Advanced-Flow Reactors: Made for Industrial Productions

Marc Winter and Alessandra Vizza, Corning, France

RSC Symposium Chemspec Europe 2017
Munich, 2017 June 1st
Presentation Outline

1. Introduction

2. Seamless Scale-Up

3. Industrial Examples

4. The Challenge of Solid handling

5. Outlook
Presentation Outline

1. Introduction

2. Seamless Scale-Up

3. Industrial Examples

4. The Challenge of Solid handling

5. Outlook
About Corning

Corning is one of the world’s leading innovators in materials science. For more than 160 years, Corning has applied its unparalleled expertise in specialty glass, ceramics, and optical physics to develop products that have created new industries and transformed people’s lives.

Corning succeeds through: sustained investment in R&D, a unique combination of material and process innovation, and close collaboration with customers to solve tough technology challenges.
Corning’s continuous flow reactors build on the company’s 160 years of innovation

- Glass envelope for Thomas Edison’s light bulb (1879)
- Heat-resistant PYREX® glass (1915)
- Dow Corning silicones (1934)
- Processes for mass producing the television bulb (1947)
- Glass ceramics (1952)
- Fusion overflow process (1964)
- First low-loss optical fiber (1970)
- First low-loss liquid crystal display (LCD) glass (1982)
- Ceramic substrates for automotive catalytic converters (1982)
- Thin, lightweight cover glass with exceptional damage resistance (2006)
- Environmentally conscious LCD glass (2006)
- Label-free screening platform for drug discovery (2012)
- Ultra-slim, flexible glass for thin and lightweight applications (2013)
- First all-optical converged cellular and Wi-Fi solution (2013)
- First EPA-registered antimicrobial cover glass (2013)

© 2017 Corning Incorporated
History of Corning Reactor Technologies: More than one decade of expertise

- 2002: Concept development & customers collaborations
- 2007: Collaboration with European platforms
- 2009: MIT collaboration
- 2011: Low Flow reactor
- 2013: G2 SiC Reactor
- 2015: Turn key industrial solution
- 2016: G1 SiC Reactor
- 2017: Lab Reactor
- 2017: Photo Module

- G1 reactor
- G2 bank concept
- G2 lab
- China Application lab
- India Application lab
- G3 reactor
- G4 SiC Reactor
A worldwide presence
Corning® Advanced-Flow™ Reactor Value Proposition
Revolutionary Improvement vs. Batch
Corning AFR: Unique concepts and advantages

<table>
<thead>
<tr>
<th>High Mixing</th>
<th>High Heat Exchange</th>
<th>Durable Materials</th>
<th>Seamless Scale-Up</th>
<th>Complete Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patented HEART shape</td>
<td>Combines heat exchange and reactive path in a sandwich structure</td>
<td>Glass and Ceramic</td>
<td>Reactors are designed for seamless scale-up</td>
<td>Complete turn-key solutions</td>
</tr>
<tr>
<td>Ideal for immiscible and multiphase systems</td>
<td>Independent thermal control</td>
<td>Superior corrosion resistance</td>
<td>Direct from Lab to Production</td>
<td>Engineered and customized units</td>
</tr>
</tbody>
</table>
The unique concept of a Fluidic Module

Increase throughput with similar:
- Mixing
- Residence time distribution
- Heat Exchange
- Mass transfer in heterogeneous systems
Comprehensive Solutions from Lab, to Process Development, and to Industrial Production

Lab scale stepping into flow chemistry, Application process development

Application Process Development & Small Production

Industrial Production

- G4
- GP4
- 3500 t/y
- 2000 t/y
- 1000 t/y
- 250 t/y
- 80 t/y

G1 Glass
G1 SiC
G1 Photo

G2 SiC

G3 Glass

G4

G2

G1

© 2017 Corning Incorporated
Auxiliaries – Up Stream Process

• Up Stream process is an important part of the success in Flow Chemistry

• Accuracy of the flow is a key parameters
  • Simple HPLC pumps
  • To more complex Dosing Lines

• Heat Exchanger will allow to reach full potential of Volumetric Heat transfer

• Other solution could be added such as: electrical heat tracing, safety valve, sensors, etc.
Auxiliaries – Up Stream Process
Auxiliaries – Down Stream Process

• Less critical than the up-stream process, but will allow optimisation of the global system

• Several step could be added after the reactor

• Online/Inline analytics:
  • Quick answer during development
  • Allow automatisation
  • Follow-up of critical parameter during production

*Pictures from Marqmetrix, Magritek and Zaiput
Presentation Outline

1. Introduction
2. Seamless Scale-Up
3. Industrial Examples
4. The Challenge of Solid handling
5. Outlook
What is really a Seamless Scale-Up?

A seamless scale-up will be achieved, when moving form a small continuous reactor, to a larger one, if you apply the same parameter as in lab (temperature, residence time, concentration, stoichiometric ratio), you will get the same result in production (conversion, yield, impurity profile…)

A seamless scale-up do not require any pilot study, nor any process optimization. It is a straightforward process, that does not require much time.

How to demonstrate a seamless scale-up???

As nearly every chemical reaction is specific (mixing or temperature sensitive, fast, exothermic or not, with concurrent reactions, parallel ….), making a specific reaction “seamless” does not mean at all that the scale-up will be always seamless.
## Reactor Capabilities vs. Reaction's Need

<table>
<thead>
<tr>
<th>MIXING / MASS TRANSFER</th>
<th>Contact between the molecules of the reactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence Time</td>
<td>Keep the molecules in contact during a sufficient time to allow the completion of the reaction</td>
</tr>
<tr>
<td>Residence Time Distribution</td>
<td>Does not keep the molecules to many time in contact to avoid side reactions</td>
</tr>
<tr>
<td>HEAT TRANSFER</td>
<td>Isothermal condition / reaction enthalpy release</td>
</tr>
</tbody>
</table>
Volumetric mass transfer coefficient: A seamless scale-up

Patented HEART-shape design:
- Superior mixing performance in multiphase systems\(^1\)
- Higher performances in L/L mass transfer coefficient \((k_L a)\)^2
  - Up to 10^3 compared to packed column
  - 2x - 4x better than other “micro-channel” devices

Similar mass transfer performances from lab to production


**Heat transfer coefficient**

~100x-1000x higher than batch

Seamless scale-up: similar heat transfer coefficient from G1 to G4

<table>
<thead>
<tr>
<th>Method</th>
<th>Volumetric heat transfer coefficient (MW/m²K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramic SiC fluidic modules</td>
<td>1.5</td>
</tr>
<tr>
<td>*Corning glass fluidic modules (water/water, ~ 0.7 m/s)</td>
<td>1.6</td>
</tr>
<tr>
<td>*Plate (metallic, 4 mm spaced; water/water, 1 m/s)</td>
<td>1.25</td>
</tr>
<tr>
<td>*Shell and tubes (metallic; water/water; 1 m/s)</td>
<td>0.2</td>
</tr>
<tr>
<td>*Batch with external heat exchanger</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>*Jacketed batch</td>
<td>$10^{-3}$</td>
</tr>
</tbody>
</table>

Scale-up Principle: Same Residence Time

**G1 Platform**

Channel size: ~1mm; Internal Volume: 8 ml

**Reactor Residence Time**

$= \frac{\text{Reactor Internal Volume}}{\text{Mixture Volumetric Flow Rate}}$

**G1 Case:**

Reactor Volume = $6 \times 8 ml = 48 ml$

Mixture flow = 150 ml/min

$= 9 l/h$

$= 64.8 m^3/yr$

Residence time = $\frac{48}{150} = 0.32 \text{ min} = 19.2 s$

**G4 Production**

Channel size: ~5mm; IV = 250 ml

**G4 Case:**

Mixture flow = 2 160 m$^3$/yr

$= 300 l/h$

$= 6 000 ml/min$

Residence time = $19.2 s = 0.32 \text{ min}$

Internal V = $0.32 \times 6000 = 1920 ml$

# of FM s in reactor = $1920 \div 250 = 8$
Scale-up from G1 to G4 and numbering-up

Production increase versus lab: 100 time higher

- $1 \times 1.7$
- $1 \times 30$
- $1 \times 2$

10 minutes after start-up, the product was on specs (purity > 99.6%)

Yearly throughput: 5 000 t/y
Yearly production: 2 200 t/y
2 G4 reactors in parallel
Presentation Outline

1. Introduction

2. Seamless Scale-Up

3. Industrial Examples

4. The Challenge of Solid handling

5. Outlook
Seamless Scale-Up from G1 (80 t/y) to G3 (1000 t/y)

Installation in Shandong, China (2013)

Yield of G1 and G3
G4 SiC industrial installation in Jiangsu, China (2012)
More and more production cases in various chemistry fields

**Fine Chemistry Production on G4**

**API Production on G1**
Continuous production of fine chemicals is real: Seamless scale-up from G1 to G4

- Scaled flow up by $>25$ times from G1 to G4
- 1st sample fully met product specs (2014.1)
- Same yield (99.8%) achieved in G1 and G4
- Manpower reduced 70%

Seamless Scale up from G1 to G4: Significantly changes equipment layout and safety management
Angelini Pharma G4 reactor system for Active Pharmaceutical Ingredient (API) production

- Development done with a G1 SiC reactor
- Seamless scale-up to a G4 size reactor
- Installation of a G4 reactor with related dosing lines
- ATEX and FDA compliance requirement
- Timeline from first talk to chemistry running in G4: less than 2 years.

*Pictures are a courtesy of Angelini (Italy)*
Anupam G4 reactor system for specialty chemistry production

- Installation of a G4 reactor with related dosing lines
- Continuous manufacturing of products where difficult chemistries can be manufactured in a safer and more sustainable manner

*Pictures are a courtesy of ARIL (India)
From lab-scale to pilot/industrial-scale

G1 Corning reactor → G4 Corning reactor

**Corning AFR seamless scale-up principle:** Keep only residence time constant, assuming same mixing and heat exchange properties are provided by this technology

Test at pilot/industrial scale by using a G4 reactor:

- 96% conversion at 25°C with a residence time of 82 seconds
- 8 plates of G4 reactor → achieve 1/3 of the industrial productivity

To achieve the required industrial production: add plates (ΔP < 18 bar) and numbering-up
Multipurpose industrial flow system in a GMP and FDA inspected API manufacturing plant

- 3 fully automated pumping units Atex compliant
- 1 industrial G4 Corning reactor (SiC)
- 1 Heating and cooling capacity from +200°C to -60°C

**Outcome**

- Low temperature reaction not scalable in batch
- 10 industrial batches of API intermediate produced
- Smooth and Quick scale-up from Kilo-lab to Industrial scale
- COGS savings of more than 30% vs external sourcing
Production Plant Installations

Courtesy of Medichem (Spain)
Corning G4 reactor system with 2 dosing lines, 1 temperature zone control and DCS monitoring with a footprint of 15m²
Presentation Outline

1. Introduction

2. Seamless Scale-Up

3. Industrial Examples

4. The Challenge of Solid handling

5. Outlook
Selective Hydrogenation

Customer issues:
- Highly exothermic (>400 kJ/mol)
- Catalyst in slurry (30 µm)

Batch Process:
- Product 35% w/w
- 30°C
- 0.4% of catalyst

Ref: Chemistry Today • Vol 27 n 6 / November-December 2009
Selective Hydrogenation

Batch Process:
- significant catalyst reduction
- >98% conversion & selectivity
- Impurity profiles within specification

![Image of excellent G/L mixing](image)

![Graph showing performance comparison between Batch and Corning® AFR](graph)
Grignard Reagent (RMgX) Preparation

RX + Mg  \[\text{Solvent} \rightarrow \text{Temperature} \rightarrow \text{RMgX}\]

**Advantage from AFR technology:**
- Superior heat transfer ensured uniform temperature
- Superior mixing between liquid and solid particle happened
- Plug-flow behavior leads to narrow residence time distribution
- Short & precise contact time

**Results:**
- Precise control leads to better purity of final products
- Better purity & solubility delivered for the final products comparing with “batch” process
- Generated Grignard reagents react with a variety of carbonyl derivatives
Particle Handling in Corning® AFR

- Corning Reactors can handle solids with a variety of particle sizes, solid types and loading.
- Enabling Solid/Liquid, Solid/Liquid/Gas application (e.g. heterogenous catalytic hydrogenation, diazo dye, etc.)

<table>
<thead>
<tr>
<th>Slurry type</th>
<th>Particle size (µm)</th>
<th>Solid loading</th>
<th>Slurry Hydrodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd/C</td>
<td>30-50</td>
<td>2.5 g/L</td>
<td>OK</td>
</tr>
<tr>
<td>Silica beads</td>
<td>63-200</td>
<td>2.5 g/L</td>
<td>Ok</td>
</tr>
<tr>
<td>Silica beads</td>
<td>63-200</td>
<td>20 g/L</td>
<td>OK</td>
</tr>
<tr>
<td>Organics*</td>
<td>&lt;50</td>
<td>500 g/L</td>
<td>OK</td>
</tr>
<tr>
<td>Diazo*</td>
<td>&lt;50</td>
<td>0.2 M</td>
<td>OK</td>
</tr>
</tbody>
</table>

*Based on typical values and experiments. Other conditions or products than tested should be validated by preliminary tests
Continuous Crystallization

- NiTech – DN15 Lite
- COBR : Continuous Oscillatory Baffled reactor
- Pressure: max 2 bar
- Temperature: max 100°C
- Materials: Borosilicate glass and PTFE
- 3 thermostats
- 1 peristaltic pump
Continuous Crystallization

- Reactor G1 6FM

- Final Parameters
  - Total G1 flow of 20 ml/min
  - Water flow of 30 ml/min
  - Temperature gradient 50°C/30°C/15°C (2/3/3 tubes)
  - Frequency 1.5 Hz, amplitude 35mm

- Full conversion and crystallization yield 60% (not optimized)
Continuous Crystallization
Continuous Crystallization
Presentation Outline

1. Introduction

2. Seamless Scale-Up

3. Industrial Examples

4. The Challenge of Solid handling

5. Outlook
Concluding Remarks

• Corning Advanced-Flow Reactors provide
  • High Mass transfer
  • High Volumetric Heat transfer
  • Seamless Scale-up

• Corning Advanced-Flow Reactors deliver
  • High performance reactors
  • Turn key solution with the required auxiliaries
  • Customised solution to fit individual needs

• Corning Advanced-Flow Reactors offer
  • Dedicated support to customers all over the world
  • Technical data obtained by a dedicated R&D team
  • Solutions for customers to move faster to production
What is new? The AFR® Lab Reactor

A complete **Plug and Play Lab System** (reactor + auxiliaries)

**Ready to start** & easy to use

Being **seamless scalable with AFR® products**
AFR® Lab Reactor with Lab Photo Reactor add on
Thank you for your attention

Questions?
Advanced-Flow™ Reactor Technologies
www.corning.com/reactors