Sustainable Manufacture of Fine Chemicals by Flow Processes

Bert Dielemans; Peter Poechlauer; Raf Reintjens; Mehul Thathagar; June 2013
Content:

- Who is DSM?
- The fine chemicals industry - present boundary conditions - present priorities
- flow processes meet industry priorities
- Process intensification: how?
DSM Corporate Sustainability - A Century of Successful Self-Transformation

- Biomaterials / Biologics
- Life Science Products
- Performance Materials
- Petrochemicals
- Fertilizers
- Coal


Technological competences
- Mechanical engineering
- Chemical engineering
- Polymer technology
- Material science
- Fine chemicals
- Biotechnology
DSM: A Global Leading Life Sciences/Material Sciences Company

- Active in 49 countries,
- 5 continents, 200 locations

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
</tr>
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<tbody>
<tr>
<td>Net Sales</td>
<td>9,131</td>
</tr>
<tr>
<td>EBITDA</td>
<td>1,109</td>
</tr>
<tr>
<td>Net profit</td>
<td>437</td>
</tr>
<tr>
<td>ROCE</td>
<td>8.9%</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>490</td>
</tr>
<tr>
<td>Workforce</td>
<td>23,498</td>
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DSM has been #1 in the Global Chemical Industry 5 of 7 years

Dow Jones Sustainability World Index

Sales(*) per cluster

- Nutrition: 42%
- Pharma: 8%
- Performance Materials: 31%
- Polymer Intermediates: 18%
- Innovation Center: 1%

(*) per cluster
what keeps us in business?

our customers think that there are 4 major drivers for future development:

- quality / trust
- sustainability / greenness
- variability of chemistry
- flexibility of production

Continuous flow technology has an answer to each
Quality & trust: the ideal reactor ...

Quickly provides ideal conditions for every phase of the reaction:

- Mix starting materials quickly
- Heat / cool
- Ensure right stoichiometry everywhere

- Heat /cool
- Add reagent
- Remove product

- Leave for
  - complete
  - conversion
Compare: process control...

Batch recipe:
Start stirrer
Heat jacket to ..°C
Add .. kg of A
Add in total .. kg of B
at a rate to keep
the temperature
below ..°C
Stir at ..°C for .. more hours until IPC ok.

Continuous flow recipe:
Heat system to ..°C
Add A at a rate of .. kg/h
Add B at a rate of .. kg/h
( .. until batch has desired size.)
A definition of „Quality by design“ states:
• Variability is controlled by the process
• All critical sources of variability are identified and explained
• Product quality attributes can be accurately and reliably predicted over the design space established for
  - materials used,
  - process parameters,
  - environmental and other conditions
Example: Ritter Reaction

"old process": loop
1st change: MR + loop
2nd change: MR + Hex
sustainability / greenness

the following technologies will further grow in importance:

- chemocatalytic and biocatalytic methods will win over stoichiometric methods

- supply and use of high-quality starting materials and intermediates from sustainable sources (green economy vs. fossil economy)

- methods using solvents and reagents that are “sustainable according to agreed metrics”: the “GCI® pharma round table” has edited “key green engineering areas1” to define the focus:
  • Continuous Processing,
  • Bioprocesses,
  • Separation and Reaction Technologies,
  • Solvent (Selection, Recycle and Optimization),
  • Process Intensification

Sustainability of production

...slowly pumped into reactor

Reagents diluted by solvent...

40% idle time

...heavy cooling

Below maximum capacity
Could carry 9 people at 1l/100km/person

Could do 180km/h

Would consume 4l/100km

Could deliver 20 to “just in time”

Could do 1,5 cars/sec

Sustainable? Green?
Process intensification - a different approach to synthesis

From...

Which chemicals may I use?
How do I tailor my synthesis into my plant?
How do I control my plant to deliver constant quality?
How do I analyze my product?

To...

Which route would be most effective?
Which sequence of conditions will make my synthesis perform best?
Which plant setup will deliver quality by design?
How will I improve my process?

Performing a reaction in flow mode allows us to specifically meet its needs. This improves yield, saves energy, time and space.
Process chemistry of a nitration

Performed in microreactor
Development steps of nitration process
How green is green? Metrics

E-factor (“environmental factor”): how much waste is produced per kg of product?

Waste / product =19:1  \( E=19 \)

PMI (“process mass intensity”): more detailed, relates product output to chemicals input

input /product=20:1  \( PMI_{\text{total}}=20 \)

PMI_{\text{water}}=10;  \( PMI_{\text{solvents}}=5 \)

Reduction of PMI in nitration process:
variability

- ...of chemistry applicable on full scale production: a continuous expansion of the chemistry and biochemistry toolbox by using
- “lab reagents” produced and used in situ on demand in a continuous plant (phosgene, diazo compounds, acroleine, diimine..)
- demanding process conditions (pressure; temperature; time [sec] )
- “lab” separation technologies: SFC; continuous multi-step extraction;

we have developed the following elements flow syntheses on various scales:

- continuous analytics
- cation chemistry
- generation of diazomethane
- low temp metallation
- azidation
- chlorination
- hydrogenation
- nanoparticle formation
- ethyl diazoacetate and carbene reaction

avoid process changes during scale-up
**Ethyl diazoacetate & carbene reaction**

The synthesis of ethyl diazoacetate is seemingly simple:

\[
\text{Cl}^- + \text{H}_{3}\text{N}^+ + \text{O} + \text{O} + \text{Cl}^- \text{NaNO}_2 \text{CH}_3\text{COOH} \rightarrow \text{N} = \text{N} = \text{O} + \text{O}
\]

ethyl aminoacetate *HCl
(glycine ethyl ester *HCl)
103.12
C4H9NO2 * HCl

ethyl diazoacetate
114.12
C4H6N2O2

“To a cooled acidic solution of glycine ethyl ester hydrochloride add sodium nitrite solution and extract the product with an organic solvent”.

**Pure EDA is dangerous:**
- Start of decomposition at 65 °C
- Energy of decomposition 1605 J/g
- Positive result in “drop hammer” test“ at 29,4 J

Do not transport
Do not store
No mineral acids
No metal ions
Ethyl diazoacetate: flow equivalent of lab recipe:

“To a cooled acidic solution of glycine ethyl ester hydrochloride =:A add sodium nitrite solution =:B and extract the product with an organic solvent” =:S.
Further reaction of ethyl diazoacetate

Carbene formation & cyclopropanation of unreactive olefin:

EDA in solvent → olefin

“Dilute EDA solution using the olefin add carbene forming catalyst and heat up; cool after reaction”.

High rate of dimer formation vs. cyclopropanation requires high excess of olefin prior to carbene formation.
High dilution (1mol%) of EDA prior to carbene formation and reaction (10 sec):

1 mol/min EDA ➔ 100 mol/min olefin ➔ ~ 500 kg/h distilled; reactor hold-up: <2kg
flexibility

Key factors:
• minimize the cost of goods and the total installed cost
• further accelerate scheduling for design, build and construction
• make facilities more flexible and adaptable for a range of products by
  - modularization of construction and process implementation
  - use of disposables
Hurdles to implementation 1

Design and scale-up of intensified processes: a multidisciplinary effort ...and a perceived lack of adequately educated job candidates.

- reaction order & kinetics
  - A\(\rightarrow\)P; 2A\(\rightarrow\)P; A+B\(\rightarrow\)P
  - Reaction rate
  - energy demand/release
  - Rate=\(f(c,T)\); P=\(\Delta H_R \times \text{Rate}\)

- reactor performance
  - U (heat transfer); \(t_{\text{mix}}\); Re;..

- reactor features:
  - dimensions, temp / pressure resistance
  - order of reactant addition
Hurdles to implementation 2

There is an uncertainty about scale-up concepts from lab to pilot and production. Simply take costs per capacity:

Invest costs per unit of production capacity

Teaming up with the right supplier is essential
(material+method+cost)
Choice of the right construction material

Influence of construction material and method on manufacturing cost

<table>
<thead>
<tr>
<th>Construction material</th>
<th>polymer</th>
<th>glass</th>
<th>ceramic</th>
<th>metal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrosion problems</td>
<td>org.solvent</td>
<td>base</td>
<td>none</td>
<td>acids, halogens</td>
</tr>
<tr>
<td>Heat conductivity</td>
<td>low</td>
<td>medium</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Mechanical strength</td>
<td>low</td>
<td>medium</td>
<td>medium</td>
<td>high</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Construction methods</th>
<th>machining, laser, etching, sandblasting, punching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel shaping</td>
<td>multiple channels per sheet, stacking of sheets</td>
</tr>
<tr>
<td>Paralellization</td>
<td>diffusion bonding, clamping</td>
</tr>
</tbody>
</table>

Construction material and method of processing have a big influence on manufacturing.
DSM / Chemtrix Alliance: Value Proposition

Flow scan
Equipment design
Equipment manufacture
Equipment provision

Novel chemistries
Feasibility study
Lab production

Process development
Pilot manufacturing
Scale-up
cGMP production

TOGETHER we address ALL your Flow Chemistry needs, from conception to delivery
Chemtrix Flow Chemistry Equipment
Scalability & System Flexibility from Lab to Production

**DISCOVERY**
Labtrix®
(μg to mg’s)
-20 to 195 °C
Turnkey system
- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

**DEVELOPMENT**
KiloFlow®
(g to kg’s)
-15 to 150 °C
Turnkey system
- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

**PRODUCTION**
Plantrix® Reactor
(kg to ton’s)
-30 to 200 °C
Turnkey system
(with partner)
- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

PRODUCTION Plantrix® Reactor
(kg to ton’s)
-30 to 200 °C
Turnkey system
(with partner)
- Facile up-scaling
- Forbidden chemistry
- Safe production
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Status and activities of large fine chemicals and pharmaceutical producers

• The vast majority of large fine chemicals and pharmaceutical producers have implemented or consider implementing intensified & continuous flow processes.

• Most have done so in an opportunistic way (immediate advantage), for the following communicated reasons:
  - Speed up development phases
    • Avoid process changes during development
    • Speed up product supply
  - Improve on environmental footprint
  - Decrease investment for capacity build-up or expansion
  - De-bottleneck existing processes to increase throughput.
Conclusions

- Continuous processing in the manufacture of fine chemicals is moving from embryonic to maturity.

- It simplifies QbD solutions that meet authorities’ guidelines
- It helps companies to meet their sustainability / greenness goals

- We consider intensified processes to:
  - Shorten development times
  - Improve productivity and safety
  - meet quality goals
  - meet sustainability goals
Thank you

DSM Pharma Chemicals

Dr. Peter Poechlauer
Principal scientist

E-mail: peter.poechlauer@dsm.com

Internet: www.dsm.com
www.dsmpharmachemicals.com