Continuous Flow Reactors: An Opportunity for Discovery, Process Development & Production?

Dr Charlotte Wiles, April 2016
Conventional Synthetic Methodology: Challenges and Limitations

- If we look to how synthetic chemistry has been taught and performed, little has changed over the past century, with all chemists being familiar with standard glassware and equipment.

Batch Reactions:

- In batch reactions parameters such as time, temperature, stoichiometry, order of addition and solvent are investigated with the aim of increasing yield and product purity.

- If more product is required then a larger vessel is normally employed.

- Changes in surface to volume ratio mean that differences in thermal and mass transfer occur and reactions often need to be re-optimised.
With all of this in mind, when considering process development for scale-up, **PROCESS UNDERSTANDING IS KEY**, an ideal flow reactor for process development employs:

- Pre-heating to give assurance of reaction temperature & active thermal regulation
- Rapid mixing to maximise reactor volume used for reaction
- *In-situ* quenching to stabilise product(s) & prevent decomposition (where needed)

→ Giving the necessary process understanding required for scale-up
Identifying where Flow has Benefits

Process development in flow allows the researcher to;

- Use small quantities of material
- Rapidly screen the effect of reaction parameters
- Access conditions not available in batch
- Use new solvent systems or solvent-free conditions
- Develop scalable reaction methodology
- Determine implications of reaction conditions on manufacturing costs

Producing in flow allows;

- Safe, efficient production
- Stable product quality
- Small footprint manufacturing
Fundamentals of Flow Chemistry: Opportunities for Greater Process Control

Flow reactors give the user repeatable control over heat transfer & mass transfer properties

Couple this with ‘Advanced Process Control (APC)’ strategies which have the ability to perform corrective actions that mitigate process disruptions

1. Define target product quality profile & design a manufacturing process to meet target
2. Identify & control critical raw material attributes, process parameters & variability
3. Process is monitored & adapted to produce consistent quality over time
How to Approach Continuous Manufacturing: Getting Started

In order to maximise benefit of a new method of chemical manufacture, you must;

• Understand the process that you want to perform
• Define the acceptable product quality & target production rate
• Determine the manufacturing strategy – campaign based or 8000 h/annum operation
• Evaluate at the lab-scale the parameters that influence the product &/or by-products
• Assess the reactor options available & their suitability towards the process
• Intensify the process to maximise unit productivity
• Determine commercial viability of continuous vs. existing batch production

F3 Factory project (DE) reported;

• 30 % Reduced energy consumption
• 100 % Reduction in solvent usage (solvent-free)
• 40 % Reduction in off-spec products and 10 % reduction in product re-working

Q - What do you need to achieve to be commercially viable vs. existing infrastructure?
Continuous Azidation using Labtrix®: Manipulation and Formation of Hazardous Materials

Advantages:
• New reaction space (temperature & pressure)
• Use small quantities of hazardous material
• Assess reagent types impact on cost of goods

Continuous Azidation using Labtrix®:
Manipulation and Formation of Hazardous Materials

Limit of conventional batch glassware

‘Novel Operating Window’ at the mg-scale

Decreasing material costs

Conversion (%)

Temperature (°C)

X = OMe, Cl, and Br

\[
\text{X} = \text{OMe, Cl, and Br}
\]

\[
\text{NaN}_3 (aq)
\]

\[
\text{EtOH}
\]

Used in Rufinamide synthesis by Hessel et al.\textsuperscript{1}

Cyclodehydration using Labtrix®: Rapid Mixing to Afford Reaction Times < 1 s

Employing Deoxo-Fluor®, Ley and co-workers demonstrated a series of cyclodehydrations

- Using a tube reactor the reaction was found to be flow rate dependent = mixing limitation

Employing Labtrix® affords rapid mixing - enabling reaction times of 100 s to be reduced to 1 s

Advantages:
- High yields *cf*. batch
- Rapid process development
- 100 x reduction in reaction time *cf*. tube
- Scalable

Multi-step Reactions using KiloFlow®: Flow4API – Consortium led by TNO

Disadvantages:
- Different temperatures for both steps
- Unstable intermediate on isolation
- Excess anhydride
- Complex purification
Exploration of Reaction Space using Labtrix®: Telescoping at the Micro-scale

Connecting two Labtrix® Start systems in series, the reaction steps were telescoped to confirm the ability to perform the reactions without purification;

Offline analysis confirmed ester formation
- No in-line analysis performed at this stage
- Allowed ‘Cold’ Step 1 & ‘Hot’ Step 2
- Reduced excess of anhydride
- No intermediate isolation
- Same reaction solvent throughout
Facile Up-scaling from Labtrix® to KiloFlow®: Scale-up of Telescoped Reactions

Having identified the optimal conditions for each step & demonstrated at the micro-scale the ability to connect the steps in series, plans for up-scaling were developed.

**Goal:** Demonstrate at the bench-scale feasibility of telescoping – suitable for 10 kg/y

- Reactor platform selected was KiloFlow®
Facile Up-scaling from Labtrix® to KiloFlow®: Scale-up of Telescoped Reactions

Bench-scale demonstrator – two thermal zones with in-line IR analysis

- 96.9 % yield cf. 96.5 % in Labtrix®
So 10’s ml reactors allow for g-kg production, what if you want to produce at tonne-scale?

- In the early 2000’s, numbering-up was proposed
- Economically unfeasible for most transformations
- Complex peripherals & flow distribution

Smart dimensioning is key;

- Increase channel dimensions whilst maintaining the key properties;
  - Efficient mixing
  - High thermal control
  - Select a material of construction suitable for long-term use
As the advantages of flow reactors stem from the small dimensions, channels must be designed for secondary flow:

- Maintain plug flow
- Afford efficient mixing
- Have a low pressure drop

Choose function specific channel types:
- Mixing – smaller, high thermal demand
- Residence volume – large, low pressure drop

Employ efficient thermal regulation:
- Electric heating or air cooling is no longer enough
- Thermal fluid frequently used

Ref: OPRD, Roder et. al
Fundamentals of Flow Chemistry: Production Scale

Materials of construction must be carefully selected to ensure;

- Long term stability to reaction conditions
- High fouling resistance
- Required thermal performance
- Manufacturability

3M™ SiC Grade C – Continuous operation for 2.5 yr, 180 °C with 50 % aq. NaOH
New Production Techniques:
Metal 3D-printed Flow Reactors

Selectivity Laser Melting (SLM):
- 3D printing of metal
- Strong enabling technology
- Major impact on the production of flow reactors!

Available standard sizes: 1, 2, 4 & 8 ml

<table>
<thead>
<tr>
<th>MR module</th>
<th>Channel volume (ml)</th>
<th>Channel diameter (mm)</th>
<th>Channel length (cm)</th>
<th>Typical performance (@ visco 1mPa.s)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pressure drop (bar)</td>
</tr>
<tr>
<td>Flow 1</td>
<td>1.0</td>
<td>1.13</td>
<td>100</td>
<td>0.1 – 0.3</td>
</tr>
<tr>
<td>Flow 2</td>
<td>2.0</td>
<td>1.60</td>
<td>100</td>
<td>0.1 – 0.3</td>
</tr>
<tr>
<td>Flow 4</td>
<td>4.0</td>
<td>2.26</td>
<td>100</td>
<td>0.1 – 0.3</td>
</tr>
<tr>
<td>Flow 8</td>
<td>8.0</td>
<td>2.26</td>
<td>200</td>
<td>0.3 – 1.0</td>
</tr>
</tbody>
</table>

- Larger 3D printed flow reactors can be made available
- Customized configuration for your specific process on request.
Plantrix® Industrial Flow Reactors: 
Intensified Processing Conditions

Owing to the excellent thermal & corrosion resistance of 3M™ SiC, users employ Plantrix® in harsh environments, for example:

- Lithiations
- Nitrations
- Oxidations
- Chlorinations
- Brominations
- Fluorinations
- Wolff-Kishner reductions
- Alkylations
- Controlled polymerisations (RAFT)
- Diels-Alder reactions

Suitable for control of exothermic processes

- Plantrix® MR260 $U = 10,000 \text{ Wm}^{-2} \text{ K}^{-1}$ at 25 l/h $H_2O$
Plantrix® Industrial Flow Reactors: Customer Application

The synthesis of energetic materials via nitration reactions can be problematic owing:
- Inefficient heat & mass transfer
  → Strong exotherms lead to by-product formation & product decomposition

<table>
<thead>
<tr>
<th>HNO₃:H₂SO₄</th>
<th>HNO₃:hexanol (eq.)</th>
<th>Product</th>
<th>By-product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0</td>
<td>3.1</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>1:0.286</td>
<td>2.5</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>1:0.767</td>
<td>1.5</td>
<td>Minimal</td>
<td>✓</td>
</tr>
<tr>
<td>1:1.130</td>
<td>1.25</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1:1.726</td>
<td>1.0</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>

✓ No by-product formation observed under optimal conditions

Advantages:
- Small hold-up volume
- Rapid mixing & efficient heat transfer allows intensified process
- Solvent-free production technique
- Metal-free modules facilitate use of highly corrosive reagents
Plantrix® Industrial Flow Reactor: Customer Application

Challenges in Batch:
- Corrosive reagents & product
- Highly exothermic reaction (~150 kJ mol\(^{-1}\))
- High dilution employed & reaction prone to polymerisation

Optimised in Labtrix®, scaled in Plantrix® - failed in tubular reactor (due to poor heat exchange)

Process Conditions:
- Reaction time = 120 s
- Reaction temperature < 100 °C
- Throughput = 2.1 l/h
  = ~ 16 tonne/annum production

Advantages:
- Thermal control = intensification
- Metal-free reactors
- Increased product purity
- Reduced isolation costs
Plantrix® Industrial Flow Reactor: Customer Application

Challenges in Batch:
- Corrosive reagents & unstable product
- Highly exothermic reaction
- High dilution employed & long reaction time

Advantages:
- Thermal control
- Metal & glass-free reactors
- Increased product purity
- Addition minimises peroxide decomp.

Process Conditions:
- Reaction temperature < 30 °C
- MR260 Throughput = 5.7 l/h
  = 10,000 m³/annum target production
Plantrix® Industrial Flow Reactor: Customer Application

Reaction Challenges:
• Biphasic
• Competing dinitration & decomposition products
• Corrosive media
• Challenging product isolation

Initially the reaction was investigated in a series of tube reactors (as illustrated)
• A need for continuous mixing was identified
DSM uses Micro Reactors made of 3M™ (SiC) in a pharmaceutical production plant

Plantrix® Industrial Flow Reactor:
Customer Application

Plantrix® gave DSM;
- Continuous mixing
- Thermal control
- High corrosion resistance
- High productivity
Plantrix® Industrial Flow Reactor: Customer Application

cGMP Continuous Production

Solution - Plantrix®:
- Compact
- Robust
- Corrosion resistant
- Quality
- Solvent reduction

DSM uses Micro Reactors made of 3M™ (SiC) in a pharmaceutical production plant

Tonne scale API production
Plantrix® Industrial Flow Reactor: Customer Application

Challenges in Batch:
- Corrosive reagents & unstable product
- Highly exothermic reaction
- High dilution employed
- Not possible in batch at > 15 l scale

Advantages:
- Thermal control = increased safety
- Solvent-free process
- Increase production rate of material
- Target product specification achieved

Process Conditions:
- MR260 = 5.0 l/h; MR500’s = 697 l/h
Plantrix® Industrial Flow Reactor: Customer Highlights

Peracid Synthesis:
- Highly exothermic – thermally sensitive product
- For direct use – no storage required - target 250 kg/h – operated at 11 s

Dakin Oxidation:
- Metal-free reactor reduces Customers risk of H₂O₂ handling
- 15 s reaction time cf. 6 h in batch & reduced caustic soda

Oxidative Effluent Treatment:
- Highly energetic – not scalable in batch beyond ml scale
- Waste valourisation application – increased batch process sustainability

Epoxidation using PAA:
- Selectivity increase compared to batch
- Dramatic reduction in reaction time 8 h to 15 - 40 s (Substrate dependent)

Lithiation using n-BuLi:
- Multi-step, lithiation – 15 sec processing 20 kg n-BuLi/8 h shift
“Though making the switch from batch to continuous manufacturing may be difficult, costly and time consuming, pharma manufacturers and CMOs should begin to consider the switch as in the long-run it will end up saving companies time, money and space, FDA’s Director Janet Woodcock told congressmen in a hearing Thursday.”

http://www.in-pharmatechnologist.com/Processing/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production
The advantage of a flow reactor is that once on steady state the material produced is of a consistent quality – this gives you choices on how to manufacture;

Option 1: Campaign based

Option 2: Continuous operation

Target Production Time for 1000 kg:
- /2 weeks = 240 ml reactor
- /year = 10 ml reactor

Target: 1000 kg/annum production
Is it Time for a Change of Business Models & Manufacturing Strategies?

• World plants vs. Distributed manufacture

• Dedicated vs. Flexible (plants & product types)
Innovative Technology: Flow Reactor Benefits

1. Safe Use of Extreme Reaction Conditions
   - Efficient mixing
   - Excellent thermal control
   - Process intensification of hazardous reactions

2. Reduced Development Time
   - Small hold-up volume
   - Rapid reaction optimisation
   - Minimal scale-up steps

3. Improved Process Control
   - High level of reaction control
   - Process reproducibility
   - Quality by Design (QbD)

4. Reduced Production Costs
   - Increased product quality
   - Reduced safety investments
   - Higher unit productivity

- Efficiency
- Quality
- Safety
- Sustainability

Strategic Partner of 3M
Join us in Continuing an Industry Change!

- Reduced energy consumption, sustainable & safe manufacturing
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