obs}} = 0.0143 \text{ s}^{-1}$ for $p$-nitrophenyl acetate hydrolysis
Epoxidation of Alkenes: Improved Safety

- Epoxides are very useful reaction intermediates
- Traditionally prepared using organic peracids
  - Hazardous on a large scale
- Enzyme ‘greener’ but usually denatured by the reaction conditions
- Avoided using a flow reactor where peracid generated in situ

Experimental set-up:
- Reactor packed with Novozyme 435
  - Immobilised catalysts also simplify work up procedures
- Alkene 0.1 M and $H_2O_2$ 0.2 M in EtOAc

Epoxidation of Alkenes: Rapid Evaluation

- Evaluation of optimum reaction conditions
- Alkene 0.1 M and H$_2$O$_2$ 0.2 M in EtOAc

- Optimum conditions:
  - Temperature 70 °C
  - Residence time 2.6 minutes
- Higher temperatures denatured the enzyme

Translation of Microwave Methodology

• Whilst microwaves have found widespread use in medicinal chemistry labs for the rapid screening of thermally activated reactions, scaling is challenging

Advantages of Flow:

Reactions can be readily pressurised and ‘super-heated’ like microwaves, but;
• No solvent dependency on the actual reaction temperature
• Efficient heating and accurate control of reaction time
• Reactions can be scaled

Model Reaction:

• To demonstrate this, the following etherification reaction was performed using Labtrix\textsuperscript{®} S1 and the data obtained compared with the literature\textsuperscript{1}

\[
\begin{align*}
\text{O}_2\text{N} &\quad \text{Cl} \\
\text{Cl} &\quad \text{MeO} \\
+ &\quad \text{DBU} \quad \text{DMA} \\
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{N} &\quad \text{Cl} \\
\text{Cl} &\quad \text{OMe} \\
\end{align*}
\]

Translation of Microwave Methodology

Reaction Conditions:
- Residence time 10 mins
- 1.30 M Phenol and DCNB in DMA
- Performing the reaction in MeCN
  - Equivalent conversions obtained
Facile Up-Scaling

• Rapid scale-up is a ‘strategic competitive advantage’
  – Process chemists require methodology that increases reactor throughput without lengthy re-optimisation steps

• Reaction channel dimensions increased
  – ‘micro’ 300 µm x 120 µm to ‘meso’ 1.4 mm x 1.0 mm
Efficient Scale Up - Mixing Technology

- Need to ensure that the mixing is the same in all reactor designs
- Staggered Oriented Ridges (SOR) fabricated in the channels
Mixing Efficiency using Fourth Bourne Reaction

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
+ \quad \text{NaOH} & \quad \stackrel{\text{HCl}}{\text{aq. EtOH}} \\
\text{MeO} & \quad \text{OMe} \\
\text{NaCl} \quad + \text{H}_2\text{O} & \quad \text{MeO} \quad \text{OMe} \\
& \quad \text{MeO} \quad \text{OMe} \\
\text{MeO} \quad \text{OMe} & \quad \text{NaCl} \quad + \text{H}_2\text{O} \\
& \quad \text{MeO} \quad \text{OMe} \\
& \quad \text{MeO} \quad \text{OMe} \\
\end{align*}
\]

\[ k_1 = \text{fast and } k_2 = \text{slow} \]

<table>
<thead>
<tr>
<th>[DMP] (M) (^a)</th>
<th>Mixing Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>31.7</td>
</tr>
<tr>
<td>(2.5 \times 10^{-2})</td>
<td>63.5</td>
</tr>
<tr>
<td>(1.25 \times 10^{-2})</td>
<td>127.0</td>
</tr>
<tr>
<td>(6.25 \times 10^{-3})</td>
<td>254.0</td>
</tr>
</tbody>
</table>

\(^a\) After mixing but before reaction (50 % Stock)

< 4 % hydrolysis = efficient mixing
Mixing Efficiency using Fourth Bourne Reaction

Validate the Scaling Principle:
- The reaction was repeated in a 0.8 ml containing same SOR mixer as a micro reactor
Mixing Efficiency using Fourth Bourne Reaction

- > 99 % < 254 ms
- > 96 % Mixing < 159 ms

![Graph showing mixing efficiency versus residence time.]
Plantrix® Production Capacity

Chemical Appraisal:
• Plantrix chemically evaluated by a multi-national pharmaceutical company
  — Details of the process are confidential

Model System:
• 0.5 M Product concentration (MW = 200), 1 min reaction time

<table>
<thead>
<tr>
<th></th>
<th>Labtrix®</th>
<th></th>
<th>Plantrix®</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micro Reactor</td>
<td>1 Channel</td>
<td>8 Channel</td>
<td>8 Channel</td>
</tr>
<tr>
<td>Volume per Reactor Channel</td>
<td>10 µl</td>
<td>0.8 ml</td>
<td>6.5 ml</td>
<td>6.5 ml</td>
</tr>
<tr>
<td>Micro Reactors</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. Reactors per Holder</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Volume per Holder</td>
<td>10 µl</td>
<td>0.8 ml</td>
<td>6.5 ml</td>
<td>65 ml</td>
</tr>
<tr>
<td>Throughput*</td>
<td>60 mg hr⁻¹</td>
<td>4.8 g hr⁻¹</td>
<td>39.0 g hr⁻¹</td>
<td>390 g hr⁻¹ (9.36 kg day⁻¹)</td>
</tr>
</tbody>
</table>

• Using a range of product configurations, you can;
  — Minimise reagent use (0.8 ml), or tailor production rates
Conclusions

• Micro reactors allow the rapid optimisation of reactions
  – Rapid process development
• Increased reaction control
  – Higher purity
  – Higher conversion
  – Higher selectivity
• More reproducible synthetic procedures
  – Operator independent synthesis
• Increased catalyst turnovers and lifetimes
  – Easier purification/isolation
• Increased process safety
  – Due to rapid dissipation of heat of reaction
  – Low reactant hold-up
• Equipment for method development and production developed
Research Workers and Collaborators

- **Researchers**
  - Dr. Charlotte Wiles
  - Dr. Bongkot Ngamsom
  - Dr. Joe Dragavon
  - Dr. Vicki Hammond
  - Dr. Gareth Wild
  - Dr. Tamsila Nayyar
  - Dr. Julian Hooper
  - Dr. Linda Woodcock
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  - Dr. Victoria Ryabova
  - Dr. Vinod George
  - Dr. Leanne Marle
  - Dr. Mairead Kelly
  - Dr. Ben Wahab
  - Dr. Lucia Marra
  - Francesco de Leonardis
  - Matthew Simmons

- **Collaborators**
  - Hull colleagues
  - Strathclyde University
  - Prof. J. A. Littlechild (Exeter)

- **Funding**
  - EPSRC
  - Sanofi-Aventis
  - LioniX
  - Astra Zeneca
  - EU FP6
  - EU FP7
  - Yorkshire Concept