Advanced Manufacturing of Solid Dose Products using ConsiGma 4.0 Continuous Manufacturing solutions

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Background to Continuous manufacturing and the drivers behind it

GEA ConsiGma 4.0 product portfolio

Key Technology differentiators

Case study: OEE on Direct compression systems
Case study: Optimising table coating using the GEA Tablet coater
CM in Pharma industry – benefits & challenges

CM in the view of 13 Pharmaceutical companies (incl. 7 GEA ConsiGma® clients) representing 60% of the global pharma supply!

**Benefits Expected from CM**
- CM benefits include reduced cost, higher quality, agility and faster scale-up

**Challenges Companies Are Facing Today**
- Regulatory Approvals
- Legacy Infrastructure
- Change Management

**Source:** Accenture Strategy 2018
“Scale-out” not “scale-up” gives a vastly more agile platform to conventional batch

- Products have been developed on the same line through the drug development:
  - Early development batches
  - Clinical trial material
  - Commercial production
- Eliminating scale up allows for a more rapid development timeline
- Using Conti early develop runs can last under an hour, whilst longer production runs can be flexible to meet demand
Increasing OEE increases the NPV of manufacturing plants

OEE = 90% x OEE = 80% x OEE = 50% x OEE = 50% x OEE = 80% x OEE = 40%

OEE = 6%

OEE = 90%
CM can provide significant savings in costs of GMP facilities

- 60% to 70% footprint reduction – 2 instead of 34 machines and 230 instead of 680 sqm
  - Using a cost of €3,746/m² (1) for GMP space this equates to capital savings of €1,685,000 in buildings
- Savings power consumption up to 40%
- 50% less manpower – 208 down from 430 FTEs
  - Based on average US Pharma salary of $27,730 (2) annual savings of $6,156,060
- Capex Continuous technology 1.4x versus the Batch process

(1) c$600/ft² for GMP space based on https://bioprocessintl.com/manufacturing/facility-design-engineering/construction-and-start-up-costs-for-biomanufacturing-plants-182238/. Canadian dollar to Euro rate of 1$ = €0.65

(2) Average pharma salary US taken from https://www1.salary.com/Pharmaceuticals-Salaries.html

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Easier Product transfer

Savings in time and material costs during development

No Scale Up = Taster time to Market

API savings depending on the API value

<table>
<thead>
<tr>
<th>Stage</th>
<th>Batch manufacturing API used</th>
<th>Continuous Manufacturing API used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation Development</td>
<td>90 kg</td>
<td>35 kg</td>
</tr>
<tr>
<td>Pilot Scale</td>
<td>120 kg</td>
<td>Together with Formulation development</td>
</tr>
<tr>
<td>Commercial</td>
<td>1650 kg</td>
<td>350 kg</td>
</tr>
<tr>
<td>Total Amount of API used</td>
<td>1860 kg</td>
<td>385 kg</td>
</tr>
</tbody>
</table>

Difference in API consumption: approx. 1475 kg (huge potential savings !)
Confirmed Customer Cases

Experiment Time Comparison

- 2 scientists performing a DoE of 11 trials
- Lab = 1 kg scale, Pilot = 10 kg scale
- Continuous train from granulation to tableting

AstraZeneca: 2 to 3 days instead 13 to 30 days!

Roche: 1 – 2 weeks instead 7 weeks!

Rapid & efficient Development
Project X full factorial DoE

- Batch Process → fractional design DoE’s
- Conti Process:
  - Better database at time of filing (full instead of fractional DoE’s)
  - More rapid development & no Scale-Up as big benefit for accelerated products:
    → earlier NDA filing
    → earlier medicine availability for patients

AstraZeneca: 2 to 3 days instead 13 to 30 days!
GEA Key Technology Platforms
GEA is the leading supplier of continuous manufacturing solutions to the Pharmaceutical industry with over 17 year experience.

Our product range, ConsiGma® is designed to fit the needs of todays market:
**ConsiGma® Integrated Direct Compression**

<table>
<thead>
<tr>
<th>Scope</th>
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<tbody>
<tr>
<td>Up to 6x GEA LiW feeders and 2 GEA blenders with variable configuration for maximum blending flexibility</td>
</tr>
<tr>
<td>Fully integrated single story direct compression line</td>
</tr>
<tr>
<td>Available in two size ranges to suite throughput needs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capability</th>
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</thead>
<tbody>
<tr>
<td>Throughput ranges proven between 1 – 130 kg/hr</td>
</tr>
<tr>
<td>API range from 0.25 to 93%</td>
</tr>
<tr>
<td>OEB 4 Proven containment using SMEPAC testing</td>
</tr>
<tr>
<td>WIP enabled for easy washing prior to disassembly</td>
</tr>
</tbody>
</table>
ConsiGma®
Dosing & Blending DB LB/RB

**Scope**

- Flexible feeder table with multiple feeder options (GEA & K-Tron)
- Three options of GEA blending technology to suite application
- Interface with existing customer equipment (RC, WG, press)

**Capability**

- Throughput ranges of 5 - 400 kg/hr
- OEB 4 containment capability for potent formulations
- WIP enabled for washing prior to disassembly
- Multiple uses: IBC, RC, WG, Capsulator or HME
## ConsiGma® Tablet Coater TC

### Scope
- Loading from IBC, tablet press or CM line
- Modular system allows for multiple units to work together
- Range of wheel sizes to tailor throughput to needs

### Applications
- Aesthetic coatings
- Enteric coatings
- API coatings

### Benefits
- Improved coating quality – more consistent film thickness
- Less coating solution required – e.g. 5% vs 12% for enteric
- Small footprint
- No scale up

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Test before you invest
GEA Platform Capabilities:
Case study
Integrated DC
Process Yield – Short run example
180 minute run with non competitive relevant formulation:

- 400 mg tablet image, 10% mAPAP DL
- Set-up based on preceding process development work packages
- Process run with commercial control system active.
- Limits set to produce tablets within 97-103% DL prediction.

<table>
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<tr>
<th>Ingredient</th>
<th>Quantity</th>
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<tr>
<td>Lactose (PD2)</td>
<td>23.500 kg</td>
</tr>
<tr>
<td>mAPAP (PD3)</td>
<td>8.173 kg</td>
</tr>
<tr>
<td>Avicel (PD4)</td>
<td>47.134 kg</td>
</tr>
<tr>
<td>CCM Na (PD5)</td>
<td>2.460 kg</td>
</tr>
<tr>
<td>Mag St (PD7)</td>
<td>0.818 kg</td>
</tr>
</tbody>
</table>

In Spec Tablets: 99.61%
Manual Tablets: 0.27%
Rejected Tablets: 0.12%

Tablet Press:
- Man tabs: 543
- Good tabs: 201049
- Reject tabs: 249
- Total tabs: 201841

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Integrated DC Process Yield – Long run example

Lactose 316 FF: 1816.044 kg
Avicel PH102: 3443.766 kg
pAPAP: 611.053 kg
Ac-di-sol: 181.873 kg
Mag St: 60.970 kg

Total raw materials 6113.706 kg

Samples: 7.836 kg
120 hours One Process
Reconciliation: 31.068 kg

400 mg tablet production over entire run
15,043,590 tabs
6,030.96 kg

Rejected tablets 120,473
Manual start up 10,345
Auto start up (first revolution rejects) 1,400

Overall Tablet press performance 15,043,590
In specification tablets 14,923,118

In specification tablets 99.20%
Rejected tablets 0.80%
Manual start up 0.72%
Auto start up (first revolution rejects) 0.07%

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GEA coater technology – what's different?

Q1. What is required to coat a tablet?

Q2. How can we achieve this in reality?
GEA Tablet Coater Case study

Traditional

Data generated in collaboration with Colorcon Inc, coating material Acryl-EZE®
Aspirin (325 mg) tablets were used as the coating substrate. The coating was a fully formulated aqueous enteric coating solution, Acryl-EZE® prepared at 20% concentration.

A 12% WG was targeted based on known batch processes. Samples were withdrawn from the system at 5%, 6%, 8%, and 10% apparent weight gain and assessed for 2 hours at 0.1N HCL before being transferred to a pH 6.8 phosphate buffer for dissolution and drug release testing.

Slight differences in the rate of drug release were observed in the buffer phase depending upon the applied coating WG. As expected, higher WG resulted in slightly slower release initially, but all samples reached >90% release within 20 mins. The total coating time to reach 12% WG was 30 minutes.

Passing enteric results were achieved in 12.5 minutes of coating at just 5% WG indicating an excellent coating uniformity. The early protection and the absence of any visible edge defects indicated a low tablet stress in this dynamic process.
Continuous Manufacturing has proven benefits

Both for NCE development and high efficiency manufacturing
Starting to see significant development in

Using GEA’s 17 years experience in providing CM platforms there is a range of solutions for every need:

Simple applications to solve specific pain points such as feeding and blending only, or tablet coating
Full integrated lines for maximizing the OEE of a facility

Proven case study’s and test centers that can be utilized for customers formulations