Maison Européenne des Procédés Innovants

Success Stories and Trends of Flow Chemistry at Industrial Scale

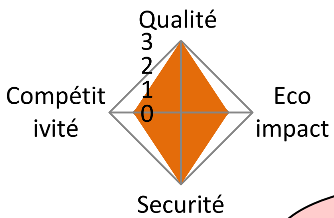
Laurent PICHON
MEPI

« SCALEUP : Du rêve de la paillasse à la réalité d'une usine industrielle »

BIOCITECH, Romainville, 21 novembre 2017

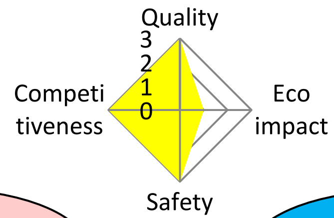
4 axes of improvment

PROJECT A



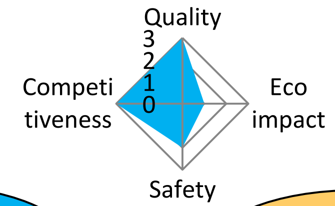
Pharma Fluorination

PROJECT B



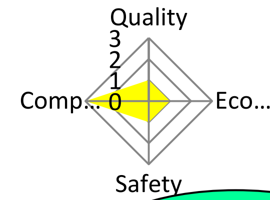
Pharma NaN3 interm

PROJECT C



Cosmetics

PROJECT D



Spec. Chem Crytallization

- Manufacture eco friendly products (renewable raw materials when possible)
- Design safer and cleaner processes with available equipments
- Save energy & costs to be competitive
- Monitor the quality of the chemical reaction with adequate on line analytic tools

10 000 times smaller reaction volumes for equal productivity !

100 % green chemistry

MEPI Alternative Chemistry

Achievements

Chemistries of interest

Organometallic (synthesis & reaction)

Nitrations (mono, di…; catalysts)

Amine deprotection, Hydrazine synthesis

Electrophilic and nucleophilic additions & substitutions

Oxydations (H_2O_2, NaOCl,…**HOF**),

low T° reactions, Polymerisations, Biocatalysed reactions,

Gas reaction (**F_2**, HCL, H_2…)

NaN_3 chemistry,

New flow catalysis (H_2, C-C couplings)

Photochemistry, Micro-wave like heating...

Epychlorohydrin, ionic liquids,

Effluent treatment , isolations,

Formulations, Emulsions

Crystallizations,

- Liquid
- Liquid / Liquid
- Liquid /Gas
- Liquid /Liquid / Gas
- Solid/Liquid
- Solid/Liquid/Gas
- Anhydrous medium(S/S)
- Viscous media
- Solid generation

T : -40 to 180°C

P : up to 80 bars

> 120 STUDIES

A large range of innovative technologies

Synthesis :

Micro, meso, super meso HEX-reactors, reactive extrusion, COBR, Spinning disc, Taylor Couette, static mixers.

Separation :

Thin film evaporator, centrifugator, continuous crystallization, sonocrystallization.

Alternative chemistry :

Sonochemistry, micro-waves, supercritical fluids, photochemistry, On line Spectroscopy (Raman, UV, IR).

Materials :

Glass, SiC, Hastelloy, stainless steel, titanium, polymers.

Media :

Mono, bi, tri-phasic ; liquid, gas, solid, High viscosity products , (solid/solid).

Engineering :

Knowledge in milliplants set up design & operation

mEPi
Alternative Chemistry

Key parameters for equipment choice

Reaction kinetics : Residence times up to 15 mn /up to 2 h => type of reactor,

Heat generation & associated kinetics => type of reactor & heat exchange materials,

Chemical corrosion => type of reactor / auxiliairies material,

Chemical stability => temperature range,

Type of media :
Mono, bi, tri phasic
Gas /Liquid/ solid
Viscosity and evolution (pressure drop)
Type of high viscosity media (sticky, slurry…),

Initial Reaction conditions :
Pressure,
Temperature range
Gas generation
Solid generation,

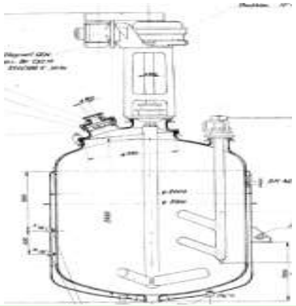
Industrial production volume & productivity expectations.

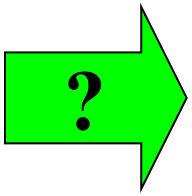
Assessment : Probability of success (go/no go), Preliminary study ? (batch Alternative chemistry : solvent, catalyst ?) Milliplant set up for faiseability…

MEPI Alternative Chemistry

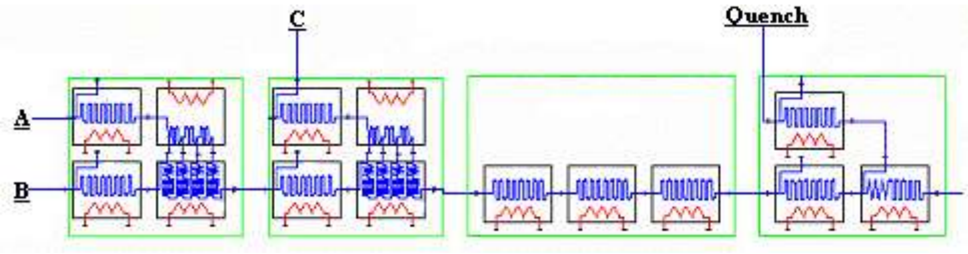
Technology benefits

Initial Process





Intensified Process



Improve yields / selectivity (e.g. enantiomers ratios)

Control strong exothermic reactions

Good mixing necessary (incl. Formulations, extractions)

Handling unstable intermediates

Dealing with hazardous chemicals (free your mind !)

Work in easier T° range (**cryogenic reactions**) or higher T° to speed up reaction (small residence time)

Fast heating or cooling down

Reduction of reagent excess, diluted processes

Avoid solvent use (distillation..)

Regulated environment (FDA driven)

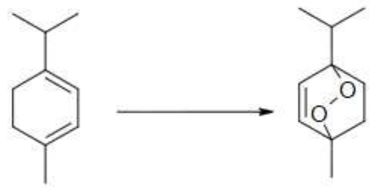
And………. ***Better economics***

mEPi Alternative Chemistry

Oxidations in continuous

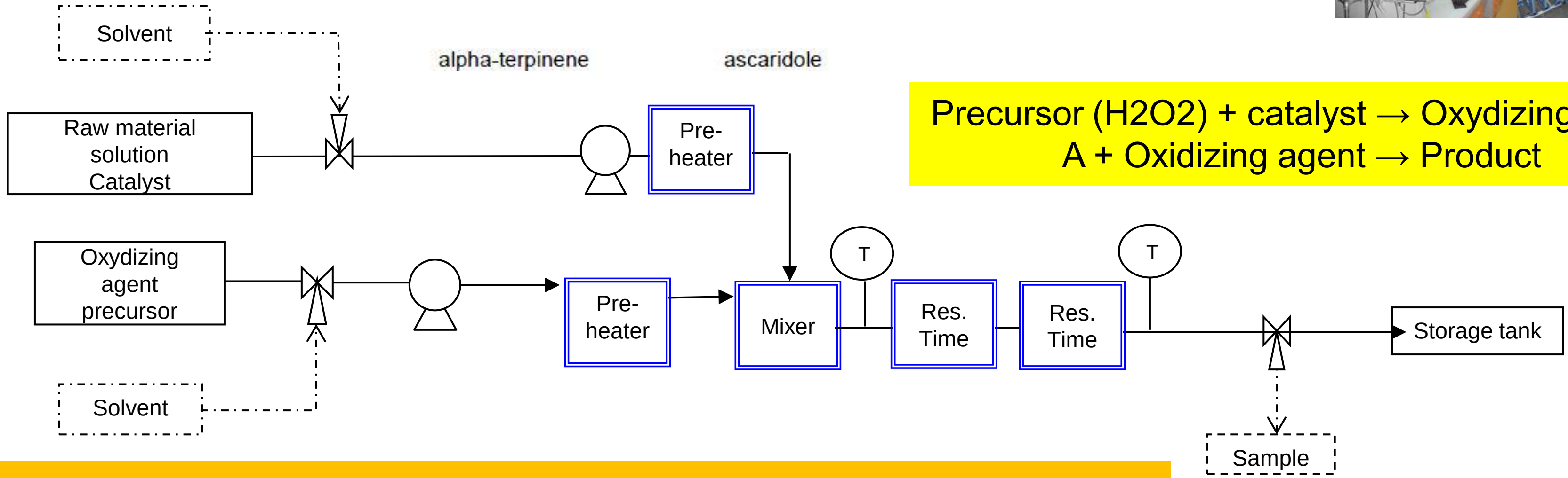
H_2O_2
NaOCl
$KMnO_4$

EXAMPLE 1 – di oxygen bridge generation



alpha-terpinene ascaridole

Precursor (H_2O_2) + catalyst → Oxydizing agent
A + Oxidizing agent → Product



No existing industrial batch process with these operating conditions:

Oxidizing agent lifetime < 1s
High exothermicity and fast kinetics → Safety issues

Continuous process :

- *In situ* generation and instantaneous comsuption of oxidizing agent.
- Exothermicity managment : isothermal behaviour
- Results : 60% conv. to the desired product in 10 seconds

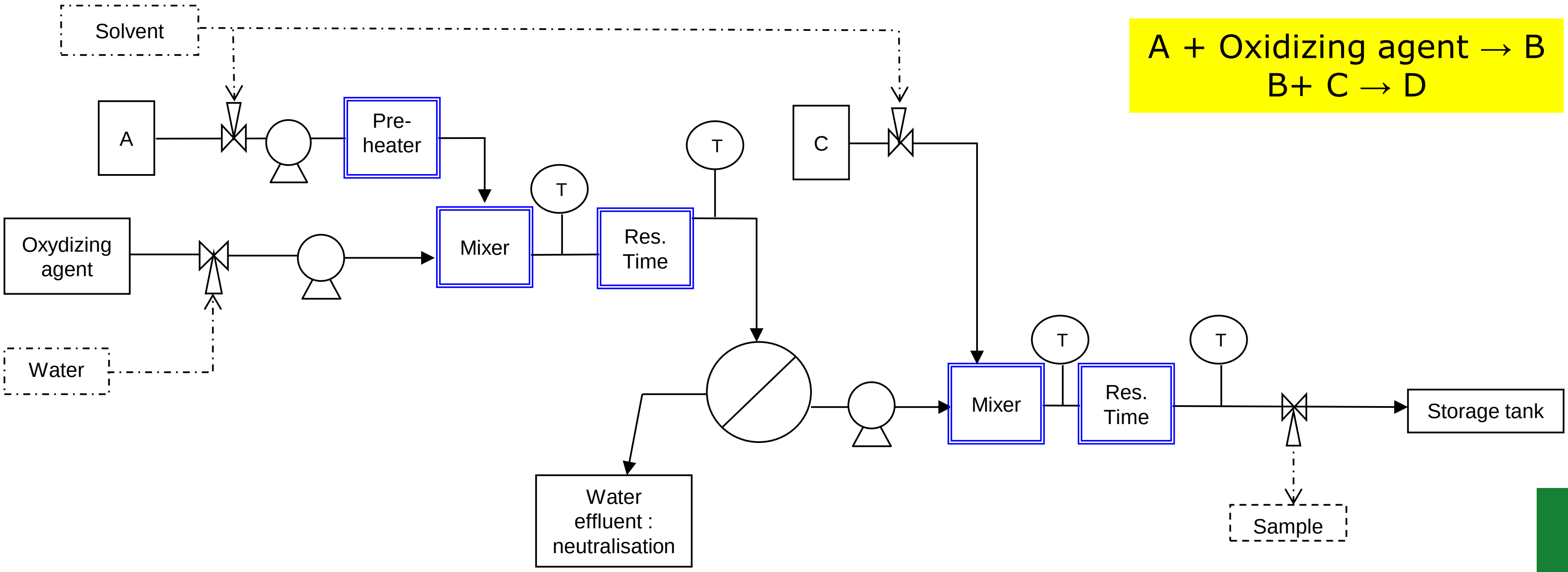
MEPI Alternative Chemistry

EXAMPLE 2 – Oxidation + Coupling

Batch process : lab (yield 92%) and pilot scale (yield 67%)

Oxidizing agent (NaOCl) n the water phase.
Unstable intermediate B : fast degradation in aqueous conditions.
C can be oxydized too.

A + Oxidizing agent → B
B+ C → D



Continuous process :

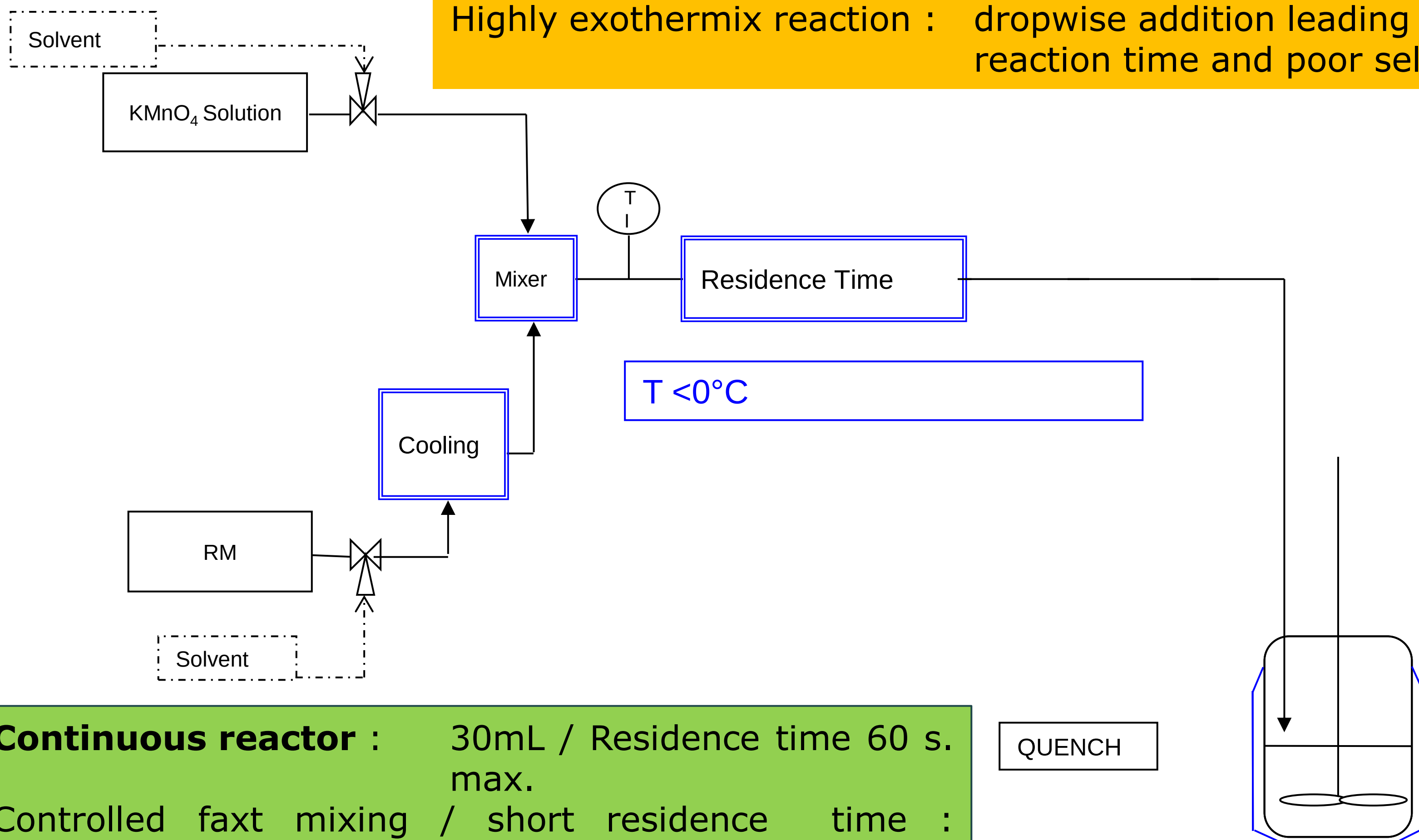
- Two step continuous process.
- Stabilization of B by continuous phase separation.
- Residence time : 10 s for step 1/ 2 min for step 2.
- Yield : 94%.

mEPi Alternative Chemistry

KMnO4 Oxidation

Hazardous batch conditions : oxydizing agent slowly degrading the solvent

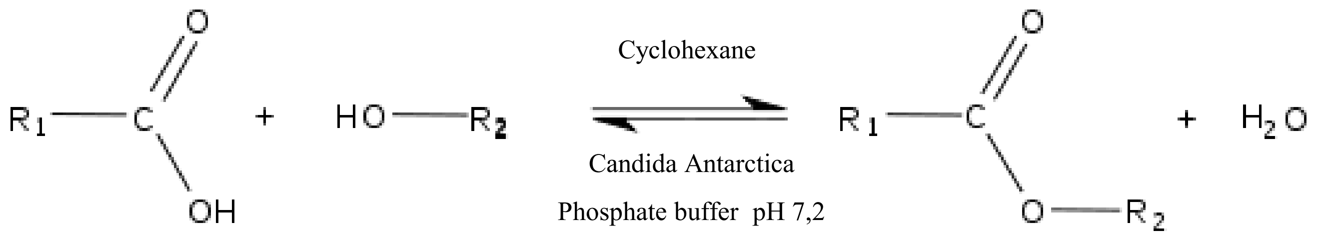
Highly exothermix reaction : dropwise addition leading to high reaction time and poor selectivity



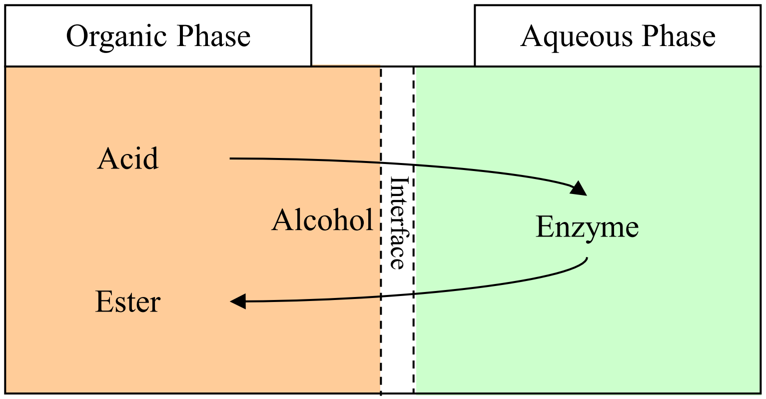
- **Continuous reactor** : 30mL / Residence time 60 s. max.
- Controlled faxt mixing / short residence time : Improvement of safety – No solvent degradation.
- Regulation of exothermicity : no heating at the outlet of the mixer.
- BUT solubility problems : Dilution increased, still selectivity issues.

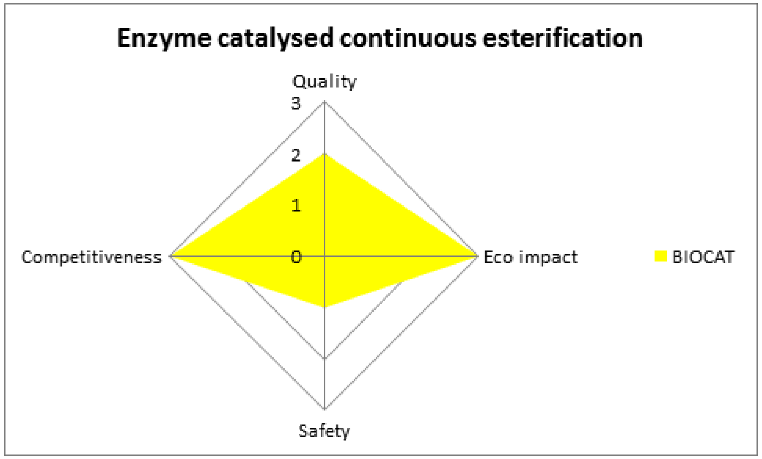
Enzyme catalysed continuous esterification

Enzyme catalysed continuous esterification



Phase transfer catalyst





Enzyme catalysed continuous esterification

Reaction constraints

Two phase reaction

- Phase transfer catalyst in order to reach high conversion level
- High interfacial area required (strong mixing performances)

Kinetics

- Important reaction time (≈ 5 h in batch)
- Intermediate regime (kinetic and diffusion regimes compete)

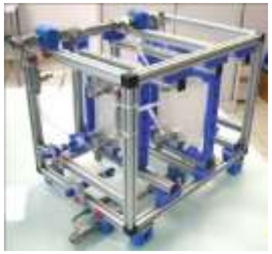
Process

- Define an alternative continuous process to classical batch and loop reactors
- Possibility to reach important productivity

Enzyme catalysed continuous esterification

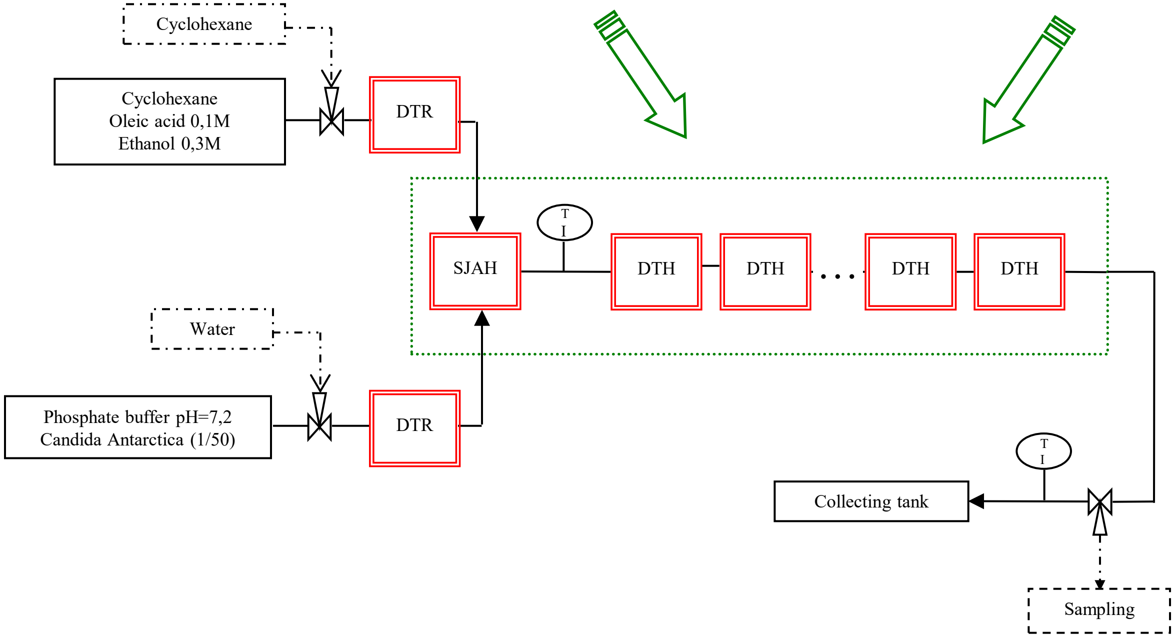
Design of continuous intensified process

Corning Advanced-FlowTM Reactor



Or

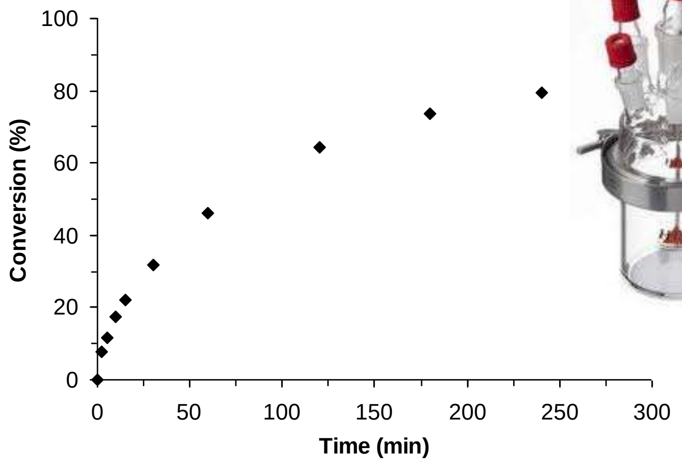
Chart Shimtec® Reactor

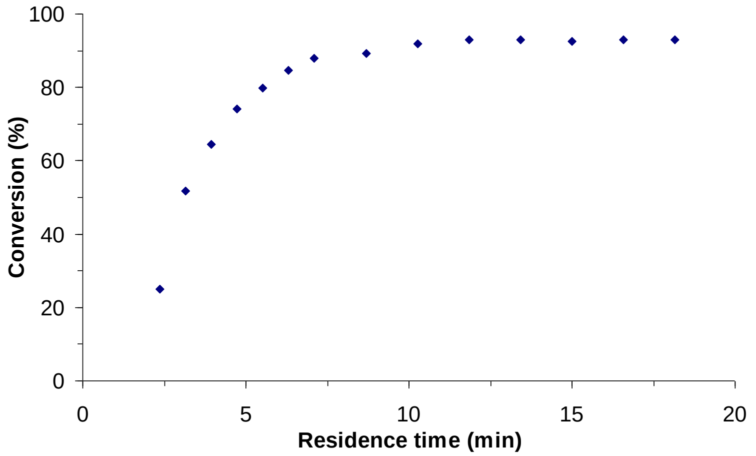


Enzyme catalysed continuous esterification

Design of continuous intensified process

- Feasibility demonstrated !





CORNING

- PI: Definition of an alternative technology !

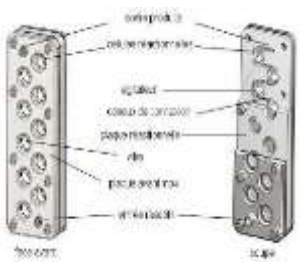
MEPi Alternative Chemistry

Enzyme catalysed continuous esterification

Benchmark of mass transfer performances

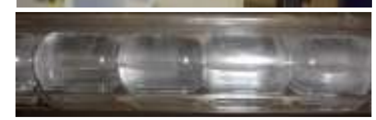
- Comparison of the ability to create interfacial area

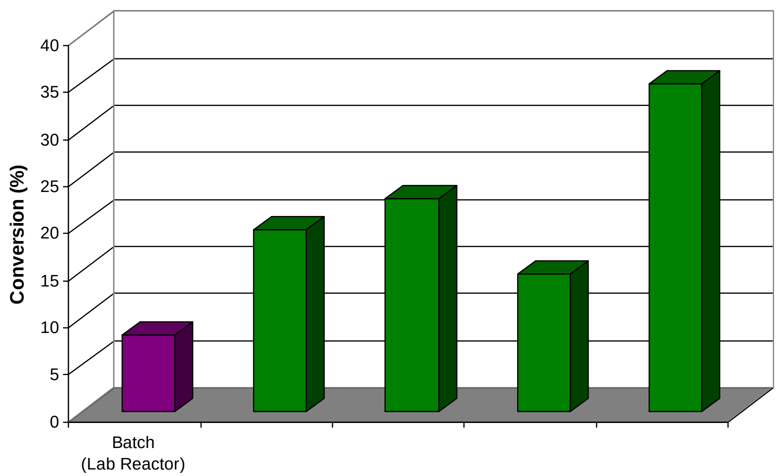
AM Technology
Engineering Chemistry

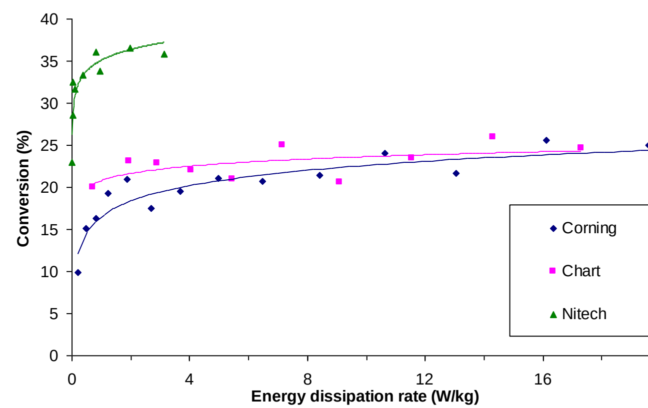


CORNING

NiTech
SOLUTIONS



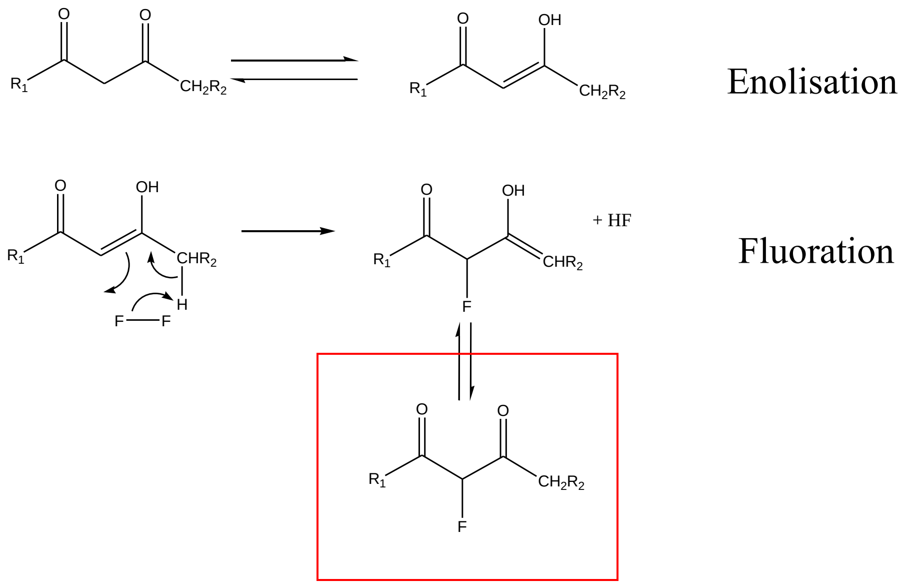


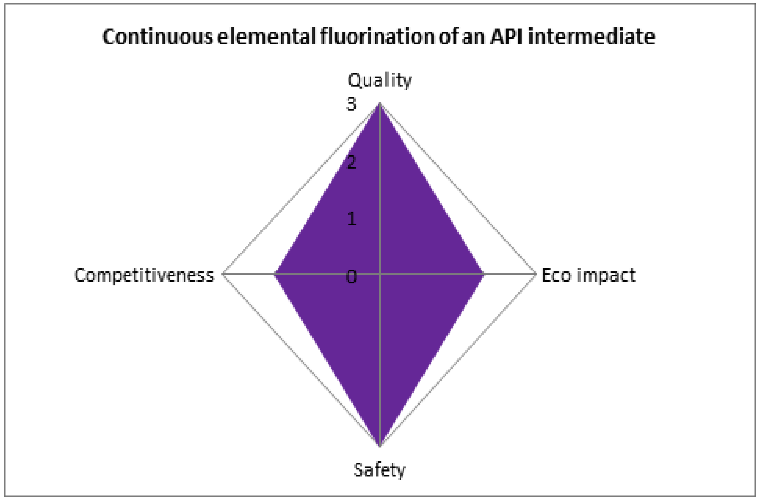


mEPi
Alternative Chemistry

Continuous elemental fluorination of an API intermediate

Direct fluorination of 1,3-dicarbonyl compound





Objectives

- Prove feasibility of a continuous production process at pilot scale
- Screening of optimal operating conditions in term of solvent and catalyst
- Check possibilities of a flexible industrial unit

Continuous elemental fluorination of an API intermediate

Reaction constraints

No existing data related to the application

- No existing procedure for synthesis or extraction
  - Thermo-kinetics (Safety !)
  - Solvents, catalysts
- No analytical standard available for the desired product

Mixing

- Two phase reaction (Liquid / Gas)
- Strong gas hold-up (fluorine could be only purchased diluted in Nitrogen from 5 to 20%)

Safety

- Handling of a hazardous reagent (Fluorine)
- Corrosion (HF generation during reaction)

mEPi Alternative Chemistry

Design of continuous intensified process

Thermal performances

- Absorb any heat generated by the reaction to avoid thermal runaway

Mixing + Mass transfer performances

- Liquid-gas system
- Strong gas hold-up

Pressure resistance

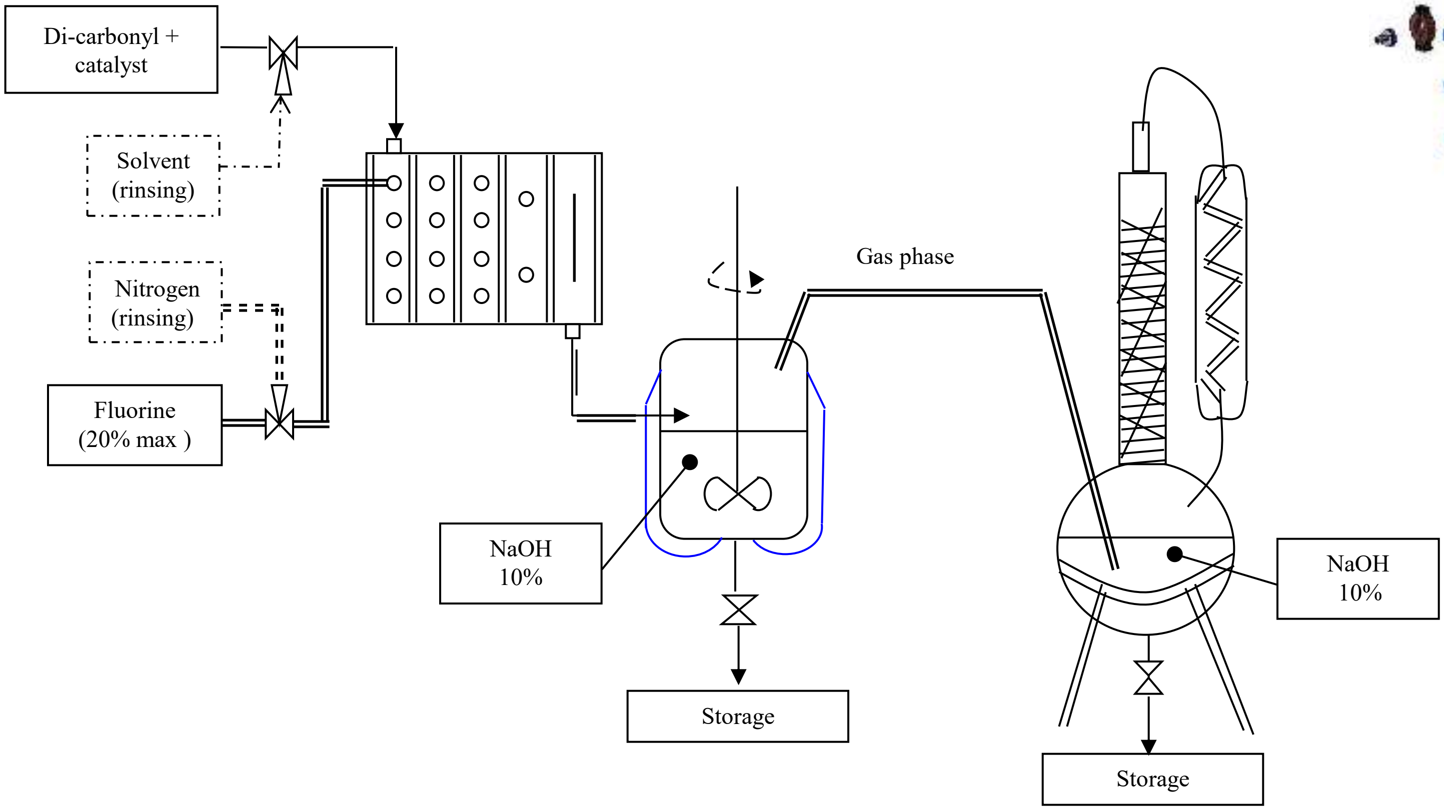
Corrosion resistance

One single reactor ?

→ Combination of different technologies ?

Continuous elemental fluorination of an API intermediate

Design of continuous intensified process



Continuous elemental fluorination of an API intermediate

Design of continuous intensified process

Continuous elemental fluorination of an API intermediate

Definition of the optimal operating conditions

- Results of the screening study

Solvent nature

Solvent nature	Catalyst nature	Molar ratios / Di-carbonyl Catalyst	Molar ratios / Di-carbonyl Fluorine	Temperature (°C)	GC results (based on peak area)
ACN	$Ni(NO_3)_2$	0.2	3.1	0	Partial conversion
50/50 solution	$Ni(NO_3)_2$	0.2	3.1	5	Full conversion
Acetic acid	$Ni(NO_3)_2$	0.2	3.1	20	Partial conversion

Catalyst nature

Solvent nature	Catalyst nature	Molar ratios / Di-carbonyl Catalyst	Molar ratios / Di-carbonyl Fluorine	Temperature (°C)	GC results (based on peak area)
acetonitrile / acetic acid mixture (50/50 w.)	$Ni(NO_3)_2$	0.20	3.1	5	100 %
	$Cu(NO_3)_2$		3.1		96 %
	CH_3COONa		3.2		48 %

Maximum Productivity = 200 g/h

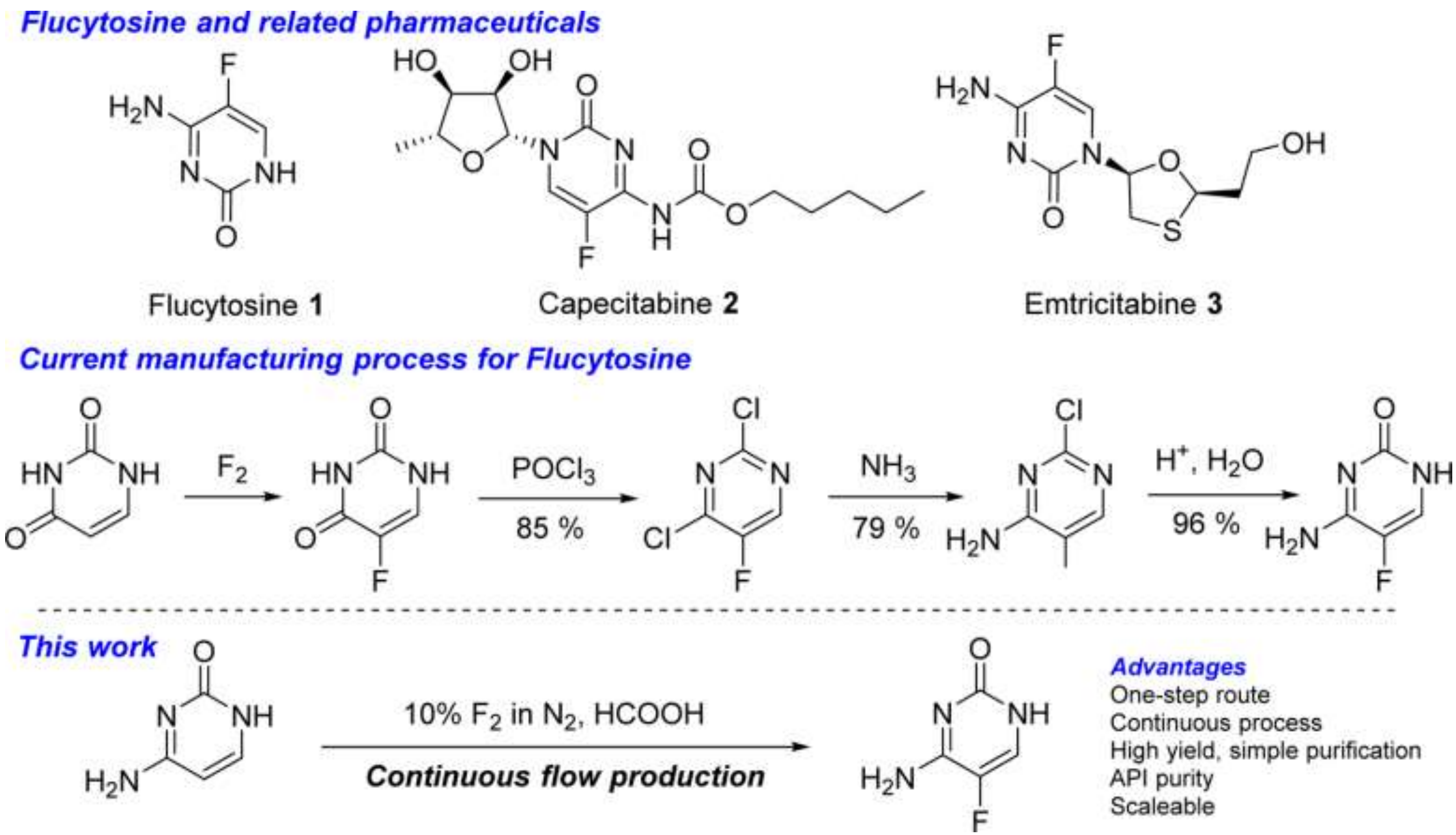
MEPi Alternative Chemistry

Continuous elemental fluorination of an API intermediate

Route scouting

SANOFI

Durham University

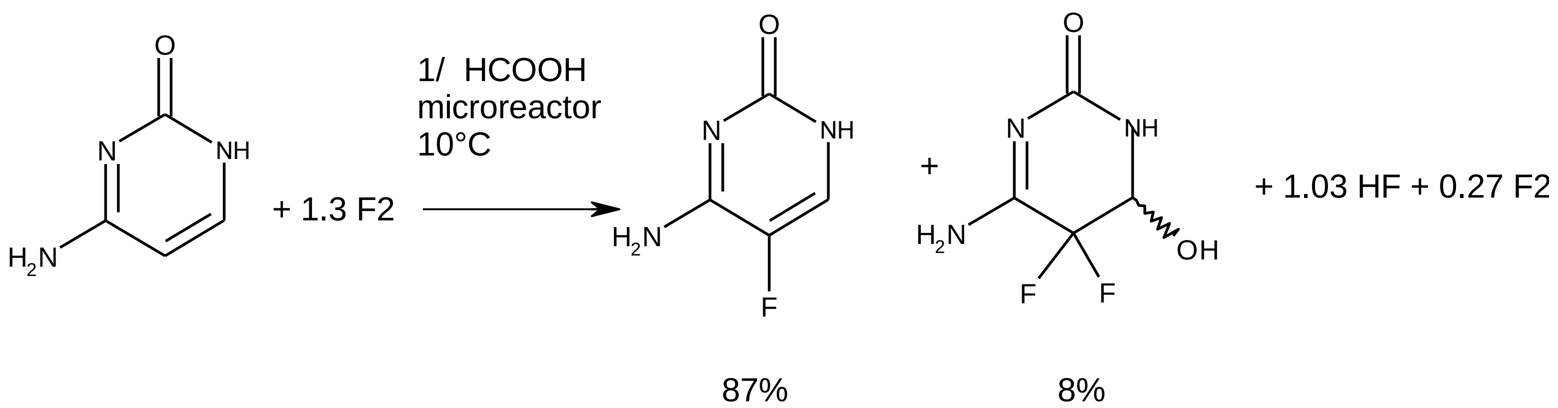


Continuous elemental fluorination of an API intermediate

SANOFI

Durham University

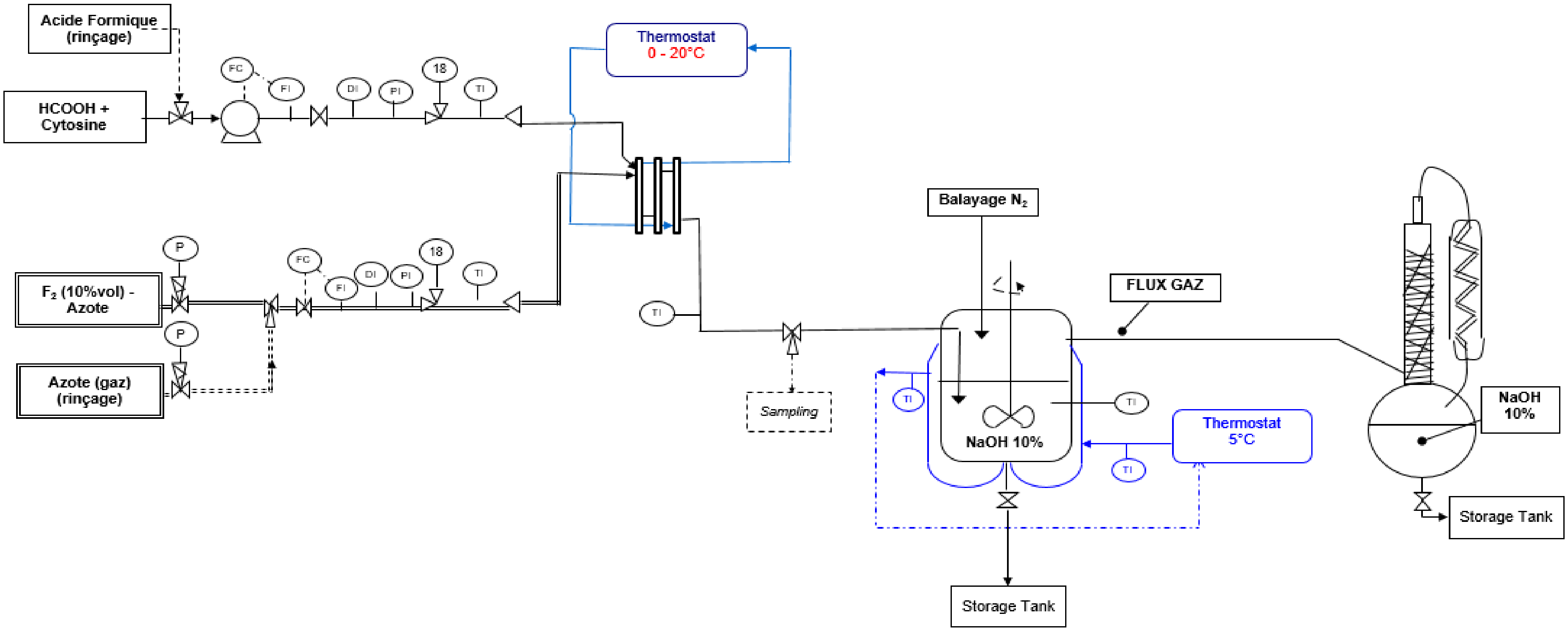
Flucytosine:MEPI / SANOFI / University of Durham (uk)



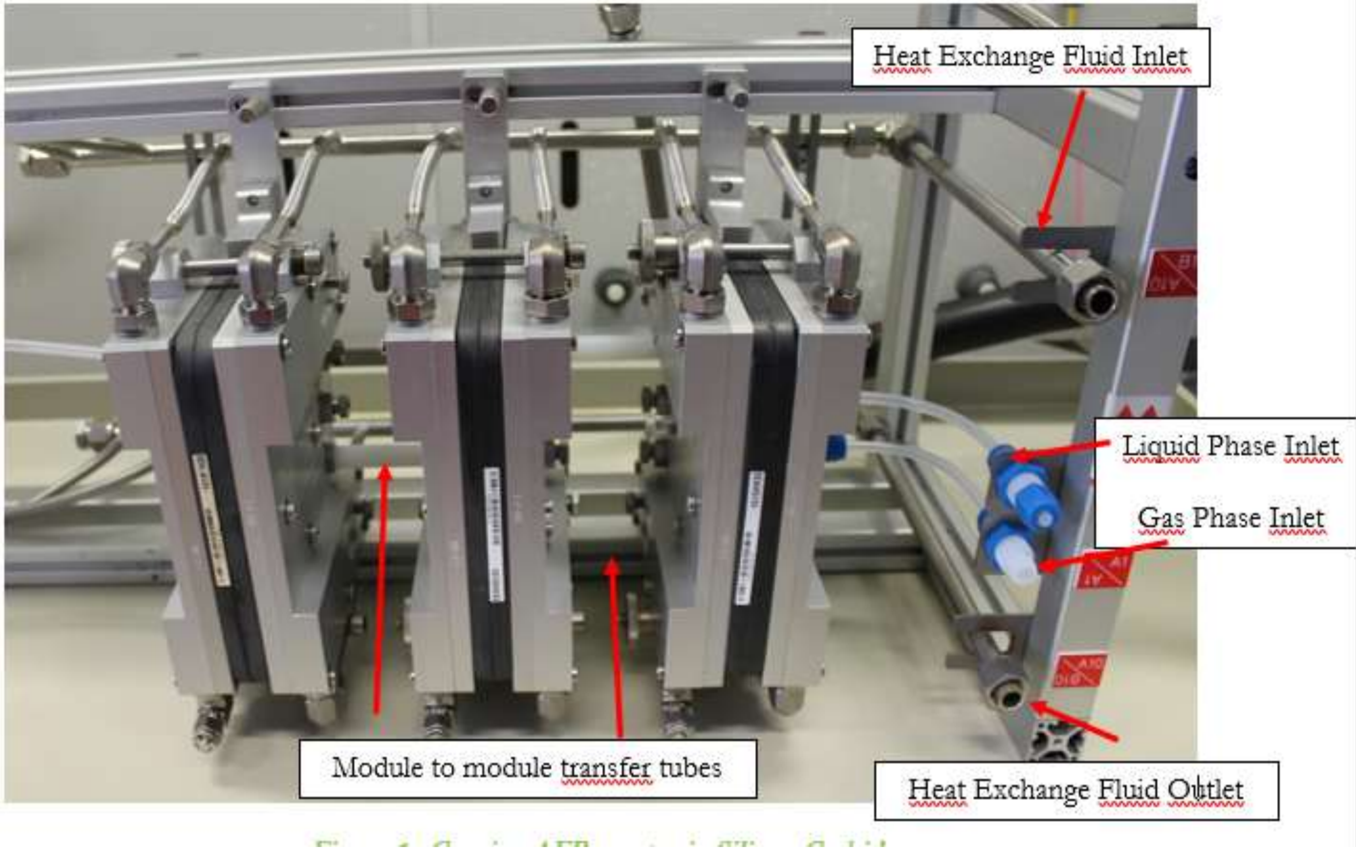
Organic Process Research & Development, Feb. 2017

MEPI Alternative Chemistry

Design of continuous intensified process



Corning G1 SiC flow reactor



mEPi Alternative Chemistry

Continuous carbonate synthesis

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

CORNING

Parker

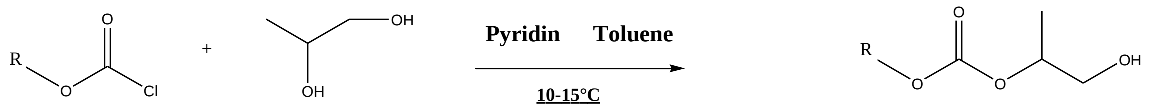
KAISER OPTICAL SYSTEMS, INC.

CPAC

mEPi
Alternative Chemistry

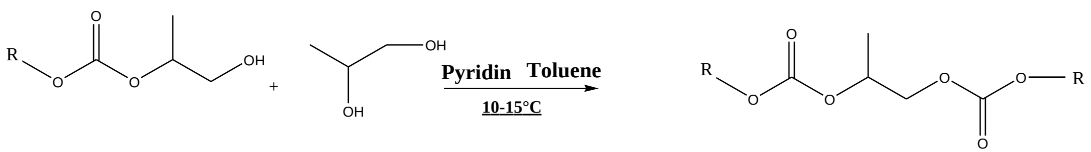
Continuous carbonate synthesis

Addition of Chloroformate on a diol



A B P

Main reaction

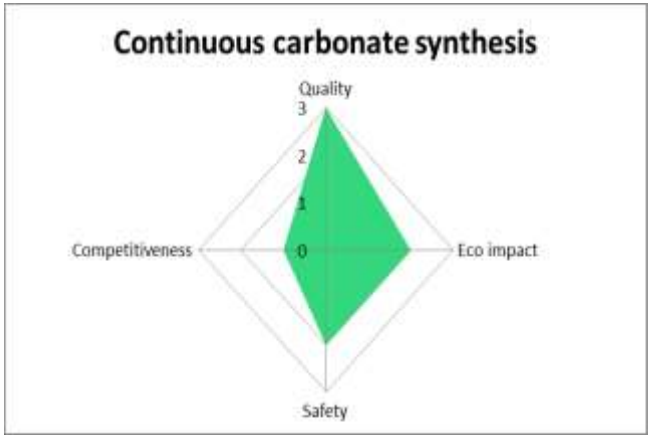


P B S

Side reaction

Objectives

- Prove feasibility of a continuous production process
- Improve selectivity (Impurity < 2%)
- Estimate the benefits related to PI technologies



Continuous carbonate synthesis

Reaction constraints

Two phase system (Liquid-Liquid)

- Chloroformate, Carbonate, Impurities → Toluene Phase
- Diol → Non miscible

Selectivity

- Necessity to slow down the main reaction (moderate temperature, reactant feeding)
- Large excess of Diol
- Constraint of less than 2% of dimer

Viscosity

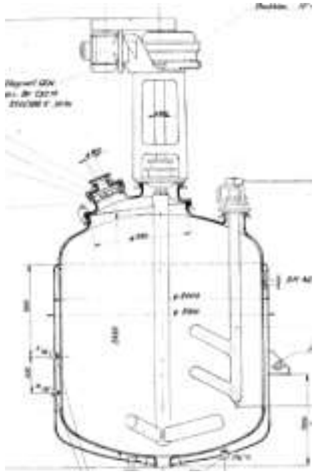
Few data available

- No information on thermo-kinetics
- No data on solubility and phase equilibria
- Operating batch data at the production scale

Continuous carbonate synthesis

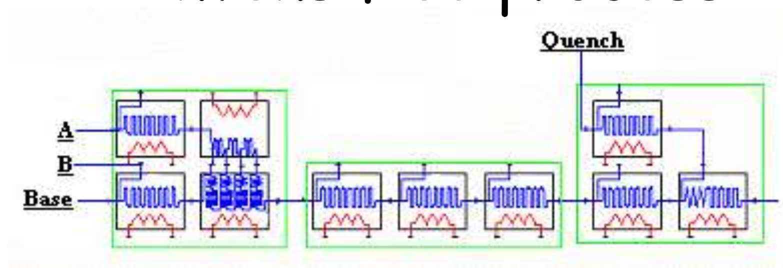
Benefits of the proposed PI process

Present Process



- Reactor volume : 4 m3
- Conversion > 95 %
- Selectivity : ≈ 2.3 %
- Excess of B : 10 equivalents
- Temperature : 15-20°C (1 atm)
- Operating duration : 4h (A feeding: 2h)
- Production : 20 T/y
- Analysis : at the end: GC

Intensified process



Increase of selectivity

Decrease of reactant excess

Decrease/removal of solvent

- Reactor volume : 100 mL
- Conversion : > 95 %
- Selectivity : in average 1.5 %, best 0.99 %
- Excess of B : 4 to 5 equivalents
- Temperature : 60°C (3;5 bar)
- Operating duration : 2 min
- Production : 17,5 T/y (≈ 40 g/min)
- Analysis : on-line : Raman Spectroscopy

mEPi Alternative Chemistry

Continuous carbonate synthesis FDA study

FDA collaboration : demonstrate the concept of QbD

- Demonstrate the benefits of improved reactor design, effective sampling and online analytics to increase process understanding (QbD)

- Improve reaction development and optimization through the use of continuous flow reactors, NeSSI and online analytics

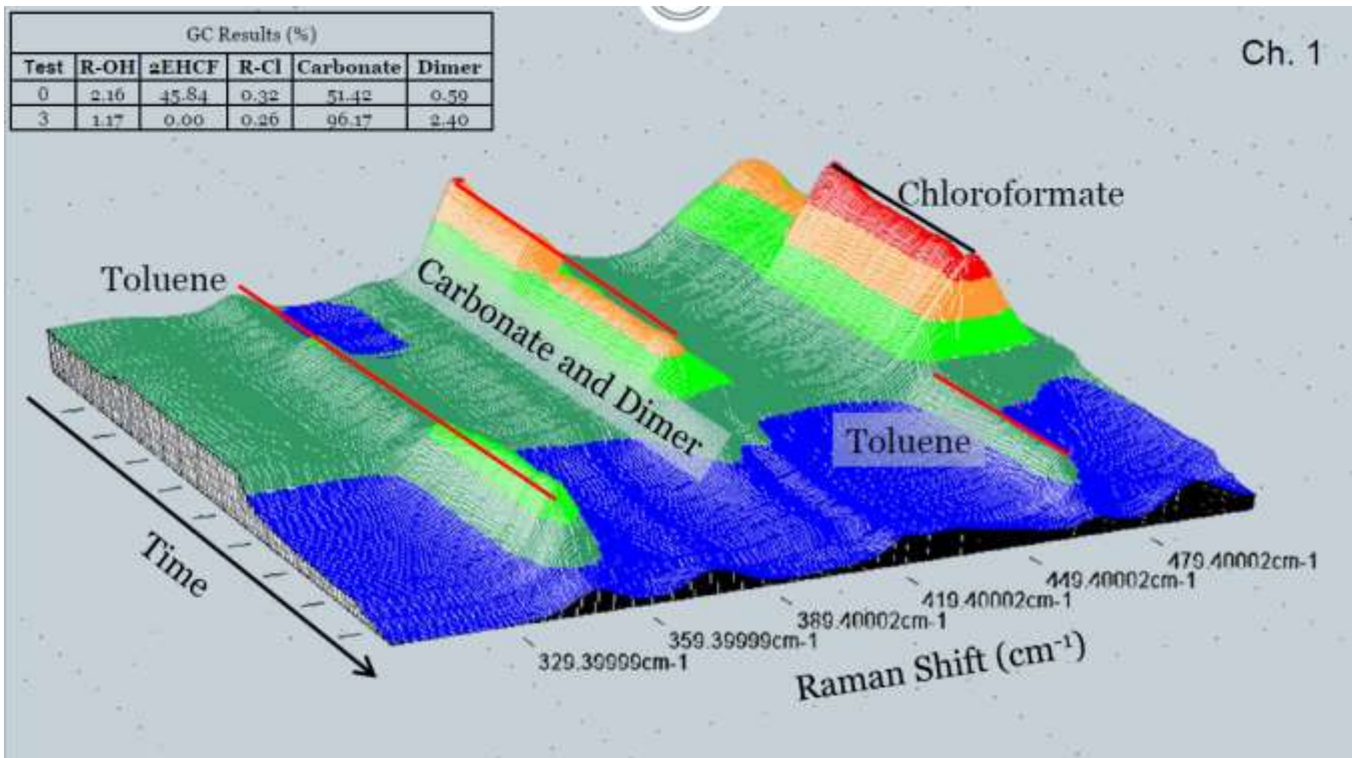
Continuous carbonate synthesis FDA study

In-line analysis – Supervision and control of the production process

NeSSI Sampling and Raman Probes

Continuous carbonate synthesis FDA study

In-line analysis – Supervision and control of the production process



GC Results (%)					
Test	R-OH	2EHCF	R-Cl	Carbonate	Dimer
0	2.16	45.84	0.32	51.42	0.59
3	1.17	0.00	0.26	96.17	2.40

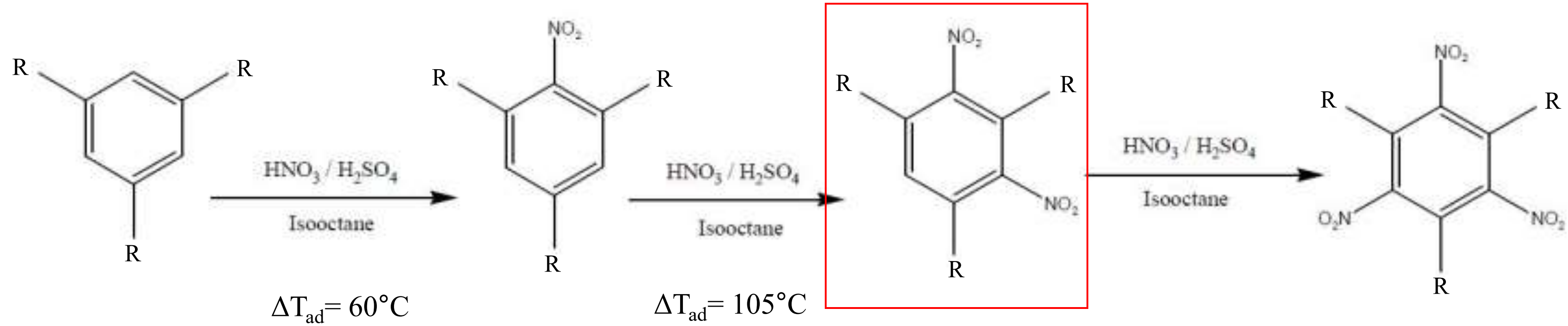
saltigo

Industrial production of a Di-Nitrated compound

mEPi Alternative Chemistry

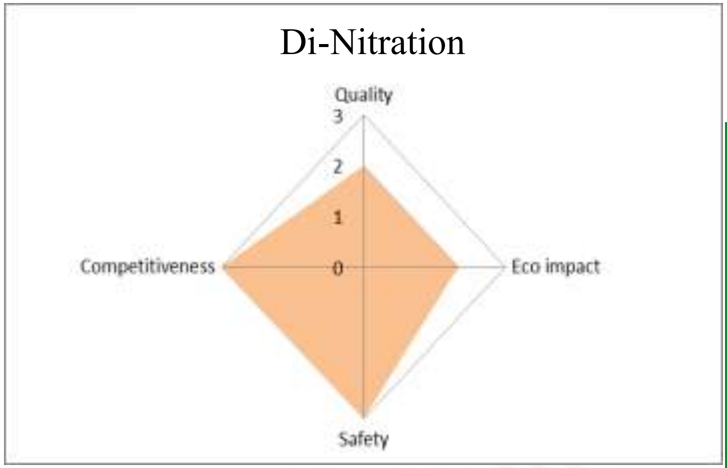
Industrial production of a Di-Nitrated compound

Di-Nitration reaction



Objectives

- Prove feasibility of a continuous production process
- Estimate the benefits related to PI technologies
- Check possibilities of increasing Productivity



Industrial production of a Di-Nitrated compound

Design of continuous intensified process : Reaction constraints

Accurate management of reactive medium temperature

- T < 35°C during feeding to avoid thermal runaway
- T > 60°C during reaction to avoid solid generation (Di-Nitro compound)

  ↳ Fed-Batch process – Operating time of 14h !

Selectivity

- Excess of sulpho-nitric acids
- Strong influence of water contents

  ↳ Use of high purity acids (HNO_3 = 99%, H_2SO_4 = 98%)

Mixing

- Two phase reaction
- Strong difference of density (aqueous d ≈ 1.7, organic d ≈ 0.7)

Corrosion

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Industrial production of a Di-Nitrated compound

Design of continuous intensified process : Batch reaction at lab-scale


Beginning of dropwise addition (35°C)


End of dropwise addition (35°C)


Beginning of contact time (65°C)


End of contact time (65°C)

- Poor thermal control
- Poor mixing

→

- Low kinetics
- Poor selectivity

64 % max. of Di-Nitro after 4h

Industrial production of a Di-Nitrated compound

Design of continuous intensified process

Thermal performances

- Estimation of the minimum required (UA/V)

Mixing + Mass transfer performances

- Estimation of the mixing time required
- Determination of flow-rates and injections design
- Solid handling (?)

Corrosion

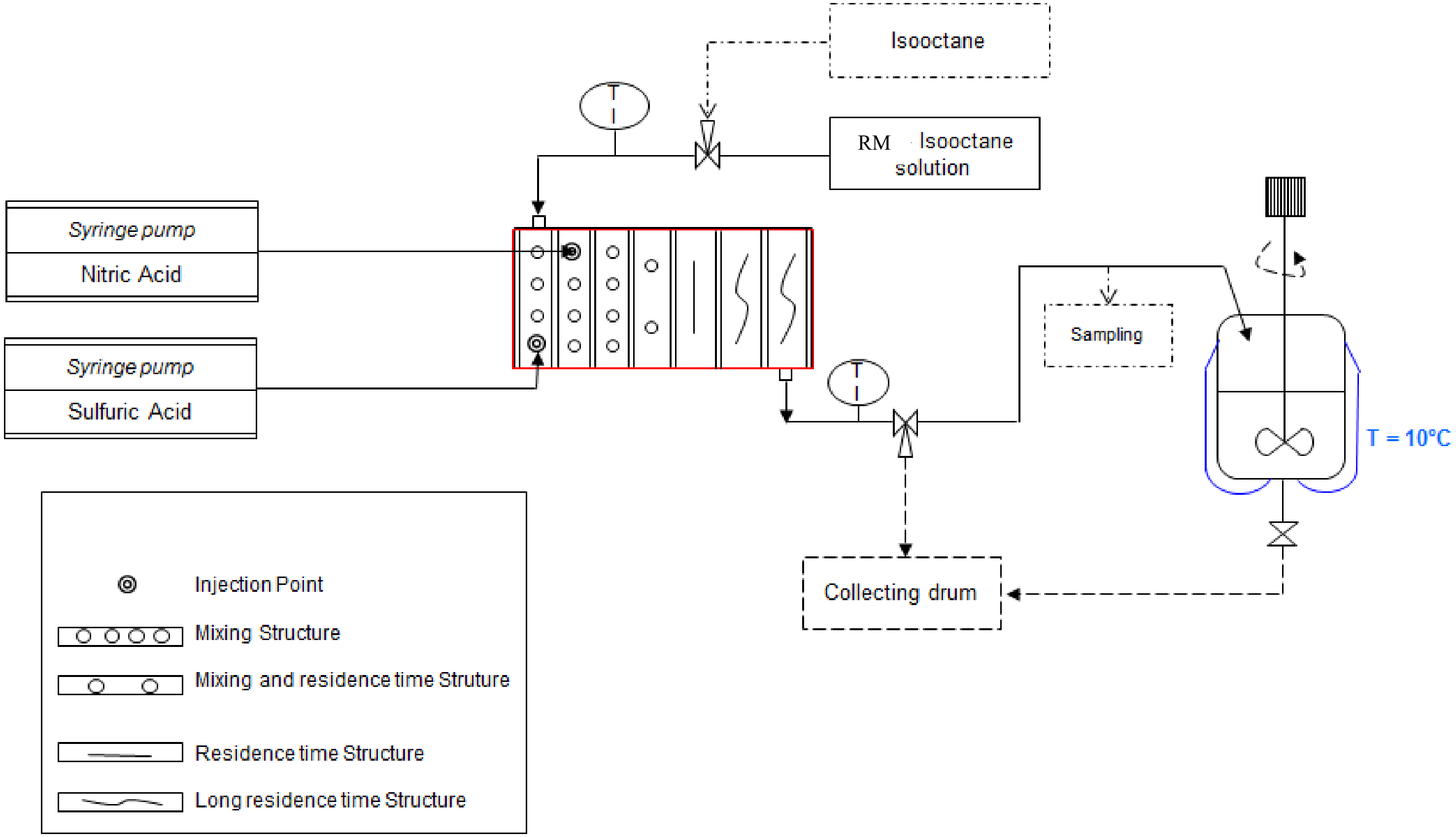
➡ One single reactor ?

Combination of different technologies ?

Industrial production of a Di-Nitrated compound

Design of continuous intensified process

Transposition to continuous : "One pot" process



Industrial production of a Di-Nitrated compound

Design of continuous intensified process

Transposition to continuous : "One pot" process

Industrial production of a Di-Nitrated compound

Design of continuous intensified process

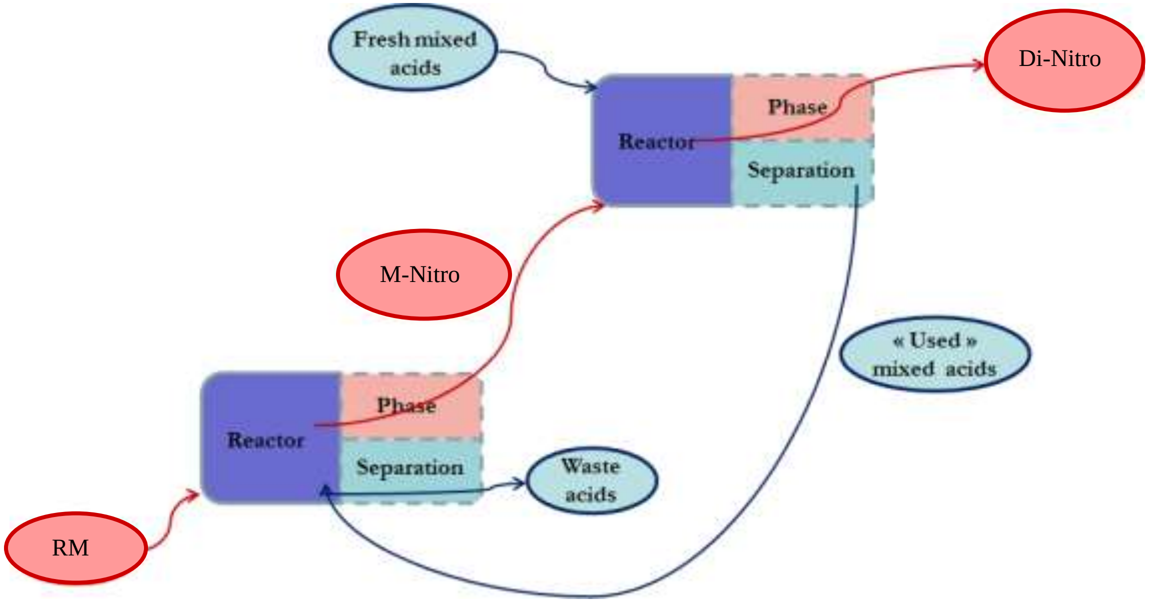
Transposition to continuous : "One pot" process

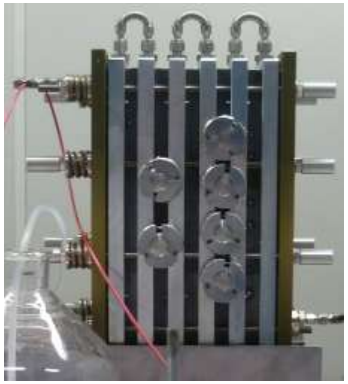
99 % of Di-Nitro obtained in 2 min

Industrial production of a Di-Nitrated compound

Design of continuous intensified process

Alternative solution : "2 steps" di-nitration process





Feasibility demonstrated !

Crossed expertises

Chemical reactions
Crystallyzations
Distillations
Extractions
Isolation
In line analysis

Formulations

Temperature control

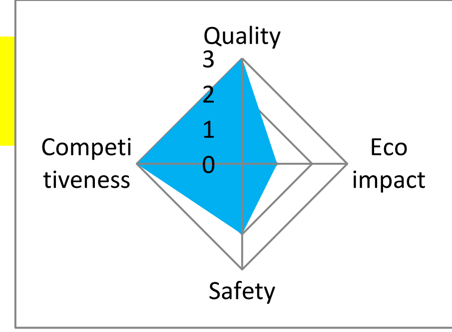
Mixing

Pharmaceuticals
Agrochemicals
Fine chemicals
Specialty chemicals
Nutraceuticals
Flavour & Fragrances
Cosmetics
Galenic
Paints

MEPI Alternative Chemistry

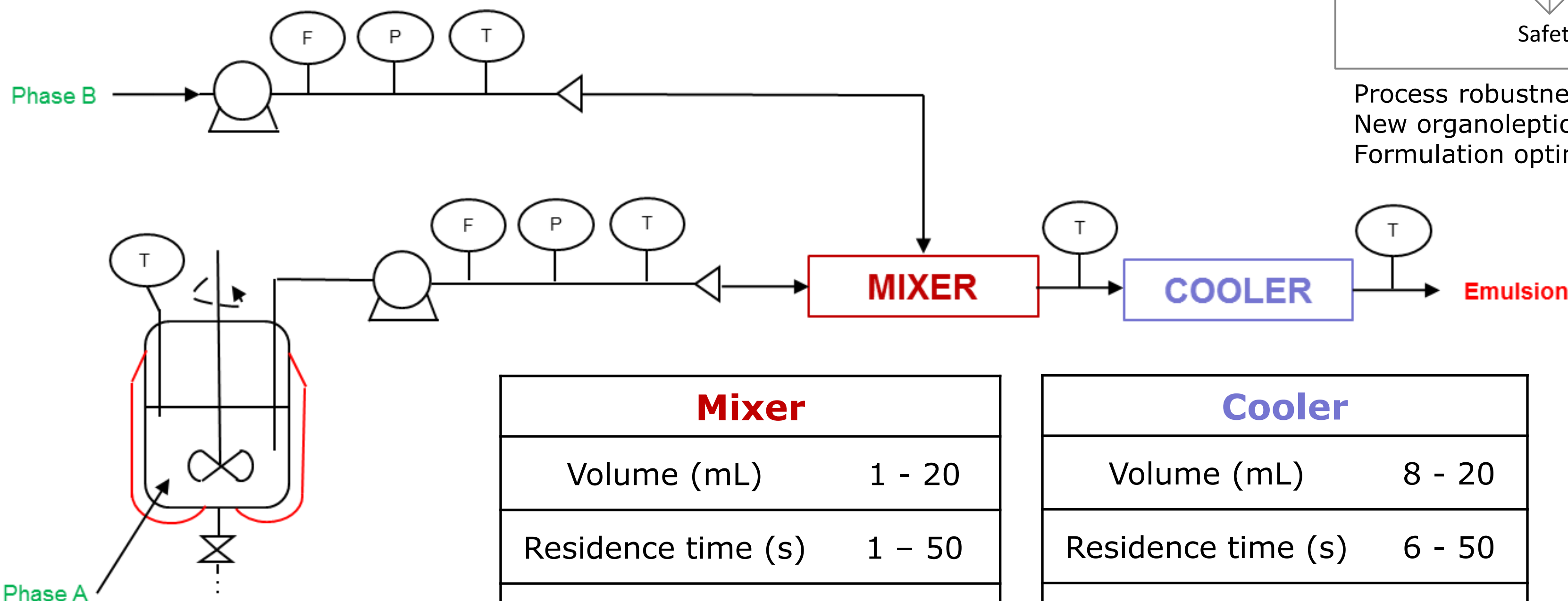
NEW

Continuous formulations



Process robustness
New organoleptic properrties
Formulation optimizations

Emulsification in continuous with mixers



Mixer	
Volume (mL)	1 - 20
Residence time (s)	1 – 50
Temperature (°C)	25 - 90

Cooler	
Volume (mL)	8 - 20
Residence time (s)	6 - 50
Temperature (°C)	25

Inlet : Phases	
Flowrate ($g.min^{-1}$)	20 - 80
Temperature (°C)	25 - 60
Viscosity (cP)	1 - 300

Outlet : Emulsion	
Appearances	Cream, Gel
Viscosity (cP)	Until 15 000

MEPI Alternative Chemistry

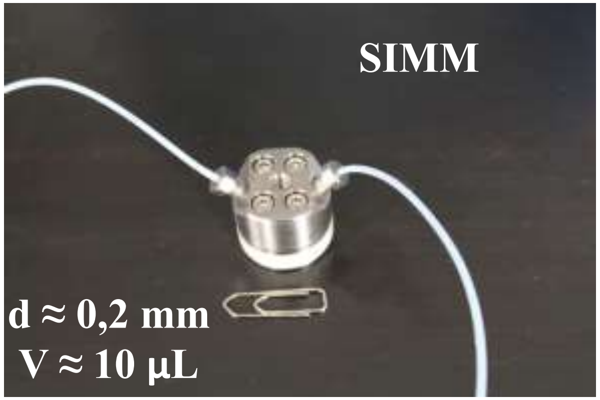
NEW

Continuous formulations

Favorite mixing devices :

T types (1/4 or 1/16 '')

IMM Micro mixers



SMX (Sulzer) static mixers

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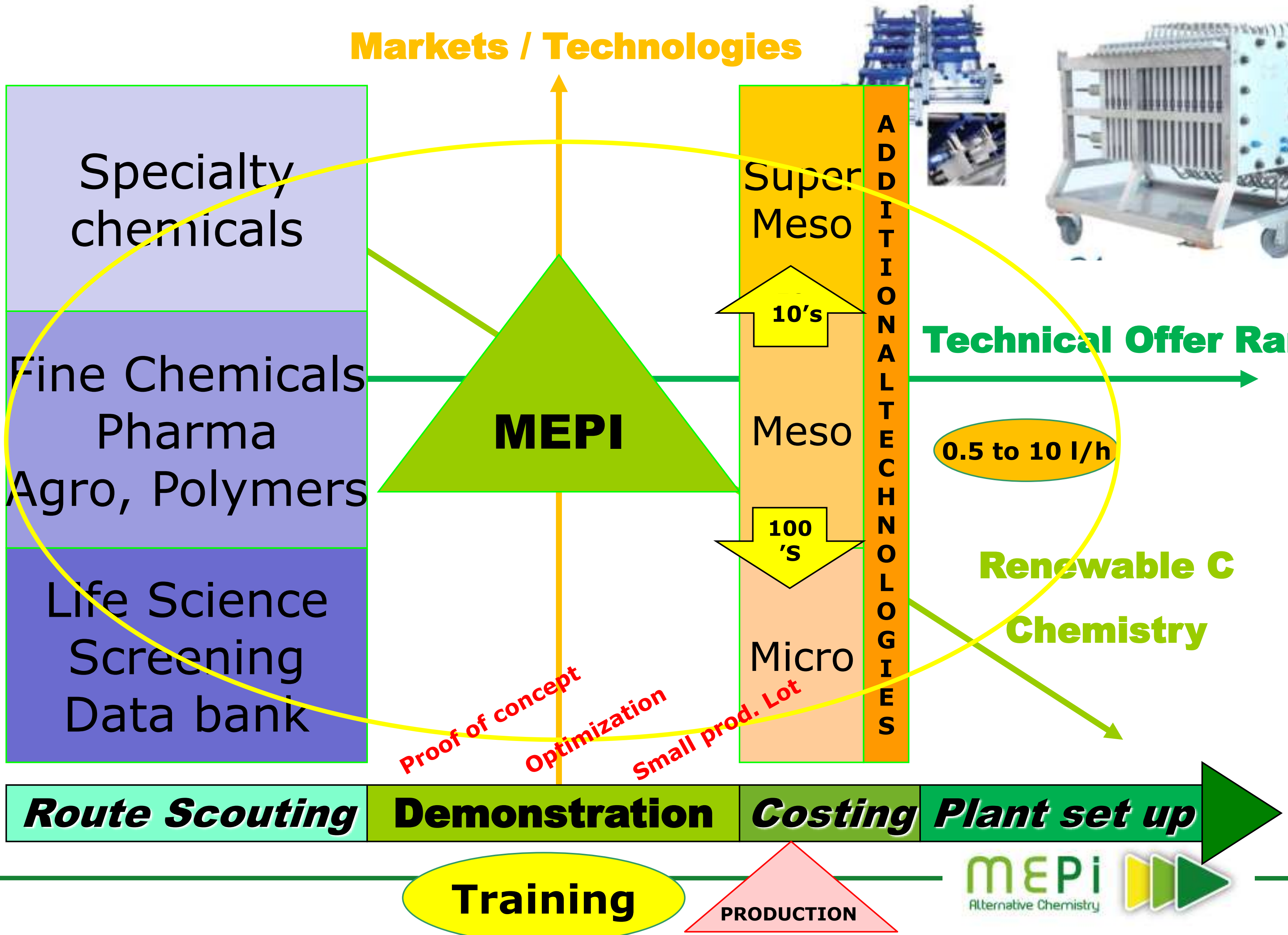
NEW

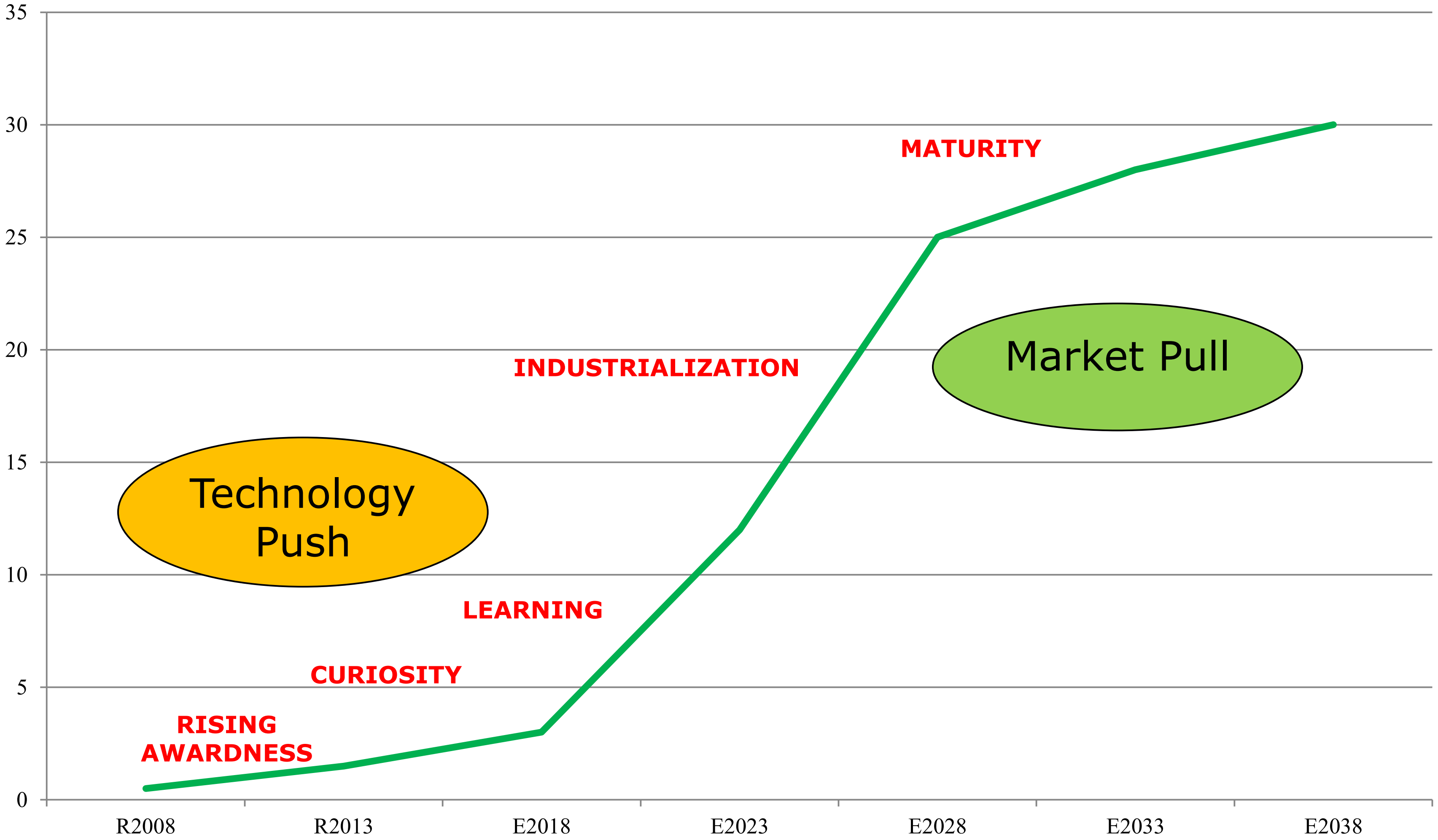
Continuous formulations

IMM Caterpillar Micro mixers

Road to Industrial Production Set up



Market trends (%)



Chemical Factory of the Future : A flexible aproach

Container factory

Implementation strategies

Hood factory

Squatter factory

Average expected Savings :

Capex reduction up to 40%
Opex reduction up to 20%
Reduction in energy consumption up to 30%
Solvent reduction up to 100%
Footprint reduction up to 50%

Paul Hodges , ICIS, Aug. 29th 2013

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Publications

Chemistry Today, July 2012 issue :
« Direct fluorination of 1,3-dicarbonyl compound in a continuous flow reactor at industrial scale”

Chemistry Today, Nov-Dec 2013 issue :
« Two-phase enzymatic reaction using Process Intensification technologies »

Specialty Chemicals Magazine, June 2014 issue :
« From batch to continuous for a selective nitration »

Chemistry Today, Sept/Oct 2015 issue :
“Photochemistry at industrial scale”
http://www.teknoscienze.com/articles/chimica-oggi-chemistry-today-flow-photochemistry-a-meso-scale-reactor-for-industrial.aspx

Organic Process Research and Development, Feb. 2017 issue :
“One-Step Continuous Flow Synthesis of Antifungal WHO Essential Medicine Flucytosine Using Fluorine »
https://www.acs.org/content/acs/en/pressroom/presspacs/2017/acs-presspac-february-1-2017/cheaper-way-to-make-who-designated-essential-medicine.html

For further articles, visit our website :
http://www.mepi.fr/en/news/

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Mentors

« Simplicity

is the utmost

sophistication ! »

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