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Continuous Flow Reactors: Applications of Discovery, Process Development & Material Production

Dr Charlotte Wiles, 31st May 2017

Process Intensification:

What is it?

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‘use **LESS** to produce much **MORE** & **BETTER**’

‘LESS’ refers to;

- Investment
- Space
- Time
- Raw materials
- Energy
- Inventory
- etc…….

© DSM (USA)

To employ the principles of Process Intensification, you must identify the limitation within the process;

a) Chemical *i.e.* catalysis, reaction conditions etc…
b) Transport phenomena *i.e.* heat & mass transport
c) Equipment *i.e.* restrictions in terms of capabilities

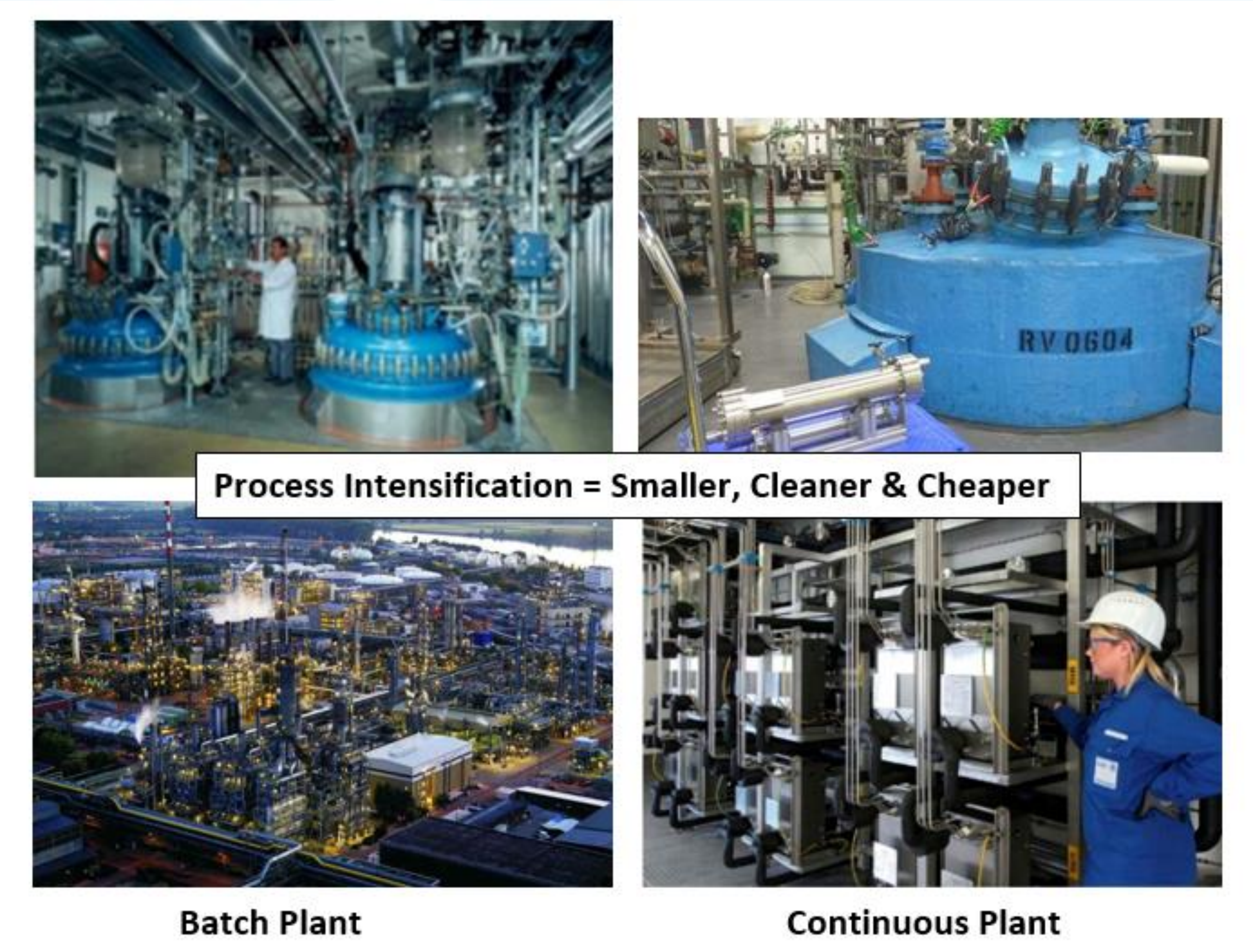
- We will learn through the talks how continuous reactors can address these topics!

[1]. Gourdon *et al. OGST*, 2015, **3**, 463-473

Process Intensification:

What Does it Look Like?

The past five years have shown PI entering the Fine Chemical & Pharmaceutical industry;



Process Intensification = Smaller, Cleaner & Cheaper

Batch Plant

Continuous Plant

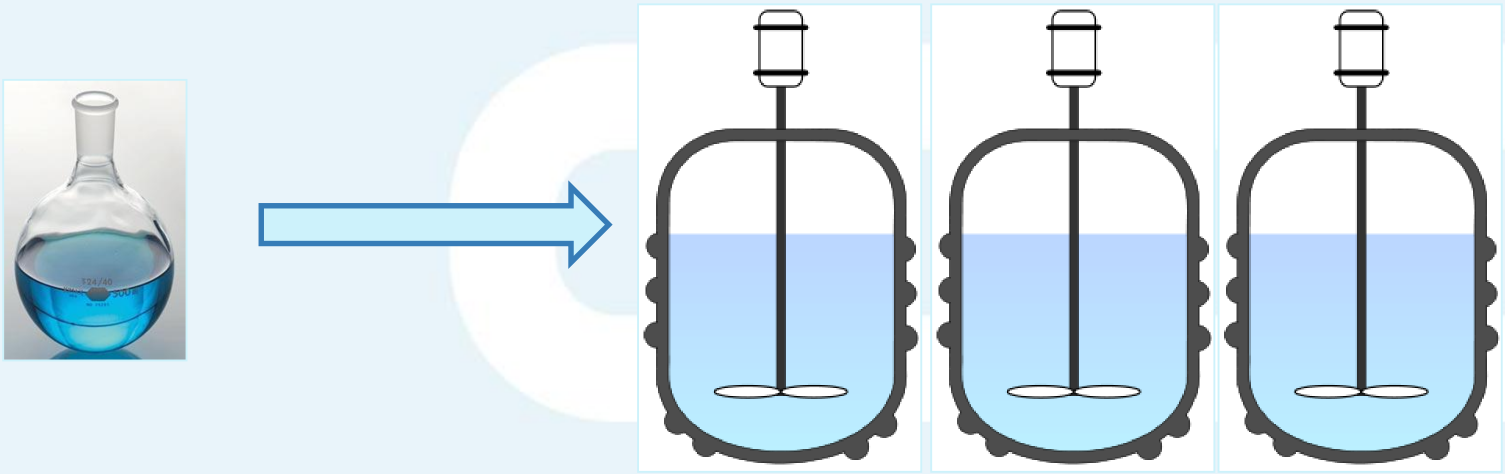
Conventional Synthetic Methodology:

Challenges and Limitations

- If we look to how synthetic chemistry has been taught and performed, little has changed over the past century, with all chemists being familiar with **standard glassware** and equipment

Batch Reactions:

- In batch reactions parameters such as time, temperature, stoichiometry, order of addition and solvent are investigated with the aim of increasing yield and product purity
- If more product is required then a **larger vessel** is normally employed



- Changes in **surface to volume ratio** mean that differences in thermal and mass transfer occur and reactions often need to be re-optimised

Fundamentals of Flow Chemistry:

Key Features of a Flow Reactor

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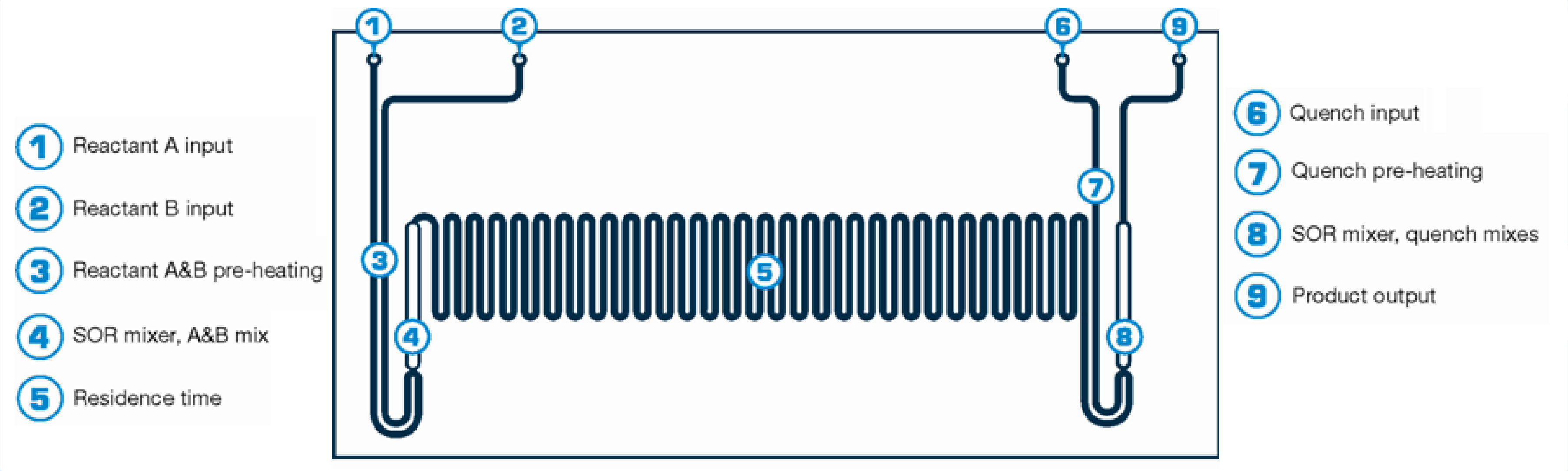
With all of this in mind, when considering process development for scale-up, **PROCESS UNDERSTANDING IS KEY**, an ideal flow reactor for process development employs;

- Pre-heating to give assurance of reaction temperature & active thermal regulation
- Rapid mixing to maximise reactor volume used for reaction
- *In-situ* quenching to stabilise product(s) & prevent decomposition (where needed)

→ Giving the necessary process understanding required for scale-up



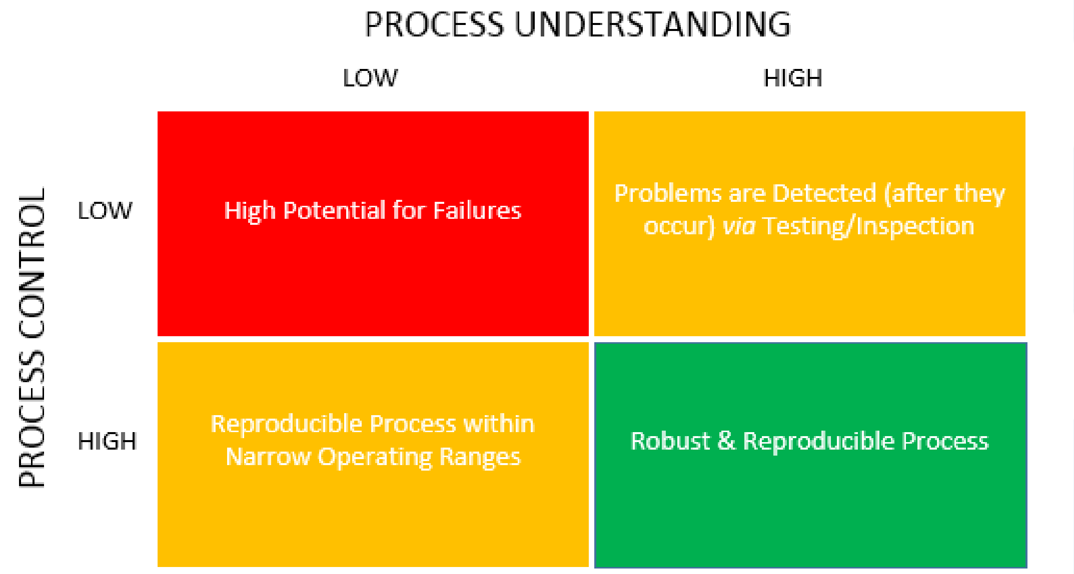
Fundamentals of Flow Chemistry:

Opportunities for Greater Process Control

Flow reactors give the user repeatable control over heat transfer & mass transfer properties

Couple this with ‘Advanced Process Control (APC)’ strategies which have the ability to perform corrective actions that mitigate process disruptions

1. Define target product quality profile & design a manufacturing process to meet target
2. Identify & control critical raw material attributes, process parameters & variability
3. Process is monitored & adapted to produce consistent quality over time



		PROCESS UNDERSTANDING	
		LOW	HIGH
PROCESS CONTROL	LOW	High Potential for Failures	Problems are Detected (after they occur) *via* Testing/Inspection
	HIGH	Reproducible Process within Narrow Operating Ranges	Robust & Reproducible Process

How to Approach Continuous Manufacturing:

Getting Started

In order to maximise benefit of a new method of chemical manufacture, you must;

- Understand the process that you want to perform
- Define the acceptable product quality & target production rate
- Determine the manufacturing strategy – campaign based or 8000 h/annum operation
- Evaluate at the lab-scale the parameters that influence the product &/or by-products
- Assess the reactor options available & their suitability towards the process
- Intensify the process to maximise unit productivity
- Determine commercial viability of continuous vs. existing batch production

Q - What do you need to achieve to be commercially viable vs. existing infrastructure?

F3 Factory project (DE) reported;

- **30 % Reduced energy consumption**
- **100 % Reduction in solvent usage (solvent-free)**
- **40 % Reduction in off-spec products and 10 % reduction in product re-working**

Continuous Processing:
What Scale & What Equipment?

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Depending on the scale that you want to use continuous processing, you may want to consider different aspects;

Flow principles can be applied to >14 orders of magnitude in scale, from earliest chemistry to late manufacturing

nano | micro | meso | kilo lab | pilot plant | manufacturing

ng → µg → mg → g → kg → 10 kg → 100 kg → multi-ton

<u>Lab-scale:</u> **mg-g**
- Speed
- New reaction space
- Selectivity
- Flexibility

<u>Process R&D:</u> **g-kg's**
- Speed
- Safety
- Robustness

<u>Production:</u> **kg's to multi-tonnes**
- Speed
- Safety
- Robustness
- Cost reduction
- Quality

1. What process?
2. What production volume & production rate?
3. Heat & mass transfer requirements

<u>Example:</u> Micro reactors are not used to produce tonnes & spinning disks not for mg's

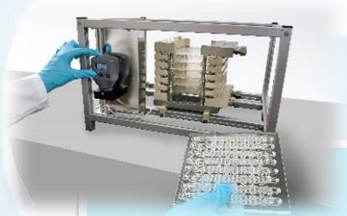
Innovative Technology:
Scalability & System Flexibility

DISCOVERY

Labtrix®
(µg to mg’s)

- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

DEVELOPMENT



KiloFlow®
(g to kg’s)

- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

Protrix®
(g to kg’s)

PRODUCTION

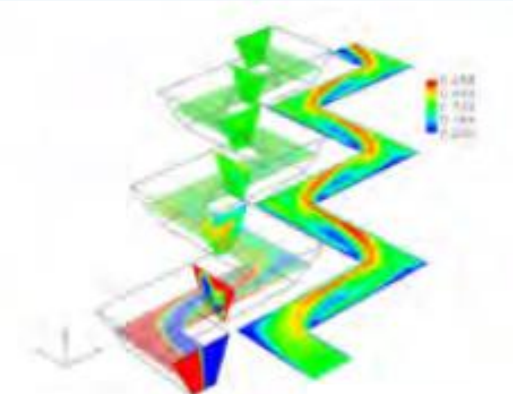
Plantrix®
(kg to 1000’s of ton’s)

- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

Fundamentals of Flow Chemistry:
Production Scale

As the advantages of flow reactors stem from the small dimensions, channels must be designed for secondary flow;

- Maintain plug flow
- Afford efficient mixing (along the flow path)
- Have a low pressure drop

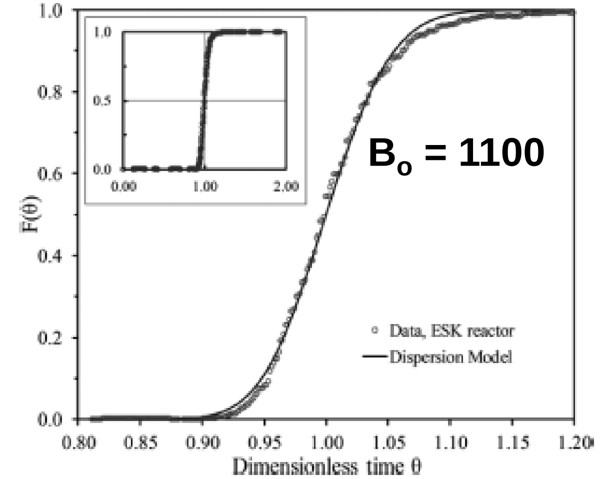


Choose function specific channel types;

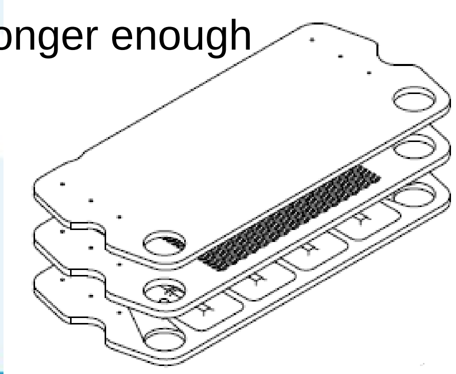
- Mixing – smaller, high thermal demand
- Residence volume – large, low pressure drop

Employ efficient thermal regulation;

- Electric heating or air cooling is no longer enough
- Thermal fluid frequently used



Measured F-function and model fits for the ESK production reactor at a total flow rate of 50 mL/min.



Ref: OPRD, Roder *et. al*

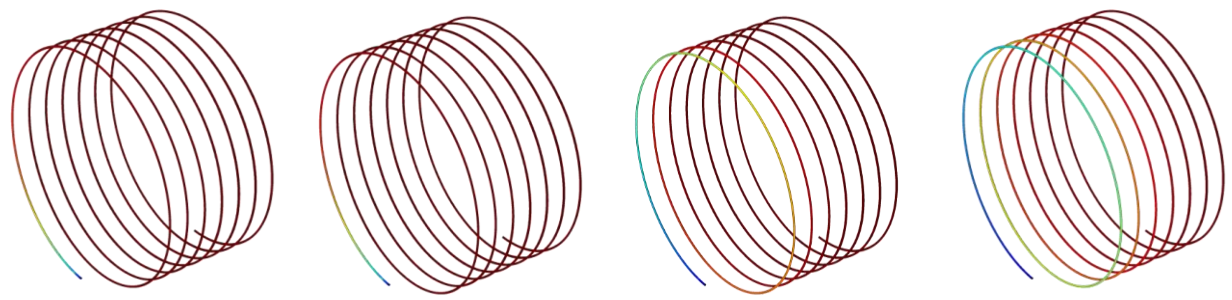
Fundamentals of Flow Chemistry:

Thermal Control

Techniques for thermal control include;

- Water or oil bath; Hot plate or Peltier; Re-circulating thermostat or hot air

Materials of construction, thermostat technique & reaction channel size all influence the thermal efficiency of a flow reactor

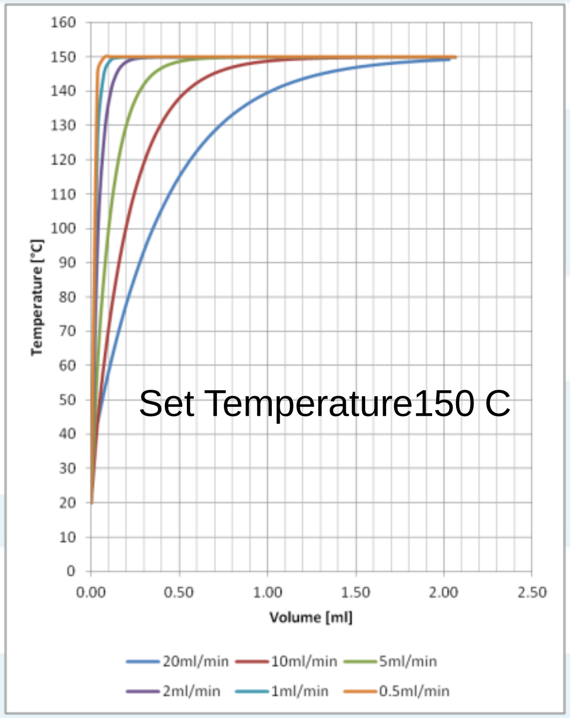


0.5 ml min^{-1} 5 % (for T_{set})

2 ml min^{-1} 10 %

10 ml min^{-1} 80 %

20 ml min^{-1} 95 %



Set Temperature150 C

Increasing flow rates need increasing volumes to reach T_{set}

- Reducing effective reaction volume
- In some cases you do not reach the set temperature

Consider also removal of heat in the case of exothermic reactions;

- If you are only inputting heat an exotherm will not be controlled

Fundamentals of Flow Chemistry:

Production Scale

Thermal control is important for obtaining a high product yield & selectivity;

- Integrated heat exchangers combined with a TF provide the most efficient regulation
- High surface area to volume ratio *cf.* batch
- Rapid temperature change *cf.* batch
- Multiple temperature zones allow process needs to be met

Sandwich construction of process & service channels give highest degree of thermal control

- Low DP for service fluid layer allows high flow *cf*. process fluid
- **Braze-free**, sintered modules give increased pressure & chemical resistance

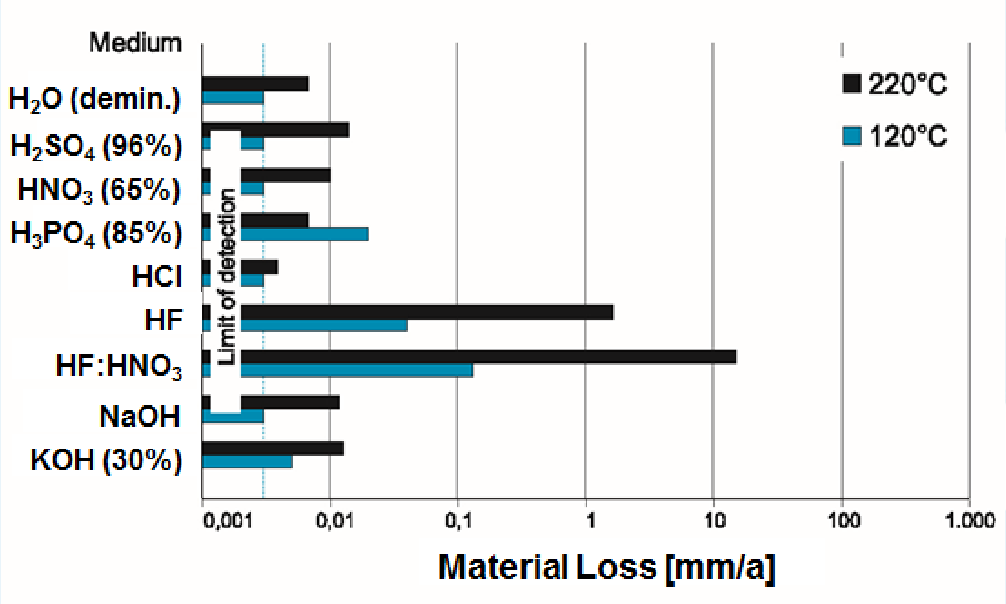

TÜV SÜD

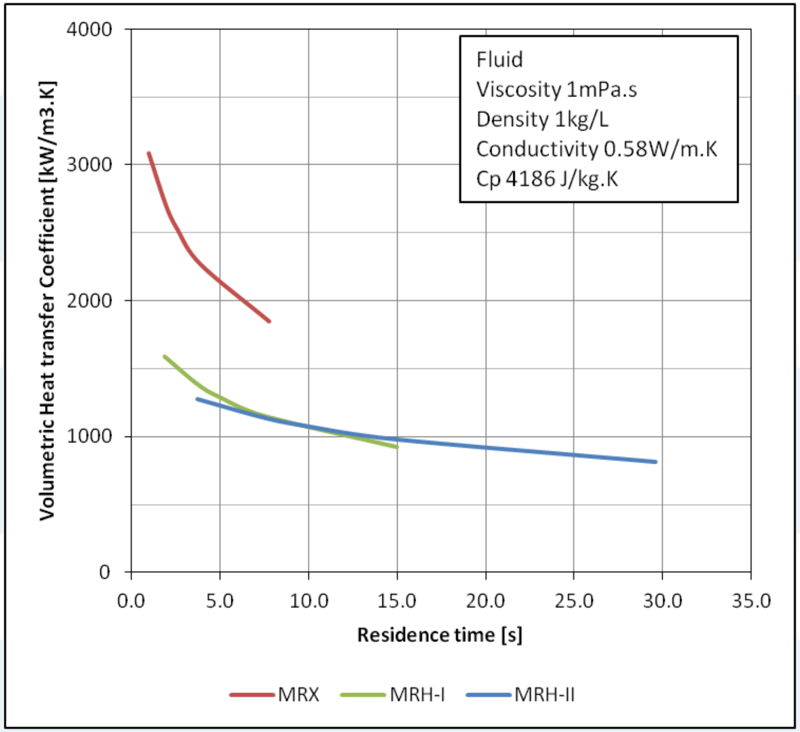
Fundamentals of Flow Chemistry:

Production Scale

Materials of construction must be carefully selected to ensure;

- Long term stability to reaction conditions
- High fouling resistance
- Required thermal performance
- Manufacturability at intended scale

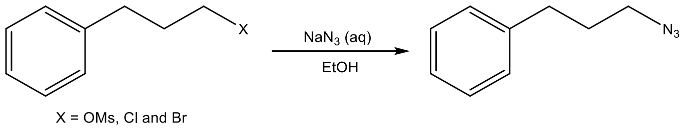




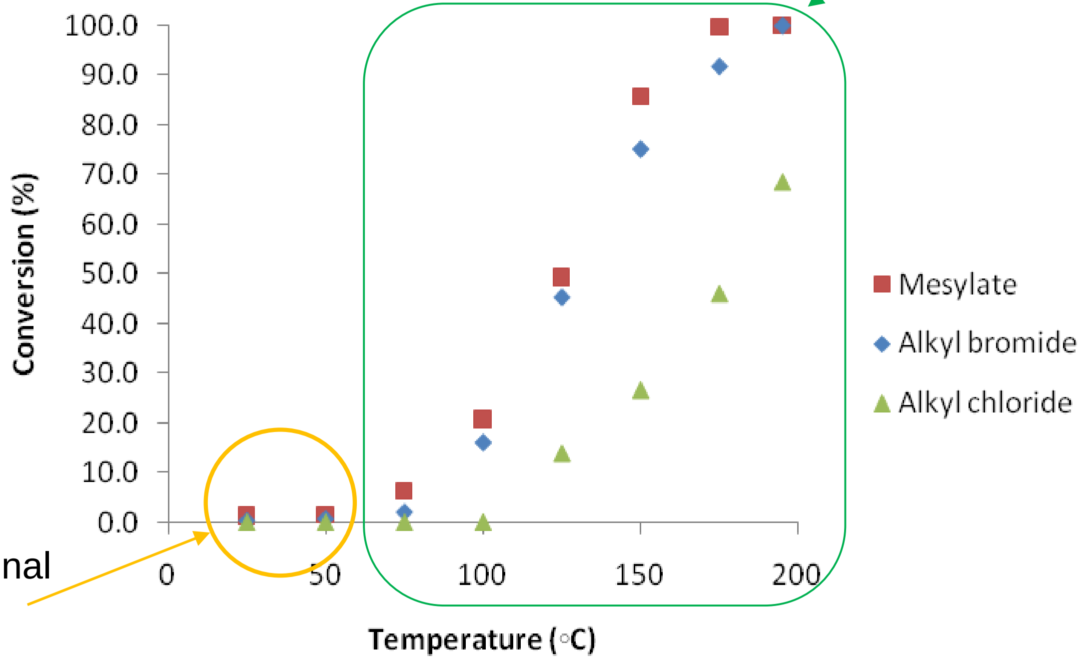
3M™ SiC Grade C – Continuous operation for 2.5 yr, 180 °C with 50 % aq. NaOH

Continuous Azidation using Labtrix®:

Manipulation and Formation of Hazardous Materials



‘Novel Operating Window’ at the mg-scale



Decreasing material costs

Limit of conventional batch glassware

Advantages:

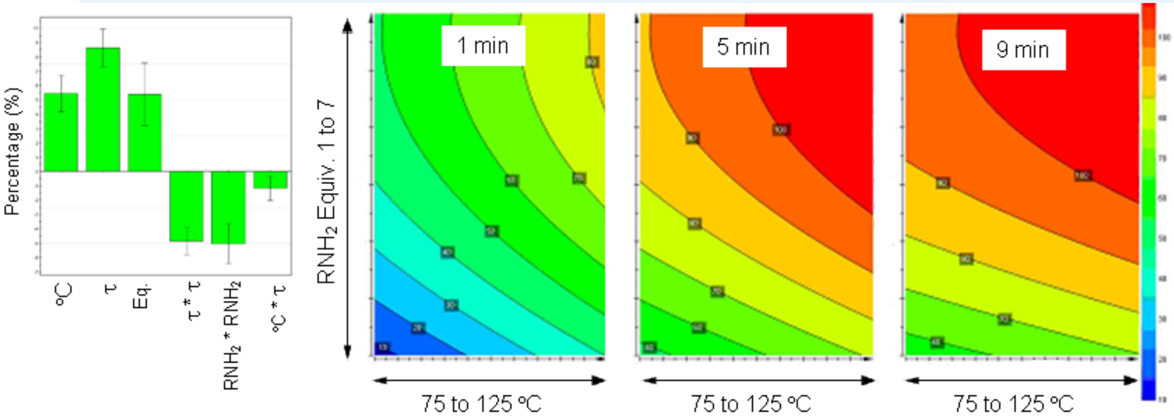
- New reaction space (temperature & pressure)
- Use small quantities of hazardous material
- Assess reagent types impact on cost of goods

Used in Rufinamide synthesis by Hessel *et al.*[1]

[1] Hessel, *Green Chem.*, 2015 DOI:100.1039/C5GC01932J

Rapid Reaction Optimisation using Labtrix®:
Design of Experiment (DoE)

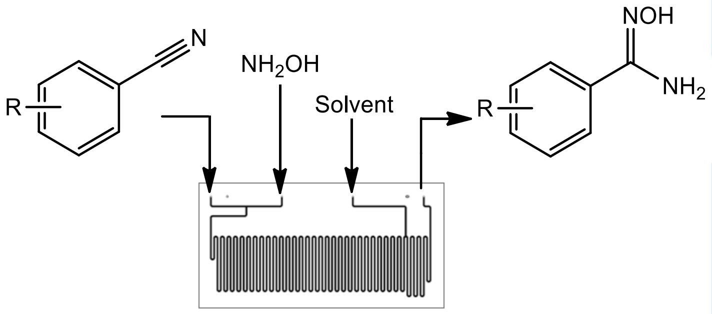
Combining micro reactors & DoE, Sanofi (Budapest) used Labtrix®-S1 to develop a process for the large-scale synthesis of amidoximes



Advantages:

- Fast - only 17 reactions required
- Metal-free reactors - ‘safety concerned reagents’
- Identify interaction effects in complex reactions
- Determine cost effective conditions for manufacture

Results used to scale x450 for material production

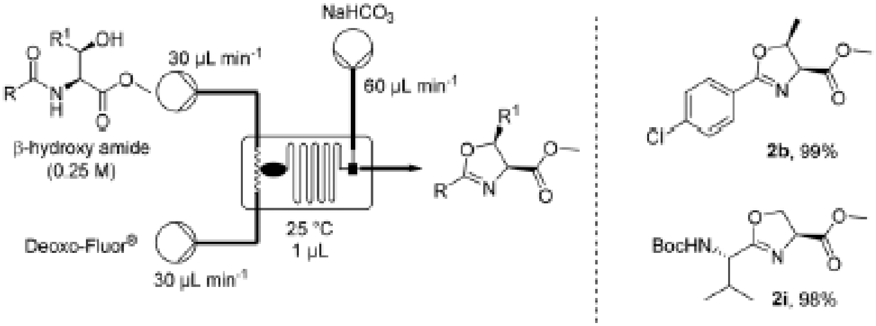


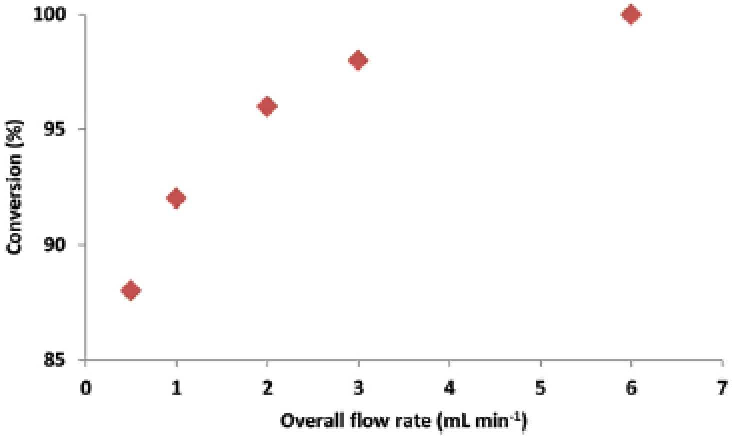
Org. Proc. Res. Dev., **2012**, *16* (11), 1717–1726.

Cyclodehydration using Labtrix®:

Rapid Mixing to Afford Reaction Times < 1 s

Employing Deoxo-Fluor®, Ley and co-workers demonstrated a series of cyclodehydrations



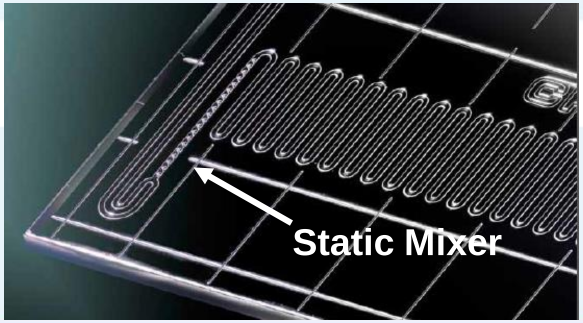


- Using a tube reactor the reaction was found to be flow rate dependent = mixing limitation

Employing Labtrix® affords rapid mixing - enabling reaction times of 100 s to be reduced to 1 s

<ins>Advantages:</ins>

- High yields *cf*. batch
- Rapid process development
- 100 x reduction in reaction time *cf*. tube
- Scalable



Ley & Battilocchio, *Org. Biomol. Chem*., 2015; DOI: 10.1039/c4ob02105c

Multi-step Reactions using KiloFlow®:

Flow4API – Consortium led by TNO

Synthon

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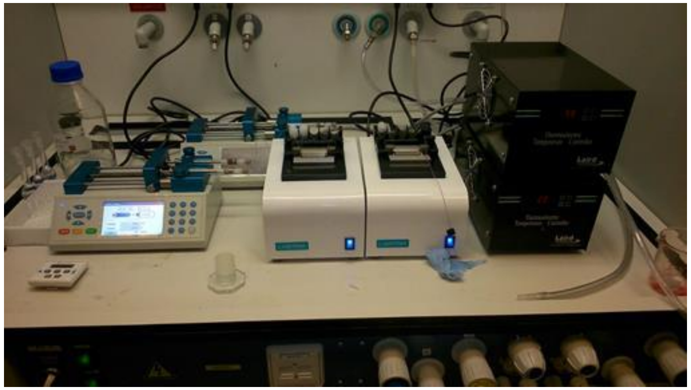
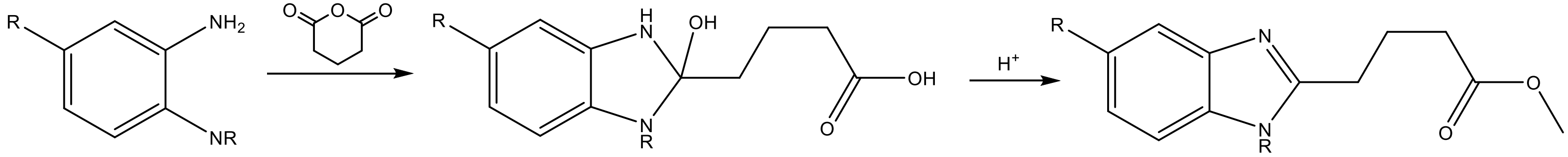




Disadvantages:

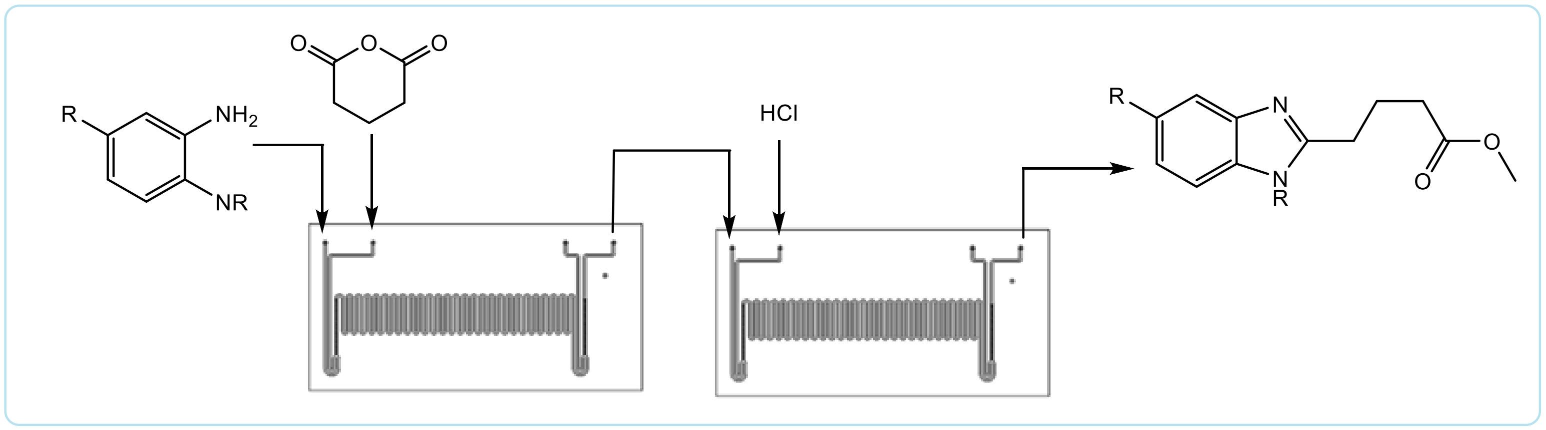
- Different temperatures for both steps
- Unstable intermediate on isolation
- Excess anhydride
- Complex purification

METTLER TOLEDO

Exploration of Reaction Space using Labtrix®:

Telescoping at the Micro-scale

Connecting two Labtrix® Start systems in series, the reaction steps were telescoped to confirm the ability to perform the reactions without purification;



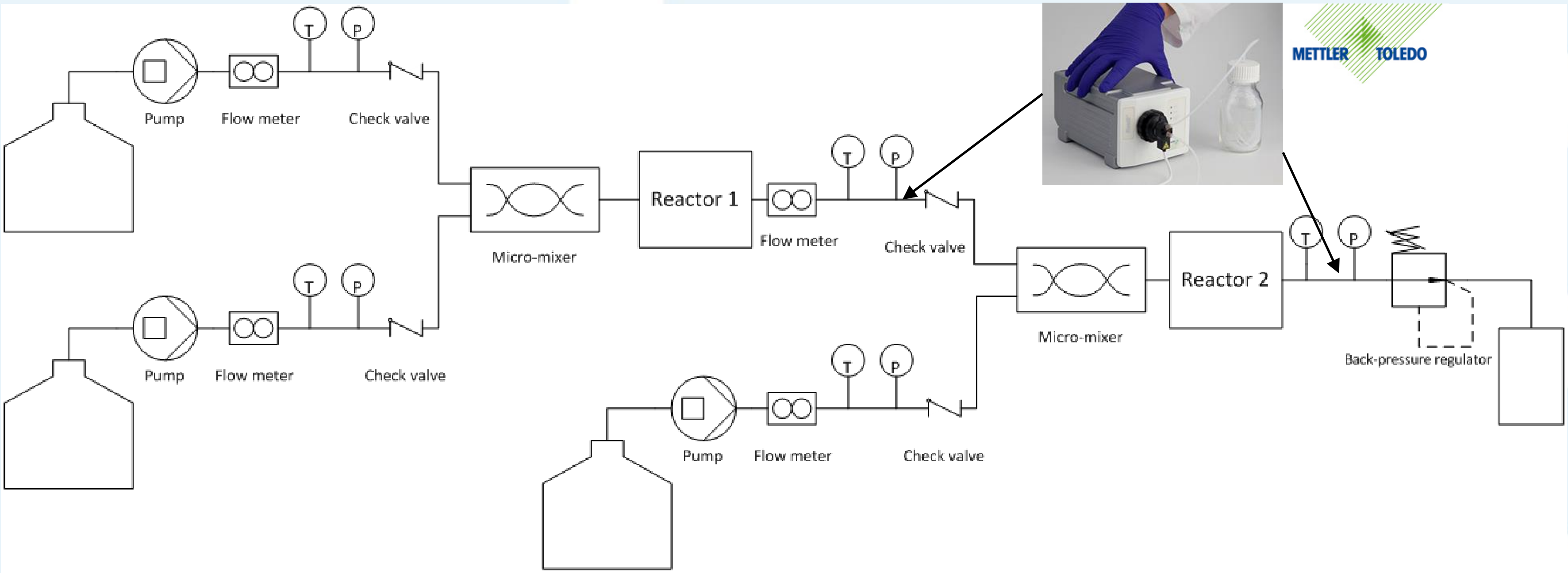
Offline analysis confirmed ester formation

- No in-line analysis performed at this stage
- Allowed ‘Cold’ Step 1 & ‘Hot’ Step 2
- Reduced excess of anhydride
- No intermediate isolation
- Same reaction solvent throughout

Facile Up-scaling from Labtrix® to KiloFlow®:

Scale-up of Telescoped Reactions

Having identified the optimal conditions for each step & demonstrated at the micro-scale the ability to connect the steps in series, plans for up-scaling were developed



<u>Goal:</u> Demonstrate at the bench-scale feasibility of telescoping – suitable for 10 kg/y

- Reactor platform selected was KiloFlow®

Facile Up-scaling from Labtrix® to KiloFlow®:

Scale-up of Telescoped Reactions

Bench-scale demonstrator – two thermal zones with in-line IR analysis

- 96.9 % yield *cf.* 96.5 % in Labtrix®

Fundamentals of Flow Chemistry:

Scale Out vs. Scale Up

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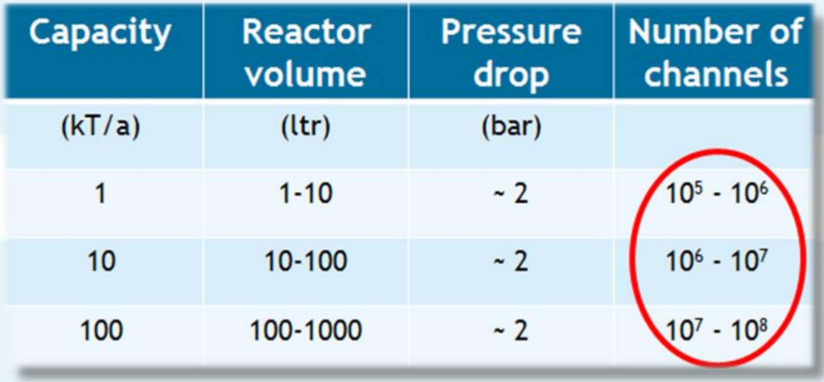
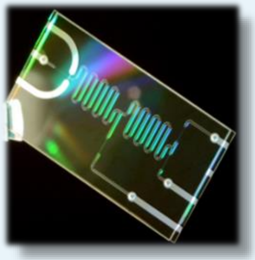
So 10’s ml reactors allow for g-kg production, what if you want to produce at tonne-scale?

- In the early 2000’s, numbering-up was proposed
- Economically unfeasible for most transformations
- Complex peripherals & flow distribution



Capacity	Reactor volume	Pressure drop	Number of channels
(kT/a)	(ltr)	(bar)	
1	1-10	~ 2	$10^5 - 10^6$
10	10-100	~ 2	$10^6 - 10^7$
100	100-1000	~ 2	$10^7 - 10^8$



100 µm

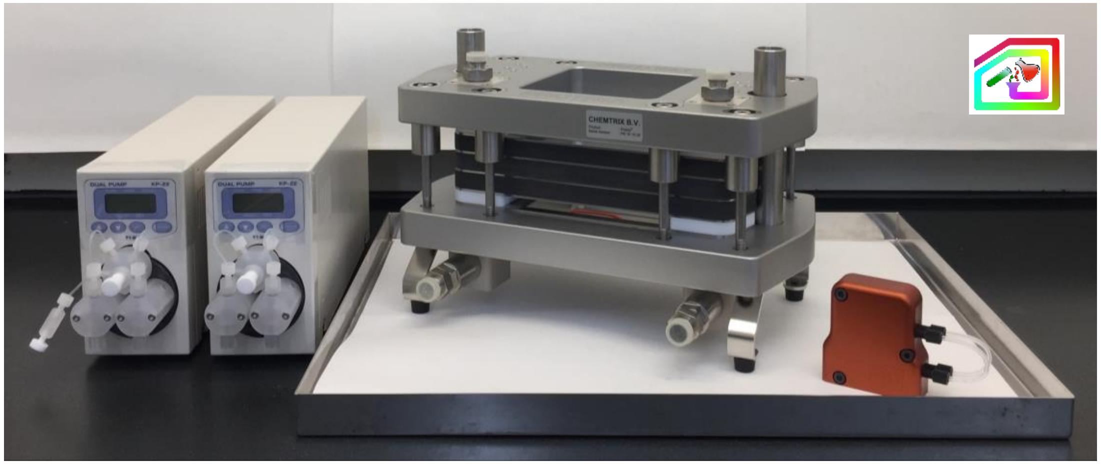
1-4 mm

Smart dimensioning is key;

- Increase channel dimensions & maintain the key properties;
  - Efficient mixing
  - High thermal control
  - Select a material of construction suitable for long-term use

SiC Corrosion Resistant Flow Reactors:

Pilot to Production Scale - Protrix® & Plantrix®



	Lab-scale	Production-scale
Reactor Volume	~1 to 12.5 ml	4000 ml
Flow Rate (ml min^{-1})	0.2 to 20	400 l/h
Scale Ratio	1/340	1
Working Name	Protrix®	Plantrix® MR555

* Patented bonding technique = braze-free reactor modules

Fundamentals of Flow Chemistry:

Production Scale

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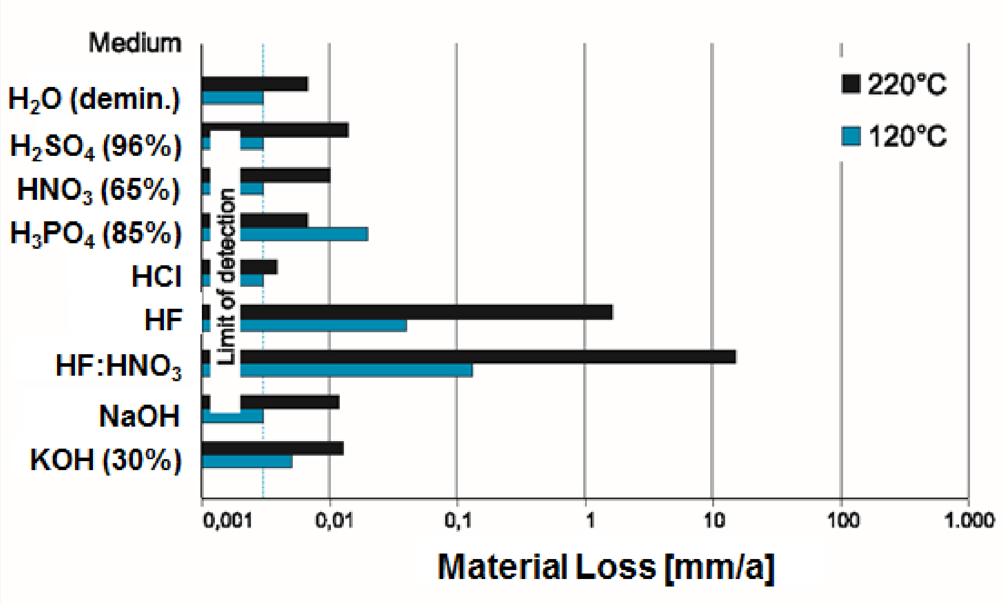
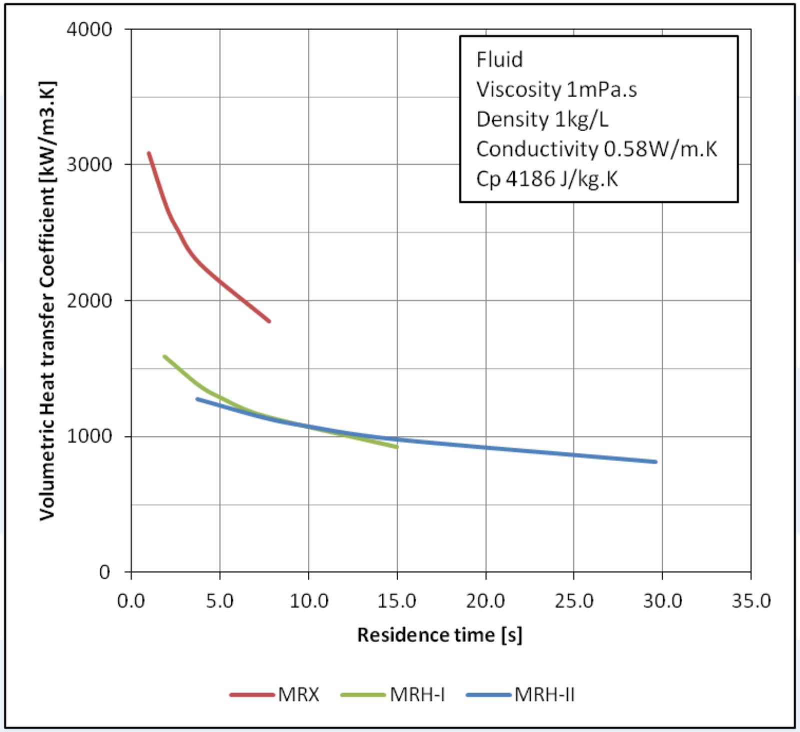
Materials of construction must be carefully selected to ensure;

- Long term stability to reaction conditions
- High fouling resistance
- Required thermal performance
- Manufacturability





3M^{TM} SiC Grade C – Continuous operation for 2.5 yr, 180 ^{o}C with 50 % aq. NaOH

Plantrix® Industrial Flow Reactors:

Intensified Processing Conditions

Strategic Partner of 3M

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Owing to the excellent thermal & corrosion resistance of 3M™ SiC, users employ Plantrix® in harsh environments, for example;

- Lithiations
- Nitrations
- Oxidations
- Chlorinations
- Brominations
- Fluorinations
- Wolff-Kishner reductions
- Alkylations
- Thioacetalisations
- Basic hydrolyses
- Controlled polymerisations (RAFT)
- Diels-Alder reactions

Suitable for control of exothermic processes

- Plantrix® MR260 U = 10,000 $Wm^{-2}\ K^{-1}$ at 25 l/h H_2O

Plantrix® Industrial Flow Reactors:
Customer Application

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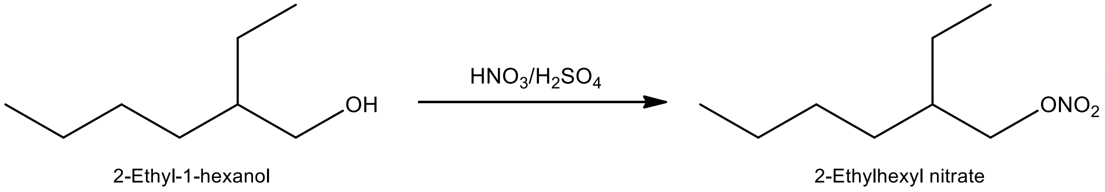
The synthesis of energetic materials *via* nitration reactions can be problematic owing;

- Inefficient heat & mass transfer

→ Strong exotherms lead to by-product formation & product decomposition

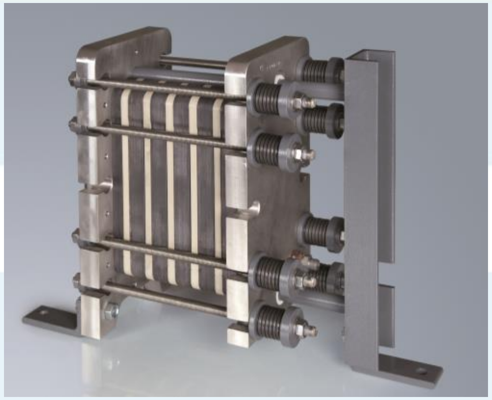


$HNO_3:H_2SO_4$	HNO_3:hexanol (eq.)	Product	By-product
1:0	3.1	×	×
1:0.286	2.5	×	✓
1:0.767	1.5	Minimal	✓
1:1.130	1.25	✓	✓
1:1.726	1.0	✓	×

✓ No by-product formation observed under optimal conditions

<u>Advantages:</u>

- Small hold-up volume
- Rapid mixing & efficient heat transfer allows intensified process
- Solvent-free production technique
- Metal-free modules facilitate use of highly corrosive reagents



Plantrix® Industrial Flow Reactor:
Customer Application

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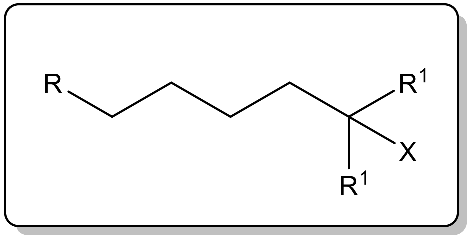


Challenges in Batch:

- Corrosive reagents & product
- Highly exothermic reaction (~ 150 kJ mol^{-1})
- High dilution employed & reaction prone to polymerisation

Optimised in Labtrix®, scaled in Plantrix® - failed in tubular reactor (due to poor heat exchange)

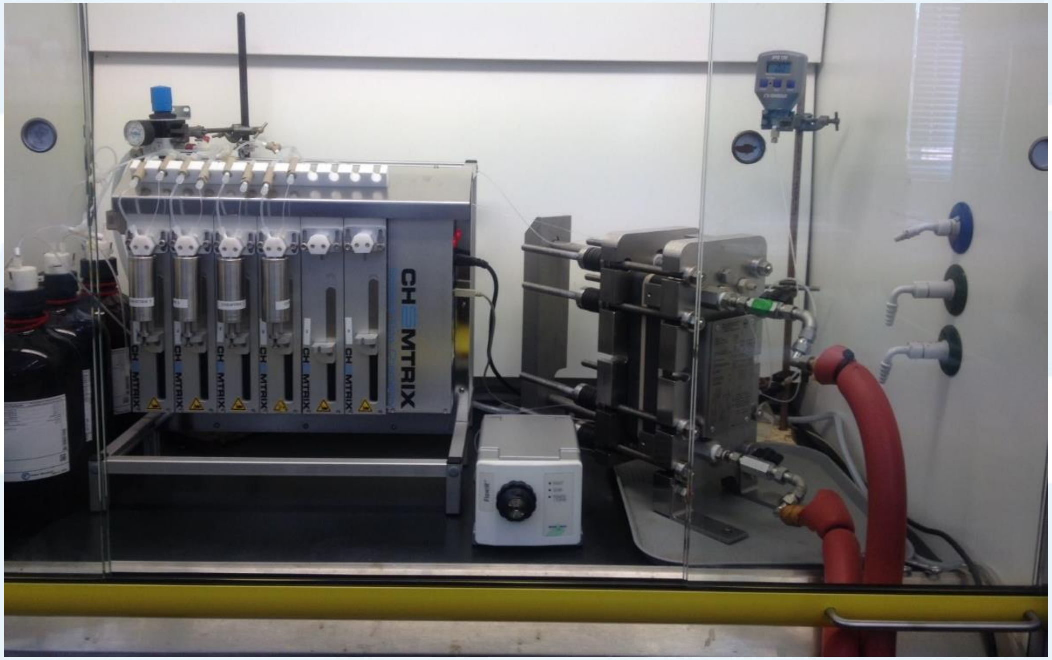
Process Conditions:

- Reaction time = 120 s
- Reaction temperature < 100 °C
- Throughput = 2.1 l/h

= ~ 16 tonne/annum production

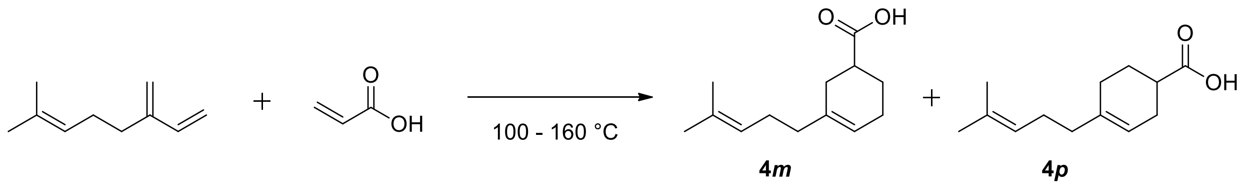
Advantages:

- Thermal control = intensification
- Metal-free reactors
- Increased product purity
- Reduced isolation costs

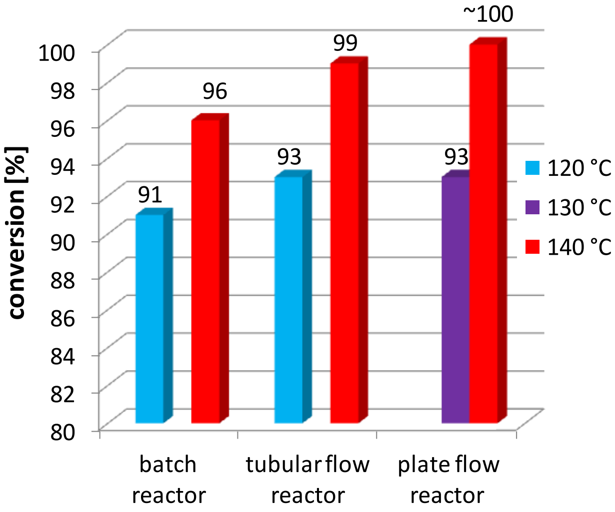


Plantrix® Industrial Flow Reactor:

Customer Application – Fragrances



tubular flow reactor
(Vapourtec R-series)



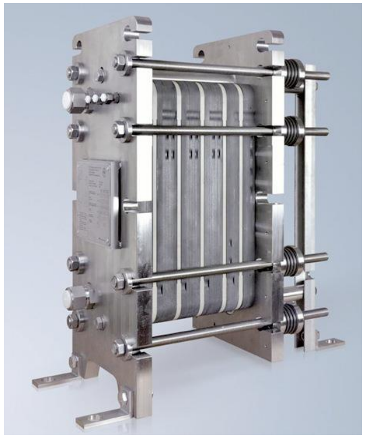


plate flow reactor
(Chemtrix MR260)

Failed in SS tubular reactor
- Memory effects of metal

Process Conditions:

- Reaction time = 30 min; Reaction temperature 160 °C; Throughput = 2.8 kg/day

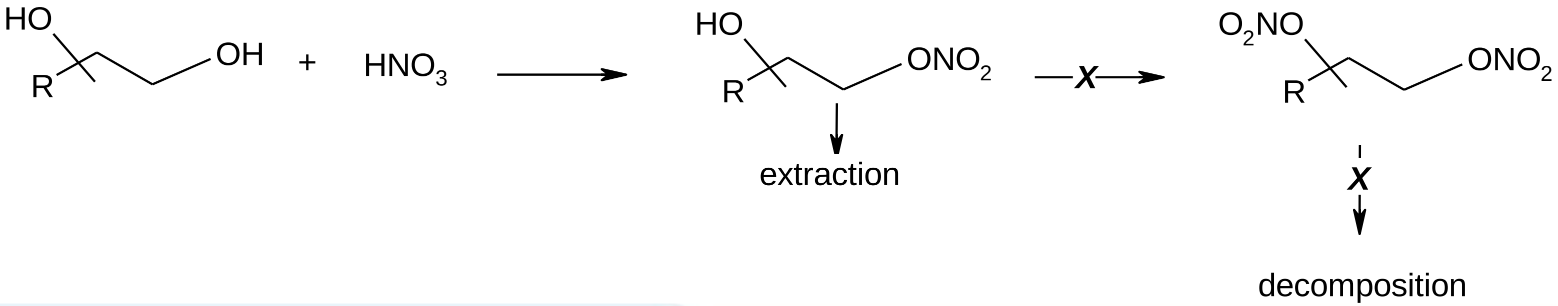
Advantages:

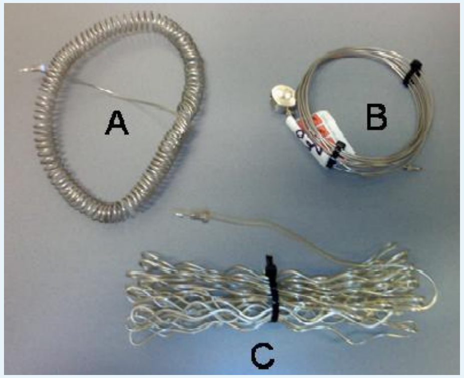
- Production technique for a novel surfactant & fragrance
- Thermal control prevented side reactions & polymerisation

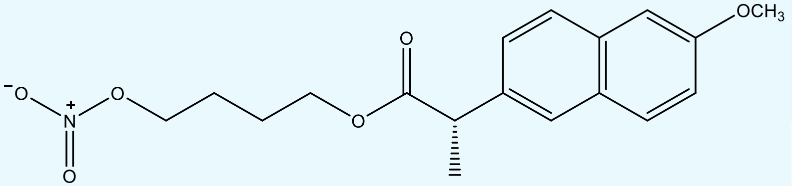
1. Hornung *et al. Beilstein J. Org. Chem*, 2016 in press.

Plantrix® Industrial Flow Reactor:

Customer Application







Reaction Challenges:

- Biphasic
- Competing dinitration & decomposition products
- Corrosive media
- Challenging product isolation

- Initially the reaction was investigated in a series of tube reactors (as illustrated)
    - A need for continuous mixing was identified

Plantrix® Industrial Flow Reactor:

Customer Application

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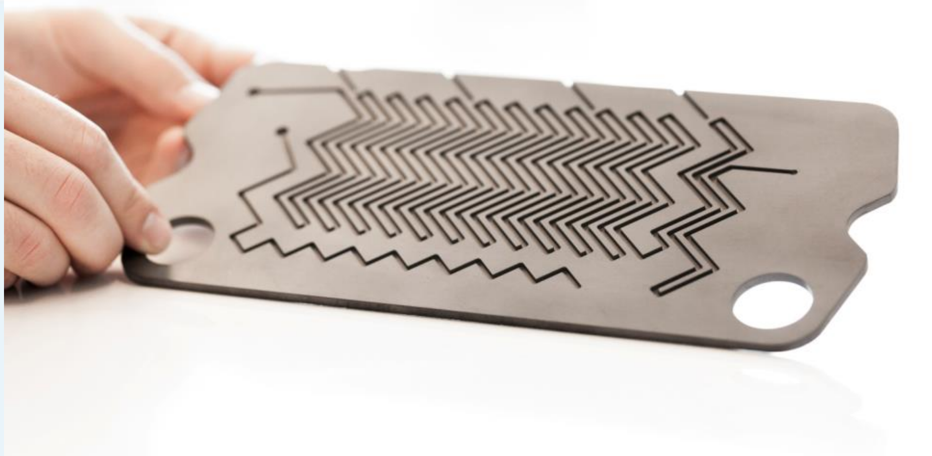
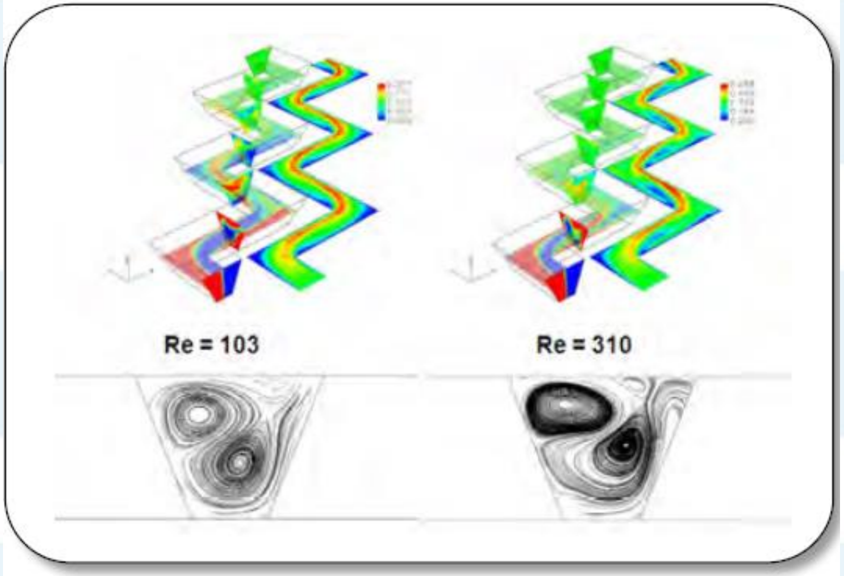
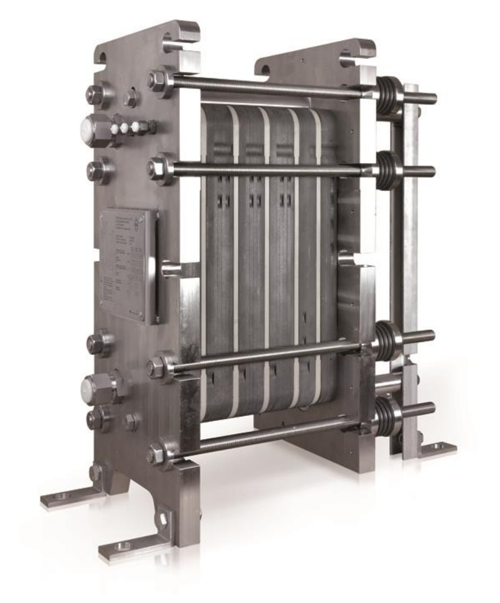






Plantrix® gave DSM;

- Continuous mixing
- Thermal control
- High corrosion resistance
- High productivity

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

DSM uses Micro Reactors made of 3M$^{\text{TM}}$ (SiC) in a pharmaceutical production plant

Plantrix® Industrial Flow Reactor:

Customer Application

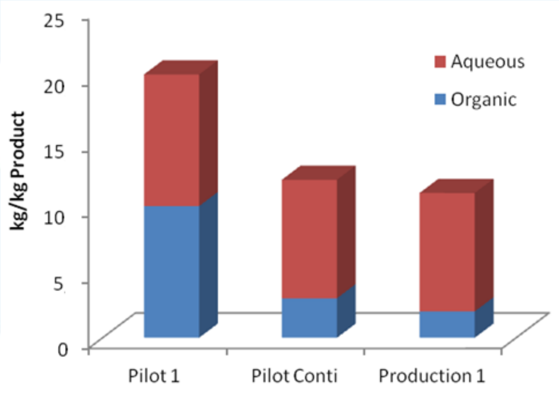
Strategic Partner of 3M

CHEMTRIX

cGMP Continuous Production

Solution - Plantrix®:

- Compact
- Robust
- Corrosion resistant
- Quality
- Solvent reduction



Tonne scale API production

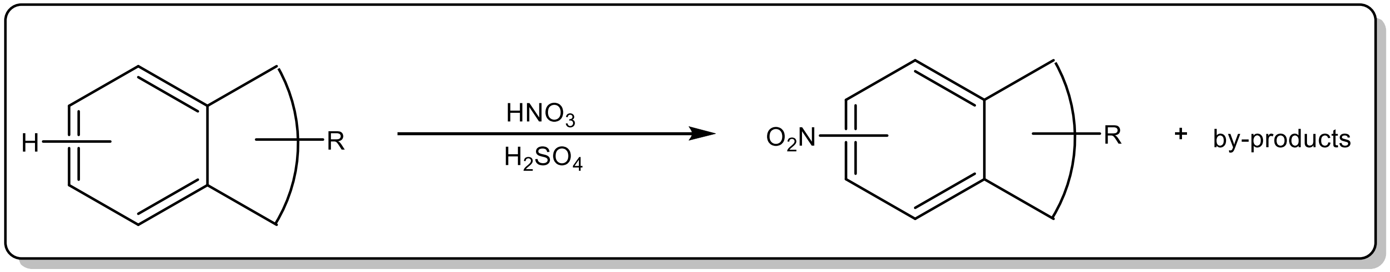
DSM uses Micro Reactors made of $3\mathrm{M}^{\mathrm{TM}}$ (SiC) in a pharmaceutical production plant

Plantrix® Industrial Flow Reactor:

Customer Application

Strategic Partner of 3M

CHEMTRIX



Challenges in Batch:

- Corrosive reagents & unstable product
- Highly exothermic reaction
- High dilution employed
- Not possible in batch at > 15 l scale

Advantages:

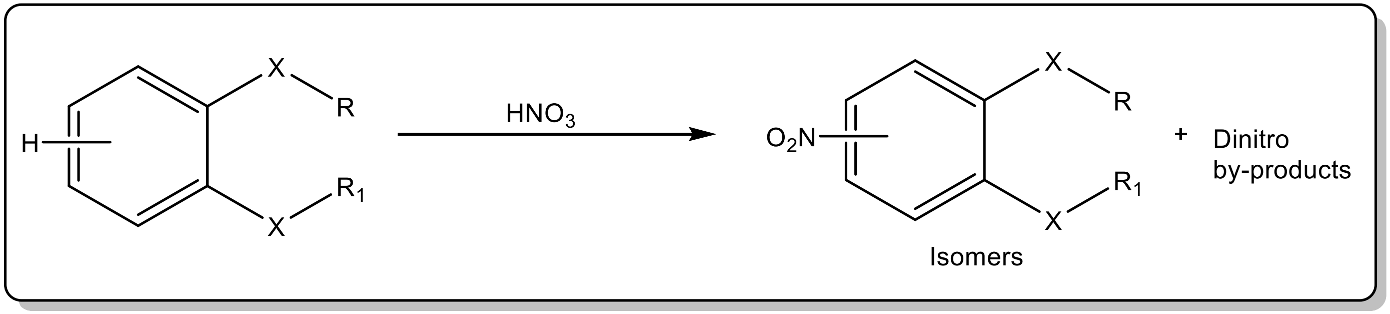
- Thermal control = increased safety
- Solvent-free process
- Increase production rate of material
- Target product specification achieved

Process Conditions:

- MR260 = 5.0 l/h; MR500's = 697 l/h

Plantrix® Industrial Flow Reactor:

Aromatic Nitration



Challenges in Batch:

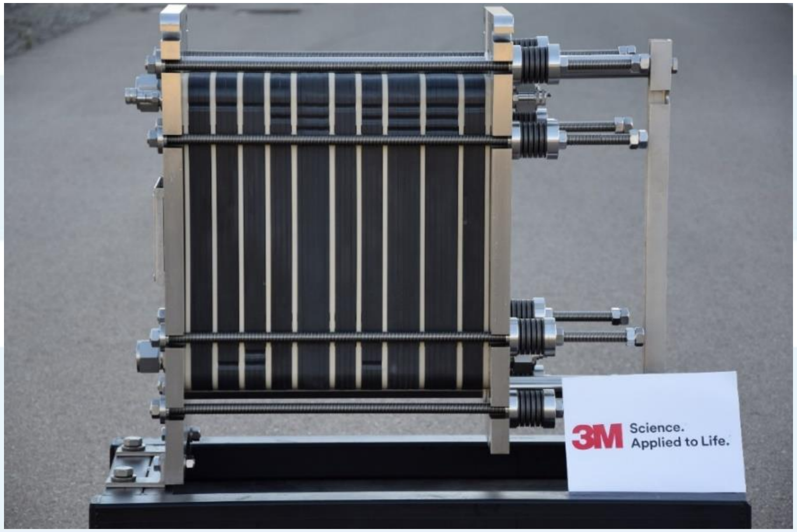
- Excess HNO_3 required
- Significant impurity
- Safety risk
- High volume of effluent

Advantages:

- Thermal control = increased safety
- No competing di-nitro
- Stoichiometric HNO_3
- Target product specification achieved

Process Conditions:

- Pilot = 5.6 l/h
- Target = 100-150 tonnes/annum



Plantrix® Industrial Flow Reactor:

Customer Highlights

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Peracid Synthesis:

- Highly exothermic – thermally sensitive product
- For direct use – no storage required - target 250 kg/h – operated at 11 s

Dakin Oxidation:

- Metal-free reactor reduces Customers risk of H_2O_2 handling
- 15 s reaction time *cf*. 6 h in batch & reduced caustic soda

Oxidative Effluent Treatment:

- Highly energetic – not scalable in batch beyond ml scale
- Waste valourisation application – increased batch process sustainability

Epoxidation using PAA:

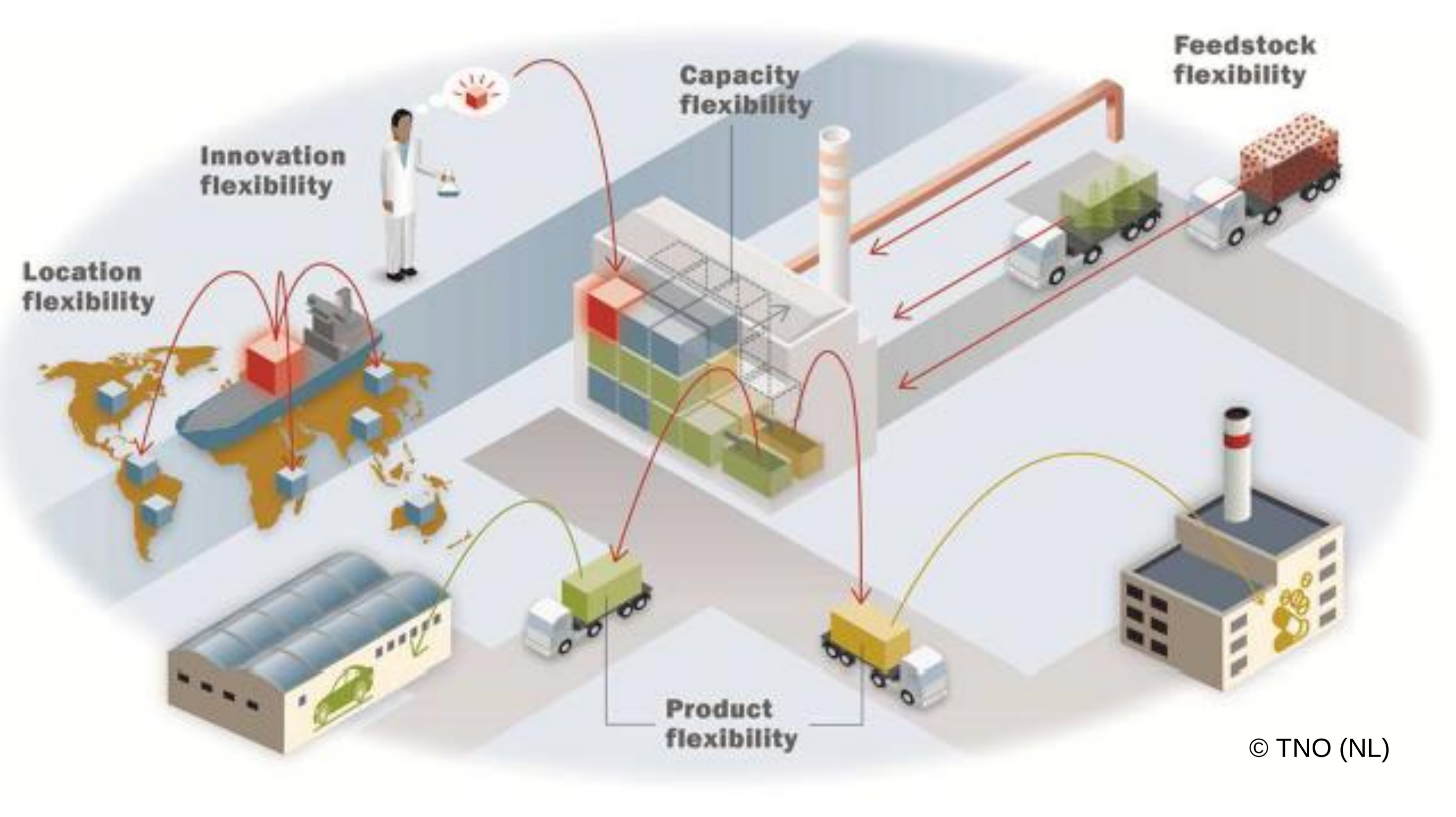
- Selectivity increase compared to batch
- Dramatic reduction in reaction time 8 h to 15 - 40 s (Substrate dependent)

Lithiation using n-BuLi:

- Multi-step, lithiation – 15 sec processing 20 kg n-BuLi/8 h shift at -10 °C

Is it Time for a Change of Business Models & Manufacturing Strategies?

- World plants vs. Distributed manufacture



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- Dedicated vs. Flexible (plants & product types)

FDA Support for Continuous Manufacturing:

Review Article Journal of Pharmaceutical Innovation
September 2015, Volume 10, Issue 3, pp 191-199

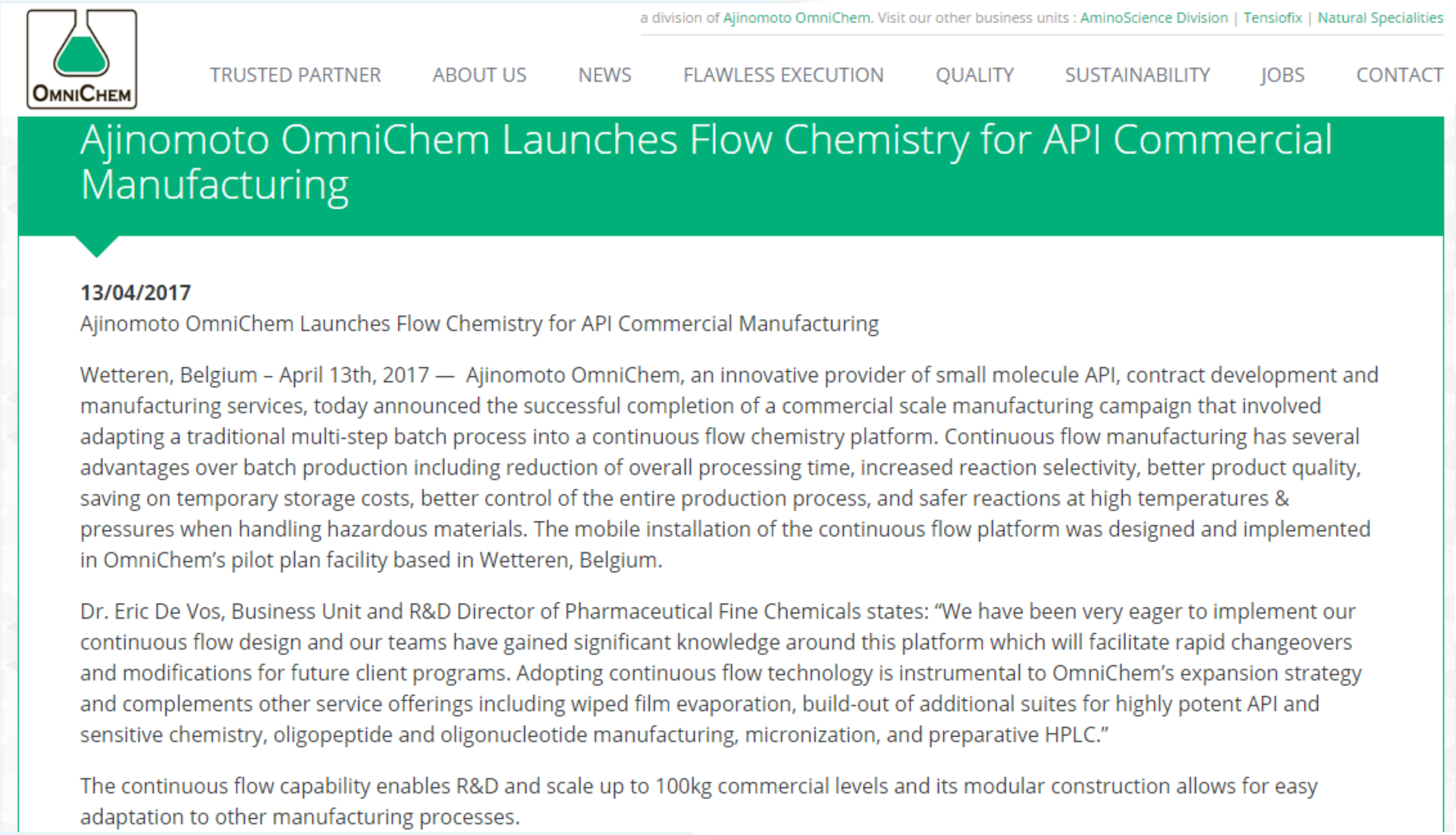
Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

Lawrence X. Yu and colleagues
Office of Pharmaceutical Quality, Center for Drug Evaluation and Research,
Food and Drug Administration

"Though making the switch from batch to continuous manufacturing may be difficult, costly and time consuming, pharma manufacturers and CMOs should begin to consider the switch as in the long-run it will end up saving companies time, money and space, ***FDA's Director Janet Woodcock*** told congressmen in a hearing Thursday."
http://www.in-pharmatechnologist.com/Processing/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production

Plantrix® Industrial Flow Reactor:

OmniChem (NV) CRAMS



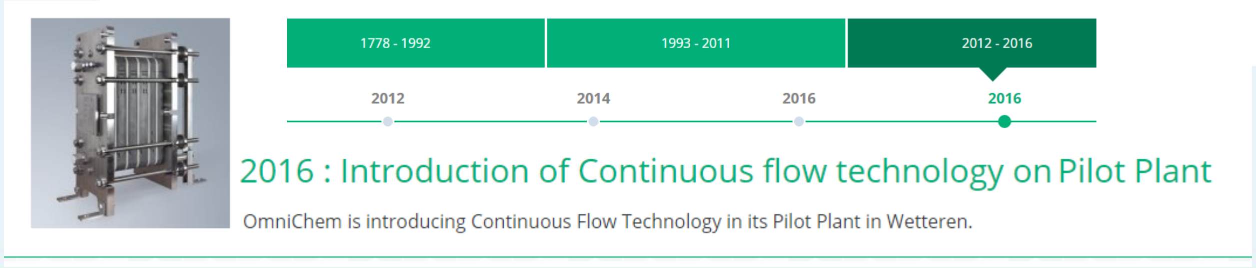
Ajinomoto OmniChem Launches Flow Chemistry for API Commercial Manufacturing

13/04/2017
Ajinomoto OmniChem Launches Flow Chemistry for API Commercial Manufacturing

Wetteren, Belgium – April 13th, 2017 — Ajinomoto OmniChem, an innovative provider of small molecule API, contract development and manufacturing services, today announced the successful completion of a commercial scale manufacturing campaign that involved adapting a traditional multi-step batch process into a continuous flow chemistry platform. Continuous flow manufacturing has several advantages over batch production including reduction of overall processing time, increased reaction selectivity, better product quality, saving on temporary storage costs, better control of the entire production process, and safer reactions at high temperatures & pressures when handling hazardous materials. The mobile installation of the continuous flow platform was designed and implemented in OmniChem's pilot plan facility based in Wetteren, Belgium.

Dr. Eric De Vos, Business Unit and R&D Director of Pharmaceutical Fine Chemicals states: "We have been very eager to implement our continuous flow design and our teams have gained significant knowledge around this platform which will facilitate rapid changeovers and modifications for future client programs. Adopting continuous flow technology is instrumental to OmniChem's expansion strategy and complements other service offerings including wiped film evaporation, build-out of additional suites for highly potent API and sensitive chemistry, oligopeptide and oligonucleotide manufacturing, micronization, and preparative HPLC."

The continuous flow capability enables R&D and scale up to 100kg commercial levels and its modular construction allows for easy adaptation to other manufacturing processes.



2016 : Introduction of Continuous flow technology on Pilot Plant

OmniChem is introducing Continuous Flow Technology in its Pilot Plant in Wetteren.

Innovative Technology:

Flow Reactor Benefits

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1. Safe Use of Extreme Reaction Conditions

- Efficient mixing
- Excellent thermal control
- Process intensification of hazardous reactions

2. Reduced Development Time

- Small hold-up volume
- Rapid reaction optimisation
- Minimal scale-up steps

3. Improved Process Control

- High level of reaction control
- Process reproducibility
- Quality by Design (QbD)

4. Reduced Production Costs

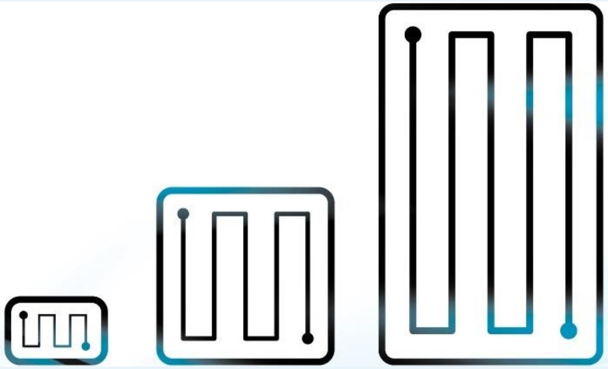
- Increased product quality
- Reduced safety investments
- Higher unit productivity

✓ Efficiency

✓ Quality

✓ Safety

✓ Sustainability



Closing Remarks:
When to Consider Flow?

A significant aspect of flow chemistry relates to performance versus scale

Reducing the reactor size can have a beneficial impact on;

- Heat transfer
- Mixing speed & mixing shear

The degree these parameters affect the process/chemistry is application specific

General benefits of continuous systems;

1. Smaller equipment, smaller buildings & reduced overall plant footprint
2. Energy savings
    - Smaller buildings have lower HVAC costs
    - Less hardware to heat/cool
    - Reduced peak loads on process utilities (smaller boilers and chillers)
3. Greater flexibility, a flow reactor can handle a wider range of throughputs
4. Improved safety via smaller in-process inventories & pressure containment

Let your process/chemistry lead your choice of what to use & what scale!

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