Continuous MDI Manufacturing Process

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1. Background

Metered Dose Inhaler (MDI)

- Deliver drug substance in a pre-measured dose to the target site (lungs) via inhalation
- Use in treatment of pulmonary diseases like cystic fibrosis, COPD, and asthma

Batch Production

- Mixing of formulation almost strictly as single, manual batch inputs since the 1950s

2. Introduction

Product Components

- Formulation: suspension of propellants and powders
- Device: canister, actuator, and metering valve

Continuous Production

- Mixing of formulation done via integration of multiple inputs at once
- Batch defined as an amount of material with uniform characteristics and product quality

Filling Modes

- Single-stage versus Two-stage: powder dosed with propellant **or** prior to propellant
- Pressure versus Cold: maintain volatile propellant as a liquid with high pressure **or** low temperature

3. Business Case

Environment and Waste Considerations

- Estimated revenue loss of $1.4 million per batch
- Decrease in incineration of and production release of greenhouse gases
- Less waste generated overall for continuous process

Resource Use and Automation

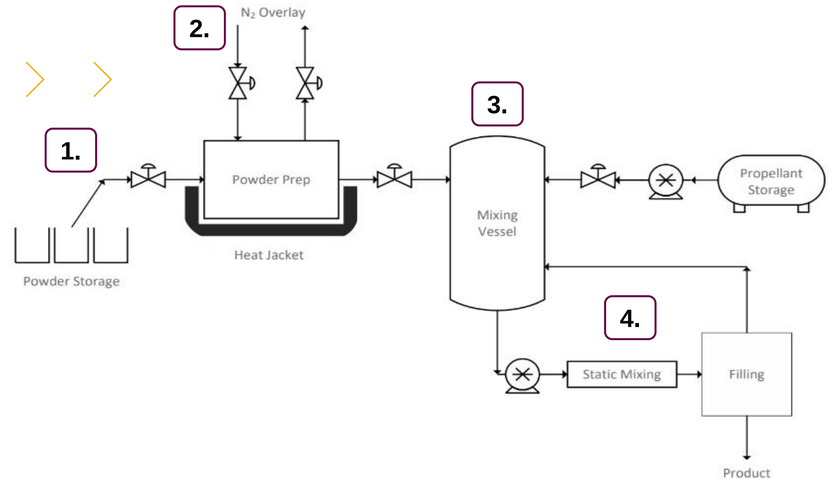
- Less room for error with seamless system integration
- Higher overall equipment efficiency
- Ability for predictive maintenance and shorter shutdown times
- Isolation of smaller amounts of defective material

4. Process Flow Diagrams

Pressurized, Single-Stage Design

1. Powder fed at desired concentration
2. Powder preparation includes heating to remove excess moisture and pressurization
3. Prepared powder and propellant mixed via agitation in vessel
4. Formulation fed with static, in-line mixing to fill-line process with recycle line

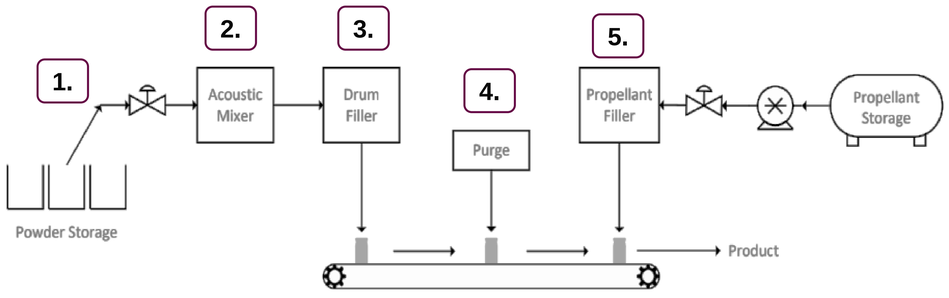
Utilizes current AstraZeneca fill-line with a partial rework of mixing method



Pressurized, Two-Stage Design

1. Powder fed at desired concentration
2. Powder mixed using low-frequency sound energy
3. Prepared powder compacted and dosed
4. Ambient air purged as canister is fitted with valve
5. Crimping occurs, and propellent dosed to the purged canister

Involves a total rework to mixing method and fill-line



5. Conclusions

- ✓ Semi-continuous and fully continuous integration reduces waste
- ✓ Proposed designs offer unique perspectives and challenges
- ✓ Process Analytical Techniques (PAT) provide real-time control to improve the product makeup
- ✓ Integration allows for flexibility with future inhalation products.

6. Next Steps

Full financial analysis
PAT analysis
Small-scale proof of concept

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