TOOL - BOX

FLOW CHEMISTRY & Downstream Operations

IGCW-2017 – FCS India Conference

Vijay Kirpalani
CEO : Pi – PROCESS Intensification Exp. LLP
President : Flow Chemistry Society - India
FLOW REACTORs – WHEN?

have a look at your reactions

➢ are the reagents/intermediates/product hazardous/toxic?
➢ are any unstable / labile intermediates formed?
➢ is mass transfer limiting selectivity/yield/product quality?
➢ is it a temperature-sensitive / highly exothermic reaction?
➢ is the reaction volume / product ratio v. high?

(small batches/loss of productivity & consequent high OPEX)

if 1 /5 answers is a “YES” → Flow Reactors

( & not just the micro-reactors)

* exception: handling of highly sticky substances is still a problem
Advantages of Continuous Flow Reactors

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 and cool
   • Reduced peak loads on process utilities (smaller boilers and chillers)
3. Greater flexibility. A flow reactor can handle a wider range of throughput capacities
4. Improved safety via smaller in-process inventories & easier pressure containment

The other aspect of flow chemistry relates to performance v/s 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
Process Challenges

Synthetic transformations pose many different challenges;
1. Exothermic reaction that is fast & uncontrollable above the lab-scale
2. Multiple reaction phases
3. Sequential reactions that give rise to by-products
4. Biocatalytic processes that fail to scale beyond the lab
5. Production of solids with uniform characteristics

Conclusion: Flow reactors are flexible to multiple processes, however the right reactor must be selected for the process challenge

Once you have decided to use flow, how do you select the right flow reactor?

• What criteria to consider?
  (45 Key attributes listed in Appendix)
• What reactors are out there?
What to Consider?

Based on the SCALE you wish to use in continuous processing, different aspects may be considered:

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

- \( ng \rightarrow \mu g \rightarrow mg \rightarrow g \rightarrow kg \rightarrow 10 \ kg \rightarrow 100 \ kg \rightarrow \) multi-ton

**Lab-scale:** mg-g
- Speed
- New reaction space
- Selectivity
- Flexibility

**Process R&D:** g-kg’s
- Speed
- Safety
- Robustness

**Production:** 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**

**Example:** Micro-reactors are not used to produce tonnes & spinning disks not for mg’s
Key Considerations

→ THERMAL CONTROL

→ MIXING SENSITIVITY
Key Considerations

SPEED vs CONTROL

Difficult to achieve both SPEED & CONTROL in a batch reaction

Heat-transfer

Mixing
Heat Transfer

Flow Process Benefits
Heat Transfer

Reduced equipment size delivers higher Heat Transfer Area - to - Volume

Heat transfer area per unit volume in a tubular flow reactor is 1 to 3 orders of magnitude higher than a typical batch (depending on respective size).

There is however a trade off when using tubes since heat transfer area per unit length suffers as the diameter is increased.

And then you have the “SYNTHETRON” with S/V ratio = 1,84,000 m² / m³
Heat Transfer

Heat transfer area per unit area - **BENEFITS**
Increasing the heat transfer area per unit volume (of process fluid) by orders of magnitude without reducing reaction time, the ability to heat & cool the reactor contents more efficiently reduces overall processing time compared to batch

- Increased surface area = increased thermal control
  ⇒ allows the use of upto solvent-free conditions

**Volumetric heat transfer coefficient:** kW/m².K is influenced by:
- Surface area/channel size
- Material of construction: SiC > SS-316 > Hastelloy > Glass

**Heat transfer capacity:** also depends on the ratio:

\[
\text{Thermic Fluid Flow Rate} \over \text{Process Fluid Flow Rate}
\]

**Heat transfer** is important if you have:
- Reaction exotherm
- Thermally **unstable** product
- Thermally promoted unselective reaction (consecutive reaction = by-product)
Mass Transfer

Flow Process Benefits
Mixing Time → Plug Flow?

Stirred tank / Batch reactors

In a batch reactor the process material needs to turnover ≈5 times to achieve >99% mixing*. In a large batch reactor (1,000’s of litres) this is measured in minutes / hours.


Flow reactor

The mixing path in a flow reactor tube is 1-3 orders of magnitude shorter than a batch reactor.

Mixing times in the millisecond range are seen.

Mixing time is important if you have;

1. A + B → C (desired product)
2. A + C → D (impurity)

If the mixing time is short in relation to reaction time, less secondary product is formed since reactant A is consumed more quickly by the primary reaction.

In a flow reactor time relates to distance travelled.

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Plug Flow – Examples

Plug flow is important if;

• Reactants & products can react to give side products
• Full flushing of the reactor is required

What does this look like in reality?

Assuming no dispersion, a flow reactor behaves like several batch reactors in series

Narrow Residence Time Distribution:

• All molecules experience the same conditions = uniform product quality
Plug Flow – Examples (2)

Plug flow increases **uniformity** of:
- Reaction **time**
- Reaction **temperature**
- Product **quality**

Example: **Plug Flow**
- Plantrix ‘zig-zag’ channel structure has;
  - **Fully flushed** channel
  - Plug flow = **no back-mixing**

Ref: OPRD, Roder *et. al*

Fits dispersion model = plug flow

Poor plug flow (**high back mixing**) has a serious impact on yield, purity and capacity

Bo = 1100
Plug Flow – Examples (3)

Dispersion effects

Bodenstein number (Bo) enables estimate of deviation from plug flow, i.e. BACK-MIXING

\[ Bo = \frac{ul}{D} \]

plug flow

Laminar flow

\[ D = D + \frac{u_i^2 d_i^2}{4 \beta D} \]

\[ \beta = 48 \text{ tube} \]
\[ \beta = 30 \text{ square channel} \]

Large deviations from plug flow

Bo = 10^2

"BACK-MIXED" zone

Small deviations from plug flow

Bo = 10^3

Plug flow

Plug Flow – Examples (4)

Consequence of **Back-mixing**

- variable reaction time
- variable temperature gradients
- **stagnant zones** = material can be retained in the reactor
  
  (Product stuck will react with oncoming reactant / will degrade / disturb the set molar ratios resulting in impurities.)

- **Broad RTD** (residence time distribution)

- **Not problematic** for non-consecutive, thermally insensitive or slow reactions *(very few known in organic chemistry)*

---

Turbulent or Poor Plug flow = high **back mixing** will have a **serious impact** on yield, purity and working capacity
Plug Flow – Examples (5)

Example: **Back-mixing (the heart is NOT Plug Flow)**

- Results in variable reaction time & temperature gradients
  - Can lead to **stagnant zones** = material can be retained in the reactor
  - **Broad RTD** (residence time distribution)
- Not problematic for non-consecutive, thermally insensitive or slow reactions

Poor plug flow (**high back mixing**) has a **serious impact** on yield, purity & capacity
High Back-mixing

Ocillatory Baffled Reactors
Back-Mixed Reactors are NOT Flow Reactors!

BACK-MIXING destroys PLUG-FLOW

PLUG-FLOW Reactors give excellent MIXING characteristics WITHOUT Back-Mixing.

Back-Mixing & Pulsed Flow (bad pumps) $\Rightarrow$ loss of uniform molar ratios & conditions

Result: erratic quality, yields and host of impurities.
How to Size a Reactor?

Volumetric size of a flow reactor (l) = Volumetric flow (l/s) × reaction time (s)

Residence time and volumetric capacity are major factors for choice of flow reactor.

Low throughput
- Micro reactors

High throughput fast reaction time
- Meso reactors
- Static mixers
- Spinning disk

High throughput slow reaction time
- Oscillatory flow
- CSTRs
- Stirred / shaken tubes
- Spinning disk reactors
Classifying a Flow Reactor

90% or more of flow reactors in common use fall within one of 6 basic types and can be classified according mixing and plug flow

### PASSIVELY mixed reactors

<table>
<thead>
<tr>
<th>Reactor type</th>
<th>Mixing method</th>
<th>Plug flow method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro channels and packed columns</td>
<td>Molecular diffusion and/or static mixing</td>
<td>By default</td>
</tr>
<tr>
<td>Meso/large channel plates, tubes &amp; static mixers</td>
<td>Axial velocity with or without static mixing</td>
<td>Axial velocity combined with channel length</td>
</tr>
</tbody>
</table>

### ACTIVELY mixed reactors

<table>
<thead>
<tr>
<th>CSTRs in series</th>
<th>Mechanical mixing</th>
<th>Random mixing in multiple stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stirred / Shaken tube</td>
<td>Mechanical mixing</td>
<td>Radial mixing combined with channel length</td>
</tr>
<tr>
<td>Spinning disk</td>
<td>Mechanical mixing</td>
<td>Controlled mixing in multiple stages</td>
</tr>
<tr>
<td>FUMI spinning disk</td>
<td>Mechanical mixing</td>
<td>-do-</td>
</tr>
<tr>
<td>Oscillatory Flow Tubes (OBRs)</td>
<td>Axial velocity bi-directional with static mixing</td>
<td>Axial velocity combined with channel length. (NOT really a Plug Flow reactor)</td>
</tr>
</tbody>
</table>
Materials of Construction

Depending on the reaction type & process requirements, range of MOC’s are available;

• **Glass**
• Metal (stainless steel, Hastelloy, **Tantalum**)
• Ceramics (aluminium oxide, **silicon carbide**)
• Polymers (PMMA, **FEP, PFA**)

When selecting a reactor material consider;

• **Chemical resistance**
• **Thermal** requirements (temperature range & heat transfer)
• **Pressure** requirements
• Feature sizes;
  • Reaction volume type
  • **Mixing** requirement
  • Overall reactor required
• Process **flexibility** (toward the future)
Materials of Construction

Example: Robust Material of Construction – Silicon Carbide

Robust Material of Construction – Silicon Carbide

- Excellent corrosion resistance
  - Acids, bases, organics etc.

- High thermal conductivity
- Durable – long lasting
  - 50 wt% NaOH at 180 C for 2.5 years – no corrosion
Materials of Construction

Example: Silicon Carbide: Integrated Heat Exchange

Integrated Heat Exchange

- Sandwich construction
- Minimal thermal loss
- High thermal conductivity of SiC
  - $100-120 \text{ W/m}^2\text{.K}$ at 7 mm
- Maximum control over exothermic reactions

Patented SiC Production Process

- Diffusion bonded – all SiC
- No brazing, welds or gaskets
- Metal-free, gas-tight modules
- Monolithic structure
- NOT sandwiched between 2 SS / Alu Boxes having Heat transfer fluid!

Patented (EP 637271B1 & foreign patents)
FLOW REACTORS

TECHNOLOGY PLATFORMS

Selection of apt reactor technology platform is most important for better cost benefit realization:

a) HEAT Transfer Area cost -- for Heat Transfer limited process
b) Reactor Volume cost -- for Mass Transfer & slow, kinetically limited process

Key types

- Micro-reactors / Micro-channel reactors
- Falling-film micro-reactors
- Tubular & “Dynamic-Tubular” flow reactors
- Spinning Tube-in-Tube reactors
- Spinning Disk reactors
- Spinning Disk FUMI reactors
- Oscillatory Tube/Baffled flow reactors (OBRs)
- Microwave assisted flow reactors
- Sonication-assisted flow reactors
- Multi-cell flow reactors
- Aspirator flow reactors, etc.
FLOW REACTOR
Options

Static Flow Reactors

Dynamic Flow Reactors
STATIC Flow Reactors

PASSIVE MIXING
Passive Mixing – Micro Reactors

Ehrfeld Modular MicroReaction System

Automated Process Screening System

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www.pi-inc.co
Passive Mixing - Micro Reactor

Advantages

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small volume</td>
<td>Rapid reaction screening</td>
</tr>
<tr>
<td>Flexible MOC’s</td>
<td>Available in many MOC’s – adaptable to chemistry</td>
</tr>
<tr>
<td>Turnkey systems</td>
<td>Accessible for students, training &amp; collection of kinetics</td>
</tr>
</tbody>
</table>

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Passive Mixing - Tube Reactor

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated</td>
<td>Lab-scale reaction screening &amp; g-production</td>
</tr>
<tr>
<td>Flexible</td>
<td>Versatile MOC’s retain flexibility needed at the lab</td>
</tr>
<tr>
<td>Complete system</td>
<td>Turnkey system suitable for chemists</td>
</tr>
</tbody>
</table>

R-Series

E-Series

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Passive Mixing - Plate Reactor

~10 to 400 kg/h

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Narrow RTD</td>
<td>Reactions needing plug flow</td>
</tr>
<tr>
<td>High surface to volume ratio</td>
<td>Exothermic reactions (nitrations/oxidations/chlorosulfonations)</td>
</tr>
<tr>
<td>Material of construction - SiC</td>
<td>Highly corrosive &amp; energetic reactions (120 W/m².K)</td>
</tr>
</tbody>
</table>
Passive Mixing – Plate/Tube Reactors
Passive Mixing – Plate Reactors

Tantalum Alloyed & SS-316 Plate Reactors (CORROSION Solution)
Passive Mixing – 3D Printed Reactors

Titanium, Hastelloy, SS-316L

Marketed by

INNO

Tomorrow's chemistry. Today.

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ACTIVE MIXING
Handling Solids in FLOW

Channel Blocking via Bridging
(Buchwald-Hartwig Coupling)

Handling Solids in FLOW

Channel Clogging via Constriction
(Buchwald-Hartwig Coupling)

Handling Solids in FLOW

Solids Handling in an Agitated Cell Reactor

4 mL/min 0.3 M morpholine in hexane
8 mL/min 0.15 M iodine in DCM

optimal flow setup

40 PSI

Agitating Cell Reactor

12 mL/min, 0.1 M
9 h gives 208 g
94% yield
3.88 kg/week
Active Mixing – Agitated Tube

‘Coflore’ – AM Technology

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing independent of flow rate</td>
<td>Slow reactions, multi-phase reactions</td>
</tr>
<tr>
<td>Solid/liquid/gas handling</td>
<td>Suitable for slurry processing and/or formation</td>
</tr>
<tr>
<td>Lab to production scale</td>
<td>Screening, feasibility &amp; production</td>
</tr>
</tbody>
</table>

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Active Mixing – OBR / OBC

‘COBR’ – NiTech

CRYSTALLIZERs

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing independent of flow rate</td>
<td>Crystallisations</td>
</tr>
<tr>
<td>Solid/liquid/gas handling</td>
<td>Suitable for slurry processing and/or formation</td>
</tr>
<tr>
<td>Lab to production scale</td>
<td>Controlled crystallisation at pilot &amp; production</td>
</tr>
</tbody>
</table>
Active Mixing – Spinning Disk

Advantages

High shear - independent of flow rate

Solid handling

High throughput

Applications

Excellent mixing at a wide flow rate range

Precipitations reactions or those using heterogeneous materials

Tonne-scale production

SpinPro Reactor

R-10  16 ml  (800 L / day)

SDR-300  230 ml  (14,400 L/day)

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Prevent Failures

→ PUMPS: Flow accuracy, measurement & control Critical!

When you can’t measure or control actual flow rates – it could mean that:

- reactions that should have worked may not, with no apparent explanation
- reactions results not reproducible
- scale-up failures as the measured/documentated flow rates were wrong

Early experiences with Flow Chemistry using unsophisticated equipment may well have been unsuccessful for this very reason.

→ Performance basics:

- reagents/products suitable for the flow path size (micro, meso)?
- clogging possibilities & what if this happens?
- cleanability (is it validatable?)
- pressure drop across the entire path (& its consequences)
- temperature range & max ΔT
- don’t calculate production capabilities only on clear water flows at RT -- you are sure to go very wrong
Prevent Failures (contd)

→ Selection of MOC: select the right materials, post-development trials on same MOC essential for scale-up!
  • Polymers
  • Glass (caution!)
  • Stainless Steels / Hastelloy (check quality!)
  • Ceramics, esp. SiC (↑ corrosion resistance, ↑ Solvent resistance, ↑ Thermal Conductivity (100x Glass & 4x SS), ↑ Temperature resistance)
    ~ but, ensure you pick the right “grade”, that gives you the required corrosion-resistance & mechanical strength – as there are many suppliers / qualities;
    ~ also look for certification re: leachability!
  • Fouling Resistance: extremely important in selection of MOC eg. Fouling rate of SS is 5x SiC
Prevent Failures (contd)

→ Design & Manufacturing Methods: factors

- Failure points? / LEAKAGE? (after many temp. cycles)
- Surface finish, (Ra) esp. for polymers & importantly SiC
- check how is it manufactured?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Metals</th>
<th>SiC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Diffusion bonding (actually monolithic)</td>
<td>-NA-</td>
<td>√</td>
</tr>
<tr>
<td>2 Laser welding</td>
<td>√</td>
<td>-NA-</td>
</tr>
<tr>
<td>3 Brazing!</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(what is the effect of the brazing material on your corrosion/temp properties?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Clamping / Bolting</td>
<td>√</td>
<td>-NA-</td>
</tr>
<tr>
<td>5 Shrink-fitting</td>
<td>Avoid!</td>
<td>-NA-</td>
</tr>
</tbody>
</table>

Quick & easy repair (at manufacturing site!)

Murphy’s law: “it anything can go wrong – it will” (someday)
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

“…..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
FDA Support for Continuous Manufacturing

Concluding Thoughts

• The science exists to enable continuous manufacturing of pharmaceuticals
  – Specific scientific considerations related to sampling frequency for continuous manufacturing

• There are no regulatory hurdles for implementing continuous manufacturing
  – However, there is a lack of experience

• FDA supports the implementation of continuous manufacturing using a science and risk-based approach
  – Recommend early and frequent discussion with Agency before implementation

Slide From: PQRI Workshop on Sample Sizes for Decision Making in New Manufacturing Paradigms
Bethesda, MD
September 13, 2011

Christine M. V. Moore, Ph.D., Deputy Director for Science and Policy
ONDQA/CDER/FDA
Advantages

FLOW Reactors

How the characteristics of a continuous flow reactor can affect process parameters

- Optimum separation of reactants and products
- Reduced reaction time
- Improved reaction time control
- Leaner reaction mixtures
- Hazardous reactions can be handled
- Extreme transient temperatures can be employed

Higher yield
Lower impurities
Smaller equipment
Shorter process time
Reduced solvent use
Improved safety
Reduced reaction steps


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It’s high time we understood the precision and accuracy requirements of successful Flow Chemistry practice.

Quite disturbing to see R&Ds playing around with ½” dia coils and old HPLC columns to “practice Flow Chemistry” – is it really any different from the above?
Illustrative Examples
n-BuLi Halex

Cetrizine intermediate:
Step-I: generation of p-chlorophenyllithium with n-BuLi
Step-II: trapping with benzaldehyde to provide (4-chlorophenyl)(phenyl)methanol
{ the benzydrol }

Step-I: p-chlorophenyl lithium

\[
\begin{array}{c}
\text{Cl} \quad \text{Br} \quad n-\text{BuLi} \\
\rightarrow \\
\text{Cl} \quad \text{Li} + n-\text{BuBr}
\end{array}
\]

Step-II: (4-chlorophenyl)(phenyl)methanol

\[
\begin{array}{c}
\text{Cl} \quad \text{Li} + \text{PhCHO} \\
\rightarrow \\
\text{Cl} \quad \text{H} \quad \text{OH} \quad \text{Ph}
\end{array}
\]

Cetrizine intermediate

Lab to Plant in the same equipment

SYNTHETRON

<table>
<thead>
<tr>
<th>Results</th>
<th>Batch</th>
<th>Flow (in Synthetron)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall conversion</td>
<td>82 – 88 %</td>
<td>98 % +</td>
</tr>
<tr>
<td>Isolated Yield</td>
<td>75%</td>
<td>94 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Throughput</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5” Ø Disk</td>
<td>24 L/hour, 2.8 Kgs/hour</td>
</tr>
<tr>
<td>5.0” Ø Disk</td>
<td>96 L/hour, 11.2 Kgs/hour</td>
</tr>
</tbody>
</table>

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n-BuLi Halex

Lab to Plant Scalability

100 Kg of API / day

2 Synthetrons: 15 ml vol.
200 uM gap and 5500 rpm on a 2.5” disk

270 ml SpinPro-300
1mm gap and 2500 rpm on a 6” disk

100 Kgs/day of API in 270 ml Reactor
Grignard

GRIGNARD Reaction
180 tonnes/year

Run Grignard reaction continuously in flow without Pump problems

E-series

Isolated Yield 89% +

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GRIGNARD Reaction in PlantriX
SiC Micro-Channel Reactor

ChemtriX PLANTRIX Micro Reactors made of EKasic® (SiC) in a pharma API production plant
Grignard Reactions
Diazomethane-in 2002!!

- Phoenix Chemicals, UK published their work regarding continuous **flow processing** for generating **60 tons per year** of **diazomethane**, while maintaining the **inventory** of this highly reactive & explosive toxic gas at **less than 80g**!

Applications in APIs:

- Nelfinavir (Pfizer, Roche)
- Saquinavir (Roche)
- Amprenavir (GSK)
- Atazanavir (BMS)

(proceedings of 5th Int’l conference on scale up of chemical processes)
Aromatic Nitration (Plantrix SiC reactor)

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
- Able to increase production rate of material
- Target product specification achieved

Process Conditions:
- Reaction time = 14 s, < 70 °C
- MR260 = 5.0 l/h; MR500's = 697 l/h

Solvent-free system
Highly exothermic
Corrosion resistant SiC

Also available
MR-555
upto 4.0 Litre
400 Kgs/hour
200° C at 25 bar

Scale-up Strategy:
19 ml --> 2.7 L --> 138x increase
MR260  MR500s
220 tonnes/month (2640 TPA)

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NITRATION

Industrial Aliphatic Nitration

\[ R \text{-} \text{CH}_2 \text{-} \text{OH} + H\text{NO}_3 \rightarrow R \text{-} \text{CH}_2 \text{-} \text{ONO}_2 \]

Extraction

\[ O_2\text{NO} \rightarrow R \text{-} \text{CH}_2 \text{-} \text{ONO}_2 \]

decomposition

**cGMP Continuous Production**

**Solution - Plantrix®:**
- Compact
- Robust
- Corrosion resistant
- Quality
- Solvent reduction

**Plantrix®**

DSM uses Micro Reactors made of 3M™ (SiC) in a pharmaceutical production plant

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Industrial Aliphatic Nitration

Drivers: Control reaction exotherm (runaway, explosive) for process safety
High “mono-nitro” selectivity, high-productivity & GMP production

DSM selected ChemtriX v/s Corning. Reasons: very few and “secure” connections, “non-leachable” & “diffusion-bonded” SiC (ChemtriX) v/s Glass or “brazed” SiC (Corning)
Continuous Nitration of Alcohols Plantrix®: 70 % Nitric Acid

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

2-Ethyl-1-hexanol

\[ \text{HNO}_3\text{-H}_2\text{SO}_4 \rightarrow 2\text{-EthylHexyl Nitrate} \]

10,000 tonnes / annum: CHINA

No by-product formation observed under optimal conditions

Optimal Conditions in Plantrix®:
12 s reaction time @ 18 °C (99.6 % purity by GC)
→ production 10,000 tonnes/annum

Advantages:
- 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
Aromatic NITRATION in Spinning Disk Reactor (SpinPro)

Throughput : 1550 t/yr
Product : 600 t/yr
in a 270 ml Reactor

Highly exothermic, Fast reaction

SpinPro-300
Volume : 270 ml
Reaction time : 5 s
Throughput : 194 kg/h

Lab

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HYDROGENATION with Heterogenous Catalyst in Agitated Tube Reactor

LAB Experiments using “Coflore” ACR

<table>
<thead>
<tr>
<th>Reactor capacity</th>
<th>70 ml</th>
<th>Reaction time</th>
<th>1 Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen pressure</td>
<td>3 bar</td>
<td>Temperature</td>
<td>65°C</td>
</tr>
</tbody>
</table>

![Diagram showing yield vs. pressure and impurity vs. temperature](image)

Yield v/s Pressure for 1 hr reaction

Impurity levels v/s Temperature

Optimized Commercial Hydrogenation Process (in “Coflore” ATR):

<table>
<thead>
<tr>
<th>Parameters</th>
<th>10 Lit</th>
<th>2 Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor capacity</td>
<td>10 Lit</td>
<td>2 Hour</td>
</tr>
<tr>
<td>Hydrogen Pr.</td>
<td>6 bar</td>
<td>35°C</td>
</tr>
</tbody>
</table>

Impurity levels:

- Batch Reaction: 2%
- Flow Reaction ATR: <0.1%

Volume:

- Batch Reaction: 1000 Lit
- Flow Reaction ATR: 10 Lit

Carbon savings:

- Batch Reaction: -
- Flow Reaction ATR: 45%

Scale effects are handled easily since mixing performance is determined by frequency & swept-volume of the agitator and not fluid velocity through the reactor and hence can be replicated at different scales.

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10,000 tonnes/year ALKOXYLATION Plant

at AGROCHEMICAL major
Shaoxing Eastlake Biochemical (CHINA)

Fast, highly Exothermic ALKOXYLATION 1000 L/hr \( \rightarrow \) 10,000 tonnes/year

MIPROVA millireactor 0.4 m dia x 7 mt L with 150 reaction channels

Replaced 20 large batch reactors
Reactions with Epichlorohydrin in “Coflore”

Drivers: High atom efficiency, Time & Energy conservation, high selectivity and virtually no degradation products (impurities)
Biocatalysis in “Coflore”

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Batch Reactor</th>
<th>ACR (Lab)</th>
<th>ATR (Plant) Output Qty</th>
<th>ATR (Plant) Output Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor Volume</td>
<td>2000 L</td>
<td>85 mL</td>
<td>10 L</td>
<td>85 L</td>
</tr>
<tr>
<td>Retention Time</td>
<td>26 Hr</td>
<td>0.5 Hr</td>
<td>0.5 Hr</td>
<td>0.83 Hr</td>
</tr>
<tr>
<td>% catalyst</td>
<td>1X</td>
<td>0.5X</td>
<td>0.5X</td>
<td>0.4X</td>
</tr>
<tr>
<td>% Purity HPLC</td>
<td>≤ 78%</td>
<td>92%+</td>
<td>92%+</td>
<td>88%+</td>
</tr>
</tbody>
</table>

All other process inputs/parameters kept constant (viz. substrate-loading, pH; Buffer; Temp.)

An otherwise un-economical Biocatalytic route made “commercially viable” (v low Enzyme reqd.), + ↑ Space, Time & Reagent efficiency
Biocatalysis in “Coflore”

ESTERIFICATION

- Oily starting material
- Lipozyme CaLB in water

- ACR-100mL: 7-Fold increase in conversion v/s stirred batch
- Scaling up to ATR-10L gives almost identical, excellent conversion
Process Intensification of DOWNSTREAM UNIT OPERATIONS
Process Intensification Technology Platform

Intensificator Reactor

- High solids / slurries
- Low to high sheer mixing
- ↓ reaction times to $< \frac{1}{10}$
- SS-316L / PTFE / PEEK HASTELLOY

Intensificator

Dalal Engineering

INDIA
Unit-Ops -- Extraction

SpinPro SDE-300

Volume: 300 ml
Throughput: 10,000 L/day +

Extremely High Extraction Efficiency

Drivers: Complete product extraction, ideal for recovery of solvents/organics from waste water, high-productivity & GMP equipment
Unit-Ops - Extraction/Separation
Unit-Ops -- Distillation

Reactive Distillation

Acetic Acid
Methanol
Catalyst

Reactor

Extractor

Azeo Column

Flash Column

Water

Impurity Removal Columns

Heavies

Water

Reactor Column

Color Column

Flash Column

Decanter

 Extractive Distillation

Methyl Acetate

Solvent Recovery

Water

Methanol Recovery

Eastman Chemicals
30 mt column replaced by a 1.5 mt column for MeOH Distn.

Drivers: v. high vapour-liquid contact surfaces // v. Low reflux ratios // v. Low energy consumption, v. low space requirements

HiGee Distillation
Unit-Ops -- Crystallization

Oscillatory Tube Crystallizer
Unit-Ops -- Filtration

Modular Spin Disk Filter – Dynamic Membrane
Unit-Ops -- Absorption

Pulsed-Jet Dynamic Waveform Absorber

Drivers: v. high gas-liquid contact surfaces // v. high efficiency // v. low space requirements
Instead of thinking outside the box, get rid of the box.

Deepak Chopra
CLOSING REMARKS

Process Intensification & Flow Reaction Platforms

1. small footprint & low CAPEX (a major advantage for sterile-processing & clean-room projects at a fraction of the CAPEX usually required)
2. v. small (and so low cost) Utility CAPEX -- due to v low peak-loads
3. v. high heat transfer area/volume ratios
4. discernable design-space -- QbD built-in
5. reproducible consistent quality & yields (impurity profile is more precise)
6. genuine feasibility for application of PAT (Process Analytical Tools)
7. highly flexible (key equipments can be plug-&-produce)
8. v. high turn-down ratios (1000 : 1 times production capacities)
9. High intrinsic safety due to extremely low reaction volumes, low residence times and high degree of temp/pressure control.
10. easy Lab to Plant scalability

We now see equipments giving 10,000 MT/yr at 1000 ml reaction volume!

It will be interesting to see how the scene unfolds in INDIA ......
Thank You
Questions/Comments??