



Advancements in Continuous Manufacturing Technology

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Discussion Items

- Continuous Manufacturing: An Overview
- Continuous Manufacturing: Advantages and Limitations
- Process Simplification: Enabler for Continuous manufacturing

- Pharmaceutical Continuous Manufacturing (PCM) was identified as national priority technology by US Congress
- US congress has authorized funding to support PCM
- FDA has created ETT (emerging technology team) to assist industry implement continuous manufacturing

Pharmaceutical Companies Pursuing Continuous Manufacturing

Company	Initiative
Vertex	<ul style="list-style-type: none">• Introduced continuous manufacturing of drug substances and drug products• Obtained FDA & EU approval for cystic fibrosis medications' ORKAMBI in 2015, and SYMDEKO in 2018
Janssen	<ul style="list-style-type: none">• Obtained FDA approval for antiretroviral medication (PREZISTA) in 2016
Eli Lilly Co.	<ul style="list-style-type: none">• Obtained FDA & PMDA approval for breast cancer medication (VERZENIO) in 2017

Source: Mitsui & Co Global Strategic Studies Institute

Advantages:

- Increased Worker Safety
- Standardization
- Economies of Scale
- Higher Production Rates

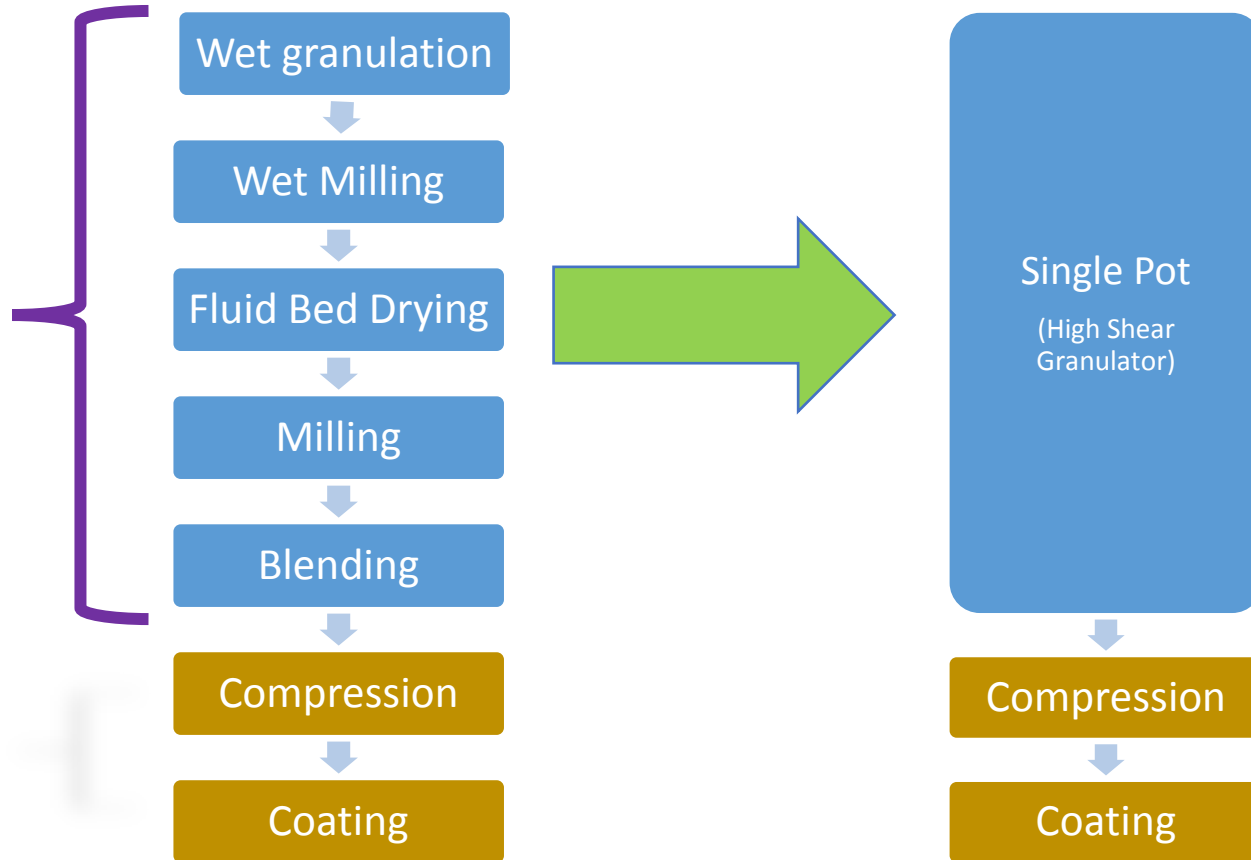
Limitations

- Requires High Investment
- Require Extremely Careful Design
- Lack of Flexibility
- May Lead to Excess Inventory

New Technologies: An Enabler for Continuous Manufacturing

Process Simplification / Efficiency Improvement / Capacity Enhancement

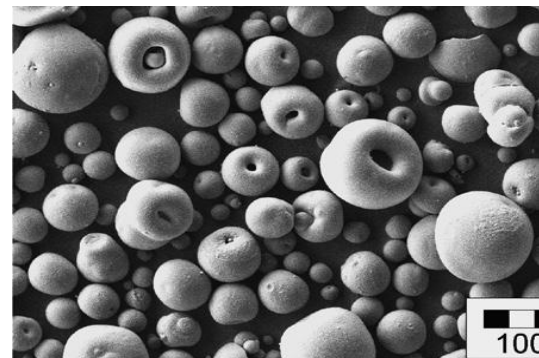
Simplification of Granulation: Conversion to Single Pot



Key Enablers



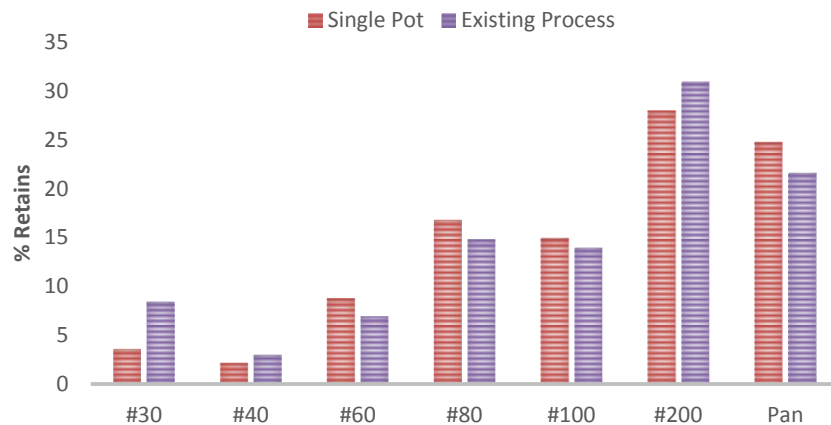
Mist



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Materials

Results: Particle Growth



Conversion to Direct Compression: Glidant Mixing Process

- Conversion of multi-stage processes to direct compression
- Glidant grades, and high shear are key enablers:
 - reduce Van der Waals
 - produce ball-bearing action

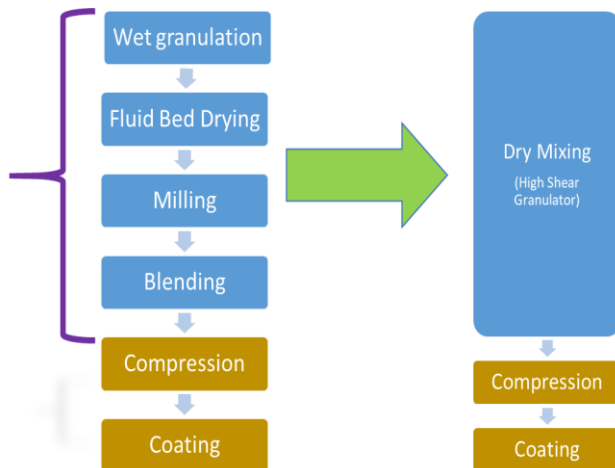
Application: Remediation of a DRL Commercial Product

Challenges:

- Very poor bulk flow
- COPE due to physical defects, excursions in-process parameters
- Longer processing times
- Low throughput

Improvements:

- Excellent bulk flow
- Elimination of physical defects
- Increase of compression speed from 20 to 40 rpm
- 75% reduction in process time



Continuous Manufacturing: Direct Compression and Coating



Continuous Coater



Benefits

- Operators Delight: elimination of major powder exposure/handling operations (sifting, milling, blending and drying)
- Improves product quality – eliminates thermal and shear stresses
- Reduction in energy usage – greener process
- No CapEx requirement
- ~ 75% reduction in process time
- Consolidation of operations – reduction in manufacturing areas/equipment usage
- Amenable for conversion to continuous manufacturing

Limitations

- Increase in raw materials (excipients) cost in some cases
- Difficult to implement for formulations that have hydrophobic drugs in large concentrations