Process Intensification: A Prerequisite for Success in Custom Manufacturing

Chemspec 2016, Basel

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Dr. Guido Giffels
Saltigo
Who are we and where do we come from?

A globally operating company for exclusive synthesis and innovative fine chemicals

Saltigo profile
- customers: ca. 150
- employees: ca. 1,250
- products/projects: ca. 400
- 10 production plants
  Leverkusen + Dormagen (Ger)

Lanxess profile
- spin off from Bayer 2004
- employees: 16,225
- sales: € 7.9 billion in 2015
- global footprint: 29 countries
- 52 production sites
Saltigo – A global player in custom manufacturing serving different industries

- Exclusive production 100 - 5.000 kg/a
- Intermediates and APIs
- Regulated area (CGMP, etc.)

- Production volumes > 1.000 t/a
- Intermediates and AIs
- Regulated area (Biocides Regulation, etc.)

- Often non-exclusive products
- ISO-production or special demands
Focus on market oriented services:
Support of customer needs along the complete project lifecycle

Core competence of Saltigo

- Custom manufacturing/synthesis up to 5,000 t/a
- Enhanced service support (registration, analytics, etc.)
- Professional procurement, reliable supply chain
- Custom-made process development
- Efficient project management
- Continuous improvement process

Process Intensification: A prerequisite for successful custom manufacturing
Process intensifications drive efficiency and cost optimization
A diverse toolbox is required for a successful implementation

Project Management

- Plants
- Technology
- Process Development
- Analytics

- De bottlenecking Capacity
- Continuous Process Improvement
- Economy Investments
- Teams Mindset Customer
- Data Generation Innovation
- QA and QC
- Process Intensification

Milestones and Implementation

Chemspec Basel 2016, Saltigo Presentation

June 1st, 2016
Process intensifications –
What does it mean?

„Getting More out of Less“
## Getting More out of Less – How?

### Ways to achieve this goal

1. More **"Right 1\textsuperscript{st} Time"**, optimizing process & parameters to improve product quality, reducing/omitting number of process steps, reworks, ...

2. Changing **Equipment** (Hardware) → improve setup

3. Higher **Space-Time-Yields** by Process Optimization, e.g. shortening cycle time, increasing output/batch etc.
Process Intensification
3 Case studies

Case #1

*Increasing the bulk density* of an agrochemical product by using multivariate data analysis

Case #2

Significant *increase of production capacity & productivity* by stepwise modification of reactor setup

Case #3

*Shortening cycle time* of an exothermic reaction by use of an intelligent control factor
Case Study #1
Objective: increase the bulk density of a crystallized product

Case description

- Large-scale custom-made product crystallizes in (at least) 2 polymorphomic modifications
- Customer requires Mod. B, a defined purity (specification!) and a high bulk density

<table>
<thead>
<tr>
<th>Mod. A</th>
<th>Mod. B</th>
</tr>
</thead>
</table>
| Crystallizes **kinetically controlled** ("faster")  
Gives better & **required purity**  
Mechanically less stable  
Grinding during drying leads to low particle size and to **low bulk density**  
Bulk density is crucial, as a certain amount of product per big bag is asked by the customer | Thermodynamically more stable, **may be formed out of** Mod. A  
**Required product form** by the customer  
Gives lower purity if crystallized directly  
Mechanically more stable, larger particle size  
Gives **higher bulk density** |
Case Study #1
Objective: increase the bulk density of a crystallized product

Objective: How to get...
- the right modification (Mod. B) ?
- the right purity ?
- a good bulk density ?
... with a minimum of effort?

Crystallize Mod. B directly:
Purity not sufficient

Crystallize A first, isolate & recrystallize, seeding B:
Works, but additional (re)crystallisation (= effort)

Convert Mod. A → Mod. B on the dryer
Possible, but drying process gave varying results

"Is this the best option?"

Let's look deeper into this one
Case Study #1: Multivariate Data Analysis – Tool to pick the right parameters and values

Drying Process
Thermal impact triggers the modification change from Mod. A → Mod. B

Drying Process (not automated) gave various results in bulk density

Multivariate Data Analysis „highlighted“ the crucial process parameters during drying:

✓ **Pressure** (vacuum) – higher pressure in the beginning is better

✓ **Bulk temperature** – higher temperature in the beginning is better

✓ **Energy application** (by stirrer): lower is better – grinding!

Multivariate Data Analysis – normalized data showing effect on bulk density

Parameter data from approx. 60 batches → high amplitude = large impact on bulk density
Case Study #1: Increase Product Bulk Density
Rationale behind the “right” parameters

Possible "Routes"

<table>
<thead>
<tr>
<th>Wet</th>
<th>A - wet</th>
<th>B - wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>A - dry</td>
<td>B - dry</td>
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</table>

Mod A          Mod B

A-wet → A-dry → B-dry:
- grinding of Mod A during drying
- low bulk density

A-wet → B-wet → B-dry:
- formation of stable Mod B first, then drying,
- larger particles and higher bulk density

First tempering the wet product at higher pressure ("bad" vacuum) and resulting higher inner temperature leads to fast change from Mod. A → Mod. B = less grinding of mechanically less stable Mod. A, resulting in a better bulk density after drying.
Case Study #1: Increase Product Bulk Density

Results after optimization

<table>
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<tr>
<td>Relevant process parameters were identified by means of multivariate data analysis</td>
</tr>
<tr>
<td>Significant increase of bulk density was achieved</td>
</tr>
<tr>
<td>Requested amount of product per big bag can be filled</td>
</tr>
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</table>

Bulk Density before/after Optimization

Histogram of Bulk density

- Before Optimization
- Optimized
Case Study #2: Increasing Capacity & Productivity by Optimized Reactor Setup
Case Study #2
Increasing capacity & productivity by optimized reactor setup

Case description

- Large scale chlorination product (B) was produced in batch mode with limited capacity
- (A) reacts to target product (B). (B) reacts further to byproduct (C) in a consecutive reaction. To maximize selectivity, (A) is only partially converted and recycled during workup
- **Objective**: increase capacity / productivity to meet market demand

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<th>Reactor Setup</th>
<th>Normalized Capacity [tons/year]</th>
<th>Normalized Productivity [tons / year x m³ reactor volume]</th>
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<td>1) Base Scenario</td>
<td>100%</td>
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Target Product

Bottleneck

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Slide 15

June 1st, 2016
Case Study #2
Increasing capacity & productivity by optimized reactor setup

Szenario 2): First expansion

- Add 2nd distillation unit
- Change to continuous operation of distillation:
  Unit 1: recycle (A)  Unit 2: isolate product (B)
- Doubling chlorination unit

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<td>2) Doubled, cont. Distillation</td>
<td>333%</td>
<td>133%</td>
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Bottleneck

Chlorination Unit 1
batch

Chlorination Unit 2
batch

Distillation Unit 1
continuous

Distillation Unit 2

(C)
Case Study #2
Increasing capacity & productivity by optimized reactor setup

Szenario 3): Debottlenecking distillation

- Reactor setup as szenario 2, plus ...
- Improved column for distillation unit 1

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<td>3) Distillation 1 improved</td>
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<td>160%</td>
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Case Study #2
Increasing capacity & productivity by optimized reactor setup

Szenario 4): Optimized Use of Chlorination Unit

- Chlorination changed from 2 batch reactors to only one CSTR (continuously stirred tank reactor) with higher throughput.
- CSTR = broader residence time distribution → higher conversion needed for the same capacity → decreased selectivity, higher portion of (C).

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<tr>
<td>4) cont. chlorination, 1 CSTR</td>
<td>400%</td>
<td>200%</td>
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Case Study #2
Increasing capacity & productivity by optimized reactor setup

Summary

- Overall, **4 fold increase of production capacity** at **doubled productivity (!)**
- Further upsides:
  - back integration into raw material via Lanxess production network
  - further conversion of byproduct (C) into sales product improves overall efficiency
Case Study #3: Shortening cycle time by intelligent use of an appropriate control factor
Case Study #3
Shortening cycle time by intelligent use of an appropriate control factor

Case description

- **Grignard reaction** of an aryl chloride (Ar-Cl → Ar-Mg-Cl)
  - sluggish, but highly exothermic
  - accumulation of reaction potential must be avoided to prevent runaway reaction

- **Standard procedure**
  → Magnesium + solvent are charged to the reactor
  → Portion of aryl chloride is added
  → Await start of reaction (exotherm = heat release; sampling)
  → Further aryl chloride is added continuously over time (fixed rate), controlling/ensuring that exothermic reaction continues

- **Objective:** How to control the reaction progress intelligently to allow maximum speed of addition – ?

Adapted from Kryk et. al., see: *Organic Process Research & Development, 2007, 11, 1135-1140*
Case Study #3
Shortening cycle time by intelligent use of an appropriate control factor

Approach for SAFE but FASTER addition rate of reagent Ar-Cl

- **Key:** Accumulation of Ar-Cl must be avoided

- Reaction is run in a *closed* reactor, allowing reaction temperature above boiling point of the solvent → faster reaction initiation and conversion of Ar-Cl → Ar-Mg-Cl

- Recording of the reactor’s calorimetric data installed, allowing a **real-time heat balance**

- From calorimetric data, the *theoretical maximum reactor pressure in case of hypothetical immediate spontaneous full conversion* (adiabatic increase of $p$ and $T$) is calculated, the so called $p_{MTSR}$ (pressure at Maximum Temperature of the Synthesis Reaction)

- The $p_{MTSR}$ is a value for the accumulated reaction potential! Always staying below the **maximum allowed $p_{MTSR}$ as lead parameter**, the maximum addition rate of the aryl halide can be applied → shorter cycle time
Case Study #3
Shortening cycle time by intelligent use of an appropriate control factor

Using the appropriate control factor allows significant cycle time reduction

Graphics adapted from H. Kryk et. al., HZDR
Summary
Take-Home Messages

Successful process intensification requires:

✓ **Knowledge**  Data, Know-How, Competence, Experience, Ideas  →  People
✓ **Ressources**  Equipment, Technology, Budget, Hands and Heads  →  People
✓ **Mindset**  Objectives, Planning, Interdisciplinary Team-Work  →  People

⇒ Acknowledgement to the Saltigo Project Teams!

Thank you for your attention!