Continuous Manufacturing

Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing

For more than 50 years, pharmaceuticals have been produced using a method known as “batch manufacturing,” a multi-step, lengthy process that involves the use of ungainly, large-scale equipment. However, recent advances in manufacturing technology have prompted the pharmaceutical industry to consider moving away from batch manufacturing to a faster, more efficient process known as continuous manufacturing.

What is Continuous Manufacturing?

- End to End Conversion of **Raw Materials** into **Final Product** in one continuous operation.
- Requires **Process Analytical Technology (PAT)** to pass material through the various unit operations.
- Requires complete understanding on how **Critical Process Parameters (CPPs)** relate to **Critical Quality Attributes (CQAs)**.
- Requires a **Control System** that allows **Feed Forward** and **Feedback** control.
- Is a **QbD** process by definition.

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Where are we heading to – Continuous Manufacturing (Future state in Pharma)

Why Continuous Process?

Quality is Assured without relying on end product testing, but process control

Release 06

Design Space 01

Exploring the design space of a production process will be in hours/ days not months

There will less product quality failures

Batch Failures 05

Scale up 02

There will be no scale up work between development and manufacturing

Quality Assurance of products is continuous, and in real time

Monitoring & Control 04

Batch Size 03

Plants will produce “batches” of any size in order to meet market demand

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Project Snapshot- *Continuous Blender*

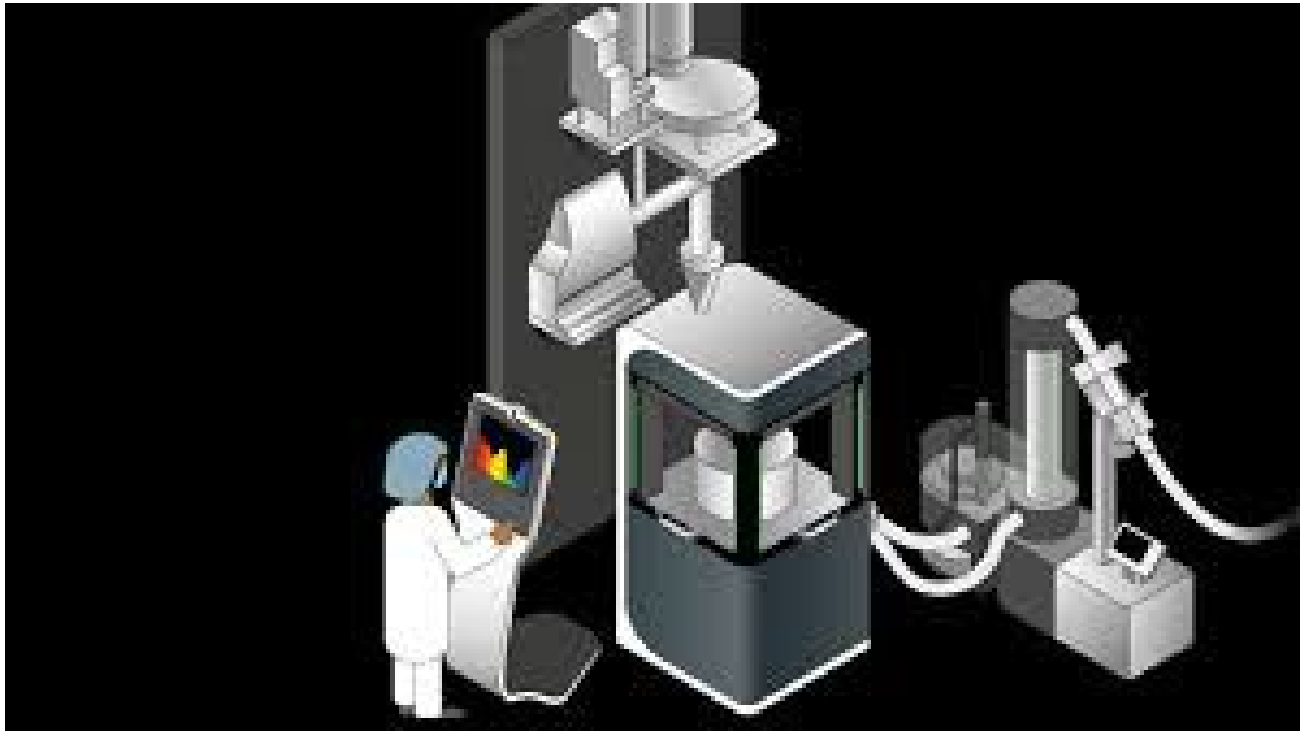
Trial Objective

1. To get uniform Content Uniformity for a MUPS product

2. To Eliminate batch wise Blending operation, Sampling and Segregation chances due to Material Handling

3. To achieve desired dissolution (avoid breakage of pellets)

4. To improve throughput / reduce cycle time



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Project Snapshot- *Continuous Blender*

Blending

Batch Staging

Bin transfer

Risk of Segregation and de mixing

Granulation

CURRENT

Compression

Continuous Blending

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Project Snapshot- *Continuous Blender*

Study Plan

Compression Stage		
S. No	**Stage (Compression)**	**Remarks**
`1	Optimum Speed (50 RPM)	Stabilisation sample- after 1 revolution
		Stabilisation sample- after 2 revolution
		Stabilisation sample- after 3 revolution
		Every 5 mins
		Pooled Sample
2	Very High Speed (80 RPM)	Stabilisation sample- after 1 revolution
		Stabilisation sample- after 2 revolution
		Stabilisation sample- after 3 revolution
		Every 5 mins
		Pooled Sample
3	High Speed (65 RPM)	Every 5 mins
		Pooled Sample

Project Snapshot- *Continuous Blender*

Trial Objective

1. To get uniform Content Uniformity for a MUPS product
2. To Eliminate batch wise Blending operation, Sampling and Segregation chances due to Material Handling

50 RPM- Stratified comp run (Every 5 min compression run)	
Avg	101.2
Min	90.9
Max	108.4
%RSD	4.70%
AV	11.4

65 RPM- Stratified comp run (Every 5 min compression run)	
Avg	101.8
Min	94.8
Max	110.3
%RSD	4.70%
AV	11.8

80 RPM- Stratified comp run (Every 5 min compression run)	
Avg	99.2
Min	92.6
Max	110.5
%RSD	4.70%
AV	11.1

Good Content uniformity at very High speed

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Project Snapshot- *Continuous Blender*

Trial Objective

3. To achieve desired dissolution (avoid breakage of pellets)

50 RPM (Commercial Bx speed)				
Time-point	1 hr	4 hrs	8 hrs	24 hrs
Limit:	NMT 20%	20 - 40%	42 - 67%	NLT 80%
Average	10.8	27.5	55.9	93.2
Min	9.7	25.5	53.1	88.5
Max	12.3	29.2	58.5	97.1
%RSD	9	5.3	3.6	3.8

65 RPM (High Speed)				
Time-point	1 hr	4 hrs	8 hrs	24 hrs
Limit:	NMT 20%	20 - 40%	42 - 67%	NLT 80%
Average	9.8	27	56.3	88.4
Min	8.6	24.5	52.4	76.9
Max	10.5	28.8	58.7	95.2
%RSD	7.3	5.4	3.9	7.1

80 RPM (Very High Speed)				
Time-point	1 hr	4 hrs	8 hrs	24 hrs
Limit:	NMT 20%	20 - 40%	42 - 67%	NLT 80%
Average	10.2	27.4	57.2	97.4
Min	9.1	25.7	55	90.3
Max	10.8	29.1	61.4	107.4
%RSD	6.3	4	4	5.8

Inference: Dissolution found Satisfactory

Project Snapshot- *Continuous Blender*

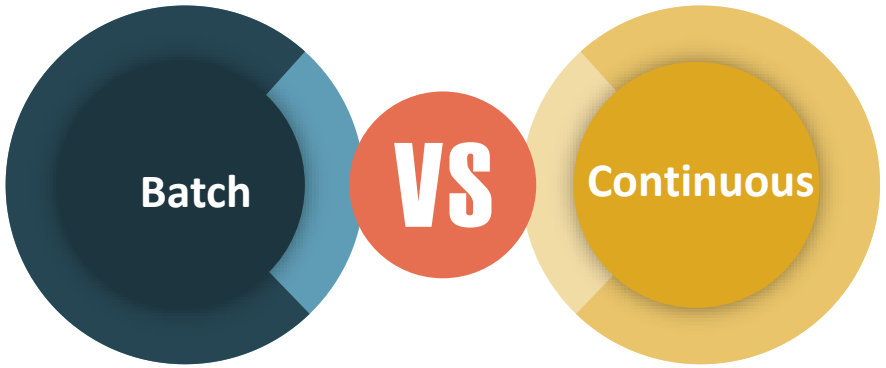
Trial Objective

4. To improve throughput / reduce cycle time

Machine Speed 50 RPM

Machine Speed 80 RPM ((60% ↑) through put improvement

Blending followed by batch staging and bin transfer to compression area



No Separate blending, Batch staging, Bin shifting (Lesser footprint)

*In process inventory * 5 days from pellet coating to compression*

No Hold up (Reduced Cycle time)

Limited Process Knowledge based on unit operation and in process control (IPC's)

Full controls integration with PAT capability provides process information real time with capabilities of advanced process control

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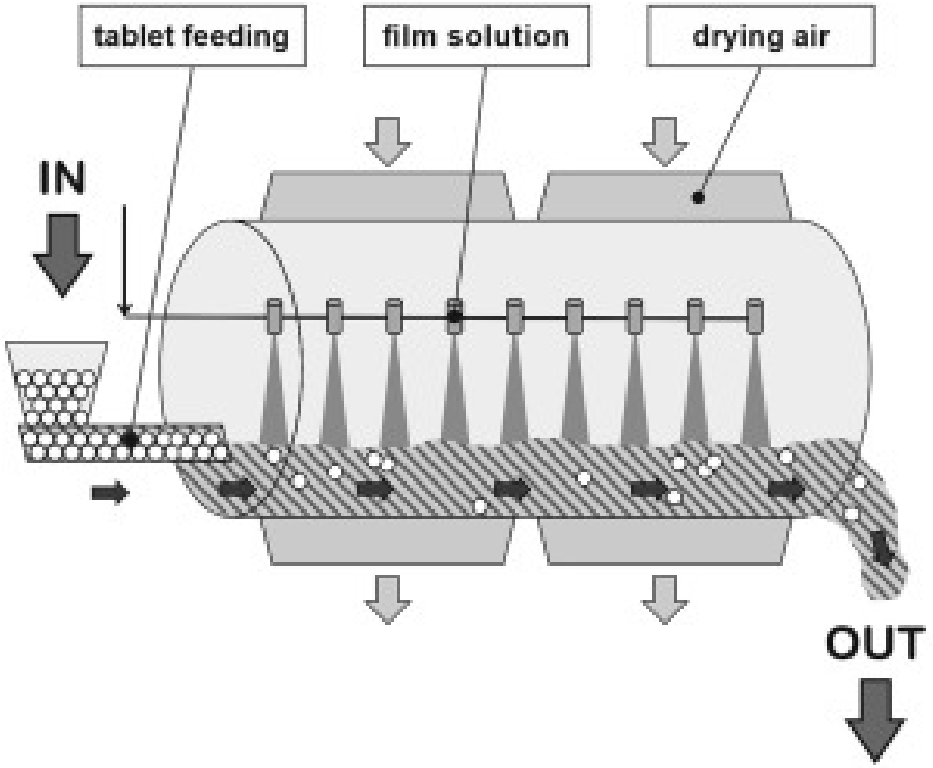
Project Snapshot- *Continuous* Coater



Classic continuous coaters

The tables are feed at one side and travel to the opposite side. While that happens the goal is to treat them in a uniform way to archive an uniform coating.

- As the traveling time and exposure time to the spray of each tablet varies the coating quality varies too
- The ability to hold the tablets for a most equal time in the zones where the spraying and drying happens defines the uniformity and quality
- Processes are used for coatings tend to be of cosmetic or a simple technical nature

Film coating is usually the final step in the manufacture of a tablet in an end-to-end continuous manufacturing system. In the continuous film coating process, uncoated tablets enter a coating drum as coated tablets are discharged. Various continuous coating systems are available to meet the requirements of different applications and processes.

Project Snapshot- *Continuous* Coater vs Batch Coater

Parameters	Continuous coating	Batch Coating
Product Contact Time in coating pan (Mins)	Maximum 10-20 Min. (Less Attrition to tablets)	Minimum 6-7 Hr. (More Attrition to tablets)
Mode of Coating process	Continuous coating	Batch Coating
	Rate Dependent Process	Time dependent Process
	Totally automated	Manual Handling
Risk to Batch/lot/ Products	Risk is low for partial quantity	Risk is high for full Lot/ Batch quantity
Scale up / Scale down Requirements	No Scale up / Scale down trial required	Parameters to be requalified for scale change
Discharging of Tablets	Totally Automated, (100 % discharging)	Manual unloading
Batch/Lot size and output / Hrs	850 Kg/ hr	Output 55 Kg/ hr.
Average Spray Rate (g/min)	1100 g	730 g
Coating Type	Suitable for immediate release	Can be used for both Immediate and Modified release

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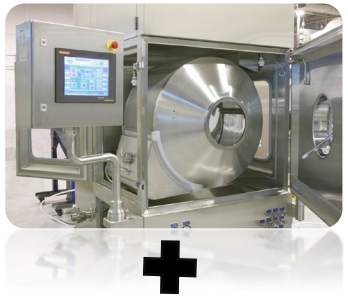
Project Snapshot- *Continuous* Coater vs Batch Coater

High space utilization
High manpower
Output : 35-55 kg/hr

BEFORE- Batch coater

1  60”

2  60”

3  60”

4  60”

After – Continuous coater

1

Benefits	Before	After
No of Machines	4	1
Space	~900 Sq. feet	~225 Sq. feet
Manpower	*12 per day	4 per day

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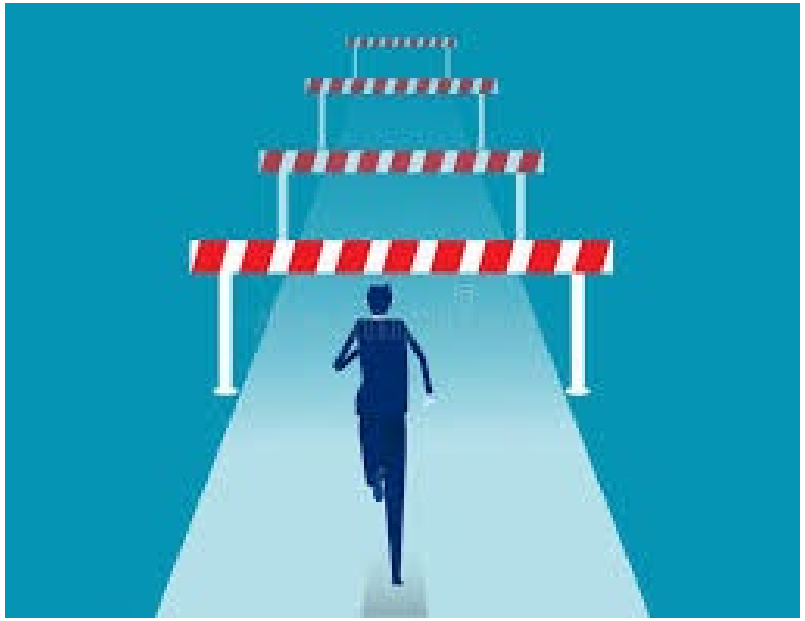
Barriers to Continuous Manufacturing



- Pharma’s hesitancy
  - Lack of prior knowledge of continuous processing
  - Formulations developed based on batch processing knowledge
  - Scale “concerns”
  - Quality assurance activities
  - R&D operations not geared for continuous process development
  - Lack of suitable equipment
  - Regulatory fear
    - Will the regulators approve the process?
    - What will the inspectors say?
  - Absence of systems integration

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Executive Summary & Key takeaways

Game Plan	• Employ continuous manufacturing concept to improve the process efficiency and product quality resulting in reduced production time and a shorter 'time to market'
Current Status	• Technology has progressed with the learnings from industry and regulators and vice versa • FDA collaboration with industry and academia via ETT(Emerging Technology Team) effort, grants, reviews, on site visits and technology forums continue to encourage adoption and development of CM. • Industry has availed the approvals for the products with CM process
Industry Direction	• Performance-based Approach for Control Strategy • Pharmacy on Demand • End-to-end CM processes
How to get there	• Right Mindset and Culture, Workforce Skill set. • Building collaborative knowledge platform • Building Standards and Guidelines Together

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Thank you