CHEMTRIX

Opportunities for the Development of Sustainable Production Processes

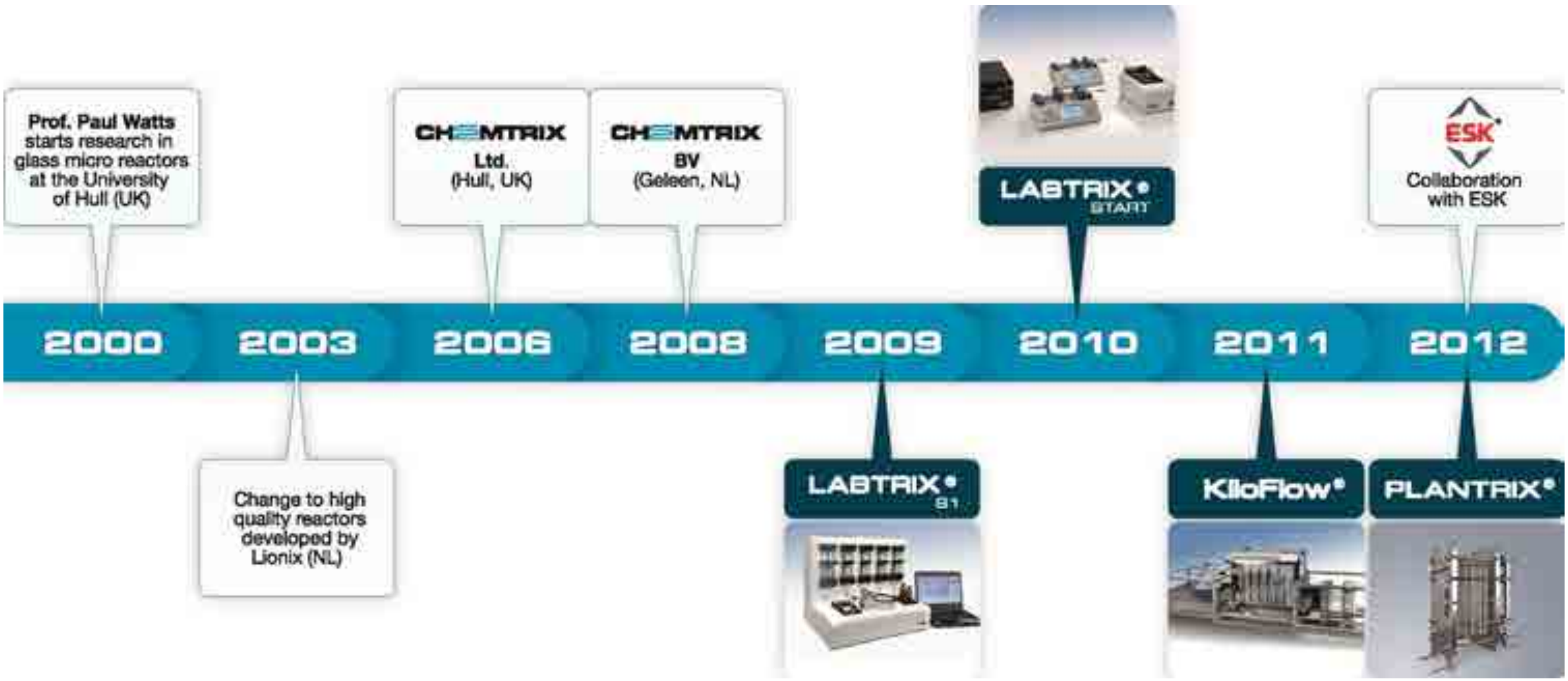
Dr Charlotte Wiles

RSC Waste Not Want Not Symposium, Budapest, Hungary

18-19th June 2014

Strategic Partner of ESK

Chemtrix Company History



More than 13 years experience in Flow Chemistry

Cooperation with DSM since 2012 together offering from concept to delivery solutions

Innovative Technology:
Scalability & System Flexibility

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Labtrix® (µg to mg's)

-20 to 195 ºC

DISCOVERY

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

KiloFlow® (g to kg's)

-15 to 150 ºC

DEVELOPMENT

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

Plantrix® (kg to ton's)

-30 to 200 ºC

PRODUCTION

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

Customised solutions are also delivered in partnership with our Customers

Conventional Synthetic Methodology:
Challenges and Limitations

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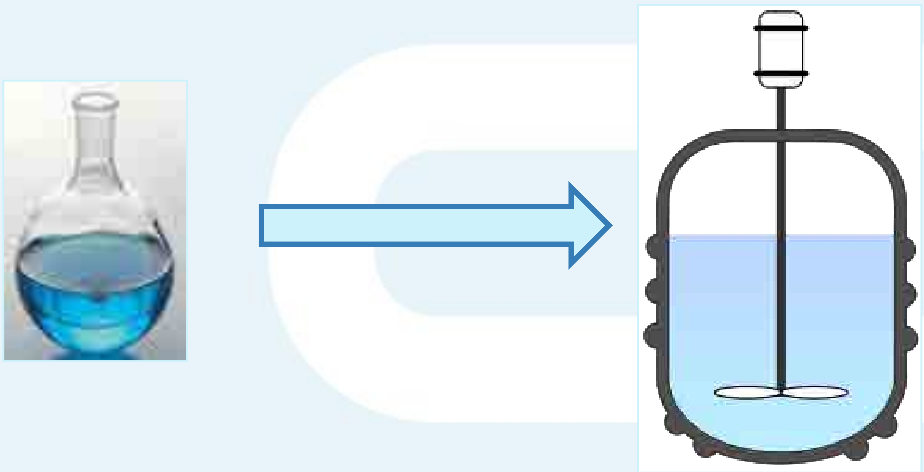
- If we look to how synthetic chemistry has been taught and performed, little has changed over the past century, with all chemists being familiar with **standard glassware** and equipment

<u>Batch Reactions:</u>

- 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

Conventional Synthetic Methodology:
Challenges and Limitations (2)

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'Batch' has been used for 100's years, so it must be good for something;

<u>Advantages:</u>

- Flexible
- Known scale-up path
- Good all round approach – liquids, solids, gases tolerated

It is however known to have its limitations;

- Mixing
- Mass transfer
- Heat transfer
- Pressure limits
- Temperature limits
- Material incompatibility
- Cost – Maintenance & labour intensive

'Batch has it issues, but time has taught ways around the problems'

Conventional Synthetic Methodology:
Challenges and Limitations (3)

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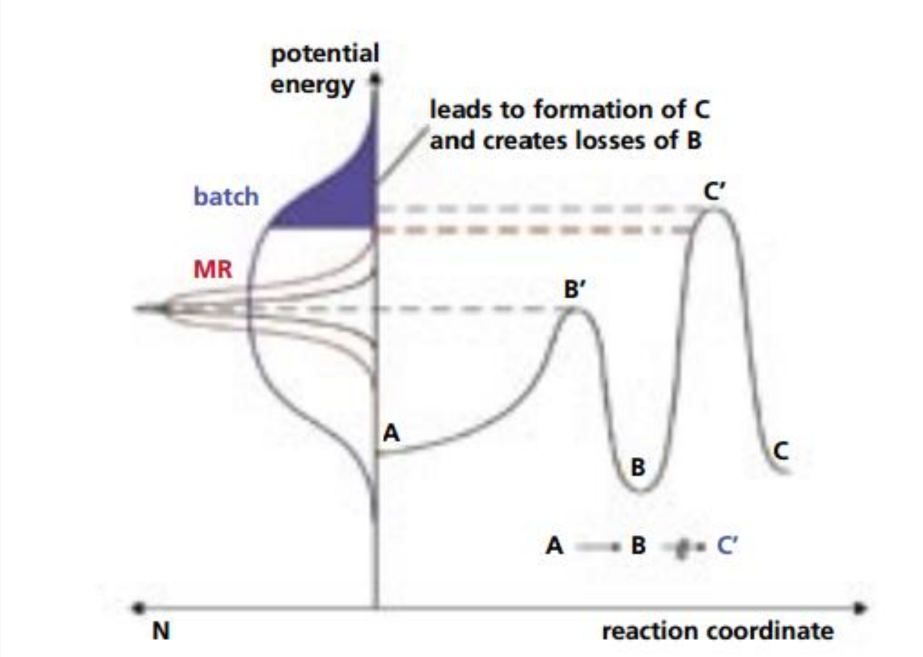
Whilst their flexibility means that as Chemists we persevere with batch vessels;

- Broad temperature, time & concentration profiles – leads to difficulties in reaction control

Here is illustrated a reaction with a competing by-product that consumes the target product



As the size increases, control is more problematic

- By obtaining a narrower temperature, time and/or concentration profile, it is possible in flow to prepare the target product without competing by-product formation

Fundamentals of Flow Chemistry:
How are Flow Reactions Performed?

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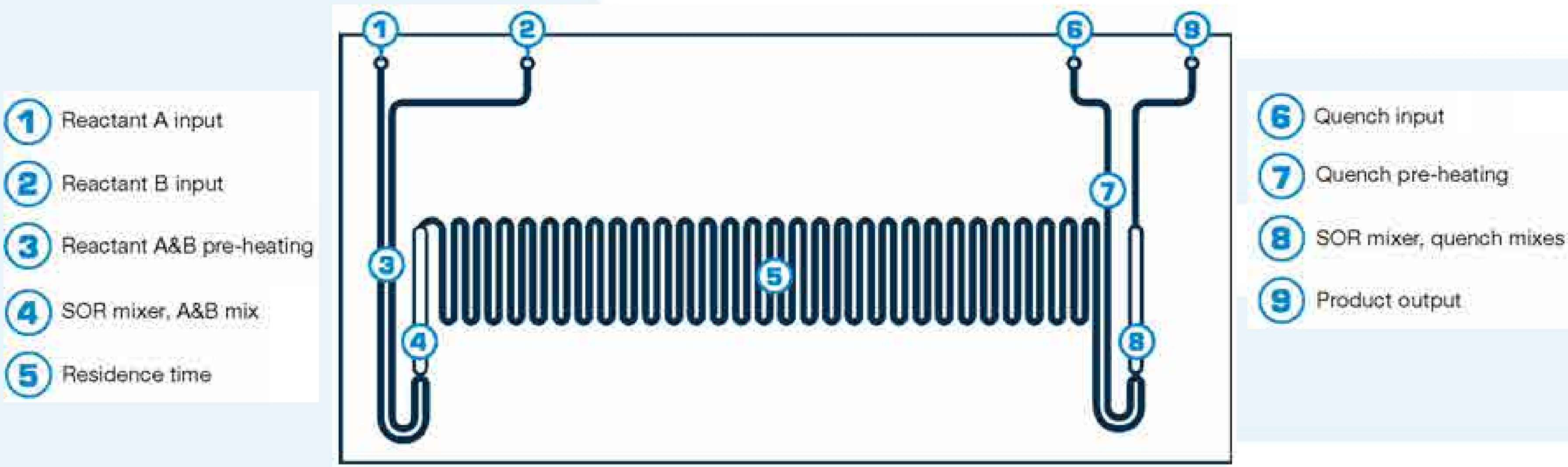
Solutions of reagents are pumped into a reactor, where they are;

- Heated or cooled ahead of mixing
- Reacted for specified period of time - based on volume of reactor & flow rate

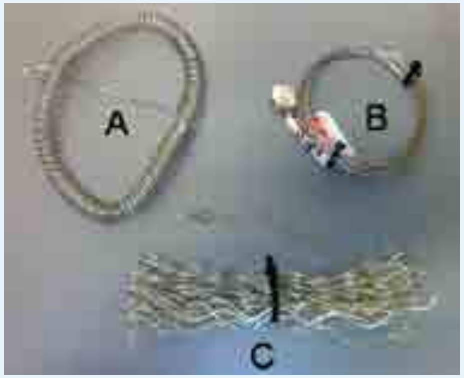


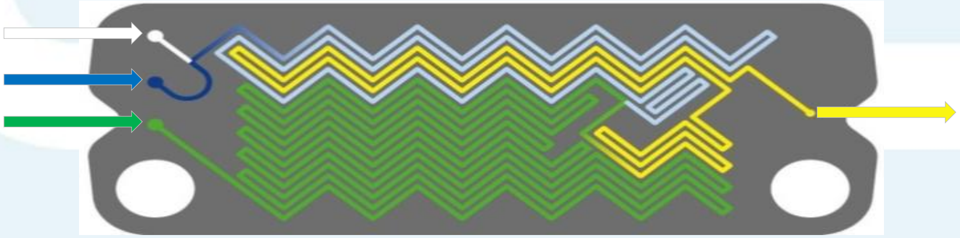
- Quenched *in-situ* (where needed)
  - To stabilise product & prevent decomposition
- Collected for batch isolation & purification (where needed)

Fundamentals of Flow Chemistry:
How are Flow Reactions Performed? (2)

- Reactor volumes can range from **μl's** to **ml's**, consequently;
  - ✓ Small volumes of reagents & catalysts used for large number of reactions
  - ✓ Steady-state is reached with low volume consumption
  - ✓ Reaction conditions can be changed rapidly
- Molecules experience similar conditions leading to increased process stability
- Volume production is **time-resolved**, increasing the volume of product can be achieved by increasing the run time <u>or</u> by employing multiple reactors <u>or</u> by increasing reactor volume
  - ✓ Theoretically no failure to scale and no changes in the safety profile of a process

Reactors can be micro structured or simple tube reactors depending on the application





Fundamentals of Flow Chemistry:
Efficient Heat Exchange & Mixing

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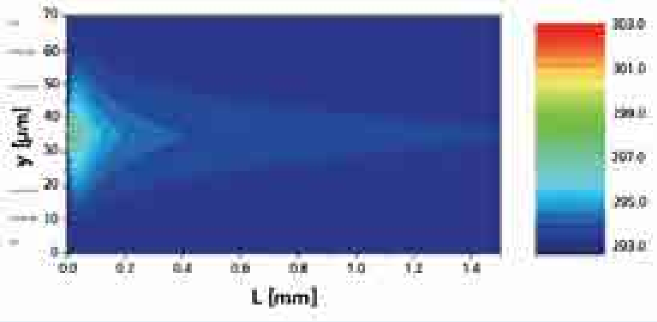
<u>Heat Exchange:</u>

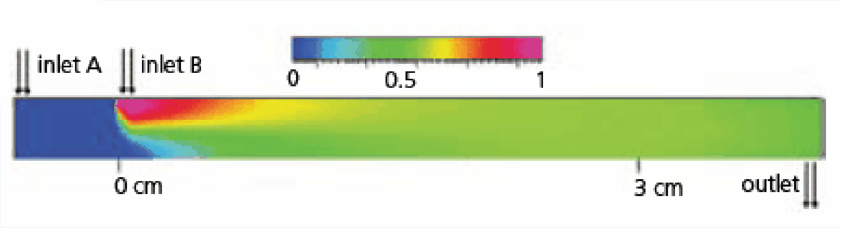
- Due to the reduced size of a reaction channel uniform temperatures are obtained
- Reduces the risks associated with exotherms
- Increases product quality
- Allows previously uncontrollable process to be executed



<u>Mixing:</u>

- Mixing occurs by diffusion only and is linked to the channel size and the reactants employed

$$t \sim \frac{d^2}{D}$$



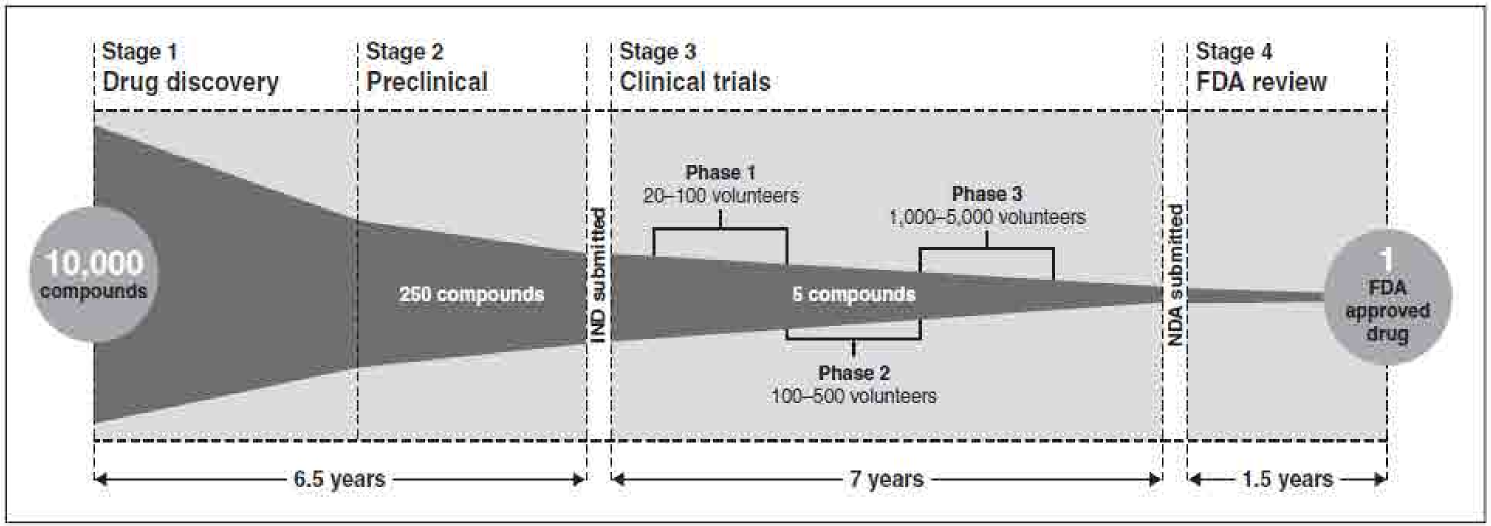
  - In a 300 μm channel this can take 10's sec
- Incorporation of static mixers can reduce the mixing time further to the ms range

Fundamentals of Flow Chemistry:
Examples of Micro Mixers

100 μl min^{-1} (left)T-mixer & (right) SOR-mixer

Flow Technology:
Drivers for Implementation

If we look to the drivers associated with the development of a process in flow;



Source: Pharmaceutical Research and Manufacturers of America.

Lab-scale:

- Speed
- New reaction space
- Reproducibility
- Selectivity
- Flexibility

Process R&D:

- Speed
- Safety
- Robustness

Production:

- Speed
- Safety
- Robustness
- Cost reduction
- Quality

As each stage has different drivers – different equipment is used

Flow Technology:
Sectors & Users

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Applications reported in;

- Pharmaceutical, fine chemical, agrochemical, specialty & commodity industries
- Research & Development
  - New chemical processes evaluated
    - Detailed investigations performed using small quantities of reagents and catalysts
  - Material production
    - Nanoparticles, colloids, pigments , polymers prepared with high specifications
- Process Development
  - Rapid translation of processes from R&D to pilot scale
  - Can stay in the research laboratory for longer to product kilograms of material
  - Can use previously inaccessible approaches for the production of materials
    - Biocatalysis, photochemistry/electrochemistry accessible at scale
- Production
  - Previously forbidden chemistries can be performed at scale with improved safety profile
  - Synthesis of fine chemicals, pigments and ionic liquids
  - Active pharmaceutical intermediate (API's) production

Continuous Azidation using Labtrix®:
Manipulation and Formation of Hazardous Materials

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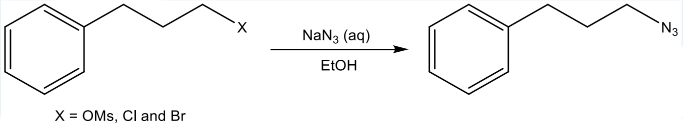
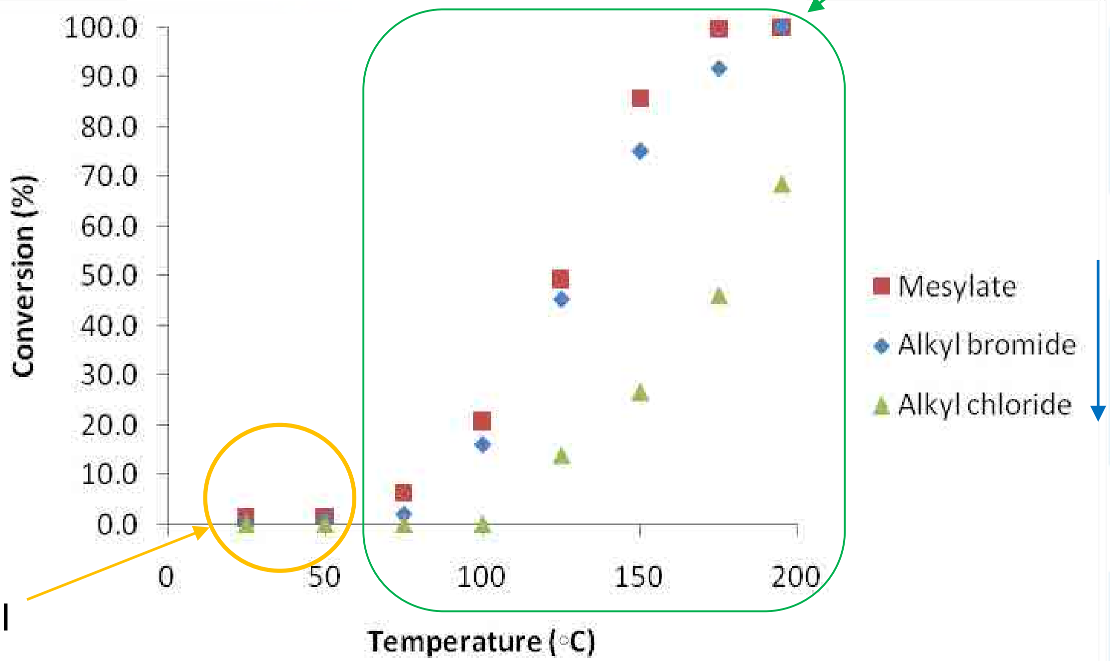
- Employing 0.66 M (EtOH) alkyl precursor and 0.66 M (50:50 aq. EtOH) NaN_3, the effect of temperature on the reaction was investigated at a residence time of 30 s



'Novel Operating Window' at the mg-scale



Decreasing material costs

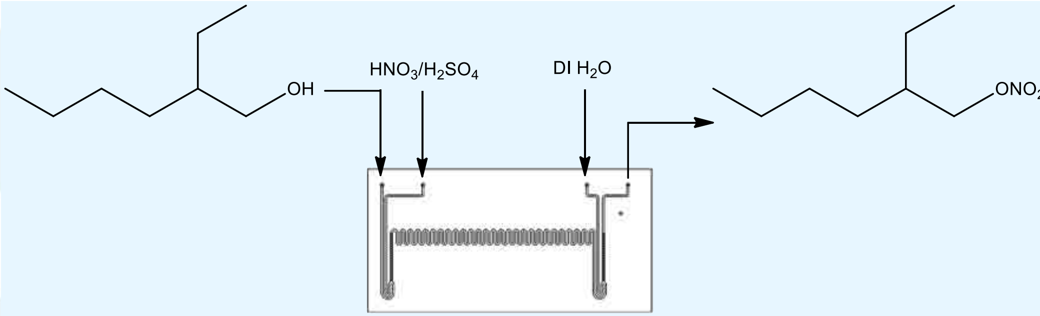
Limit of conventional batch glassware

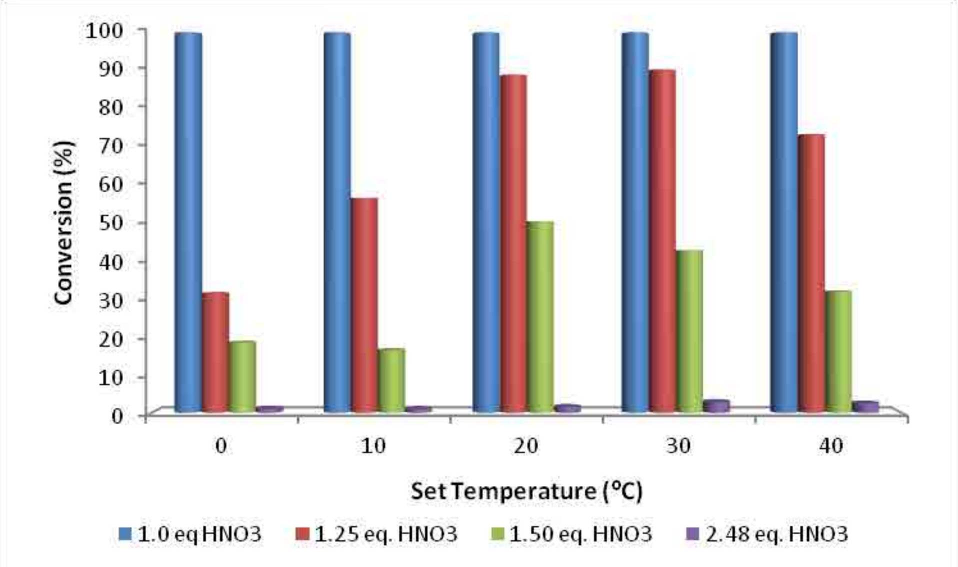
  - Using OMs derivative, azide obtained at a throughput of 79 mg h^{-1} @195 ◦C

Continuous Nitrations using Labtrix®:
Manipulation of 70 % Nitric Acid

Reaction Conditions:

- Solvent-free & mixed acid feeds
- Equal flow rates
- Reaction times = 7.5 to 60 s
- Reactor temperature = 0 to 40 ºC





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

Optimal Conditions:

- 60 s reaction time @ 40 ºC → System throughput = 336.3 mg hr^{-1}

Facile Up-scaling from Labtrix® to KiloFlow®:
No Re-optimisation Required

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KiloFlow® is a modular, **scalable** flow reactor system that can support up to **Phase 3**

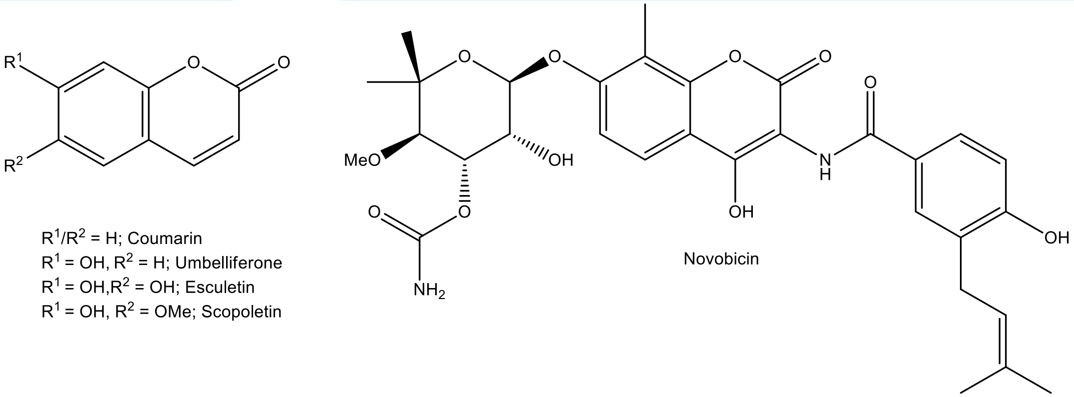
- Giving you access to a **pilot plant** within a standard laboratory fume hood

KiloFlow® Product Portfolio has a;

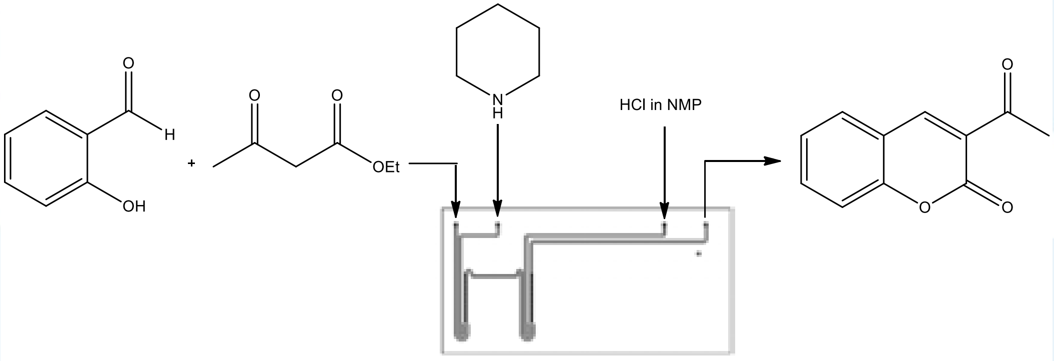
- Large working range
  - **-15 to 150 ºC**
- Flexible production volume of
  - 0.012-6.0 l h^{-1} (up to **140 l day^{-1}**)
- Small footprint
- Glass meso reactors
  - Low pressure drop
  - Efficient mixing
  - Excellent heat exchange (U x (S/V) = 3265 $kW/m^3.K$)
- Allows method transfer from Labtrix®

Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

Finding application in the pharmaceutical, agrochemical & flavours/fragrance sectors, coumarins are of significant interest to researchers



Using the condensation of salicylaldehyde and ethyl acetoacetate in the presence of an organic base, the synthesis of 3-acetylcoumarin was optimised in Labtrix®



<u>Optimal Conditions:</u>

- 60 s reaction time
- 125 C reactor temperature
- 0.4 eq. piperidine
- MeCN reaction solvent

1 μl Reactor volume (3221) consumed 5.4 mg h^{-1}

Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

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Translating the optimal conditions to KiloFlow® Basic (Reactor Volume = 13 ml)

Operating for 5.2 h, **369.6 g** of 1-(2-methyl-2*H*-chromen-3-yl)ethanone was obtained

- After aq. extraction (98.2 % yield)

Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

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13,000 x scale-up without;

- Parameter re-optimisation
- Change in product quality

Turn-key Flow Platform for;

- mg-scale optimisation to Kg production

Customer Appraisal of KiloFlow®:
Janssen Pharmaceutica NV

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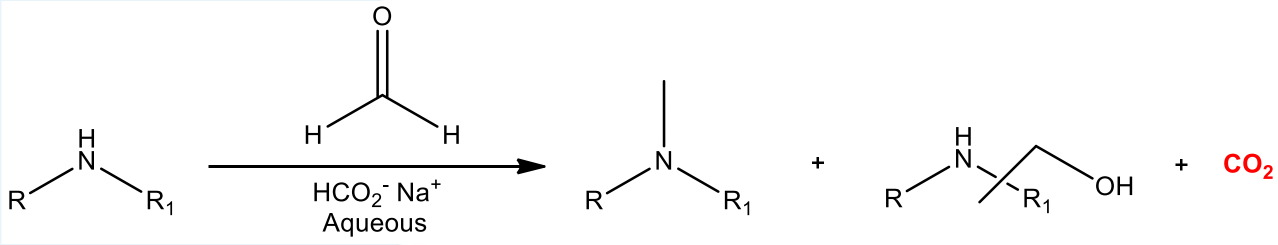
Eschweiler Clarke Reaction:



Modelling predicted the optimal to be 56 s @ 122 ºC

- Outside the conditions safely attainable in batch (time, temp & press), CO_2 ↑

	Batch	Predicted Optimal Conditions[A]	KiloFlow®
N-Methyl Derivative	87.0	95	93.5
By-product	10.0	<3.5	2.10
Others	3.0	1.2	1.0-1.2

[A] Predicted at 56 s @ 122 ºC

- Reaction translated to a 1 litre PFA reactor for 100 kg h^{-1} production of the API intermediate
- 3 Validation batches performed, results presented to the FDA who confirmed;

'no additional analytical PAT tools were required for production'

Customer Appraisal of KiloFlow®:
Iolitec GmbH

io·li·tec
Ionic Liquids Technologies

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Chemical Appraisal:

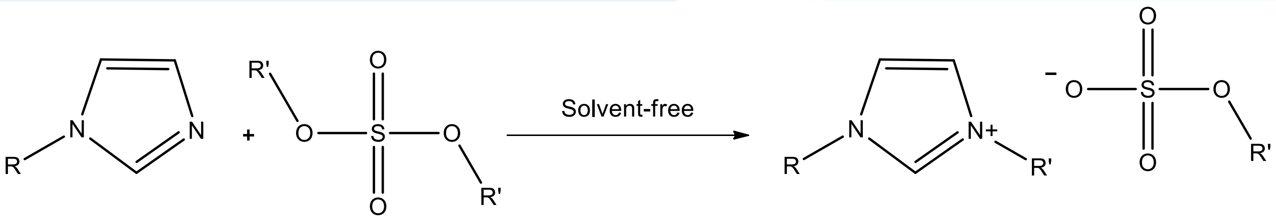
- Continuous flow synthesis of Ionic Liquids (IL's)
  - Uses include solvents, process chemicals, functional fluids, electrolytes, additives
- IL is a general term for a class of materials consisting of ions and being liquid below 100 ºC (RTIL's) consequently there are 10^{18} potential combinations of ions

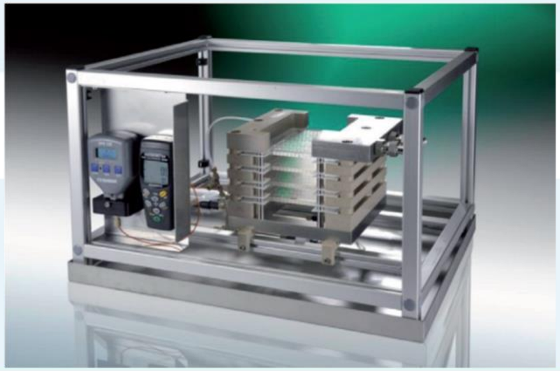
Iolitec have a diverse range of products (~ 300 IL's):

- Production quantities range from g to tonnes
- Rapid and scalable production techniques are required for high purity IL synthesis

Solution: Employ KiloFlow® with integrated heat exchangers

- Higher HE capacity than competitors; **3265 kW/m³.K**





Plantrix® made of EKasic® Silicon Carbide
Efficient Industrial Production & Superior Chemical Flexibility

CHEMTRIX

- High productivity
- High chemical flexibility
- Less scale-up risk
- Handling of solids
- Increased safety
- Environmental friendly production
- Small footprint

EKasic® Material Properties:
High Chemical Resistance

Strategic Partner of ESK

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EKasic® SiC plate: 2.5 yr, 180 °C with 50 % NaOH

✓ No sign of material corrosion

Together with exploiting the efficient thermal properties of EKasic® SiC, users also employ this material in harsh environments, for example;

- Nitrations
- Oxidations
- Chlorinations, Brominations & Fluorinations
- Wolff-Kishner reductions
- Alkylations

Suitable for control of exothermic processes

EKasic® Material Properties:
High Chemical Resistance

Strategic Partner of ESK

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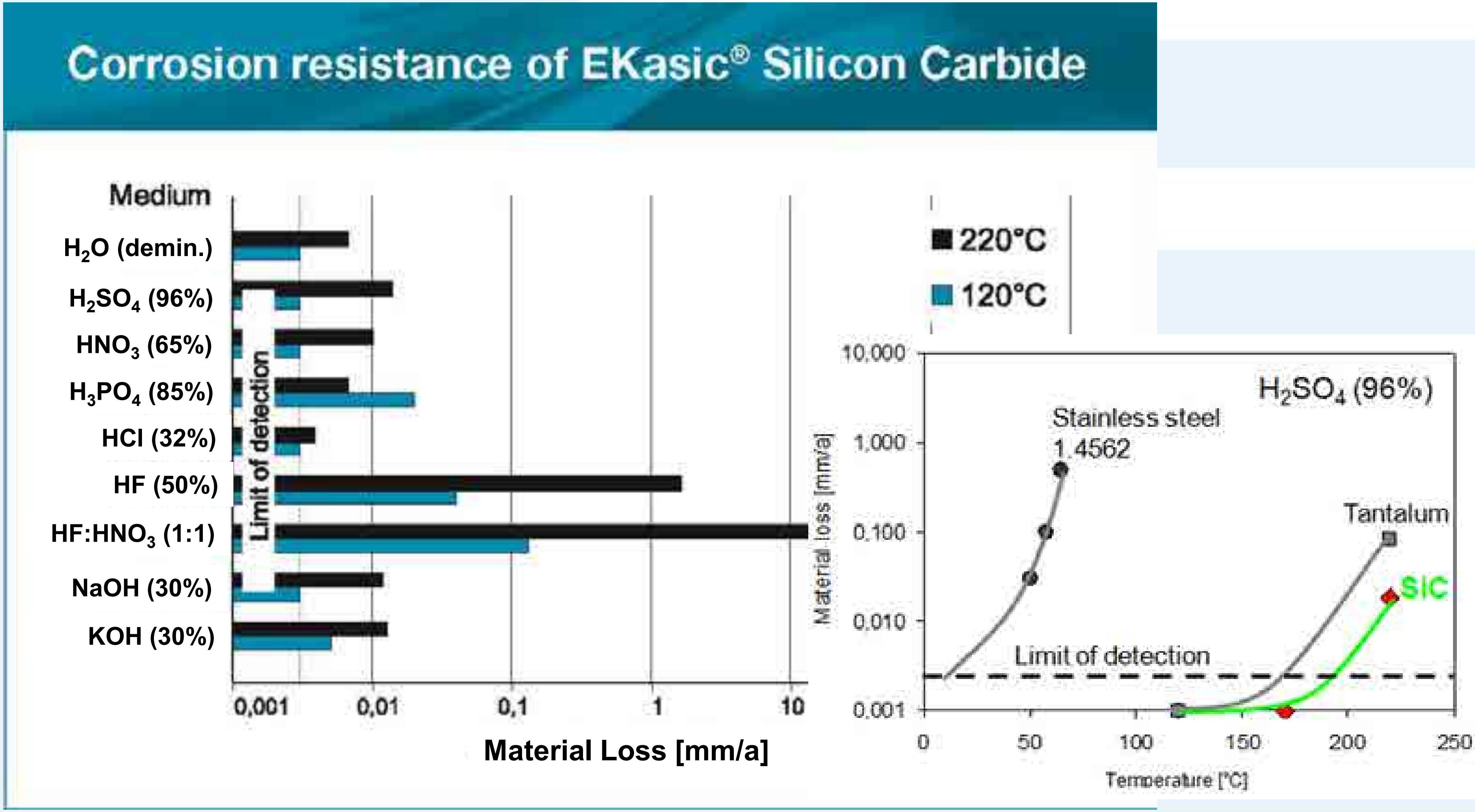
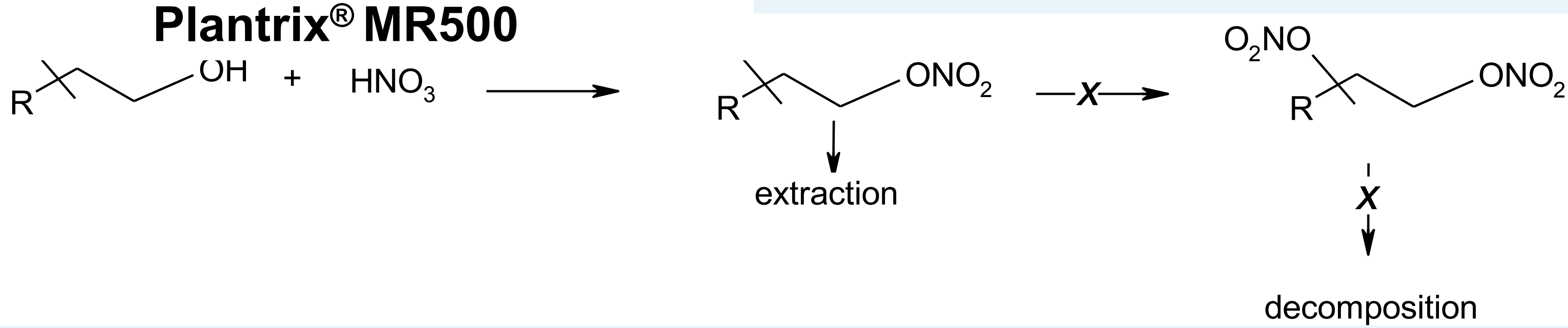
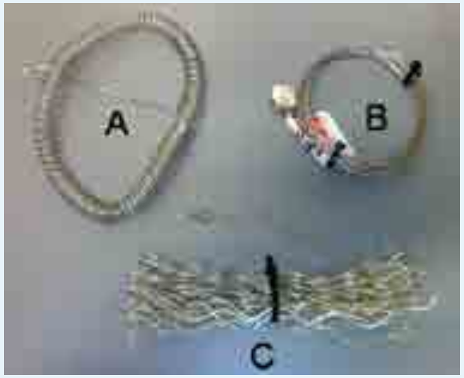


Plantrix® Industrial Flow Reactor:
Customer Application

Plantrix® MR500





<u>Reaction Challenges:</u>

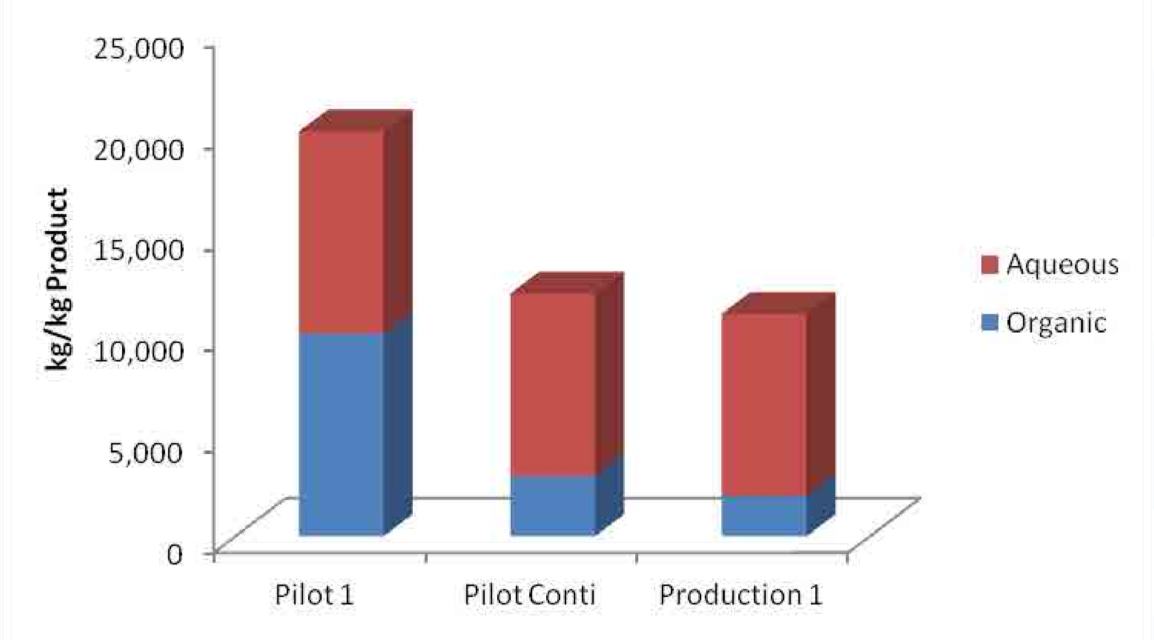
- Biphasic
- Competing dinitration & decomposition products
- Corrosive media
- Challenging product isolation

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

Plantrix® Industrial Flow Reactor:
Customer Application

Through the use of an intensified reactor, the reactant concentration & reaction temperature were increased – reducing the reaction time < 1 min

- Reduction in PMI (process mass index) across development & production



In addition to the reaction, controlled neutralisation & quenching is often key to maintaining reaction selectivity – generating waste – this can be reduced in flow

Plantrix® Industrial Flow Reactor:

Customer Application

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Strategic Partner of ESK

DSM uses ESK Micro Reactors made of EKasic® (SiC) in a pharmaceutical production plant

‘Coriac’ Project

Goal: Benchmarking of multiple flow reactor technologies for a wide range of processes

Multipurpose pilot flow reactor skid for chemical conversion of suspensions

Project Management: TNO **Timeframe:** End 2014

‘Flow4API’ Project

Goal: Explore ‘Novel Process Windows’ for API production in continuous flow

Project Partners: ISPT TNO Synthon CHEMTRIX

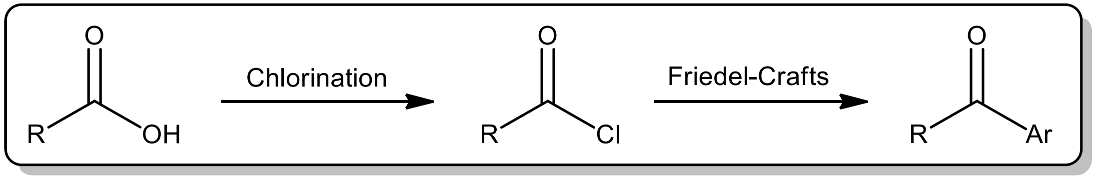
Cooperation between industrial partners and knowledge institutes

Focus: Synthetic processes that pose a challenge for pharmaceutical, flavours & fragrances, veterinary and fine chemical industries. The project will focus on processes;

Involving High-value Molecules:
- Target yield improvements

Telescope Reactions:
- Cost savings for multi-step reactions

Test Cases: Provided by Synthon BV, explored using commercially available equipment, including the scalable flow platform from Chemtrix BV



Project Management: TNO (Gerhard Reeling Brouwer: gerhard.reelingbrouwer@tno.nl)

Timeframe: End 2014

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

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