Advanced-Flow™ Reactors
High throughput continuous flow reactor technology

Dr. Pierre Woehl
New Business Development Technology Manager
Corning Incorporated

Founded:
1851

Headquarters:
Corning, New York

Employees:
Approximately 25,000 worldwide

2009 Sales:
$5.4 Billion

Fortune 500 Rank (2009):
414

• Corning is the world leader in specialty glass and ceramics.

• We create and make keystone components that enable high-technology systems for consumer electronics, mobile emissions control, telecommunications and life sciences.

• We succeed through sustained investment in R&D, more than 150 years of materials science and process engineering knowledge, and a distinctive collaborative culture.
## Corning Market Segments and Additional Operations

<table>
<thead>
<tr>
<th>Display Technologies</th>
<th>Telecom Technologies</th>
<th>Environmental Technologies</th>
<th>Life Sciences</th>
<th>Specialty Materials</th>
<th>Other Products &amp; Services</th>
</tr>
</thead>
</table>
| • LCD Glass Substrates | • Optical Fiber & Cable | • Emissions Control Products  
  − Light-duty gasoline vehicles  
  − Light-duty and heavy-duty diesel vehicles  
  − Stationary | • Cell Culture & Bioprocess | • Display Optics & Components  
  − Semiconductor Optics & Components  
  − Aerospace & Defense  
  − Stationary | • Display Futures  
  − New Business Development |
| • Glass Substrates for OLED and LTPS-LCD | • Hardware & Equipment  
  − Coaxial Connectivity Products | • Assay & High-Throughput Screening  
  − Genomics & Proteomics  
  − General Laboratory Products | • Assay & High-Throughput Screening  
  − Genomics & Proteomics  
  − General Laboratory Products | | • Drug Discovery Technology |
| • OLED Hermetic Sealing Solution | | | | | • Equity Companies  
  − Cormetech, Inc.  
  − Dow Corning Corp.  
  − Eurokera, S.N.C.  
  − Samsung Corning Precision Glass Company, LTD (SCP) |

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**Advanced-Flow™ Reactors**

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3
Outline

• Principles of our flow reactors

• Route to continuous manufacturing

• Focus on some application cases which have benefitted from the technology

• Overview of benefits for end-users

• Conclusion
The Impact of Dimensions

\[ \frac{\Delta P}{L} = 128 \cdot \frac{\eta Q}{\pi \cdot d^4} \]

Laminar flow

<table>
<thead>
<tr>
<th>Pressure drop</th>
<th>Heat transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple tube</td>
<td>U \times (S/V)</td>
</tr>
<tr>
<td>(bar)</td>
<td>(kW/m^3.K)</td>
</tr>
</tbody>
</table>

Mixing Quality

Villermaux (%)

20 bar

80 %

CORNING

450 \( \mu \text{m} \) 6 mm
Heat exchange & mixing are integrated in the Fluidic module

Heat exchange layer
Reaction layer
Heat exchange layer
## Corning Fluidic module heat exchange performance

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Specific area, m²/m³</th>
<th>Volumetric heat transfer coefficient (MW/m³K)</th>
</tr>
</thead>
<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 <em>(metallic; water/water; 1 m/s)</em></td>
<td>400</td>
<td>0.2</td>
</tr>
<tr>
<td>Plate <em>(metallic, 4 mm spaced; water/water, 1 m/s)</em></td>
<td>800</td>
<td>1.25</td>
</tr>
<tr>
<td>Corning glass fluidic modules <em>(water/water, ~ 0.7 m/s)</em></td>
<td>2500</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Glass Fluidic Modules as standard building blocks

Throughput of reaction mass: 3-15 kg/hr

Throughput of reaction mass: up to 50 kg/hr
Engineered reactor components

- Interfaces
- Frames
- Standard Fittings
- Connectors
- Tubing
- Sensing
- O-ring seals
- Fluidic Modules
- Labelling
- Add-on (insulation...)
- Instrumentation (Pressure relief valve...)

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Glass Fluidic Modules 1,2,4X – Scaling out …

1X: Throughput of total reaction mass: 3-15 kg/hr

2X: Throughput of total reaction mass: up to 50 kg/hr

4X: Throughput of total reaction mass: up to 200 kg/hr
Scaling the technology to industrial production in 2 ways:

- **Scale-out** = increase the total fluidic channel path length/fluidic module
- **Scale-up** = increase the number of fluidic modules

**Gen I**
- Process Development and Pilot Production Capable

**Gen II**
- Scale-out
- Stacking scale-out

**Gen III**
- Scale-out

Scale-up: simple numbering up to full production

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Processed liquid flow rate for one reactor

<table>
<thead>
<tr>
<th></th>
<th>1X</th>
<th>2X</th>
<th>4X (Under development)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>g/min</strong></td>
<td>15</td>
<td>160</td>
<td>400</td>
</tr>
<tr>
<td><strong>kg/h</strong></td>
<td>1</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td><strong>Tons / 5600h</strong></td>
<td>5</td>
<td>56</td>
<td>140</td>
</tr>
<tr>
<td><strong>Tons / 8000h</strong></td>
<td>7</td>
<td>80</td>
<td>200</td>
</tr>
</tbody>
</table>

- Temperature: T -60°C - 230°C
- Pressure: P up to 18 bar
… Numbering Up For Commercial Scale

FLUIDIC MODULES

REACTORS

PRODUCTION BANKS
Broad range of applications

- Reactions which have already benefited from Corning Advanced-Flow Reactor
  - Alkylation
  - Amidation
  - Bromination
  - Condensation
  - Metal Organic
  - Hydrogenation
  - Oxidation
  - Nitration

- In mono or multi phase environments
  - Miscible liquid feeds
  - Non miscible feeds – emulsions
  - Liquid and gas feeds
  - Suspensions
Selective Hydrogenation of Slurry in Corning® AFR
98%+ conversion & selectivity (impurity profiles within spec.)

- highly exothermic (>400 kJ/mol)
- ~30 µm catalyst in slurry
- significant catalyst reduction

Ref: Chemistry Today 27(6), Nov-Dec (2009)
Green Process: Glycerine to Fuel Additives in Corning® AFR
Successful feasibility demonstration for ~1000 mt/y industrial production

- 10% biofuels for transports by 2020 in EU
- 20 millions tons biodiesel capacity in 2009 (EU)
- 10 tons biodiesel => 1 ton Glycerine (*by-product*)

**Convert Glycerine to STBE (Solketal TertButyl Ether) via Solketal**

![Diagram of process](image)

**Short process development cycle:**
~4 months

- AFR: 6-10h Time
- Batch: < 2 min

- 10-12 equivalents
- 4 equivalents

- Acetone
- Solvent Reduction

- Excess

- ~80%
- ~85%

- Ratio = 2
- Ratio = 1

- STBE Yield

- isobutene

- Solvent Reduction

**11-12 kg/hr STBE (90 tons/Year)**

Ref: Chemistry Today – to be published (2010)
Nitration Reactions in Corning® AFR
Reduced solvent usage & higher yield of safer operation

- Shorten Development Cycle
- Value Generated from: Reduced Solvent Usage, Higher Yield & Significant Improvement in Safety

Preparation of Active Pharmaceutical Ingredients (API) by Continuous Processing

BRIAN MARQUARDT
WES THOMPSON
APPLIED PHYSICS LABORATORY
UNIVERSITY OF WASHINGTON
marquardt@apl.washington.edu

Slide: Courtesy of Mel Koch and Brian Marquardt, CPAC
Safer processing: Diastereoselective Ritter reaction

- Highly exothermic reaction.
- Possible reaction run-aways and decomposition of product: operating conditions (temperature, pressure, flow rate) have to be carefully managed.
- Thermal instability of the reaction mixture.
- Critical handling of reactants (corrosion and stability of H$_2$SO$_4$).
- Possible formation of Sulphate salts if in excess of H$_2$SO$_4$ before the quench and of Sodium salts during the quench.

Presented by PCAS at the Scientific Update conference, 2008
NeSSI Output example for CPAC/FDA Project

Slide: Courtesy of Mel Koch and Brian Marquardt, CPAC
Overview of End-User Benefits
Increase product quality

<table>
<thead>
<tr>
<th>END-USER CASE</th>
<th>CONVENTIONAL TECHNOLOGIES</th>
<th>CORNING Reactors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esterification from acid chloride and alcohol</td>
<td>Distillation used to bring dimer level below 2%</td>
<td>Dimer at 1% No distillation needed</td>
</tr>
<tr>
<td>Nitration (sulfonitric)</td>
<td>Impurity at 3% Semi-batch in specialized equipment</td>
<td>Impurity at 1.5% More product due to easier crystallization work-up</td>
</tr>
<tr>
<td>Hydrosilation</td>
<td>Specific impurity at 20 wt% in output feed</td>
<td>Specific impurity below 5 wt% in output feed Debottlenecking of distillation column</td>
</tr>
</tbody>
</table>
Increase yield - Decrease mass of materials involved to make one kilogram of final product

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<tr>
<td>Nitration (Nitric acid)</td>
<td>Yield: 55%</td>
<td>Yield: 75%</td>
</tr>
<tr>
<td>Autocatalytic</td>
<td>77wt% solvent in substrate feed</td>
<td>10wt% solvent in substrate feed</td>
</tr>
<tr>
<td>Condensation</td>
<td>Solvent</td>
<td>Solvent-free</td>
</tr>
<tr>
<td>Adiabatic temperature rise of 310°C</td>
<td>6 Unit Operations</td>
<td>4 Unit Operations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No distillation step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product purity &gt; 99.8%</td>
</tr>
<tr>
<td>Organometallic reaction</td>
<td>Temperature : - 70°C</td>
<td>Yield: + 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temperature: - 50°C</td>
</tr>
<tr>
<td>Organometallic reaction</td>
<td>Temperature: - 70°C</td>
<td>Yield: Same as batch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temperature: - 20°C</td>
</tr>
</tbody>
</table>
## Removal of time consuming operations

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<tbody>
<tr>
<td>Oxidation with bleach</td>
<td>Stir over 1,000 rpm for half an hour</td>
<td>Reaction completed in 60 s</td>
</tr>
<tr>
<td>Get full conversion in a 2 liquid phase</td>
<td>Slow dosage and small vessel size</td>
<td></td>
</tr>
<tr>
<td>Organometallic</td>
<td>1 batch out of 5 is out of specifications – Rework</td>
<td>Continuous processing provides constant quality</td>
</tr>
<tr>
<td>Hydrosilation</td>
<td>Loop reactor, 30 min residence time</td>
<td>Full conversion in 2 minutes</td>
</tr>
<tr>
<td>Get full conversion</td>
<td>Finishing reactor</td>
<td></td>
</tr>
<tr>
<td>Organometallic</td>
<td>Cool reaction mixture down to -70°C: 20 min</td>
<td>Cooling down and contacting completed in less than 30 s</td>
</tr>
<tr>
<td>Put two cooled liquid feeds in contact</td>
<td>Dose slowly: 1 hour</td>
<td></td>
</tr>
</tbody>
</table>
## Increased safety

<table>
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</thead>
<tbody>
<tr>
<td>Oxydation with bleach</td>
<td>Scale-up issues</td>
<td>Safe operation</td>
</tr>
<tr>
<td></td>
<td>Dangerous reaction</td>
<td></td>
</tr>
<tr>
<td>Coupling in presence of sulfuric acid</td>
<td>First production batch at 60°C damped into a quench solution</td>
<td>Operation under full control at 90°C</td>
</tr>
<tr>
<td>Autocatalytic nitration</td>
<td>Accumulation risks</td>
<td>Safe operation</td>
</tr>
<tr>
<td></td>
<td>No scale-up possible</td>
<td></td>
</tr>
<tr>
<td>Nitration reaction</td>
<td>Dedicated equipments</td>
<td>Safe operation</td>
</tr>
</tbody>
</table>
Conclusion

• Continuous flow reactors for chemicals manufacturing
  – From lower flow reactors
  – Up to production scale reactors
    • scale-up of fluidic modules
    • numbering-up / scale-out of reactors

• Examples of auxiliaries used to control and monitor processes

• Successful implementation of these solutions

• The technology enables to capture recognized PI benefits