Strategic Partner of Scalable Flow Chemistry: A Flexible Tool for the Research, Development and Production of Pharmaceuticals, Fine & Specialty Chemicals

Dr Charlotte Wiles, December 2015
Chemtrix Company History

More than 15 years experience in Flow Chemistry
Available to Customers through Equipment & Chemical Services
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.
Fundamentals of Flow Chemistry: How are Flow Reactions Performed?

Solutions (typically) of reagents are pumped into a reactor, where they are:

- Mixed
- Heated or cooled
- Reacted for specified period of time
- Collected for analysis or product isolation

A basic flow reactor comprises of:

An advanced flow reactor comprises of:

Key is to understand the requirements of your process and design the reactor accordingly – Compared to batch practices where you adapt the process to suit your vessel!
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

That said, if you will never scale beyond mg/g’s then a tube could be a viable flow reaction tool!
Fundamentals of Flow Chemistry: Key Features of a Flow Reactor – Micro Mixer

www.chemtrix.com
Fundamentals of Flow Chemistry: Key Features of a Flow Reactor – Thermal Control

Techniques for thermal control include:
- Water or oil bath; Hot plate or Peltier; Re-circulating thermostat or hot air

Materials of construction, thermostat technique & reaction channel size all influence the thermal efficiency of a flow reactor.

Increasing flow rates need increasing volumes to reach \( T_{\text{set}} \):
- Reducing effective reaction volume
- In some cases you do not reach the set temperature

Consider also removal of heat in the case of exothermic reactions;
- If you are only inputting heat an exotherm will not be controlled.
The advantage of a flow reactor is that once on steady state the material produced is of a consistent quality;
Where can you Benefit from Flow Chemistry:
Process & Economic Drivers

In addition to technical drivers such as;

• Speed, Efficiency & Scalability

When used at scale, flow reactors have the potential to;

• Reduce operating costs
• Improve product quality utilising ‘Quality by Design’
• Afford operator independent processes – ‘if I can do it, you can do it!’
• Remove ‘batch failure’
• Valourise waste & reduce process waste
• Increase production capacity within the existing asset base – small footprint systems

Consequently, the technology is being taken up by fine chemical, agrochemical & pharmaceutical Companies as a means of maintaining competitiveness

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
Innovative Technology: Scalability & System Flexibility

Labtrix® (μg to mg’s)
-20 to 195 °C

- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

Customised solutions are also delivered in partnership with our Customers
Innovative Technology: Scalability & System Flexibility

- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

Customised solutions are also delivered in partnership with our Customers
Innovative Technology:
Scalability & System Flexibility

- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

Customised solutions are also delivered in partnership with our Customers
3M™ Silicon Carbide Grade C: Excellent Thermal Conductivity

Comparative thermal conductivity of EKasic® Silicon Carbide

Thermal conductivity at least 10 times higher than other reactor materials

- Lower volumes for heating & cooling
- Allows exotherm control
- Intensification of reactions by removal of solvent
- High heat transfer reduces the need for solvent as a thermal buffer
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
Rapid Reaction Optimisation using Labtrix®: Design of Experiment (DoE)

Combining micro reactors & DoE, Sanofi (Budapest) used Labtrix®-S1 to develop a process for the large-scale synthesis of amidoximes.

Advantages:
• Fast - only 17 reactions required
• Metal-free reactors - ‘safety concerned reagents’
• Identify interaction effects in complex reactions
• Determine cost effective conditions for manufacture

Results used to scale x450 for material production.

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

Production using KiloFlow® Basic: Synthesis of 1-(2-Methyl-2H-chromen-3-yl)ethanone

Translating the optimal conditions to KiloFlow® Basic (Reactor Volume = 13 ml)

Operating for 5.2 h, 369.6 g of 1-(2-methyl-2H-chromen-3-yl)ethanone was obtained
• After aq. extraction (98.2 % yield)
Production using KiloFlow® Basic: Synthesis of \(N\)-(4-phenylthiazol-2-yl)acetamide

First optimised in Labtrix® and transferred to KiloFlow® Basic;

Optimal Reaction Conditions: 1.0 M, 40 s at 75 °C

Advantages:

- High purity product \textit{cf.} batch
- Short reaction time
- Product isolated by precipitation
- Directly scaled from Labtrix® to KiloFlow®

\[ \text{→ 1.08 kg } N\text{-}(\text{phenylthiazol-2-yl})\text{acetamide} \text{ (127 g/h)} \]
Customer Appraisal of KiloFlow®: Janssen Pharmaceutica NV

Eschweiler Clarke Reaction:

\[
\text{R}_1^+ \text{R}_2^{\text{NH}} + \text{HCO}_2^\text{Na}^+ \rightarrow \text{R}_1^+ \text{R}_2^{\text{NH}} + \text{H}_2\text{N}^+ \text{R}_2^{\text{OH}} + \text{CO}_2
\]

Modelling predicted the optimal to be 56 s @ 122 °C

- Outside the conditions safely attainable in batch (time, temp & press), CO\(_2\) ↑

Using continuous flow, the reaction was translated to 100 kg h\(^{-1}\) production (API intermediate)

- 3 Validation batches performed, results presented to the FDA who confirmed;
  
  ‘no additional analytical PAT tools were required for production’

Advantages:

- Combine modelling & continuous reactors for accelerated process development
- Use conditions not accessible in batch
- No route re-development required

<table>
<thead>
<tr>
<th></th>
<th>Batch</th>
<th>Predicted Conditions(^A)</th>
<th>KiloFlow®</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methyl Derivative</td>
<td>87.0</td>
<td>95</td>
<td>93.5</td>
</tr>
<tr>
<td>By-product</td>
<td>10.0</td>
<td>&lt;3.5</td>
<td>2.10</td>
</tr>
<tr>
<td>Sign. Others</td>
<td>3.0</td>
<td>1.2</td>
<td>1.0-1.2</td>
</tr>
</tbody>
</table>

Luc Moens, Flow Chemistry Conference, Munich
Continuous flow synthesis of Ionic Liquids (IL’s) is of interest due to their use as solvents, process chemicals, functional fluids, electrolytes, additives

- There are $10^{18}$ potential combinations of ions to give IL’s

**Challenge:**
- Exothermic reactions
- Corrosive media

**Advantages:**
- Integrated heat exchangers in KiloFlow®
  - Higher HE capacity than competitors
- Continuous mixing in channels enables solvent-free conditions
- High purity product with reduced work-up required

Customer Appraisal of KiloFlow®: Iolitec GmbH

B. Iliev, M. Smiglak and D. Schmidt; Iolitec GmbH
Multi-step Reactions using KiloFlow®:
Flow4API – Consortium led by TNO

Telescoping: Optimised using 2 x Labtrix® systems and scaled in a custom KiloFlow®

Advantages:
- Different temperatures for both steps
- No intermediate isolation required
- Reduced reactant excess
- API intermediate in high yield (96.5%)
Plantrix® made of 3M™ Silicon Carbide Grade C
Efficient Industrial Production & Superior Chemical Flexibility

- High productivity
- High chemical flexibility
- Handling of solids
- Increased process safety
- Environmental friendly production
- Small footprint

Strategic Partner of 3M
Plantrix®: Industrial Flow Reactor

Plantrix® flow reactors have desirable properties for fast & exothermic reactions:

- High thermal conductivity & temperature stability
- Metal-free modules
- Fully sintered, high strength, gas tight & leak-free systems
- Excellent corrosion resistance
- Plug flow

Plantrix® Certification & Standardisation:

- Certified by German TÜV
- FDA approved materials of construction
- Standard Swagelok fluidic connections
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:

- Nitrations
- Oxidations
- Chlorinations
- Brominations
- Fluorinations
- Alkoxylations
- 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 $\text{H}_2\text{O}$

3M™ SiC Grade C – Continuous operation for 2.5 yr, 180 °C with 50 % aq. NaOH
Continuous Nitration of Alcohols Plantrix®: 70 % Nitric Acid

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

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

Strategic Partner of

$\text{HNO}_3:\text{H}_2\text{SO}_4$

$\text{HNO}_3: \text{hexanol}$ (eq.)  

<table>
<thead>
<tr>
<th>HNO$_3$:H$_2$SO$_4$</th>
<th>HNO$_3$: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>
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<tr>
<td>1:0.286</td>
<td>2.5</td>
<td>×</td>
<td>✓</td>
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<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

Optimal Conditions in Plantrix®:
12 s reaction time @ 18 °C (99.6 % purity by GC)
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 (poor heat exchange)

Process Conditions:
- Reaction time = 120 s
- Reaction temperature < 100 °C
- Throughput = 2.1 l/h
  = Multi-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 time = 33 s
- Reaction temperature < 30 °C
- MR260 Throughput = 5.7 l/h
Plantrix® Industrial Flow Reactor: Customer Application - Nitration

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

cGMP Continuous Production

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

Tonne scale API production
• 16 Plantrix® cf. 96 Corning

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

Strategic Partner of 3M

- Efficiency
- Quality
- Safety
- Sustainability
Join us in Continuing an Industry Change!

- Reduced energy consumption, sustainable & safe manufacturing
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