# DEM-based investigation of the effect of the CPP on the CQA in a low-dose capsule filling process

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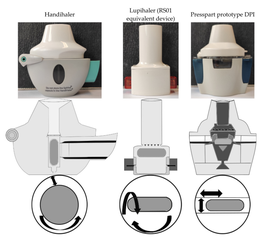
## 1. Background and Motivation

### Capsule

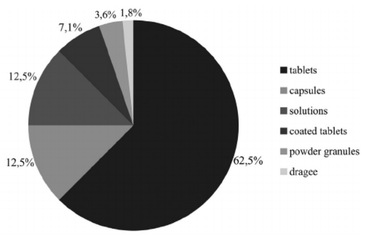
- Solid dosage forms are the most common drugs including tablets and capsules.
- Capsules are solid dosage forms in which the drug or a mixture of drugs with or without excipients is enclosed in capsule shells.
- Capsules can be also designed for a nasal spray.

Hard Galantine capsule

Soft Galantine capsule




Dry powder inhalation



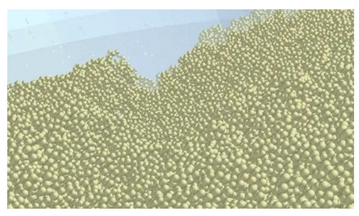

Solid dosage form[1]

### Challenges of capsule filling

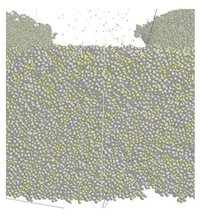
- Segregation of powders
- Automated filling machines usually require at least a kilogram scale of material to run a batch.
- Maybe extremely costly due to the cleaning and a large amount of waste generated at the end of each production cycle which is remaining powder[2].
- Raw material attributes e.g., the presence of fine particles may result in poor flowability (due to high cohesion) and deviations from the targeted CQAs (e.g., capsule weight and uniformity, API/Excipient ratio).

Segregation of powders

Challenging weight uniformity



Poor flowability powder bed



Powder bed scale

## 2.Quality by Design framework

**Our scope**

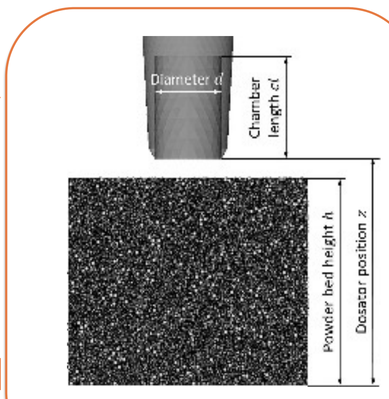
**Identity QTPP** → **Define CQA and identify CMAs and CPPs** → **Set up DoE, Establish the relationship between CQAs, CMAs and CPPs** → **Identify/Build the Design Space** → **Identify and control the sources of variability** → **Continually monitor/improve manufacturing process**

**CPPs**

- Rotation speed
- Flow rate
- Design of dozator

**CMAs**

- API:PDS/Diameter
- Excipient: PSD/Diameter
- Excipient/API



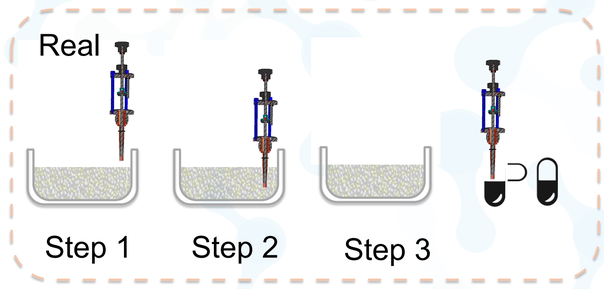

**DEM simulation[3]**

**CQAs**

- Capsule weight
- Uniformity
- PDS

## 3. Case study

- Excipient : Lactose (Diameter 100um)
- Contact model: Edinbrugh Elasto-Plastic Adhesion (EEPA)
- Software: EDEM Altair



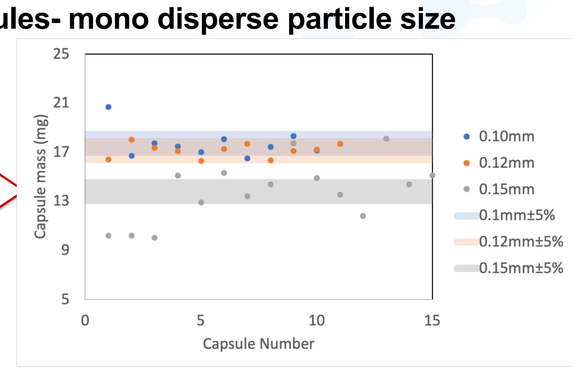

### Monitoring the weight uniformity

**Case 1 : Excipient/API only capsules- mono disperse particle size**

Lactose (Size 100)

Lactose (Size 120)

Lactose (Size 150)



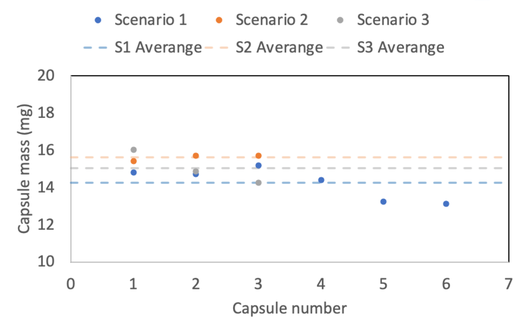

**Capsule weight is highly sensitive to the particle mean size of the raw material.**

**Case 2 : Excipient and API capsules**

Scenario 1 A/E 45%

Scenario 2 A/E 73%

Scenario 3 A/E 37%

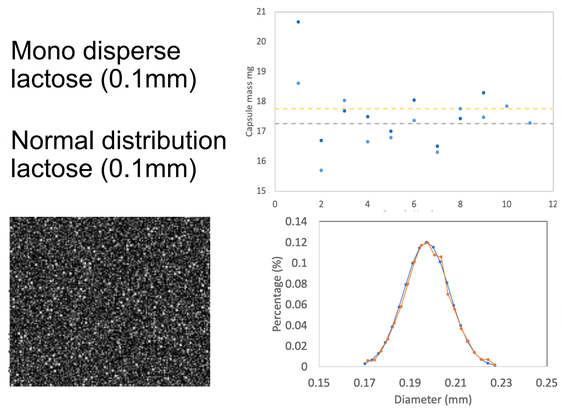



**Capsule weight uniformity is highly sensitive to the API / Excipient ratio.**

### Identifying and understanding the PSD

**Case 3 : Excipient/API only capsules-particles size distribution**

- Mono disperse lactose (0.1mm)
- Normal distribution lactose (0.1mm)




PSD in Feed VS Capsule

PSD changes in Feed will results in weights variant in capsule. However, this need more scenarios and data to explore the connection.

PSD in feed shows slightly difference between feed and capsules (in average).

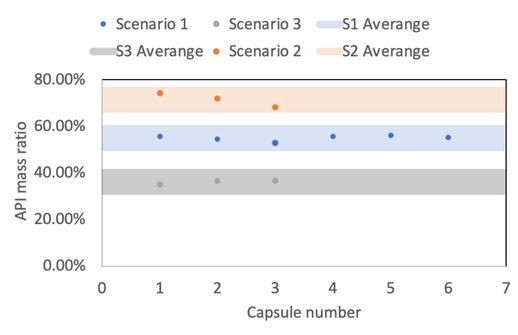
### Composition uniformity

**Case 4 : Excipient and API capsules**

Scenario 1 A/E 45%

Scenario 2 A/E 73%

Scenario 3 A/E 37%




**API ratio in capsule varies from capsule to capsule. However, all case were remains within 5% variation.**

## 4. Conclusion and future work

- Capsule weight is highly sensitive to the particle mean size of the raw material
- PSD changes in the raw material results in capsule weight deviations.
- PSD of the material in the capsules is overall consistent with the PSD of the raw material under the investigated conditions.
- Capsule weight uniformity is highly sensitive to the API / Excipient ratio.
- API ratio in capsule varies slightly from capsule to capsule but overall remains within the targeted 5% variation (CQA bounds).
- More data of capsules and experiments will be generated to improve the reliability of DEM predictions and help identify the design space

**REFERENCES:**

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