QbD in Pharmaceutical Development: Tablet formulation design spaces for direct compression and roller compaction processes

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1. Introduction to tablet formulations and challenges (CQAs, excipients, CU and dissolution)
2. Overview of processes and unit operations – choosing the most cost effective manufacturing
3. What is a standard formulation?
4. Direct compression
   1. Composition
   2. Dose homogeneity and theoretical considerations (incl. comparison to practice)
   3. NIR blend data
   4. Design space construction
   5. Conclusion and perspectives (more DC form. implementation i development through decision-making trees)
5. Roller compaction (dry granulation)
   1. Introduction to roller compaction
   2. Critical quality attributes of ribbons and the granule (porosity, fines and API in fines)
   3. Ranking of critical process variables
   4. Design space of ribbon and granule properties
   5. Future work
6. Concluding remarks
Tablet formulations and manufacturing...
Common tablet compositions

- Active ingredient (API)
- Filler(s) (+binder)
- Lubricant
- Other (not shown)

Low dose (0.5% API)

Intermediate dose (10% API)

High dose (20% API)

Very high dose (50% API)
Tablet process technologies

**Wet Granulation**
- Wet granulation
- Wet sieving
- Drying in fluid bed
- Dry sieving
- Mixing granulate with excipients
- Tablet compression

**Direct Compression**
- Dry sieving
- Mixing of API with excipients
- Tablet compression

**Roller Compaction**
- Dry sieving
- Mixing of API with excipients
- Roller compaction
- Mixing granulate with lubricant
- Tablet compression
Low dose (0.5% API)

Challenge: Dose homogeneity
- Particle size of API is critical!
- API particle size control and the blending step are very critical

Intermediate dose (10% API)

High dose (20% API)

Challenge: Making the tablet stick
- Requires good compression properties of API!
- Dry processing methods usually not applicable

Very high dose (50% API)

Usually well suited for direct compression and roller compaction
Rational selection of process technology

Example:
IR-tablet, 3 strengths, 10, 20 and 30 mg
Dose proportional formulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wet Granulation</th>
<th>Direct Compression</th>
<th>Roller Compaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit operations, no.</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Scale up</td>
<td>complex</td>
<td>simple</td>
<td>simple</td>
</tr>
<tr>
<td>QbD</td>
<td>complex</td>
<td>simple</td>
<td>simple</td>
</tr>
<tr>
<td>API- PSD criticality</td>
<td>lower</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>API supply until scale-up to production, kg</td>
<td>90</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Production cycle time, index</td>
<td>300</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Typical production throughput, kg/h</td>
<td>125</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Preferred (if applicable)
The standard formulation concept...
What is a standard formulation?

Standard formulation (SF):
- A formulation template applied to new (and suitable) HLu APIs.

Thorough and structured documentation is available for each standard formulation, describing the relationship between critical formulation- and process variables and one or several critical quality attributes.

Advantages of a SF:
- In-depth knowledge of the formulation is already available, i.e. developability well-known.
- Reduction of workload of a development project (efficiency)

A standard formulation is a platform technology (in-house term)
Design space definition

- **Design space:**
  ICH Q8: "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change”

  - Unit operations
    - Critical process parameters (CPP)
  - The formulation, raw materials
  - Critical quality attributes (CQA)
    - related to specifications

A prerequisite for the construction of a design space is DoE!
(Implementing a control strategy usually requires PAT)
Critical Quality Attributes of the final tablets

- Blending time and lubrication bleeding time (established based on preliminary experiments) - (CPP- Critical Process Parameter)

- Tableting properties
  - Compactibility and compressibility
  - Adhesion to punches

- Tablet technical properties
  - Hardness > 50 N
  - Friability < 0.5%
  - Disintegration time < 5 min.

- Content uniformity (RSD) ≤ 4% (CQA)

- Segregation properties (e.g. fluidization) (CQA)

- Dissolution? Stability? → API dependent (molecular properties)!
Direct compression formulation...
Choice of excipients
- previous knowledge / literature

- **Filler: Microcrystalline cellulose**
  - Compatible with many APIs
  - Plastic deforming material (excellent compactibility)
  - Multi-functional: Disintegrant+binder
  - Relatively good flowability

- **(Super) disintegrant: Croscarmellose sodium**
  - Cross-bound carboxymethylcellulose
  - Low conc. required
  - Effective disintegration agent
  - May be incompatible w/ API (ionin interaction)

- **Lubricant: Mg-stearate**
  - Most effective (anti-adhesive effect)
  - Disrupts internal tablet bondings (affects dissolution/disintegration)
  - May be incompatible w/ API
Formulation compositions and PSD of API’s (escitalopram)

- API (1, 11 and 20% w/w)
- Avicel PH102 ($d_{50} = 122 \, \mu m$, $d_{90}/d_{50} = 2.0$)
- 3% Ac-di-sol (croscarmellose sodium)
- 1% or 2% Mg-stearate (2% at 20% API)
- API of qualities $D_{50}=42 \, \mu m$, 67 \, \mu m, 114 \, \mu m$ and 163 \, \mu m (laser diffraction)

<table>
<thead>
<tr>
<th>API</th>
<th>$d_{10}, \mu m$</th>
<th>$d_{50}, \mu m$</th>
<th>$d_{90}, \mu m$</th>
<th>$d_{50}/d_{10}$</th>
<th>$d_{90}/d_{50}$</th>
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</thead>
<tbody>
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<td>1</td>
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<td>42</td>
<td>165</td>
<td>6.8</td>
<td>4</td>
</tr>
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<td>2</td>
<td>8.6</td>
<td>67</td>
<td>211</td>
<td>7.8</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>114</td>
<td>249</td>
<td>10</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>163</td>
<td>338</td>
<td>9.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Central Composite Face (CCF) design

42 µm API quality was added to the design without compromising the design quality.

The aim with the designed experiment is to approximate the response (CU-rsd) by a quadratic polynomial (model) in order to:

• Understand in more detail how factors: particle size and drug load influence the response; i.e. get a map of the system (response surface modelling).
• Make predictions and find a region of operability.
Thus, the design will also investigate for any interaction effects and non-linearities in the dataset.

<table>
<thead>
<tr>
<th>Drug load (%)</th>
<th>1.1</th>
<th>11</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>114</td>
<td>X</td>
<td>XX</td>
<td>X</td>
</tr>
<tr>
<td>163</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Analyze 2 tablets for content for every 2000th produced (100 min tableting)

Calculate RSD over tableting = Dose homogeneity
Blending evaluation by NIR-SentroPat

1 mg, $d_{50} = 54 \, \mu m$

20 mg, $d_{50} = 54 \, \mu m$

50 mg, $d_{50} = 54 \, \mu m$

1 mg, $d_{50} = 164 \, \mu m$

20 mg, $d_{50} = 164 \, \mu m$

50 mg, $d_{50} = 164 \, \mu m$

SentroPAT NIR spectrometer (Sentronic GmbH, Dresden, Germany)
Theoretical optimal dose homogeneity (Srel = CU%)

\[ S_{A,rel} \% = 100 \sqrt{\frac{P_B (P_B w_a + P_A w_b)}{P_A W}} \]

\[ w_a = \frac{\pi}{6} \rho \sum v_i d_i^3 \]

- \( P_{A/B} \): relative content of API and Avicel PH102, respect. (\( P_A + P_B = 1 \))
- \( w_a \): mean weight (based on volume weighted volume mean diameter) of a single particle of API and Avicel PH102, respectively, calculated from the volume size distribution (laser diffraction)

- **Assumes free flowing non-interacting binary mixtures!**
- **In this case:** \( \rho_{API} \approx \rho_{Avicel \ PH102} \) (reduces risk of segregation)
Theoretical optimal dose homogeneity versus experimental

**1 mg tablet**

**20 mg tablet**

**50 mg tablet**

Adhesion to punches!
Constructing the design space: Multiple Linear Regression (MLR)

The data from the statistical experimental design can be fitted by means of multiple linear regression (MLR) and the response, $y$, can be described by a polynomial function:

$$CU_{RSD} = b_1k_1 + b_2k_2 + \text{interaction terms} + \text{constant}$$
Design space visualization based on MLR
Conclusions for DC standard formulation based on Avicel PH102

- Theoretical calculation on optimal dose homogeneity correlates well with the actual values as a very valuable tool for prediction of the effect of API-PSD on CU% for the final tablets based on DC.
- A design space was established based on CFF design showing the effect of API on dose homogeneity in the dose range of 1-20% API.
- Below API-PSD of $d_{50} < \approx 40 \, \mu m$ adhesion to punches occur for 20% API even at 2% Mg-stearate → External lubrication.
- Avicel PH102 is an effective filler/disintegrant providing excellent compactibility and compressibility and tablet disintegration times < 20 sec with 3% superdisintegrant Ac-Di-Sol. Ac-Di-Sol might be excluded (to be investigated).
- Segregation due to fluidization is reduced when the API-PSD and dose is reduced (due to increased cohesion between particles).
On going work on DC standard formulations

- The use of using external lubrication with in-process spraying of magnesium stearate to eliminate potential incompatibility between Mg-stearate and API.

- Alternative fillers than MCC is investigated. Formulation screening has shown the best candidates to be: Flowlac 100 (lactose) and Parteck M200 (mannitol). A binder is needed to improve compactibility of the final blend.
Roller compaction formulation...
Roller compaction
Why do dry granulation

**Advantages:**
- Improve flowability
- Improve weight uniformity
- Improve content uniformity (possibly)
- Minimize segregation (possibly)

**CQAs (granulate):**
- Ribbon porosity (work hardening)
- No. of fines
- Bimodal / unimodal?
- Distribution of API in sieve fractions

**CPPs (RC):**
- Compaction force
- Gap size
- Roll speed (mostly up-scaling)
- Sieve size (tablet dose uniformity)

Work hardening (tabletability)
Determines impact of segregation on tablet content uniformity
### Critical Quality Attribute (CQA)

<table>
<thead>
<tr>
<th>Process / formulation parameter</th>
<th>Ribbon porosity</th>
<th>Fines fraction (≤ 125 µm)</th>
<th>API-% in fines fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compaction force (kN)</td>
<td>HIGH</td>
<td>INTERMEDIATE</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Gap size (mm)</td>
<td>INTERMEDIATE</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Roll speed (rpm)</td>
<td>LOW</td>
<td>LOW (upon decrease in roll speed)</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Roll width (cm)</td>
<td>NONE</td>
<td>NONE</td>
<td>NONE</td>
</tr>
<tr>
<td>Granulator angle (°)</td>
<td>NONE</td>
<td>LOW</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Granulator speed (rpm)</td>
<td>NONE</td>
<td>NONE</td>
<td>NONE</td>
</tr>
<tr>
<td>Screen type</td>
<td>NONE</td>
<td>HIGH</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Screen size</td>
<td>NONE</td>
<td>INTERMEDIATE</td>
<td>INTERMEDIATE</td>
</tr>
</tbody>
</table>
CQA specifications of intermediate product

• Ribbon porosity ∈ [35 ; 40%]
• % relative content of API in fines fractions shall be minimized (≤ 45%)
• Fines fraction shall be minimized (≤ 30%)

Porosity determination:
Assessed by oil-intrusion method (in-house)
Several other methods were initially compared

Fines fraction of granulate:
Determined by sieve analysis

Relative API content in fines fraction:
Determined by UV spectrophotometry
Calculated as % of total dose recovered in a given granule fraction

NOTE: API particle size (d_{50} fixed at 65 µm)!
Central composite face design

**3 factors**
- Drug load (% w/w)
- Compaction force (kN)
- Gap size (mm)

**2 center points**

<table>
<thead>
<tr>
<th>Load (%)</th>
<th>Comp. force (kN)</th>
<th>Gap (mm)</th>
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</thead>
<tbody>
<tr>
<td>20</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>1.1</td>
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</tr>
<tr>
<td>1.1</td>
<td>9</td>
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</tr>
<tr>
<td>1.1</td>
<td>3</td>
<td>4</td>
</tr>
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<tr>
<td>11 (CP)</td>
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<td>3</td>
</tr>
<tr>
<td>11 (CP)</td>
<td>6</td>
<td>3</td>
</tr>
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</table>
### Results from roller compaction trials

<table>
<thead>
<tr>
<th>Load (%)</th>
<th>Comp. force (kN)</th>
<th>Gap (mm)</th>
<th>Throughput (kg/hr)</th>
<th>Elastic recovery (mm)</th>
<th>d&lt;sub&gt;gw&lt;/sub&gt; (µm)</th>
<th>Porosity-%</th>
<th>Fines-%</th>
<th>API-RSD in sieve frac. (%)</th>
<th>Rel. API content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Throughput</td>
<td>Oil</td>
<td>&lt; 71 µm</td>
<td>&lt; 125 µm</td>
</tr>
<tr>
<td>1.1</td>
<td>3</td>
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<td>9.2</td>
<td>23.0</td>
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<td>0.2</td>
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<td>27.6</td>
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<td>0.3</td>
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<td>11.0</td>
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<td>0.3</td>
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<td>9.7</td>
<td>27.7</td>
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<td>4</td>
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<td>0.25&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>45.4</td>
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<td>32.1</td>
<td>33.6</td>
<td>8.9</td>
<td>25.6</td>
</tr>
</tbody>
</table>
Design space construction (PLS modeling)

- **R²**
- **Q²**
- Model Validity
- Reproducibility

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Weight fraction</th>
<th>Rel. API content of tot. dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP-porosity</td>
<td></td>
<td></td>
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<tr>
<td>Oil-Porosity</td>
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<tr>
<td>&lt;71um</td>
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<td></td>
</tr>
<tr>
<td>&lt;125um</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dqw~</td>
<td></td>
<td></td>
</tr>
<tr>
<td>API71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>API125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of CPPs on ribbon/granule properties

**Porosity (%)**

- Load: 0%
- CF: 2%
- Gap: 4%
- Load*Load: 2%

**Fines (% < 125 μm)**

- Load: 0%
- CF: 2%

**API in fines < 125 μm (%)**

- Load: 0%
- CF: 2%
Model equation: Ribbon porosity
Model equation: Fines fraction (% < 125 µm)
Model equation: API in granulate fraction (< 125 µm)

![Graph showing the relationship between API125 and Load, and between Comp. force and Load.](image-url)
Optimal process settings: Hitting the sweet spot

Sweet spot plot showing the operating region (design space) for each drug load. A red star indicates the operating conditions used in upcoming verification batches.
CQAs could be well modeled against drug load and CPPs: compaction force and gap size.

Next step: Verification of sweet spot settings in a new experimental series (on-going; larger scale) \(\rightarrow\) preliminary results show good reproducibility for porosity and mostly for fines fraction, however, new challenges are now encountered:

- Sampling related issues when measuring fines (sample divider)
- Tableting step: Adhesion to punches \(\leftrightarrow\) further decrease amount of fines in the granulate (varying the sieve size of the granulator)

Finally: Design space describing relationship between API load and API particle size (similar as for DC and using verified sweet spot settings for the RC step)
Concluding remarks...
A SF needs to be continuously modified and refined!

Results/data and finally information is useless unless used as part of a structured framework (QbD). So far there are 13 experimental plans and reports behind the SF work!

Decision-making tool in Development: Integrate SF results as flowcharts and in risk assessment templates (on-going).

Good advice: Don’t underestimate the usefulness of ‘old’ data and previous studies. Seek information and decrease the experimental work load markedly (less complex DoEs).
Thank you... Questions?