Reinventing chemical manufacturing: toward a compact and mobile factory?

Jean-Christophe M. Monbaliu
CiTOS - Department of Chemistry - ULiège
jc.monbaliu@ulg.ac.be | www.citos.ulg.ac.be

Liège créative
- April 2017 -
CiTOS - Where organic chemistry meets technology

Department of Chemistry, Research Unit MolSys

- 13 PIs
- 63 researchers

CiTOS

Expertise in organic chemistry & flow chemistry

3 main research areas:

- APIs (small molecules & peptides)
- Biomass and platform molecules
- Unconventional conditions, transient species
## Chemical manufacturing

### API vs bulk chemical manufacturing

<table>
<thead>
<tr>
<th>Industry segment</th>
<th>Product tonnage</th>
<th>E Factor (kg waste/kg product)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oil refining</strong></td>
<td>$10^6–10^8$</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4–10^6$</td>
<td>&lt;1–5</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^2–10^4$</td>
<td>5–50</td>
</tr>
<tr>
<td><strong>Pharmaceuticals</strong></td>
<td>$10–10^3$</td>
<td>25–100</td>
</tr>
</tbody>
</table>
Chemical manufacturing

API vs bulk chemical manufacturing

- Multiple steps
- Complex chemistry
- Purity is paramount
- Variable scale (fine chemicals)

- (usually) Single step
- “Basic” chemistry
- Purity is less critical
- Very large scale (bulk, commodity)

- **Macroscopic** (batch)
- **Macroscopic** reactors (flow)
Traditional manufacturing

Macroscopic batch reactors
Traditional manufacturing

Complex multistep processes on large scale
Traditional sequential batch approach

\[
A + B \rightarrow C \text{ workup + purification}
\]
\[
C + D \rightarrow E \text{ workup + purification}
\]
\[
E \rightarrow F \text{ workup + purification}
\]

- Tedious process
- Large workforce
- Stockpiling issues
- Stepwise process

lab: hours to days
prod: weeks to years
Traditional manufacturing

Multistep processes on large scale
Complex molecules, complex processes
Traditional manufacturing

Multistep processes on large scale

Drug shortages

Recent examples:
- 2010 diphenhydramine massive recall
- lidocaine and diazepam flagged on 2015 FDA drug shortage list

US national drug shortages (adapted from *P&T*, 2011, 36, 742-753).
Traditional manufacturing

Multistep processes on large scale
Bad reputation – NIMBY syndrom

• **2000-2014:** 85 (US) / 111 (EU) serious chemical incidents in organic chemistry-related industry

• **2000-2013:** 120 (US) serious incidents in organic chemistry-related academic labs

http://www.csb.gov/
Emerging manufacturing technology

A new paradigm for chemical manufacturing
Cleaner, flexible, more efficient continuous manufacturing

“Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing.”

Dr. Janet Woodcock (FDA), AAPS Annual meeting, October 2011

“Drug manufacturers typically produce drugs in batches in large factories. But a new trend is developing in the pharmaceutical industry to reduce infrastructure costs by using small continuous-flow systems to make drug doses on demand.”

Stu Borman, Chemical and Engineering News, February 2017
Emerging manufacturing technology

A new paradigm for chemical manufacturing
Mobile, compact, reconfigurable, versatile, sustainable

http://corporate.evonik.com
Emerging manufacturing technology

A new paradigm for chemical manufacturing
Technology breakthroughs

• Compact (15 m²)
• Fully integrated (up / downstream + formulation)
• Modulable (output: 20 g h⁻¹ and 100 g h⁻¹)

Org Proc Res Dev 2014, 18, 402

Ang Chem Int Ed 2013, 52, 12359
Emerging manufacturing technology

A new paradigm for chemical manufacturing
Technology breakthroughs

On-Demand Drug Production Is on the Horizon
The Drug-Making Process Is Slow and Wasteful — This Machine Could Fix That

WO 2016/025803 & Science, 2016, 352, 61
Emerging manufacturing technology

Continuous-flow manufacturing

GCI/2007: continuous manufacturing is a research top priority

<table>
<thead>
<tr>
<th>Rank</th>
<th>Main Key Areas</th>
<th>Sub-areas/aspects</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continuous Processing</td>
<td>Primary, Secondary, Semi-continuous, etc.</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Bioprocesses</td>
<td>Biotechnology, Fermentations, Biocatalysis, GMOs, etc.</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Separation and Reaction Technologies</td>
<td>Membranes, crystallizations, etc.</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Solvent Selection, Recycle and Optimization</td>
<td>Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Process Intensification</td>
<td>Technology, process, hybrid systems, etc.</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Integration of Life Cycle Assessment (LCA)</td>
<td>Life cycle thinking, Total Cost Assessment, carbon / eco-footprinting, Social LCA, streamlined tools</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Integration of Chemistry and Engineering</td>
<td>Business strategy, links with education, etc.</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Scale up aspects</td>
<td>Mass and energy transfer, Kinetics, and others</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Process Energy Intensity</td>
<td>Baseline for pharmaceuticals, estimation, energy optimization</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Mass and Energy Integration</td>
<td>Process integration, Process Synthesis, Combined Heat and Power, etc.</td>
<td>0</td>
</tr>
</tbody>
</table>
Flow chemistry
An overview of the two last decades
Emerging manufacturing technology

Flow chemistry

Job market overview

“with strong expertise in flow chemistry,... experience/expertise in photo-redox chemistry or photo-redox reaction in flow is desirable”

“Working across skills sets such as flow chemistry ...”

“A Ph.D. in chemistry with experience in flow chemistry is required, ...”

“Applies applications for new technologies to project objectives, e.g. flow chemistry”
**What is flow chemistry?**

Flow chemistry is a term widely used to describe the performance of a reaction in a continuous manner, in a micro/mesofluidic reactor.

---

<table>
<thead>
<tr>
<th>KEY FEATURES</th>
<th>Batch reactors</th>
<th>Continuous-Flow micro/mesoreactors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D internal structure &gt;&gt; $10^4 , \mu m$</td>
<td>3D internal structures &lt; $10^3 , \mu m$</td>
<td></td>
</tr>
<tr>
<td>mL &lt; internal volume &lt; kL</td>
<td>$\mu L$ &lt; internal volume &lt; mL</td>
<td></td>
</tr>
<tr>
<td>Finite volume of chemicals</td>
<td>Infinite volume (flow) of chemicals</td>
<td></td>
</tr>
</tbody>
</table>
Continuous micro/mesofluidic reactors

- Used in labs, R&D and production
- Continuous reactors with well defined micro or meso structures (< 1000 µm) and internal volumes (µL to mL)
- Inflow = outflow while reaction is being carried

What is flow chemistry?
What is flow chemistry?

Continuous micro/mesofluidic reactors

Anatomy of a continuous-flow reactor
What is flow chemistry?

End-to-end continuous manufacturing

The telescoping of complex multistep continuous-flow sequences from raw chemicals toward finalized product is often referred to as end-to-end continuous manufacturing.
Continuous micro/mesofluidic reactors

Inherent differences between macroscopic batch and microreactors

The behavior of liquids at a microscopic scale is quite distinct from that for fluids at a macroscopic level.

- At a **macroscopic scale**, pressures well above or below atmospheric pressure and gravity dominate fluid dynamics.
- Surface tension, energy dissipation, and fluidic resistance start to dominate the system, rather than gravitational forces at a **microscopic scale**.
Continuous micro/mesofluidic reactors

Inherent differences between macroscopic batch and microreactors
Batch reactors
- Macroscopic reactors
- Scale dependent
- Time-resolved
- Mixing is poor ($t_{\text{mix}} \gg t_{\text{reac}}$)
- Heat transfer is slow
- Difficult control of reaction time
- Low surface/volume ratio
- Intensification = hazard
- Chemical hazard!
- Less for transient species
- Scale-up is time consuming

Flow (micro/meso)reactors
- 3D internal structures < 1000 µm
- Scale independent
- Space-resolved
- Mixing is fast ($t_{\text{mix}} << t_{\text{reac}}$)
- Heat transfer is fast
- Control of reaction time
- High surface/volume ratio
- Intensification = safe
- Inherently safer
- Suitable for transient species
- Fast scaling-out or numbering-up

Flow chemistry redefines chemical processing
Flow chemistry: what benefits?

**Faster mixing & better heat exchange**

laminar, **transitional** and **turbulent**

**Macro- and micromixing**

**Flow chemistry** enables **faster, more selective** and inherently safer chemical transformations.
**Flow chemistry: what benefits?**

**Faster mixing & better heat exchange**

<table>
<thead>
<tr>
<th>Reactor type</th>
<th>Surface/volume (cm²/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mL reaction bulb</td>
<td>1</td>
</tr>
<tr>
<td>1 m³ reactor</td>
<td>0.06</td>
</tr>
<tr>
<td>μchannel 100 μm</td>
<td>200</td>
</tr>
</tbody>
</table>

**Flow chemistry enables faster, more selective and inherently safer chemical transformations.**
Fine tuning of reaction time

Flow chemistry enables faster, more selective and inherently safer chemical transformations.

\[ t_R = \frac{V}{\mu R} \] (Eq. 1)
Flow chemistry: what benefits?

Inherent safety – finite vs infinite volumes

Small amount of processed material / unit of time

Inherently safer transient, explosive, toxic chemicals

Flow chemistry enables faster, more selective and inherently safer chemical transformations.

Large amount of processed material / unit of time

Chemical hazard transient, explosive, toxic chemicals
Flow chemistry: what benefits?

Unconventional conditions are easily accessible

- Explosive/unstable intermediates
- Toxic intermediates
- High temperature
- High pressure
- Photochemistry
- Electrochemistry

*Flow chemistry* enables the handling of unstable/hazardous species and unusual conditions – expanding the horizon.
Flow chemistry: what benefits?

Seamless transition from lab-scale to production-scale

Flow chemistry enables fast transition from lab to pilot-scale
Pharmacy on demand
On-demand continuous-flow synthesis of 4 APIs (including formulation)

Specific requirements
- Compact (“mobile”)
- Single operator & user friendly
- Easy maintenance, adaptable, versatile, reconfigurable
- High yield, high purity of all APIs

Case studies – part I
Pharmacy on demand

Fluoxetine

**Upstream**

- DIBAL in toluene (1 eq.)
- (in toluene, 1 eq.) (14)
- 4 M HCl (aq)
- V₁ = 5 mL
- T₁ = rt
- tᵣ = 10 min
- Reactor I

- Reactor II
- ultrasound transducer
- V₂ = 5 mL
- T₂ = rt
- tᵣ = 3.3 min

- SEPM₂
- BPR
- 1.6 MPa
- aqueous waste

- 4 M HCl (aq)
- MeNH₂ (aq) (15 eq.)
- V₃ = 10 mL
- T₃ = 135°C
- tᵣ = 10 min
- Reactor III

- NaCl (aq)
- 1.6 MPa
- aqueous waste

- THF
- 0°C
- 4A MS
- 0.13 eq. in DMSO

- KO/Bu
- 18-crown-6 in DMSO
- V₄ = 10 mL
- T₄ = 140°C
- tᵣ = 2.6 min

- H₂O
- BPR
- 1.7 MPa
- TBME

**Downstream**

- 100-200 doses/24 hours

- fluoxetine hydrochloride (4)

- HCl/Et₂O
- aqueous waste
Pharmacy on demand

WO 2016/025803
Science, 2016, 352, 61
Case studies – part I

Pharmacy on demand

Modules

(A) Productions of different pharmaceuticals

(D) Flow direction

WO 2016/025803
Science, 2016, 352, 61

4500 doses d⁻¹

810 doses d⁻¹

3000 doses d⁻¹

200 doses d⁻¹

Diphenhydramine hydrochloride (1)

Lidocaine hydrochloride (2)

Diazepam (3)

Fluoxetine hydrochloride (4)
Continuous-flow process toward methylphenidate hydrochloride
Reaction telescoping with unstable/explosive intermediates

- most widely prescribed stimulant API for ADHD and narcolepsy

Work with R. Gérardy
Patent application No. EP16189458.9

2.3 billion doses year⁻¹
Continuous-flow process toward methylphenidate hydrochloride
Reaction telescoping with unstable/explosive intermediates

Previous work:
- multistep sequential batch
- inventories of hazardous chemicals
- reaction times up to 5.5 h (inter and intra)
- hazardous scale-up

This work:
- telescoped multistep continuous-flow
- no inventories of hazardous chemicals
- reaction times up to 20 min (inter) and 25 min (intra)
- scalable process with inherent safety

Patent application No. EP16189458.9
Case studies – part II

Reaction telescoping with unstable/explosive intermediates
Seamless scale-out: Corning® Advanced-Flow™ LF to G1™ reactors

- **PFA µreactor**: 21.7 g day\(^{-1}\) (1400 doses)
- **LowFlow**: 86.9 g day\(^{-1}\) (5,800 doses)
- **G1**: 4.25 kg day\(^{-1}\) (280,000 doses)

Patent application No. EP16189458.9
Concluding remarks

Expanding chemistry’s horizon

- Significant reduction of spatiotemporal requirements
- Expands the toolkit for chemical processing
- Compatible with unstable materials and unconventional conditions
- Intensification/seamless transition toward larger scales
- Safer, greener, faster processes

Concluding remarks

New challenges

“A lack of scientific talent will hold pharma back from adopting continuous manufacturing despite the imminent opening of regulatory pathways”

Tim Jamison, MIT
http://www.in-pharmatechnologist.com/Processing/Lack-of-talent-will-hamper-continuous-manufacturing-uptake-MIT-Prof

• Chemical challenges (new paradigm)
• Technology challenges (mechanical & chemical resistance)
• Increasing process/molecular complexity
Acknowledgements

- R. Gérardy
- N. Emmanuel
- N. Tshibalonza
- T. Toupy
- G. Ernotte
- V.-E. Kassin
- D. Collin
- Prof. C. Damblon
- Prof. G. Eppe
- Prof. B. Heinrichs

- Prof. K. F. Jensen
- Prof. T. F. Jamison
- Prof A. Myerson
- Dr. A. Adamo
- Dr. N. Weeranoppanant
- Dr. T. Stelzer
- Dr. P. Zhang
- Dr. D. Snead
- Dr. E. Revalor

- Dr. Y. Jiang
- Eng. M. Winter
- Dr. G. Gauron
- Dr. C. Horn
- A. Vizza
- F. Gonzalez