Process Development and Industrial production using Corning Advanced Flow Reactor

CPAC Rome Workshop
March 23, 2009

Frank Schmidt, Philippe CAZE
Outline

• Status on industrial deployment by our customers
  – Lonza public statements
  – PCAS public statements
  – DSM public statements

• Corning Advanced Flow Reactor
  – Customized reactor made of standard microstructures
  – Mass transfer
  – Heat transfer
  – Multi injection reactor module

• From lab process development to industrial production
Continuous versus batch process

- Continuous processes are much better suited for product and process optimization / understanding compared to batch
  - Almost 100% of Petrochemicals and basic chemicals processes
  - Limited implementation in Pharmaceuticals and fine chemicals production

- The current large vessels used for continuous processes do not meet the Pharma and Fine chemicals tighter requirements
  - Not providing the product quality
  - Not being economical (lower tonnage to be made)

- Microreaction Technology has demonstrated significant improvements of chemistry / product quality at the Research level
Corning focus: The reactor and its integration into your production system

Chemistry

\[ R - C = O - R' \]

Mass and heat transfer

Reactor engineering

System engineering
## Status on industrial deployment by our customers

### Typical tonnage needs (in isolated product)

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30 multistep reactors in place in 2007-08
**Status on industrial deployment by our customers**

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First installations done

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First installations done
Under development
c-SSP Track Record

- **Organolithium exchange reaction:**
  - Up to 1 ton of product; few weeks of operations
  - Corning multi-injection reactor and Lonza module

- At the end of the campaign the reactor was cleaned by standard procedure and used again for a new project.

- **Organolithium coupling reaction:**
  - Several kg of product; operation 7 consecutive days; 24 hours per day
  - Corning multi-injection reactor & Corning single-injection reactor for validation, Lonza module

- **Nitration reaction (kg-lab):**
  - Few kg of product; 24 hours operations;
  - Corning multi-injection reactor.
The RITTER reaction: Pilot unit / Continuous flow

Multi-injection with residence time for mass and heat transfer between injection points
The RITTER reaction: Pilot unit / Continuous flow

- **Conditions**: Continuous Flow Process
- **Corning Micro-Reaction Technology**
  - **Economic improvements**
    - Higher yield and selectivity
    - Reduced energy consumption
    - Continuous processing
    - Dilution reduction
    - Consistent quality
    - Ease of scale-up
  - **Safety improvements**
    - Reduced reactant inventories
    - Less handling of solvents
    - Optimized control parameters
    - Prevention of run away temperature
    - Elimination of batch critical operations
CPhI 2008 - DSM Corning announcement

- DSM as manufacturer of fine chemicals and active pharmaceutical ingredients and Corning Incorporated as manufacturer of modular micro-structured flow-through reactors have collaborated to develop and pilot a new process to perform a selective nitration under cGMP conditions. Nitration reactions are difficult to handle due to the exothermic properties of organic nitrates. In order to achieve high selectivity, classically high dilution conditions are used. DSM developed and intensified a process to utilize the capabilities of the Corning’s reactor technology, combining the advantages of the micro-structured devices with extraction equipment. This combination has resulted in a highly efficient process, which was quickly and easily transferred from the laboratory to production, resulting in the processing of more than 25 metric tons of material and in the production of more than 0.5 metric tons of the desired quality product under cGMP conditions.
Corning Advanced Flow Reactor: Industrial Production

Two production banks, each made of 4 reactor in parallel.

- 1,000 tons/year processed feeds

Includes

- Grounding
- Mechanical protections
- Containment

Conventional production environment

- Plant utilities
- Shift workers
In the lab: reactor design in order to develop a safe and highly efficient process

• Strict control of reaction parameters is crucial for both quality and safety
  • Temperature
  • Stoichiometry
  • Residence time
From lab process development to Industrial Production

- In 9 months demonstration of a commercially viable approach to a cGMP nitration reaction
  - Starting with 1 kg lab sample
  - Parallelization of 8 identical reactors, integration into the production plant
  - Execution of a campaign under cGMP conditions
  - More than 25 mT materials processed
  - More 500 kg of quality product produced
  - Safety performance and product quality were perfectly maintained
Through this successful development and production campaign, we demonstrated:

- Safe operation of a hazardous reaction in a cGMP environment
- High chemical selectivity in a nitration reaction which had the side benefit of significantly lower waste generation
- Predictable and reliable performance of highly engineered equipment customized in an extremely short period of time and transferred to a production facility
- Ability to deliver high quality chemical product on a short timeline
CORNING

Advanced Flow Reactor Technology
Customized reactors made from standard parts

MICRO-STRUCTURES

A few 10’s of designs

1000’s Product Designs
Glass Micro-structures for single and multi phase
Multi-phase mass transfer

Miscible liquids

Gas / liquid

Non miscible liquids
The micro-structure integrates mass and heat transfer

\[ \rho C_p \frac{dT}{d\tau} = kA(-\Delta H) - U \cdot \left( \frac{S}{V} \right) \cdot (T - T_c) \]

Heat generation

Heat removal

Reactants

Product
Corning micro-structure heat exchange performance

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Specific area, m²/m³</th>
<th>Volumetric heat transfer coefficient (MW/m³K)</th>
</tr>
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<tbody>
<tr>
<td>Jacketed batch</td>
<td>2.5</td>
<td>10⁻³</td>
</tr>
<tr>
<td>Batch with external heat exchanger</td>
<td>10</td>
<td>10⁻²</td>
</tr>
<tr>
<td>Shell and tubes (metallic; water/water; 1 m/s)</td>
<td>400</td>
<td>0.2</td>
</tr>
<tr>
<td>Plate (metallic, 4 mm spaced; water/water, 1 m/s)</td>
<td>800</td>
<td>1.25</td>
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<tr>
<td>Corning glass microstructure (water/water, ~ 0.7 m/s)</td>
<td>2500</td>
<td>1.7</td>
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Design Dimensions: Optimized for performance and throughput

Heat transfer
- 700 microns

Mixing
- 300 microns

Pressure drop
- 1 millimeter

4 mm

Heat exchange fluid
Reactants
Reactants
Reactants
Reactants
Multi Injection modules

A

B

HE IN

HE OUT

PRODUCT
Multi-injection module 1 with PFA piping option

- Temperature and pressure range:
  
<table>
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<td>-50°C to 40°C</td>
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- Total hold-up: ≈ 30 ml
- Reaction volume: ≈ 12 ml
- Throughput at 10 bars (water, 20°C): 220 ml/min or 13 l/h
- Mixing > 90% (Villermaux test)
Advanced Flow Reactor Technology
From lab process development to industrial production
From one reactor to industrial production
Straightforward scale-up

- Increased production duration
  3 kg/h is 1.4 Tons/month (480h)

- A limited number of reactors in parallel with engineered distribution

- Increased throughput per reactor with Gen I / II / III reactors keeping performance and operating conditions the same

Courtesy of DSM
From lab process development to industrial production

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Addition or increasing complexity of the downstream operations                                                  |
| **Corning Advanced Flow Reactor** | Develop the product to meet final requirement | - Starting from basic understanding of the chemistry  
- optimization of mass and heat transfer  
- future envisioned required throughput | Scale up made with no change in the key reactor and process parameters that are controlling the product performance and quality | Increase time under continuous flow  
Increase throughput per reactor  
Increase number of reactor in parallel  
Initial product quality is maintained  
Final requirements are met  
Continuous process allowing a larger design space |
Thank you for your attention

Courtesy of Isochem - SNPE

Courtesy of Lonza

Courtesy of DSM

Courtesy of Siegfried

Courtesy of Organon