Manufacturing of Low Fill Weight Capsules Using a Nozzle Dosator Capsule Filling Machine

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Content

- Motivation
- QbD for fill weight (5-45mg) and weight variability of capsules
  - Screening DOE to identify CMAs and CPPs
  - Developing predictive models for fill weight and weight variability (Design Space)
  - Model Validation
- Conclusions
Motivation

Progress new concepts and pharmaceutical products

- API in capsule
- Inhalation products

Why dosator nozzles?

- Scalability of the capsule filling process
- Large output at industrial scale
- Highly automated industrial capsule filling machines
- Product control: high-speed precise fill weight measurements
- Scientific knowledge on the equipment performance for standard doses
Understand how 1) material attributes, 2) the process parameters and 3) environmental conditions affect capsule weight and weight variability.
Process parameters

No compaction step
Materials and material attributes

Materials

- Respitose ML001 (milled Lactose)
- Respitose ML006 (fine milled Lactose)
- Respitose SV003 (sieved Lactose)
- Respitose SV010 (coarse sieved Lactose)
- Lactohale_GSK (blends of Lactoses)
- Lactohale_100 (sieved Lactose)
- Inhalac 230 (sieved Lactose)

Material attributes

- Particle size (VMD) and shape
- Bulk- (Bul), Tapped-(Tap) and True density (True)
- Hausner ratio (Haus)
- Wall friction angle (WFA), Angle of internal friction (AIF)
- Carr index (Carr), Basic flowability energy (BFE), Flow function (FFC) and Cohesion (Coh)
- Air Permeability (Per)
- Compressibility (Com)
- Adhesion
Screening DOE to identify CMAs and CPPs
Screening Design of Experiment

- Four process parameters = FACTORS
  1 – Speed (500, 1500, 2500 capsules per hour = cph)
  2 – Nozzle diameter (1.9mm, 2.8mm, 3.4mm)
  3 – Powder layer depth (5mm, 10mm, 12.5mm)
  4 – Size of dosing chamber (2.5mm, 3.75mm, 5mm)

- Two interactions
  1 – Size of dosing chamber and powder layer depth
  2 – Nozzle diameter and size of the dosing chamber

- Two constraints for the ratio between the size of dosing chamber and layer (Interaction 1):
  1 – Never smaller than 1:2
  2 – Never larger than 1:5

- Screening DoE (D-Optimal): 14 different combinations of process parameters = 14 experiments

- Two sets of capsules (20 capsules each) are collected with a time interval of 5 minutes in each experiment

- Weight and weight variability = RESPONSES
The weight of 5 powders is affected from diameter and chamber $\rightarrow$ volumetric filling

The effect of material attributes were subsequently analyzed.

### Results: Fill weights and standard deviations for 14 experimental conditions

<table>
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<tr>
<th>DoE</th>
<th>ML001</th>
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| CPP’s | dia/cha | dia/lay | dia/lay | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha | spa/dia | dia/cha | dia/cha | dia/cha | dia/cha | dia/cha |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|

- The weight of 5 powders is affected from diameter and chamber $\rightarrow$ volumetric filling
- The effect of material attributes were subsequently analyzed.
Identifying CPPs and CMAs

<table>
<thead>
<tr>
<th>Capsule weight [mg]</th>
<th>Weight variability – RSD [%]</th>
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<td>Investigation: DOE_ALL (PLS)</td>
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<td>Summary of Fit</td>
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<td>R²</td>
<td>Q²</td>
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</table>

### Abbreviations:
- spe = speed
- dia = diameter
- cha = chamber
- pow = powder layer
- VMD = Volumetric mean diameter
- WFA = Wall friction angle
- BFE = Basic flowability energy
- Per = Permeability
- Com = Compressibility
- Tru = True density
- Tap = Tapped density
- Bul = Bulk density
- Hau = Hausner ratio
- Car = Carr Index
- AIF = Angle of internal friction
- FFC = Flow function
- Coh = Cohesion
Identifying CPPs and CMAs

Scaled & Centered Coefficients for weight~

- N=93
- R2=0.974
- RSD=0.04557
- Conf. lev.=0.95

Scaled & Centered Coefficients for weight variability~

- N=98
- R2=0.655
- RSD=0.1538
- Conf. lev.=0.95

Scaled & Centered Coefficients for weight~

- N=93
- R2=0.972
- RSD=0.0464
- Conf. lev.=0.95

Scaled & Centered Coefficients for weight variability~

- N=98
- R2=0.675
- RSD=0.1507
- Conf. lev.=0.95
Model development and validation
Design Space for fill weight

Model I: valid for different grades of Lactose in a filling range of 6-45mg with a RSD between 7-3%
Design Space for weight RSD
Model Validation

- Inhalac 250 (Meggle) was selected for validation
- CMAs of Inhalac 250 were determined: Bulk, tapped and true density.
- Model Validation was performed within the design space for fill weight.
  Selected target weights for validation: 6.5 mg; 10 mg; 15 mg; 20 mg; 25 mg; 30 mg; 35 mg

- 4D-contour plot for three different nozzle diameters was used to identify different target weights for validation
- Prediction list was generated in MODDE
Model Validation

- Requested parameters:
  - dosator diameter
  - dosing chamber
  - powder layer
  - Densities (bulk-, tapped, true)
- Prediction list was generated in MODDE:
  - Weight (upper and lower limit)
  - Weight variability (upper and lower limit)

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Red values: New combination of process parameters
Model Validation

- Results:
  - 1,9 mm is used for weights under 10mg
  - 2,8 mm is used for ~15mg
  - 3,4 mm is used for weights from 20mg up to 35mg

- Results were within the 95% confidence interval, except for three values of weight:
  - 23,44mg → deviation: 1,5% of the lower limit
  - 29,76mg → deviation: 0,6% of the upper limit
  - 39,17mg → deviation: 6,0% of the upper limit

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Conclusions
Conclusions

- Dosator nozzles are a promising technology to manufacture capsule with low fill weight and low weight variability.
- QbD is a powerful tool to develop products with specific fill weight and weight variability: allows for CMAs and CPPs identification; developing and validating predictive models.
- Future work: Models were developed in a lab scale machine and will be tested using machines of manufacturing scale.
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- GSK
- MG2
Thanks for your attention

Questions?