
Reinventing chemical manufacturing: toward a compact and mobile factory?

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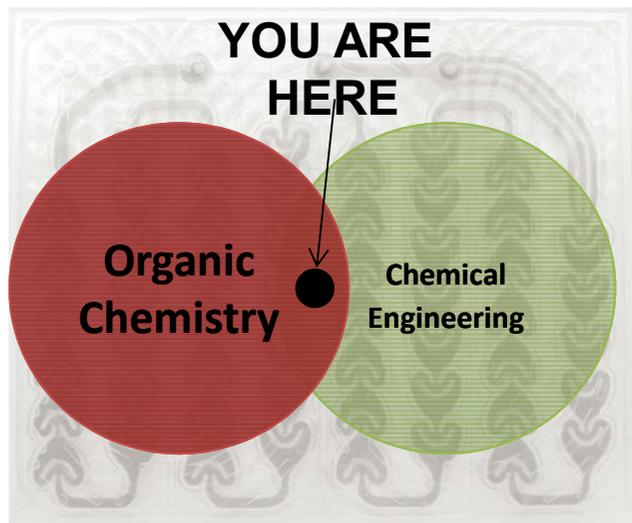
Liège créative
- April 2017 -

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



API vs bulk chemical manufacturing



| Industry segment | Product tonnage | E Factor (kg waste/kg product) |
|------------------|-----------------|-----------------------------------|
| Oil refining | 10^6-10^8 | <0.1 |
| Bulk chemicals | 10^4-10^6 | <1-5 |
| Fine chemicals | 10^2-10^4 | 5-50 |
| Pharmaceuticals | $10-10^3$ | 25-100 |

API vs bulk chemical manufacturing



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



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

Macroscopic batch reactors

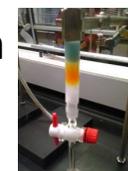
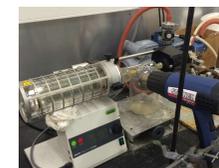


Complex multistep processes on large scale

Traditional sequential batch approach



Multistep
Organic Chemistry?



+

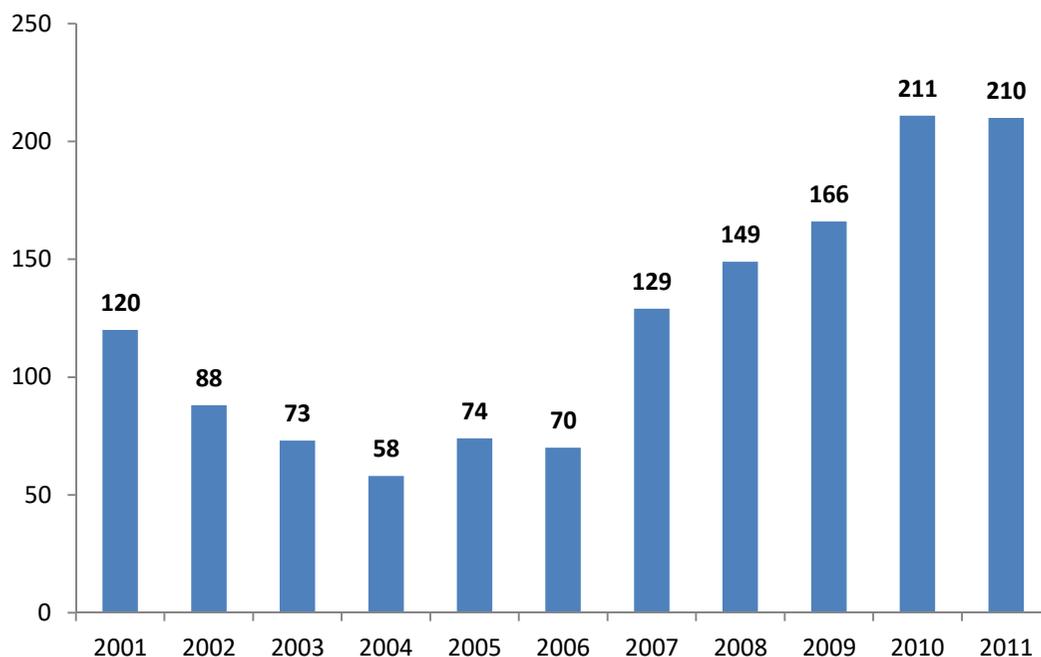


- Tedious process
- Large workforce
- Stockpiling issues
- Stepwise process

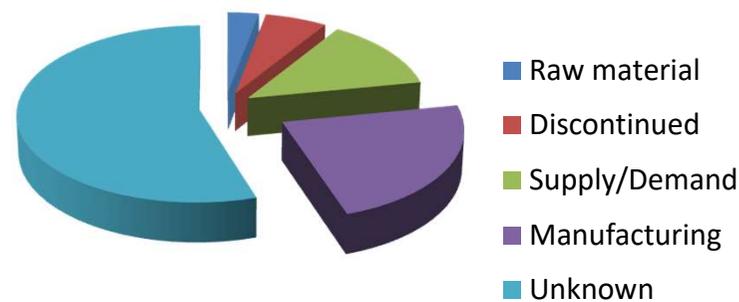
lab: hours to days
prod: weeks to years

Multistep processes on large scale

Drug shortages



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



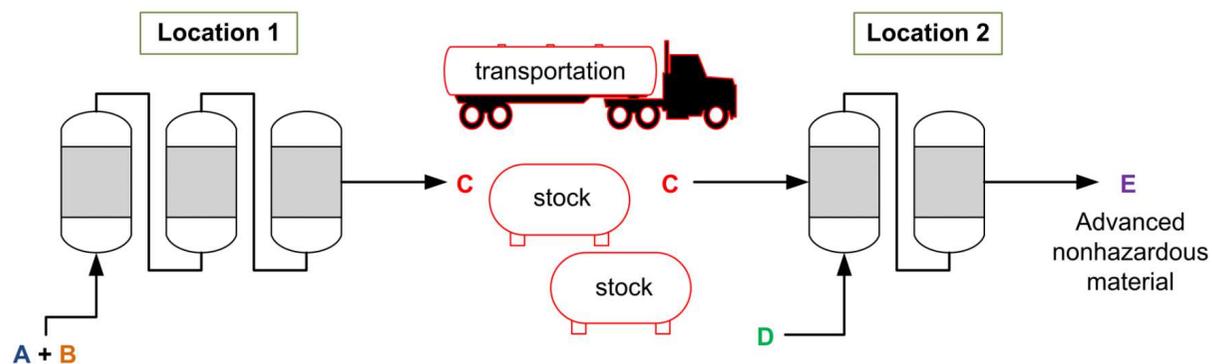
Recent examples:

- 2010 diphenhydramine massive recall
- lidocaine and diazepam flagged on 2015 FDA drug shortage list
- <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>
- <http://www.ema.europa.eu/ema/>

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/>

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

A new paradigm for chemical manufacturing

Mobile, compact, reconfigurable, versatile, sustainable



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

Concentrates

Selections from the scientific literature and news from the week

| | |
|--|----|
| ► Highlights | |
| New insights into Zika's biology | 5 |
| Microneedle patch delivers skin cancer therapy | 5 |
| New epigenetic mark for mammals | 6 |
| EPA uncovers mysterious phosphorus pollution | 6 |
| Why whiskey doesn't have a ring to it | 8 |
| Noctkatone tested as a mosquito repellent | 10 |
| Thermo Fisher wins contest for Affymetrix | 10 |
| Food firms push to phase out bisphenol A | 11 |
| EPA targets hydrofluorocarbons | 14 |
| Warm sea temperatures bleach reef off of Australia | 15 |

PROCESS CHEMISTRY

Mini drug factory up and running

Continuous-flow system efficiently produces four approved drugs

Drug companies generally make commercial medicines in batches. They carry out discrete reaction, separation, analysis, and formulation steps in large factories, sometimes in multiple locations, and then begin each process all over again to make more doses of the same drug.

Seeking a better way, researchers have now developed a refrigerator-sized flow system that continuously synthesizes and formulates hundreds to thousands of doses per day. Although the system makes only one drug at a time, an operator can switch the system to make a new drug in less than two hours.

The continuous-flow drug system is much smaller and less expensive than a conventional batch-processing facility. It could be useful for "on demand" manufacture of drugs with a short shelf life or drugs needed for small patient populations, for public health emergencies, or at specific locations, its developers say. In addition, it might reduce the need for drug transport, distribution, and storage.

Timothy F. Jamison, Klavs F. Jensen, and Allan S. Myerson of MIT and coworkers report the mini-factory in a new paper (*Science* 2016, DOI: 10.1126/science.1251337). The Food & Drug Administration has been recommending continuous-flow processing as one way to modernize drug manufacturing, and the new system helps advance that goal.

Various groups have developed integrated continuous-flow drug syntheses, but "this is the first modular, reconfigurable, plug-and-play system that can produce several drugs in final dosage forms," comments flow chemistry expert C. Oliver Kappe of the University of Graz. "Clearly, the authors had

to invent many new tools to be able to pull off the multistep chemistry they show in this paper. Five years ago, most process chemists would not have believed this was possible."

The system includes an initial "upstream" unit with reactors and a "downstream" section with precipitation, filtration, dissolution, crystallization, and formulation units. It also includes chemical analysis and computational units for process evaluation and control.

The researchers design each reaction on a micro-liter scale before translating it to the continuous-flow system. They use elevated temperatures and pressures to make reactions go more quickly and high-concentration reagents to reduce raw materials and waste, compared with batch processing.

The MIT team demonstrated the system's abilities by producing liquid oral and topical formulations of the anticholinergic diphenhydramine hydrochloride (Benadryl); the local anesthetic lidocaine hydrochloride; the depressant diazepam (Valium); and the antidepressant fluoxetine hydrochloride (Prozac or Sarafem). The researchers hope to develop the ability to produce solid pill formulations as well.

"Clearly, the structural complexity of the chosen drugs is quite simple," Kappe says. Continuous flow may be practical for more complex structures, "and batch reactors will continue to be in use for a long time. But this paper demonstrates in an impressive way what is possible" by pushing technological boundaries.

Jensen says a next version of the system will be 40% smaller and able to synthesize more complex pharmaceuticals. The researchers are patenting and plan to commercialize the technology.—STU BORMANN



Diazepam



4 CAEN | CEN.ACS.ORG | APRIL 4, 2016

On-Demand Drug Production Is on the Horizon

The Drug-Making Process Is Slow and Wasteful — This Machine Could Fix That



SHARE

RESEARCH ARTICLE

On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system

Andrea Adamo¹, Rachel L. Beingsner², Mohsen Behnam^{1,2}, Jie Chen¹, Timothy F. Jamison^{2,1}, Klavs F. Jensen^{1,3}, Jean-Christophe M. Monbaliu^{1,4}, Allan S. Myerson^{1,5}, Eve M. Revalor^{1,6}, David R. Sneed^{1,7}, Torsten Stelzer^{1,8}, Nopphon Weeranoppanant¹, Shin Yee Wong^{1,9}, Ping Zhang^{1,10}

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WO 2016/025803 & Science, 2016, 352, 61

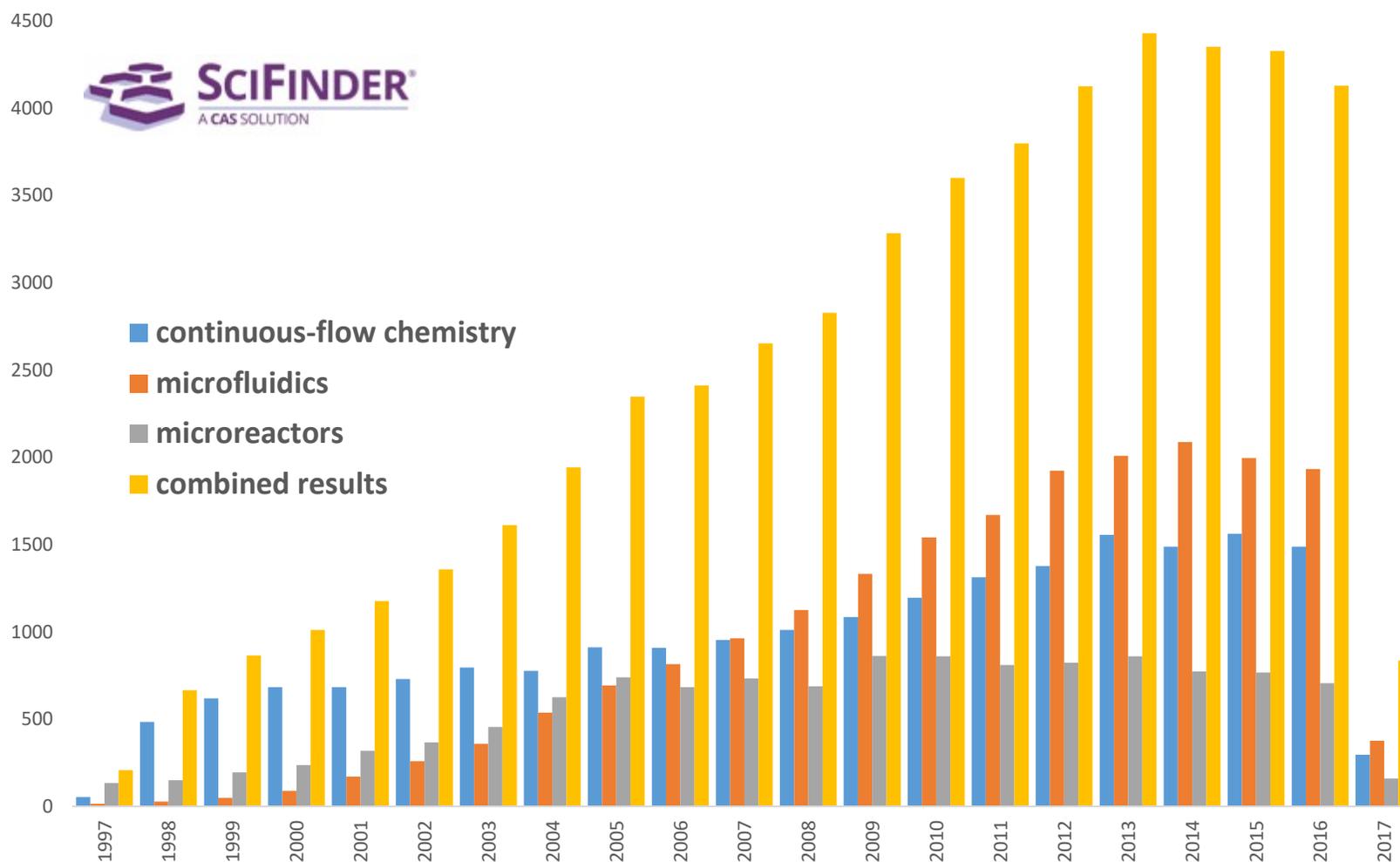
Continuous-flow manufacturing

GCI/2007: continuous manufacturing is a **research top priority**

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

Flow chemistry

An overview of the two last decades



Flow chemistry

Job market overview

LinkedIn



“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** ...”

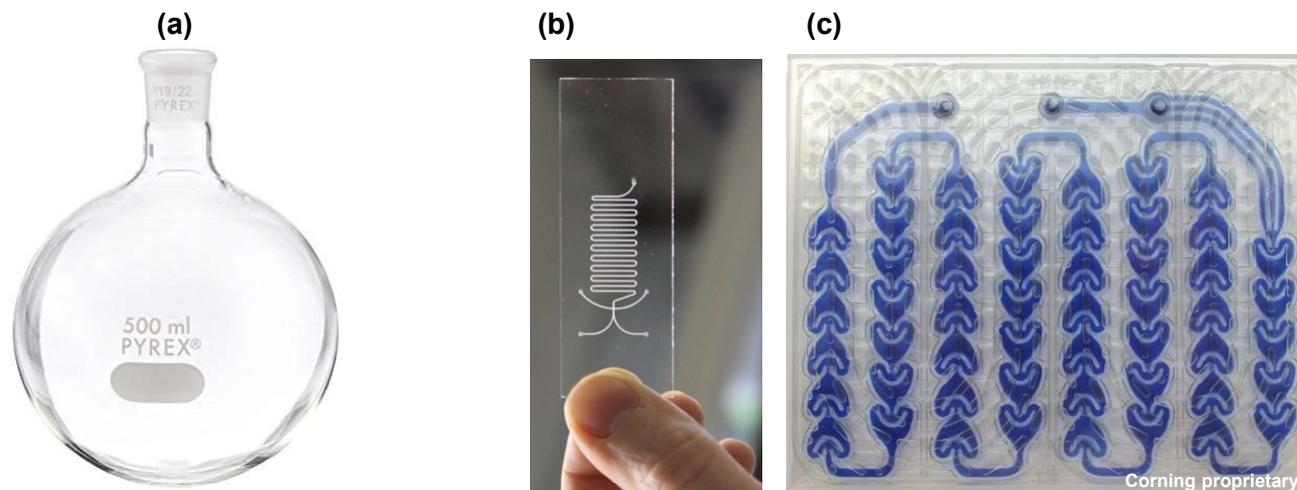


“A Ph.D. in chemistry with experience in **flow chemistry** is required, ...”



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

What is flow chemistry?



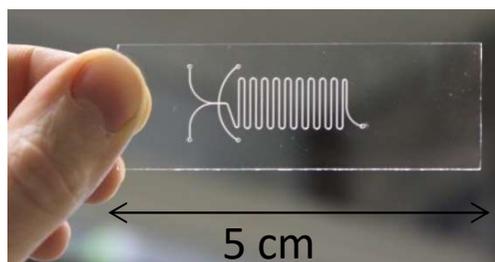
| KEY FEATURES | Batch reactors | Continuous-Flow micro/mesoreactors |
|--------------|---|--|
| | 3D internal structure $\gg 10^4 \mu\text{m}$ mL < internal volume < kL Finite volume of chemicals | 3D internal structures $< 10^3 \mu\text{m}$ μL < internal volume < mL Infinite volume (flow) of chemicals |

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

What is flow chemistry?

Continuous micro/mesofluidic reactors

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

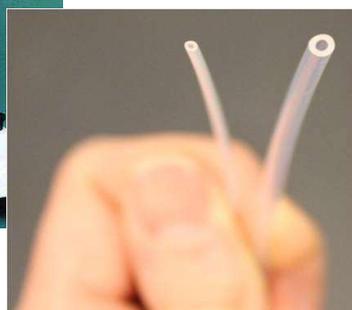


Channel \varnothing : $100 \mu\text{m}$
 V_{int} : $100+ \mu\text{L}$

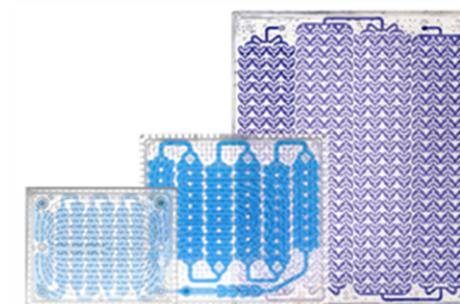
micro



meso

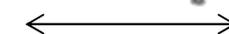


Channel \varnothing : $100-800 \mu\text{m}$
 V_{int} : up to mL



15 cm

Channel \varnothing : mm
 V_{int} : $10+ \text{mL}$

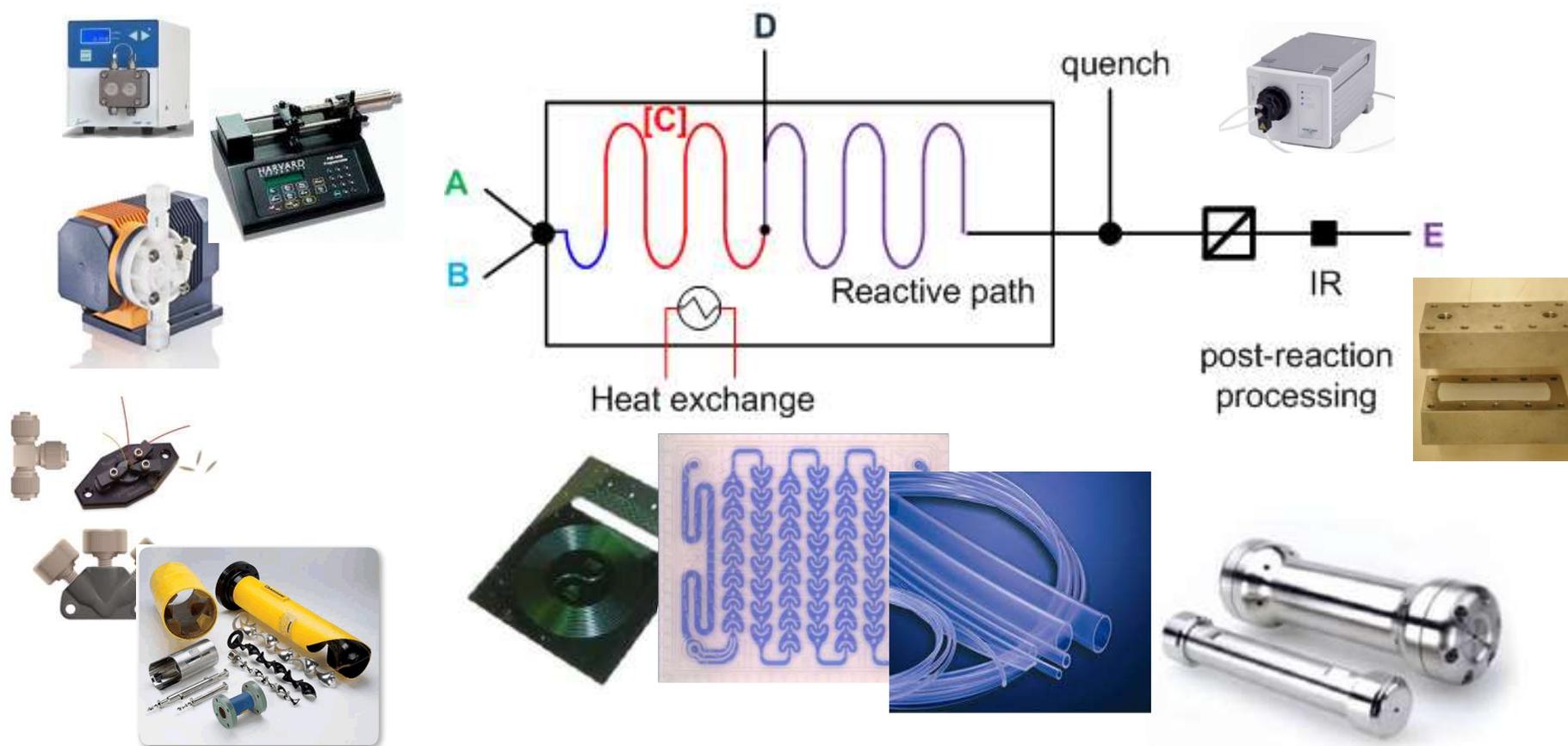


2 m

What is flow chemistry?

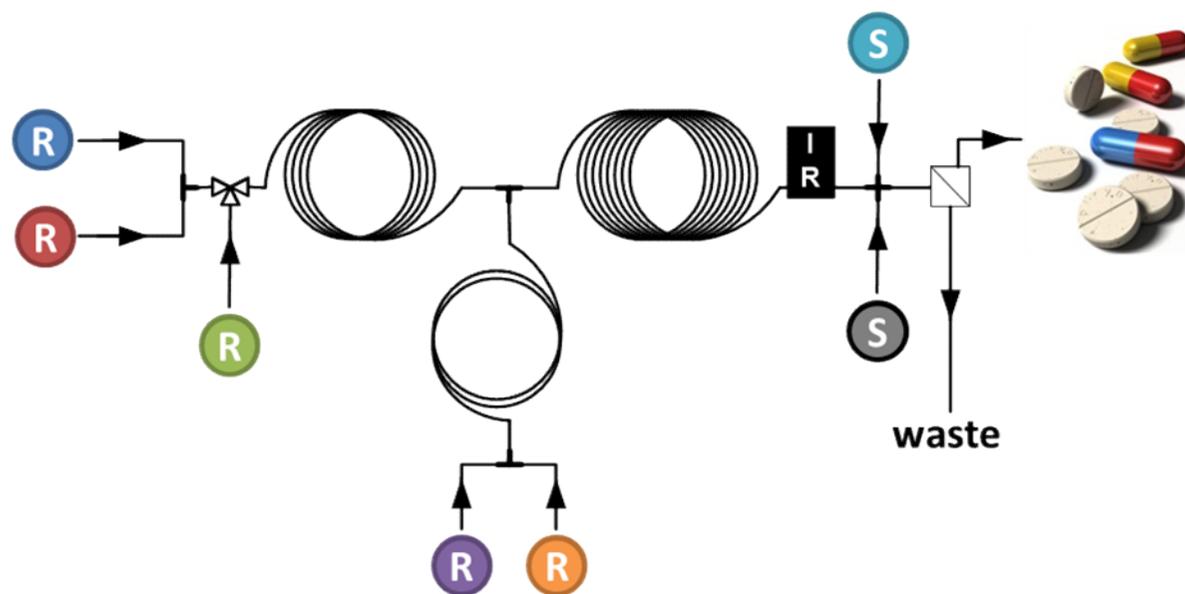
Continuous micro/mesofluidic reactors

Anatomy of a continuous-flow reactor



What is flow chemistry?

End-to-end continuous manufacturing



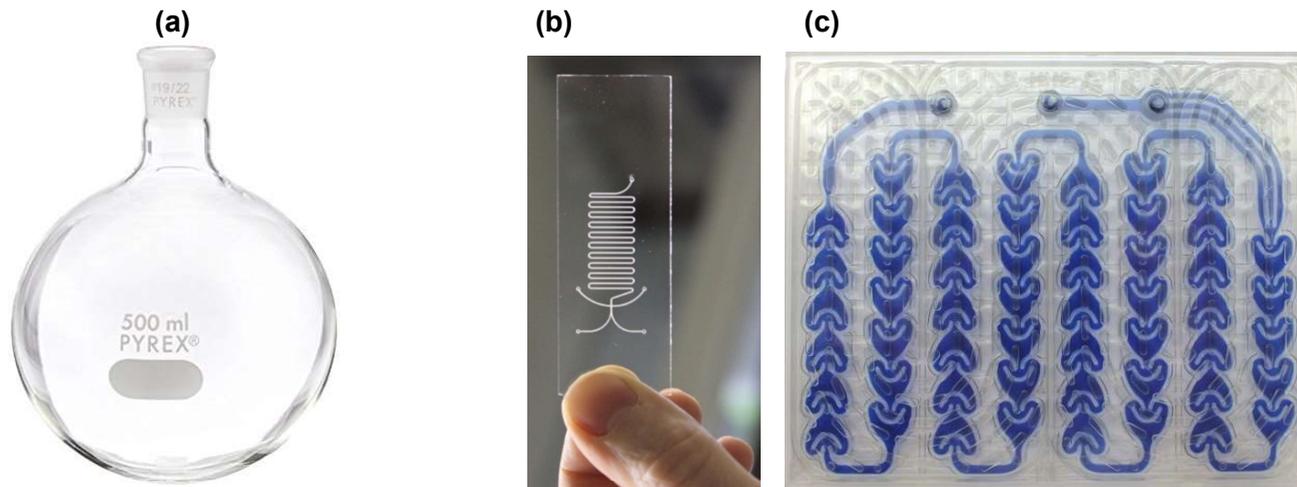
The telescoping of complex multistep continuous-flow sequences from raw chemicals toward finalized product is often referred to as **end-to-end continuous manufacturing**

Internal size matters

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

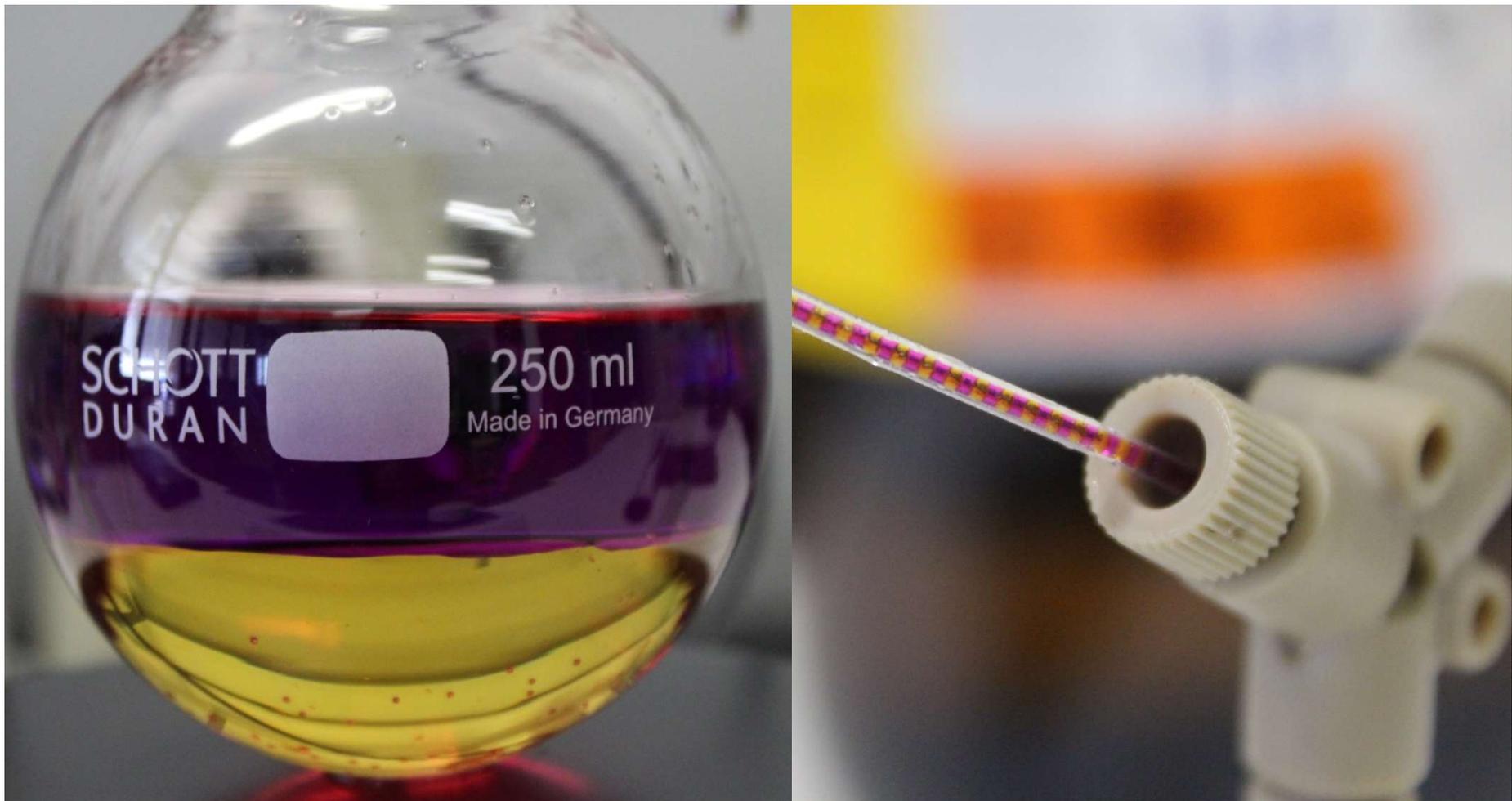


- At a **macroscopic scale**, pressures well above or below atmospheric pressure and gravity dominate fluid dynamics
- Surface tension, energy dissipation, and fluidic resistance start to dominate the system, rather than gravitational forces at a **microscopic scale**

Internal size matters

Continuous micro/mesofluidic reactors

Inherent differences between macroscopic batch and microreactors



Flow chemistry: what benefits?

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 ($t_{\text{mix}} \ll t_{\text{reac}}$)**
- **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

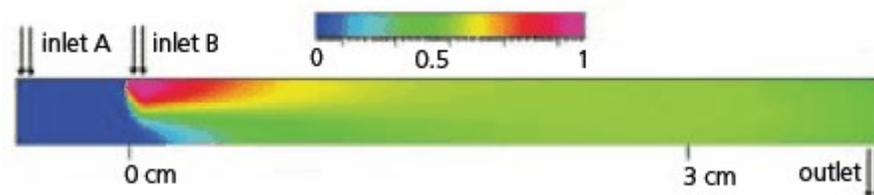
Flow chemistry: what benefits?

Faster mixing & better heat exchange



**laminar, transitional
and turbulent**

Macro- and micromixing



**laminar, transitional
and turbulent**

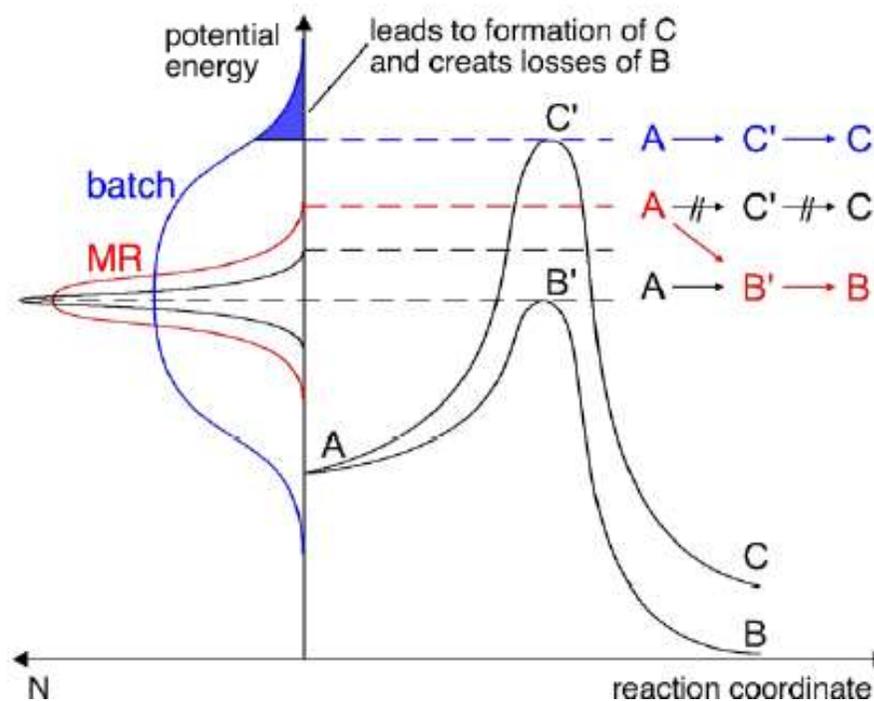
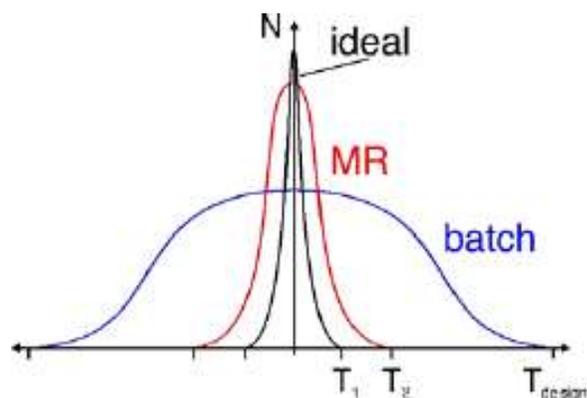
Micromixing (active & passive)

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

Flow chemistry: what benefits?

Faster mixing & better heat exchange

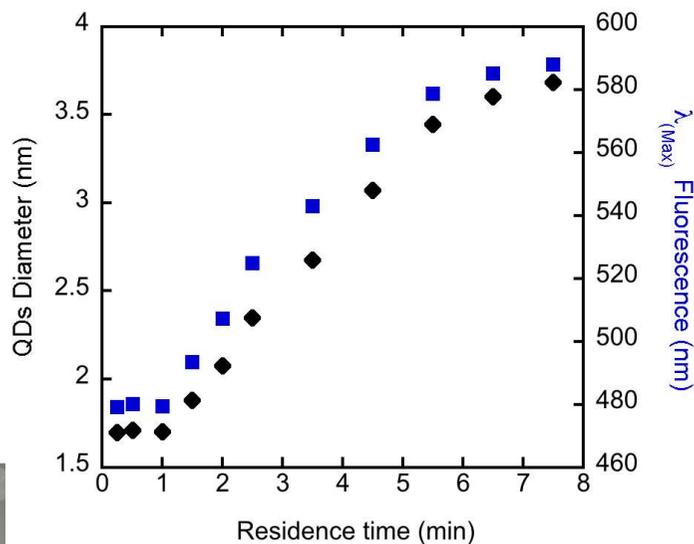
| Reactor type | Surface/volume (cm ² /cm ³) |
|--------------------------|---|
| 100 mL reaction bulb | 1 |
| 1 m ³ reactor | 0.06 |
| μchannel 100 μm | 200 |



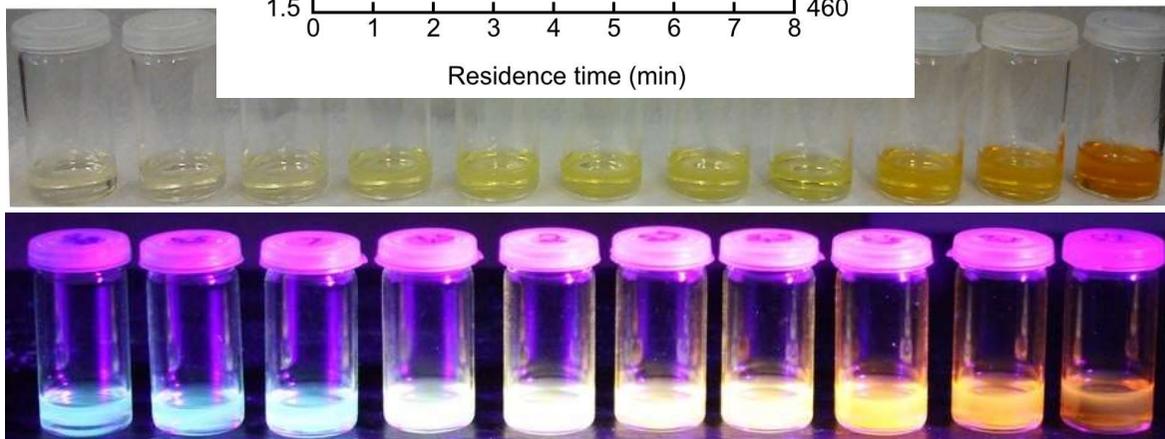
Flow chemistry enables **faster, more selective** and inherently safer chemical transformations.

Flow chemistry: what benefits?

Fine tuning of reaction time



$$t_R = \frac{V \mu R}{\phi} \text{ (Eq. 1)}$$



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

Flow chemistry: what benefits?

Inherent safety – finite vs infinite volumes

Small amount
of processed material / unit of time



Inherently safer
transient, explosive, toxic
chemicals

Large amount of
processed material / unit of time



Chemical hazard
transient, explosive, toxic
chemicals

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

Unconventional conditions are easily accessible



**explosive/unstable
intermediates**



**toxic
intermediates**



**high
temperature**



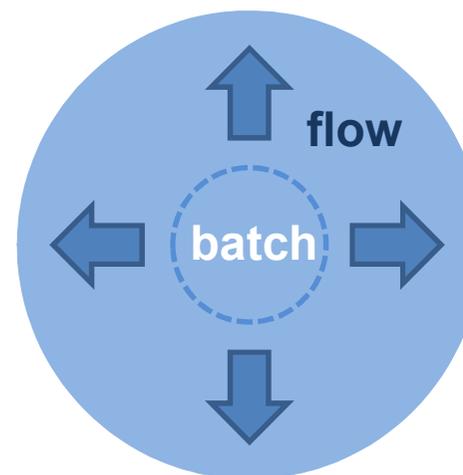
**high
pressure**



photochemistry



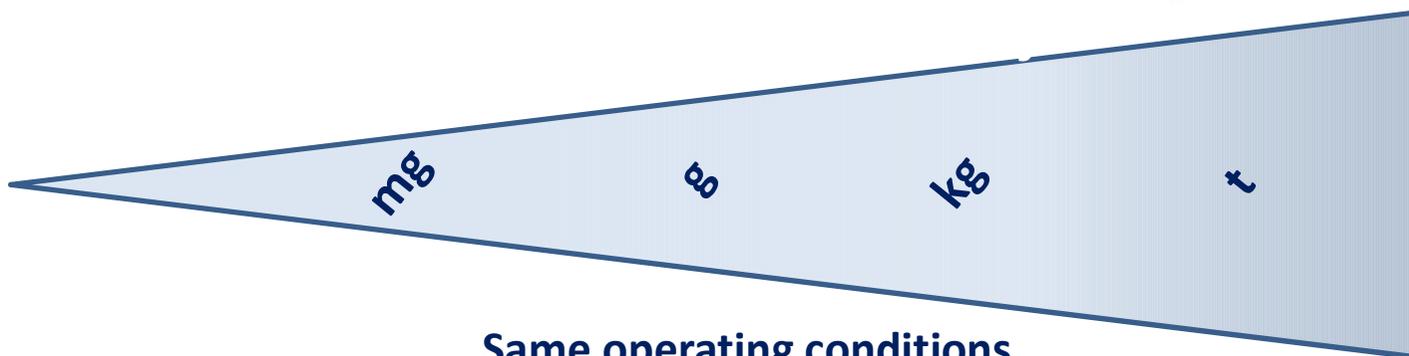
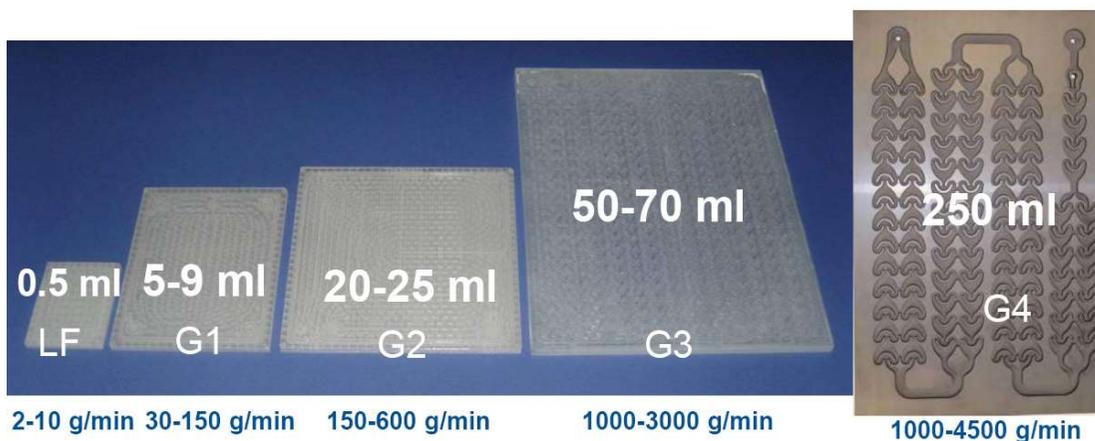
electrochemistry



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



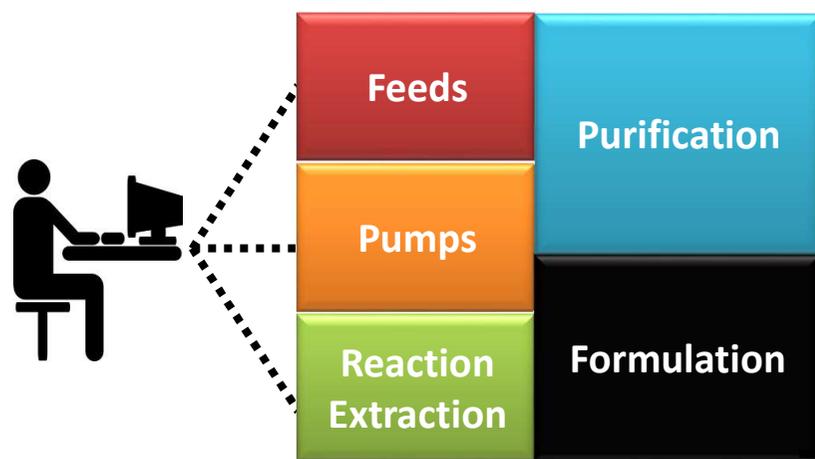
Same operating conditions
(Minimal) re-optimization

Flow chemistry enables fast transition from lab to pilot-scale



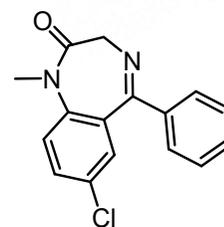
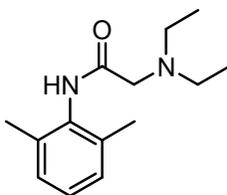
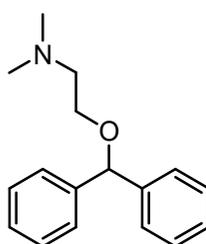
Pharmacy on demand

On-demand continuous-flow synthesis of 4 APIs (including formulation)



Specific requirements

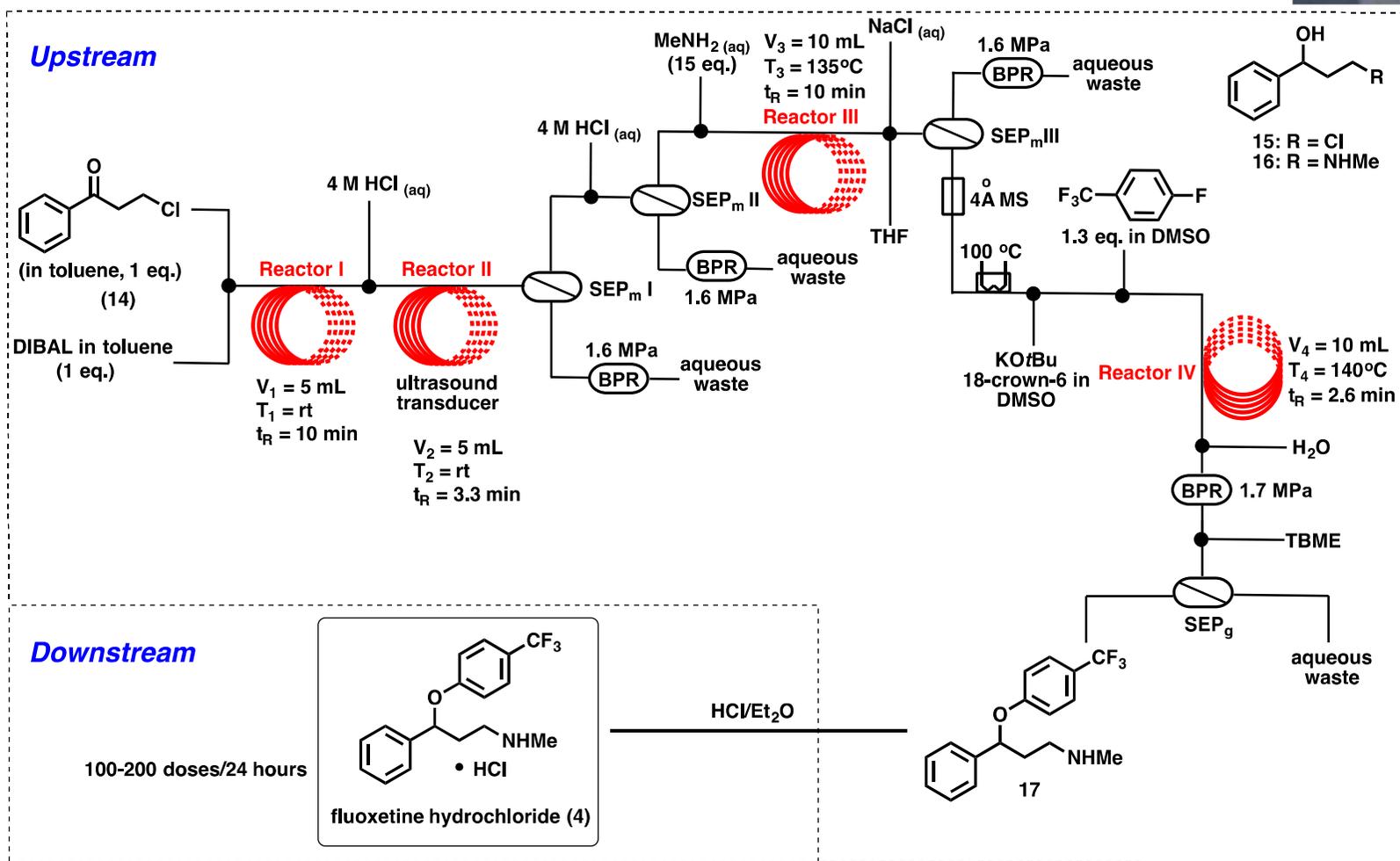
- Compact (“mobile”)
- Single operator & user friendly
- Easy maintenance, adaptable, versatile, reconfigurable
- High yield, high purity of all APIs





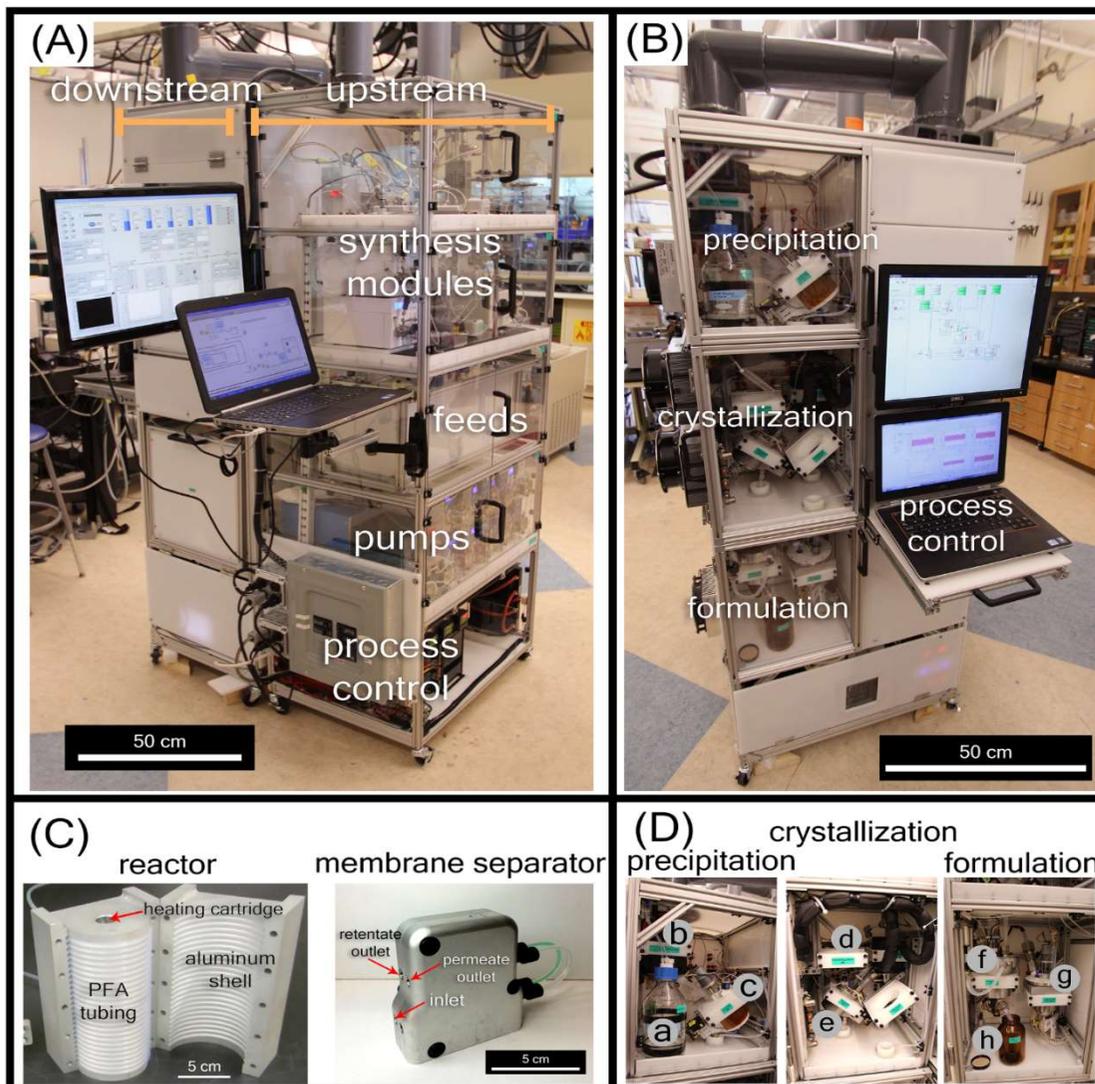
Pharmacy on demand

Fluoxetine





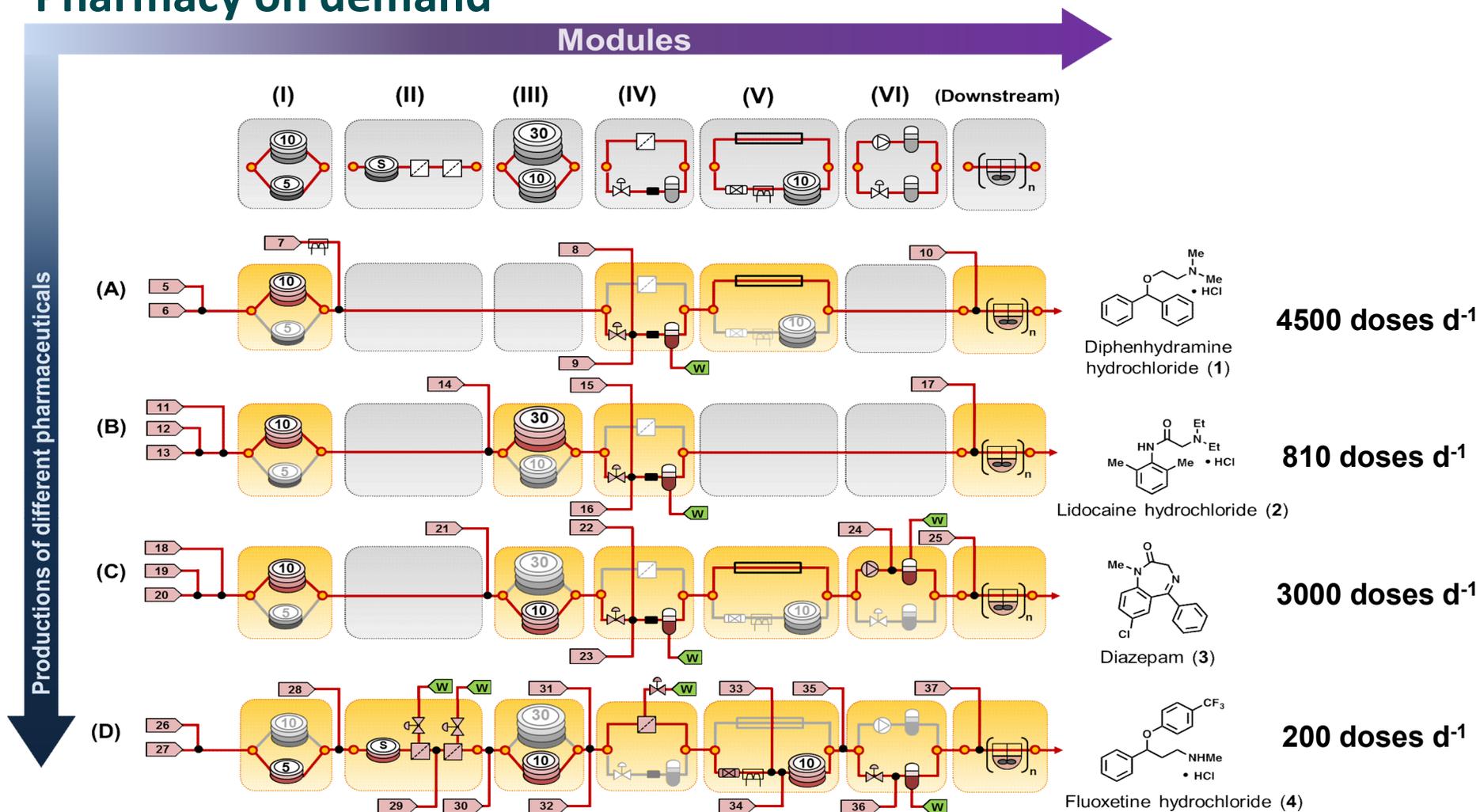
Pharmacy on demand



WO 2016/025803
Science, 2016, 352, 61



Pharmacy on demand

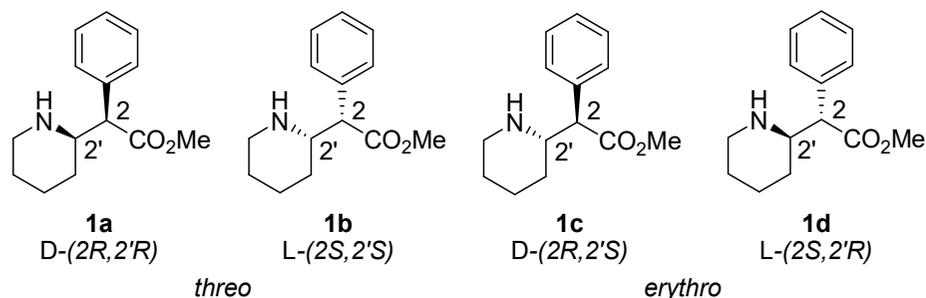


WO 2016/025803
 Science, 2016, 352, 61

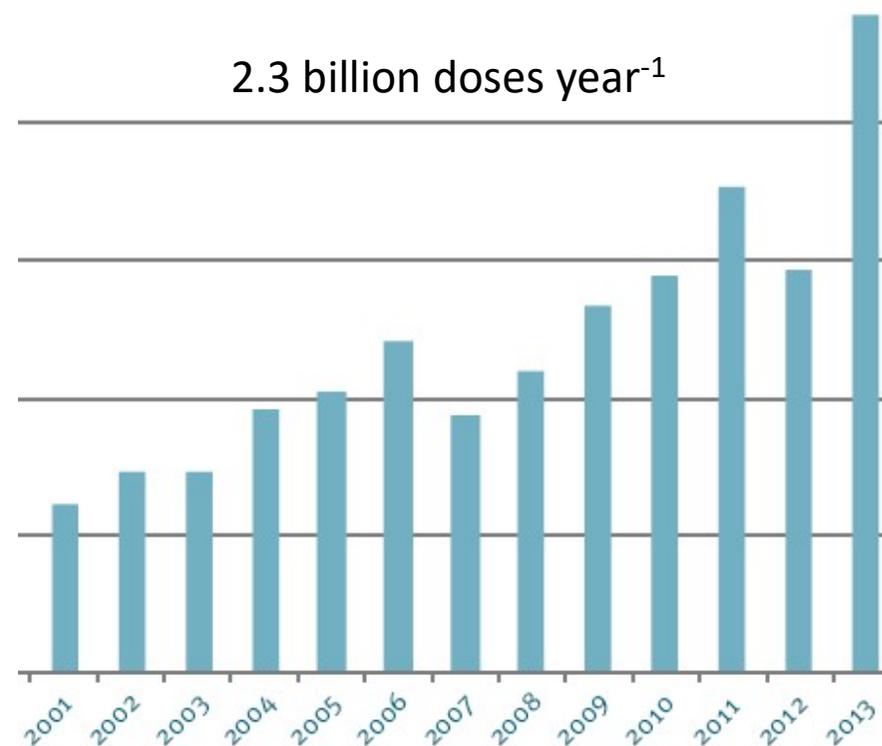


Continuous-flow process toward methylphenidate hydrochloride

Reaction telescoping with unstable/explosive intermediates



- most widely prescribed stimulant API for ADHD and narcolepsy

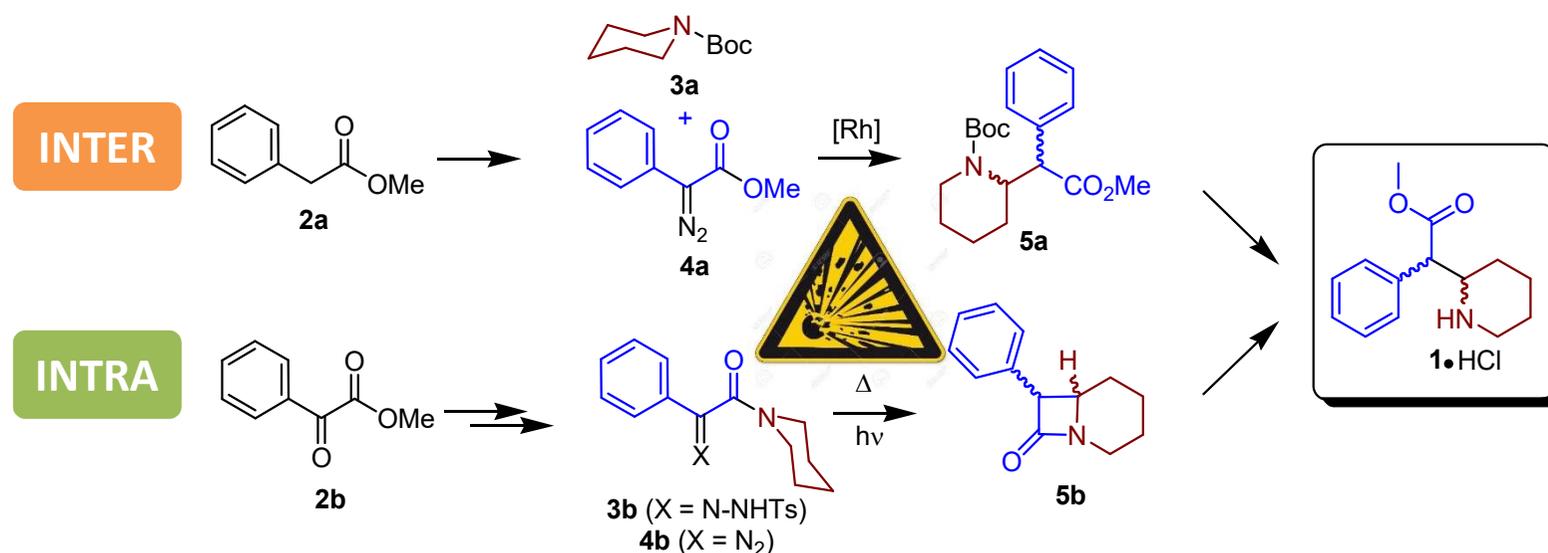


Work with R. Gérardy
 React. Chem. Eng. 2017, 2, 149.
 Patent application No. EP16189458.9



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

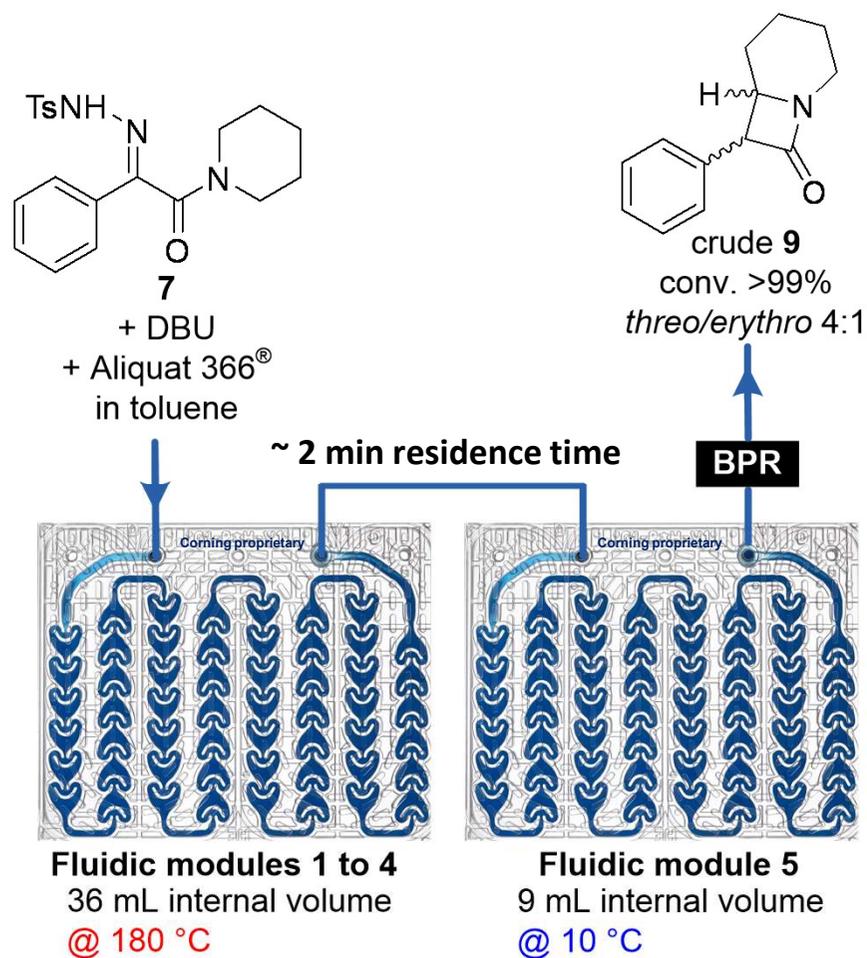
React. Chem. Eng. 2017, 2, 149.

Patent application No. EP16189458.9



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

Inspiring reading: **“Flow chemistry—Microreaction technology comes of age”** K. F. Jensen, AIChE J., 2017 doi:10.1002/aic.15642

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



LE FONDS EUROPÉEN DE DÉVELOPPEMENT RÉGIONAL
ET LA WALLONIE INVESTISSENT DANS VOTRE AVENIR

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- Prof. G. Eppe
- Prof. B. Heinrichs



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- Prof. T. F. Jamison
- Prof A. Myerson
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