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

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GEA engineering for a better world

Agenda

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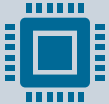
Background to Continuous manufacturing and the drivers behind it

GEA ConsiGma 4.0 product portfolio



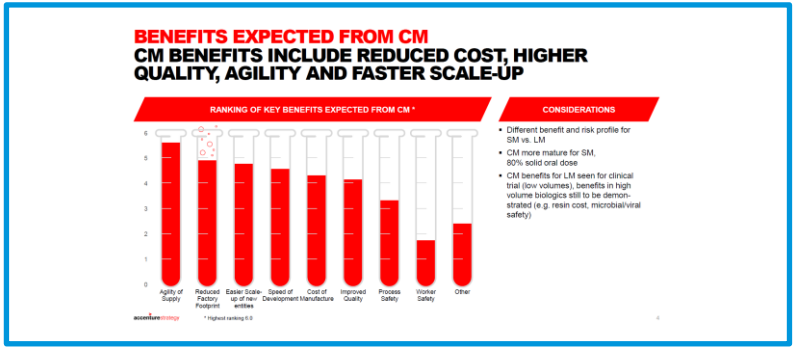
Key Technology differentiators

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 !



- Agility of Supply
- Reduced Footprint
- Easier Product Transfer

- Regulatory Approvals
- Legacy Infrastructure
- Change Management

Source: Accenture Strategy 2018

NCE's: Agile manufacturing platforms

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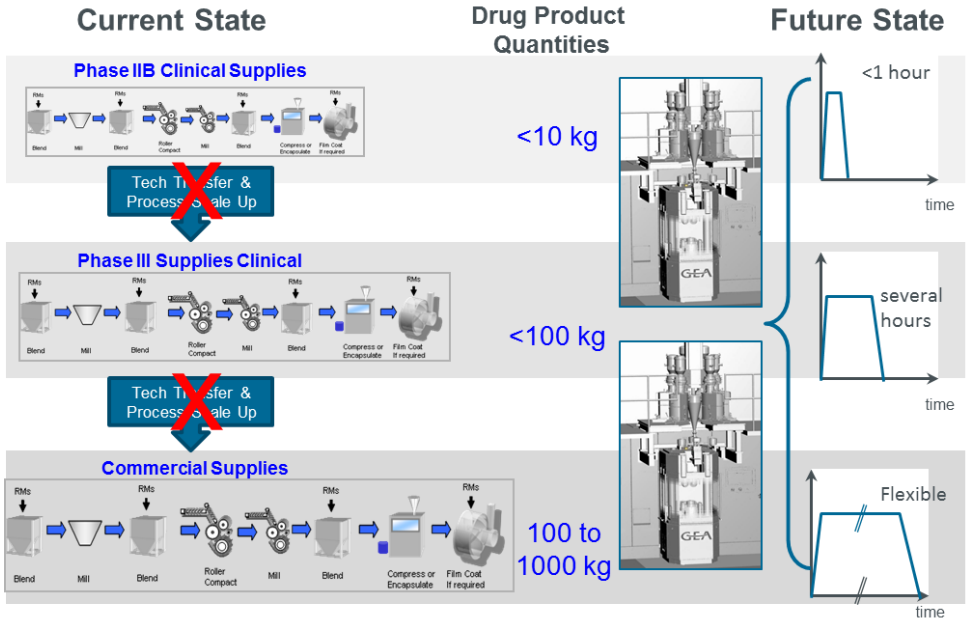
"Scale-out" not "scale-up" gives a vastly more agile platform to conventional batch

- *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*



Batch versus Continuous

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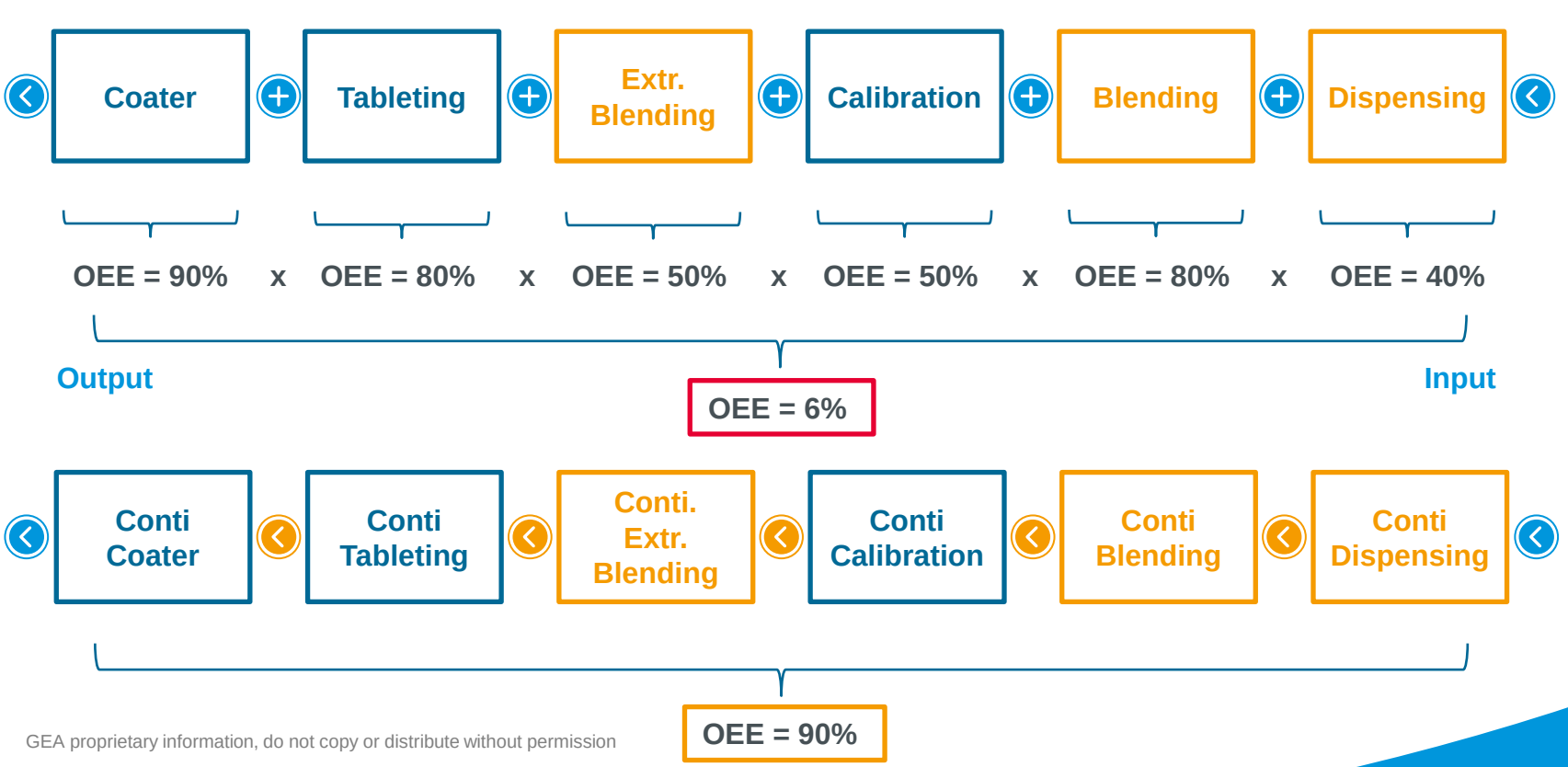
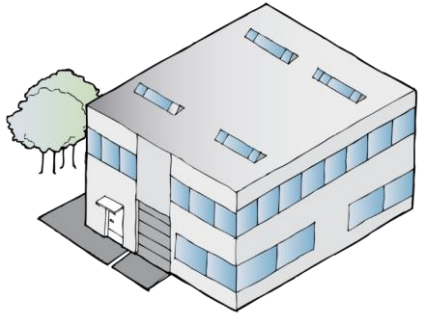
Increasing OEE increases the NPV of manufacturing plants

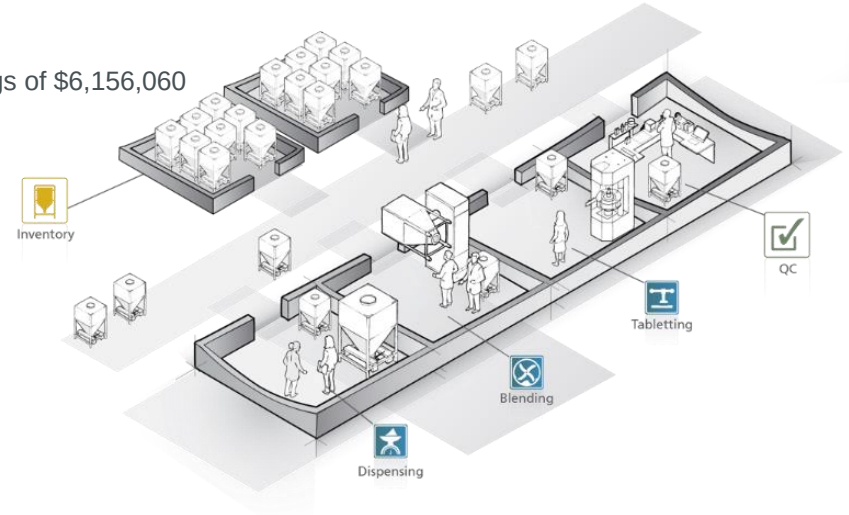


Operational Efficiency and Footprint Accenture – Business Case

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

Easier Product transfer

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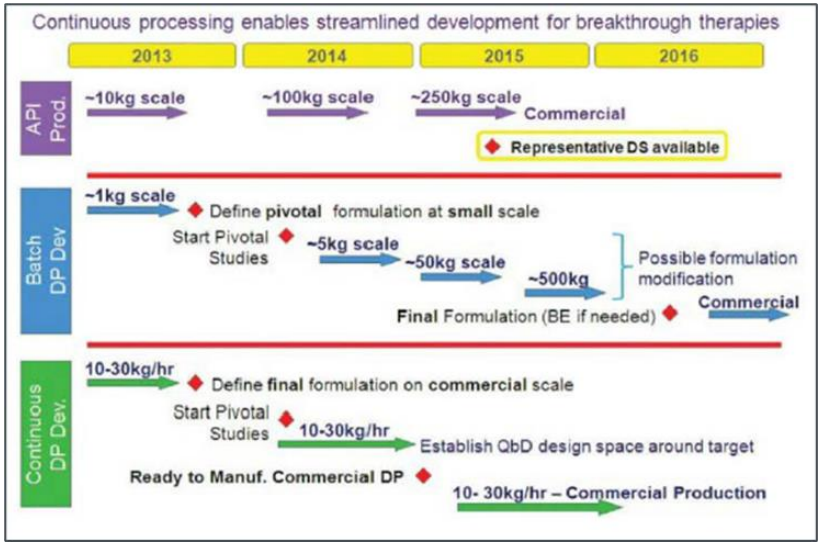
Savings in time and material costs during development



Stage	Batch manufacturing	Continuous Manufacturing
	API used	API used
Formulation Development	90 kg	35 kg
Pilot Scale	120 kg	Together with Formulation development
Commercial	1650 kg	350 kg
Total Amount of API used	**1860 kg**	**385 kg**

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

No Scale Up = Taster time to Market

API savings depending on the API value

4.0

Faster, Simpler Development

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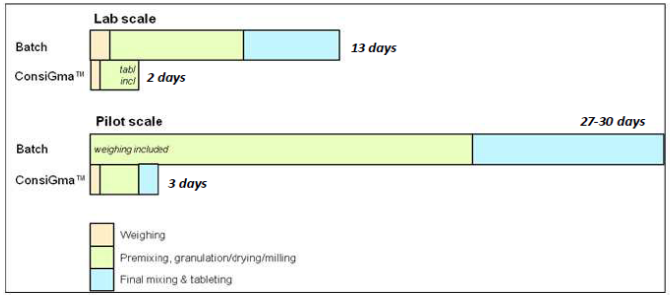
Confirmed Customer Cases

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 !

Rapid & efficient Development

Roche

Project X full factorial DoE

Exp Name	API PSD	Screw speed	Gran liquid feed rate	FBD inlet air temp
N01	P03 (6um)	700 rpm	142 g/min	50°C
N02	P02 (12um)	700 rpm	142 g/min	50°C
N03	P03 (6um)	1000 rpm	142 g/min	50°C
N04	P02 (12um)	1000 rpm	142 g/min	50°C
N05	P03 (6um)	700 rpm	162 g/min	50°C
N06	P02 (12um)	700 rpm	162 g/min	50°C
N07	P03 (6um)	1000 rpm	162 g/min	50°C
N08	P02 (12um)	1000 rpm	162 g/min	50°C
N09	P03 (6um)	700 rpm	142 g/min	65°C
N10	P02 (12um)	700 rpm	142 g/min	65°C
N11	P03 (6um)	1000 rpm	142 g/min	65°C
N12	P02 (12um)	1000 rpm	142 g/min	65°C
N13	P03 (6um)	700 rpm	162 g/min	65°C
N14	P02 (12um)	700 rpm	162 g/min	65°C
N15	P03 (6um)	1000 rpm	162 g/min	65°C
N16	P02 (12um)	1000 rpm	162 g/min	65°C
N17	P03 (6um)	800 rpm	152 g/min	58°C
N18	P02 (12um)	800 rpm	152 g/min	58°C
N19	P01 (9um)	700 rpm	152 g/min	58°C
N20	P01 (9um)	1000 rpm	152 g/min	58°C
N21	P01 (9um)	800 rpm	142 g/min	58°C
N22	P01 (9um)	800 rpm	162 g/min	58°C
N23	P01 (9um)	800 rpm	152 g/min	50°C
N24	P01 (9um)	800 rpm	152 g/min	65°C
N25*	P01 (9um)	800 rpm	152 g/min	58°C
N26*	P01 (9um)	800 rpm	152 g/min	58°C
N27*	P01 (9um)	800 rpm	152 g/min	58°C
N28*	P01 (9um)	800 rpm	152 g/min	58°C

	Consigma	Batch HSG small scale	Batch HSG pilot scale
Time need	1-2 weeks	7 weeks	7 weeks
API need	56kg	168kg	504kg
Representative for commercial scale	🙂	☹	😐

- 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

Roche: 1 – 2 weeks instead 7 weeks !

4.0

GEA Key Technology Platforms

ConsiGma®

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:

Modular & standalone

Flexible & configurable

Integrated & consolidated

ConsiGma® Focus Today

ConsiGma® Materials Handling **4.0**

ConsiGma®

ConsiGma® Control Software: **Conductor 4.0**

ConsiGma®
Granulation &
Compression (GC) Lines

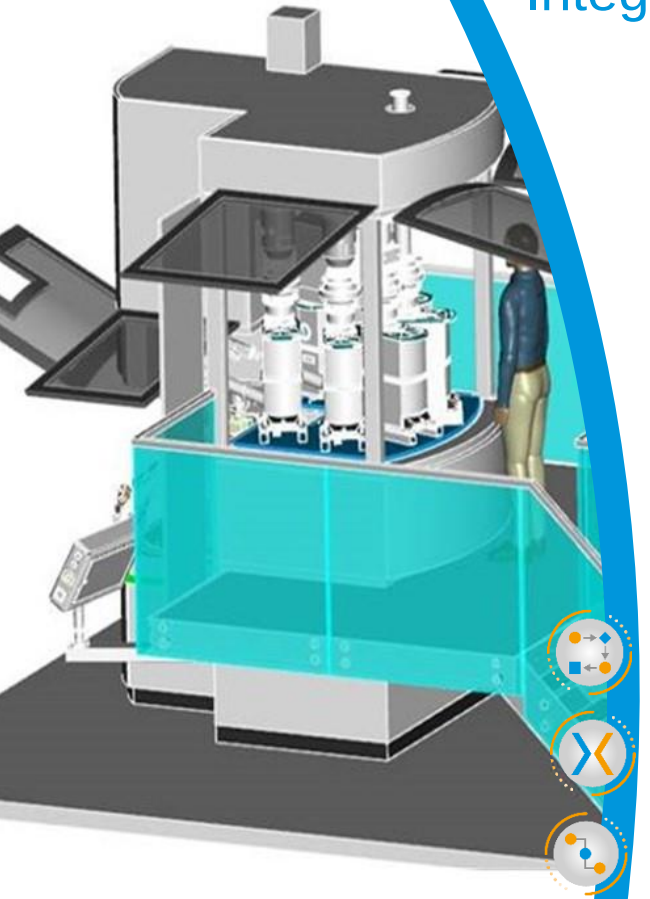
ConsiGma®
Direct Compression
(DC) Lines

ConsiGma®
Bin-2-Bin
Modules **(DB)**

ConsiGma®
Tablet Coater
Modules **(TC)**

ConsiGma®
R&D equipment

ConsiGma®
Integrated Direct Compression



Scope

- Up to 6x GEA LiW feeders and 2 GEA blenders with variable configuration for maximum blending flexibility
- Fully integrated single story direct compression line
- Available in two size ranges to suite throughput needs

Capability

- Throughput ranges proven between 1 – 130 kg/hr
- API range from 0.25 to 93%
- OEB 4 Proven containment using SMEPAC testing
- WIP enabled for easy washing prior to disassembly

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

Test before you invest

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GEA Columbia
US Pharma solids

SKKU South Korea
Batch
Continuous

GEA Wommelgem
Main pharma solids

GEA Halle
Main compression trial facility

GEANUS Singapore
Batch

RCPE Graz
Continuous

EuroTechno Tokyo
Continuous Compression

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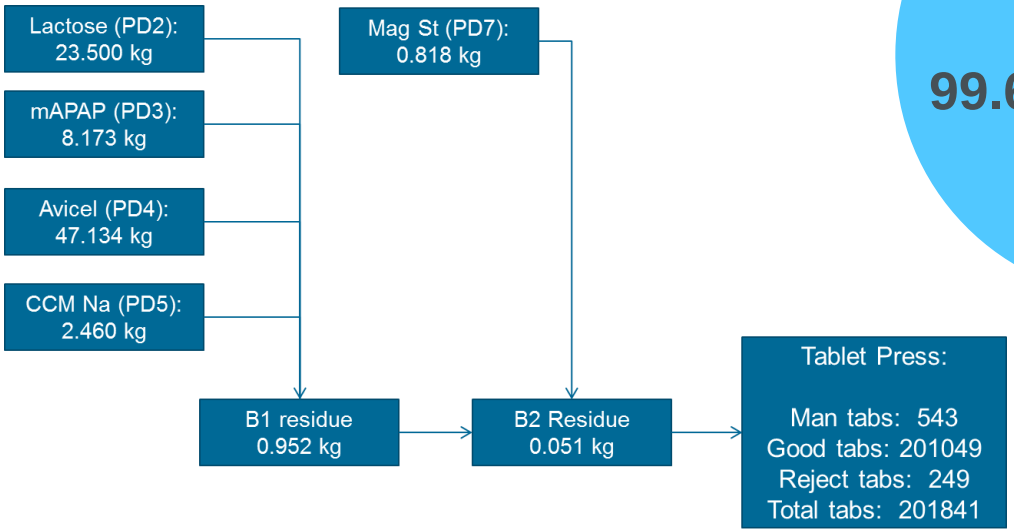
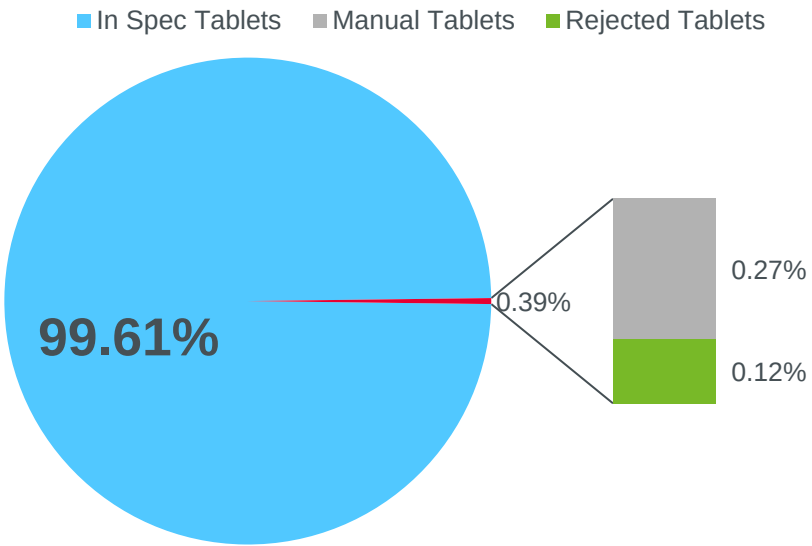
GEA Platform Capabilities: Case study

Integrated DC
Process Yield – Short run example

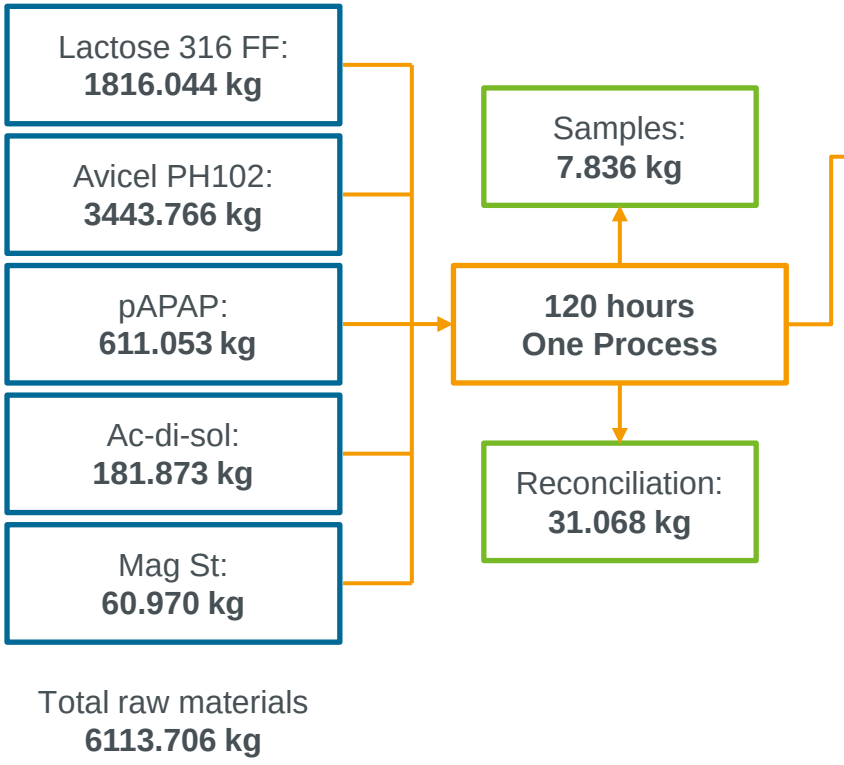
180 minute run with non competitive relevant formulation:

- 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.

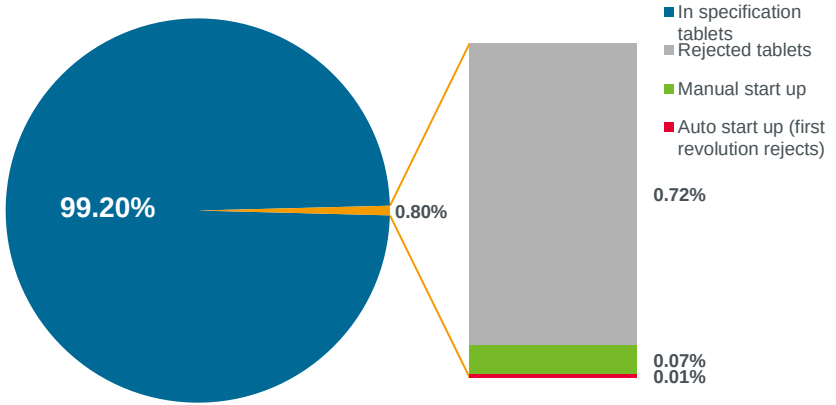




Integrated DC
Process Yield – Long run example



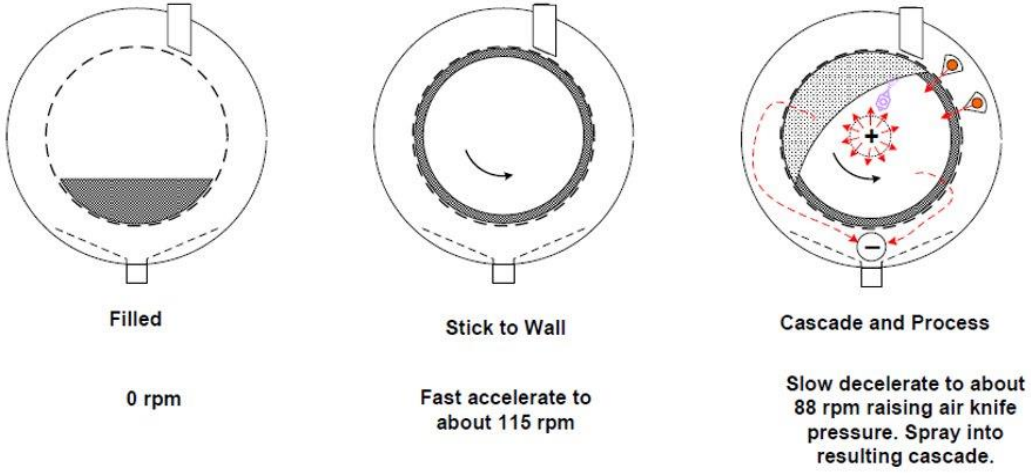
400 mg tablet production over entire run 15,043,590 tabs 6,030.96 kg	
Rejected tablets	120,473
Manual start up	10,345
Auto start up (first revolution rejects)	1,400
Overall Tablet press performance	**15,043,590**
In specification tablets	**14,923,118**

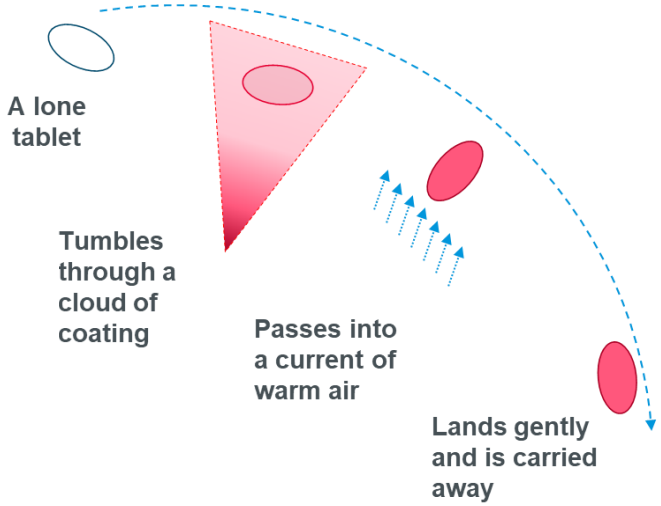


GEA coater technology – what's different?

Q1. What is required to coat a tablet?

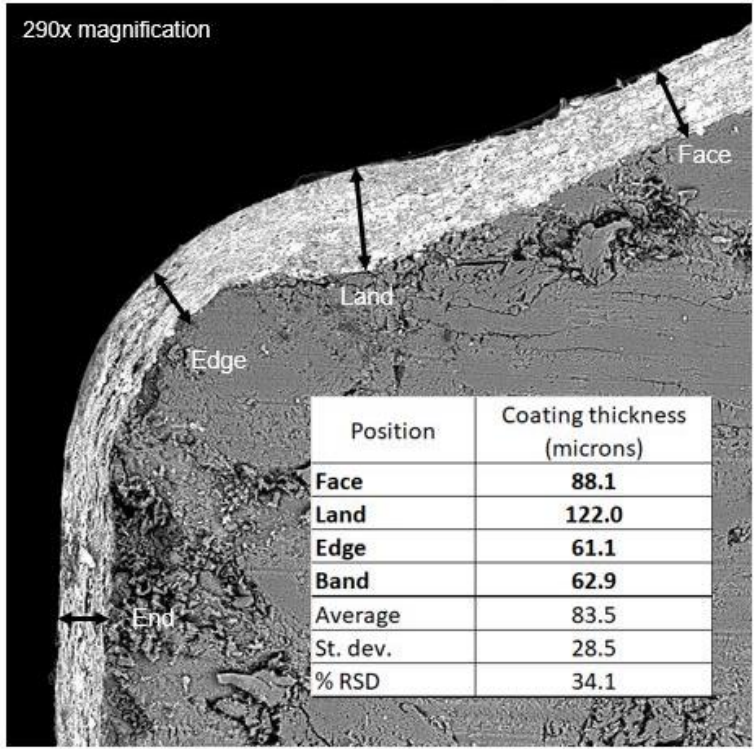
Q2. How can we achieve this in reality?





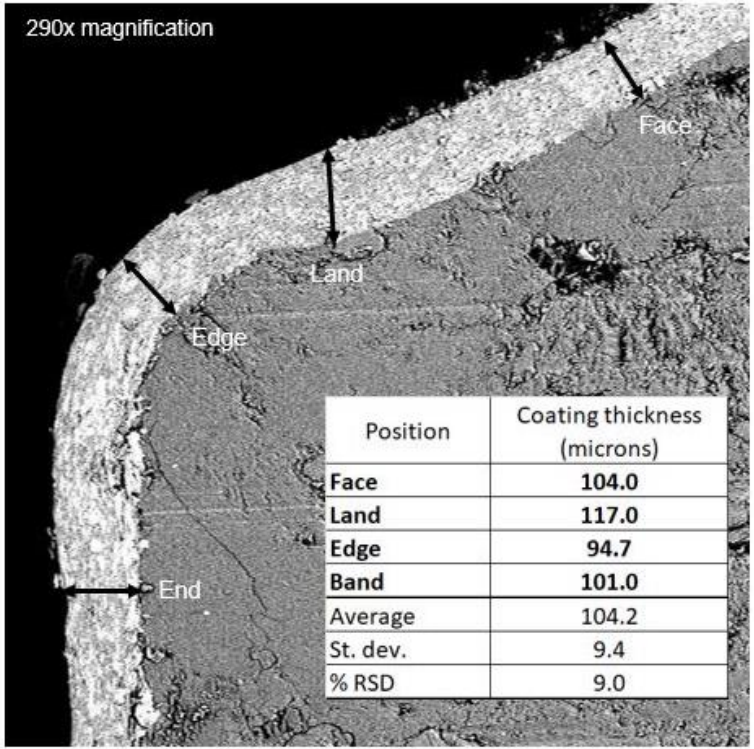
GEA Tablet Coater Case study

Traditional



Position	Coating thickness (microns)
Face	**88.1**
Land	**122.0**
Edge	**61.1**
Band	**62.9**
Average	83.5
St. dev.	28.5
% RSD	34.1

ConsiGma



Position	Coating thickness (microns)
Face	**104.0**
Land	**117.0**
Edge	**94.7**
Band	**101.0**
Average	104.2
St. dev.	9.4
% RSD	9.0

Data generated in collaboration with Colorcon Inc, coating material Acryl-EZE®

Coater studies – Enteric coating Acryl-EZE ®

Investigation of a New Semi continuous Coating Process Using a Fully Formulated Enteric Coating System

Charles Cunningham, James Gilmour, Ali Rajabi-Siahboomi, Michael Waldron, Trevor Page

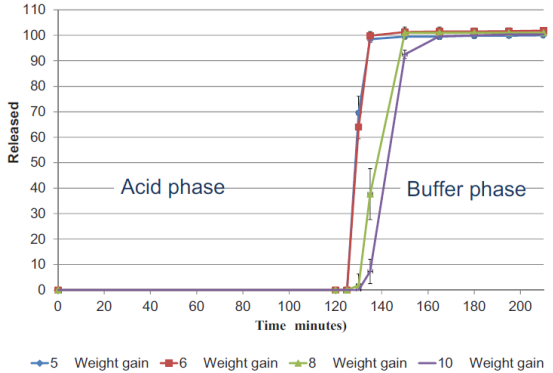
Poster Reprint
AAPS 2 13

Trial parameter description		Unit	Value
Tablet core	Dimensions	mm	10.5 x 4.9 Round
	Weight	mg	388.0
	Surface area	mm²	252.0
Process loading	Wheel size	mm	Ø440 x160
	Fill weight	g	3000.0
	Number of tablets		7732.0
	Surface area	cm²	19484.5
Handling Time	Loading / Discharge time	sec	90.0
	Preheat time	sec	15.0
	Drying time	sec	15.0
	Total	sec	120.0
Spray parameters	Solids concentration	%	20.0
	Quantity applied	g	1800.0
	Spray rate	g/min	60.0
	Dry film density	g/cm³	1.6
	Spray time	min	30.0
	Film build rate	microns/min	3.8
	Film thickness	microns	115
Output	Theoretical weight gain	%	12.0
	Output	kg/hr	5.6
Spray Pattern	Atomizing air	bar	1.5
	Pattern air	bar	1.0
Tablet Motion	Wheel speed	rpm	95/92
	Knife 1	m/bar	220.0
	Knife 2	m/bar	220.0
Drying	Flow rate	m³/hr	220.0
	Temp	°C	80.0

Aspirin(325 mg) tablets 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.

Conclusions

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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