PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
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Multivariate Analysis: A Technique to Evaluate the Risk and Impact of Raw Material Variability

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Biography and contact information

- Over five years experience in the excipient industry @DFE Pharma
- Product application specialist
- Product development experience of Oral Solid Dosage and Dry Powder Inhalation excipients
- Analytical expert
- Master of Science (cum laude) in Physical chemistry @Radboud University
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Robust formulations and processes are key to guarantee quality

In the market, there is a continuous drive from pharmaceutical companies and regulatory bodies to develop more robust pharmaceutical formulations and processes based upon knowledge.

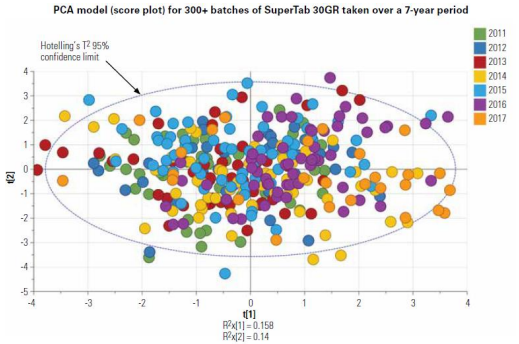
Robust formulations and processes should be able to accommodate typical variation seen in APIs, processes and excipients without compromising on the manufacture, stability or performance of the product. Excipient suppliers can help to de-risk the use of excipients, in line with QbD by:

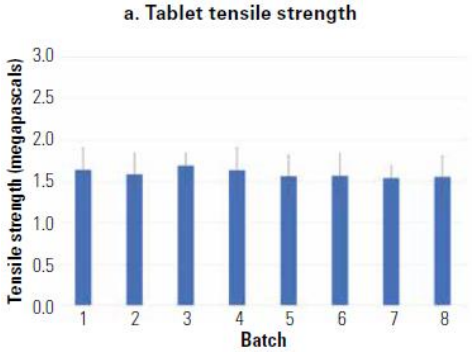
- Sharing insights on batch-to-batch consistency
- Providing insights in FRC's and/or CMA's

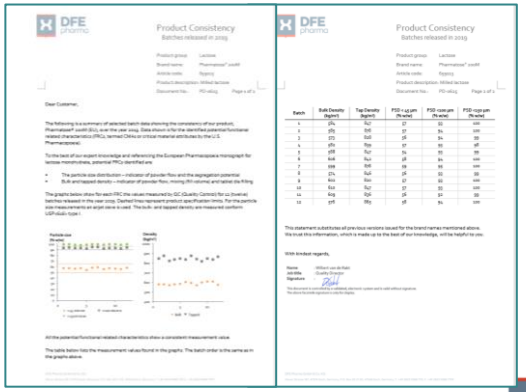
There is increased attention for Excipient Consistency in the market

ICH Q13: Continuous Manufacturing, 4.2. Control Strategy

Impact of input material attributes and their variability (e.g., intra-batch, inter-batch, different suppliers) on continuous processing **should be assessed** and proposed material attribute acceptable ranges should be justified when establishing the material specification. For input materials for which pharmacopoeia requirements exist, characterisation and control may extend beyond those requirements.







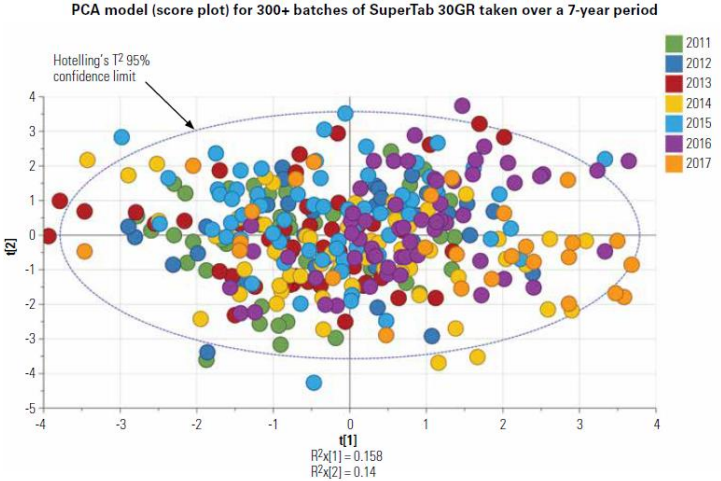
There is inevitable variation within production processes

- All production processes, including the production processes for excipients, have some inevitable degree of variation.
- Production processes can shift amongst other due to equipment getting older, variation in conditions, human intervention, variability of raw material, variability of analytical instrumentation

Variation ≠ out of control

Variation = not all batches are exactly the same

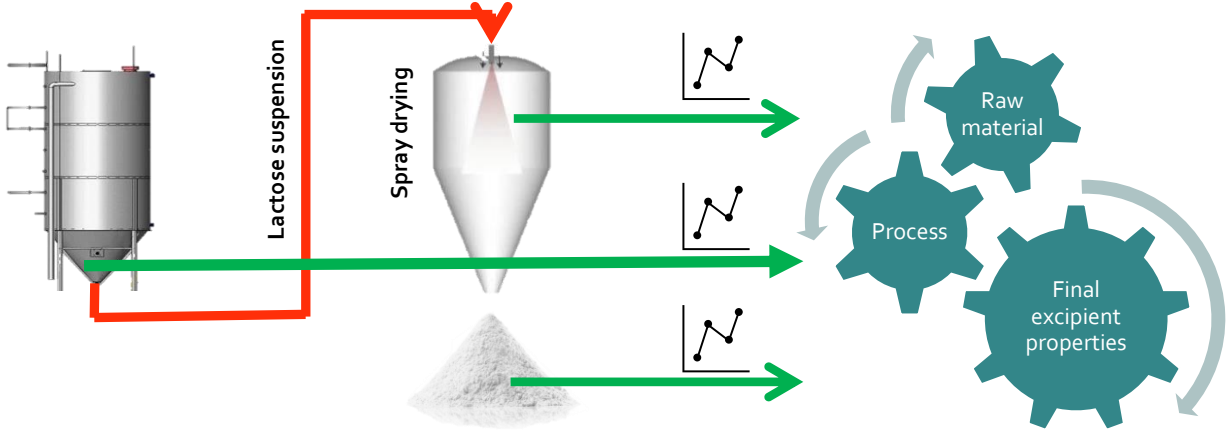
Impact of variation on the final dosage form should be understood.

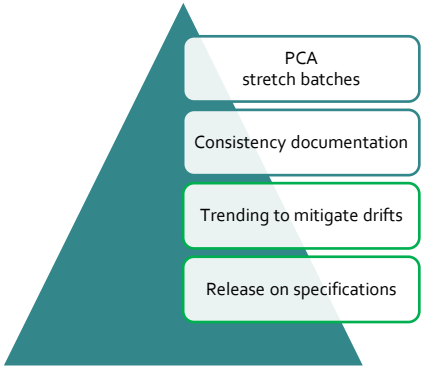


Pharma 4.0 – digitalization of manufacturing processes

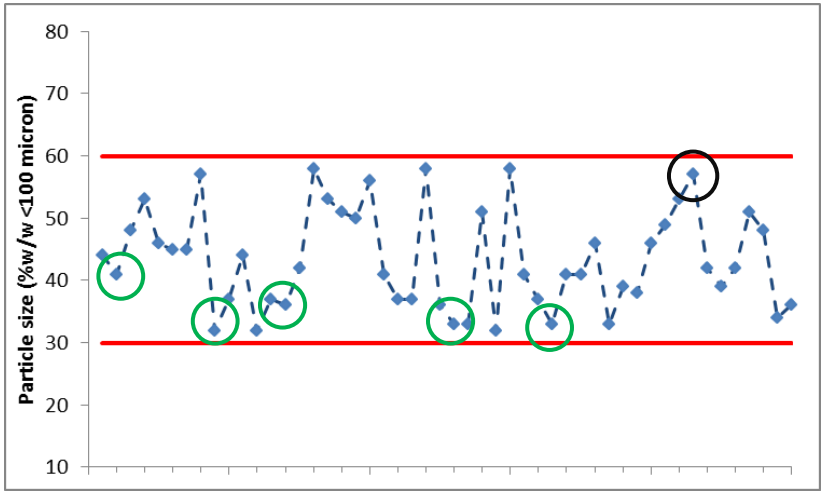
Increased understanding from linking *raw material data, process data, IPC material data, final product properties*, results in:

- Significant improvement in product consistency
- Process stability





Understanding the variation is important for evaluation of the risk

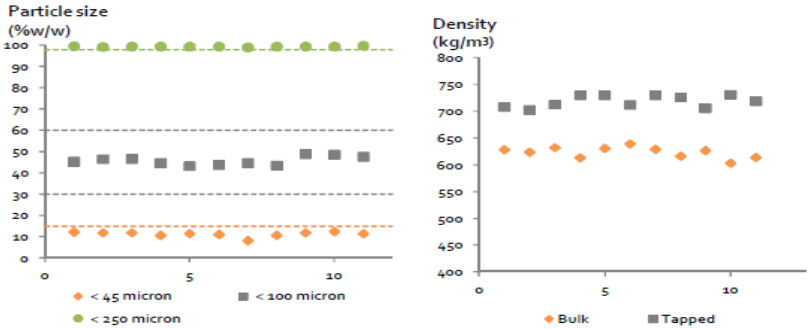


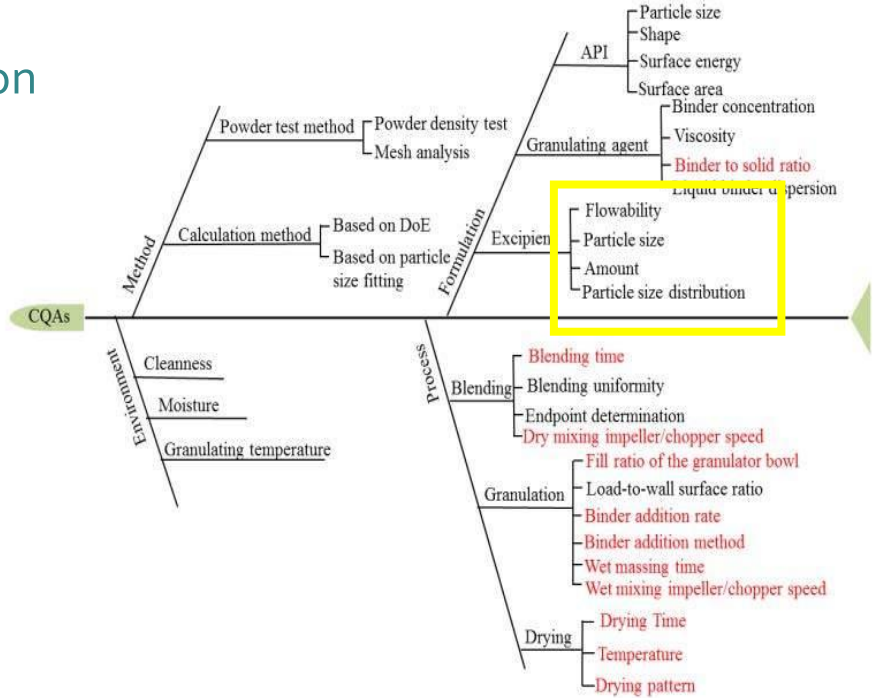
- When choosing functional excipient suppliers, users should be aware of the 'natural' variation of the excipient
- Imagine in development you used the five (5) batches highlighted in green.
- What is the risk of using the batch highlighted in black?

Suppliers know their typical variation for potential FRCs

- Typical batch-to-batch variability data on pFRCs is available at suppliers
- This data can be used to assess the risk of excipient variability

SuperTab®11SD EU

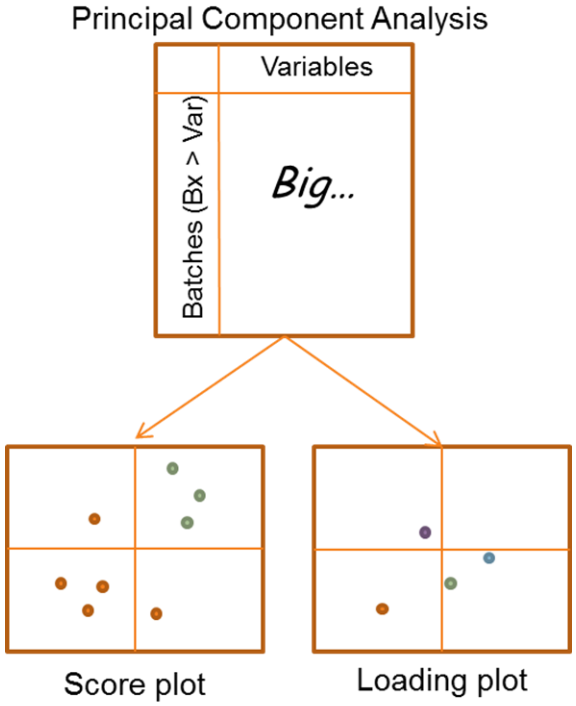




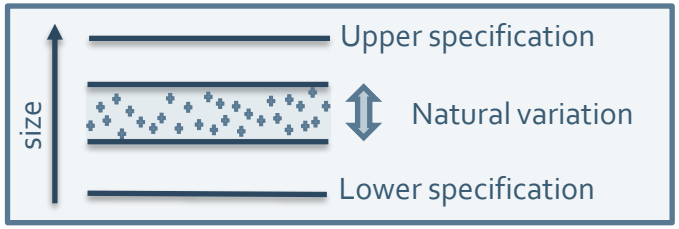
https://www.researchgate.net/figure/An-ishikawa-diagram-illustrating-factors-that-may-have-influence-on-D-50-and-tapped_fig2_314099963

Multivariate analysis can be used to evaluate variability of raw materials

- Multivariate analysis (MVA) by Principal Component Analysis (PCA)
- Statistical tool to evaluate large data sets.
- No need to follow hundreds of (univariate) control charts: two (main) graphs per product only!
- Shows the main structure in the data: no structure = no trends.
- Score plot shows how batches relate to each other. Inspection on clusters/trends.
- Loading plot shows how batches relate to the QC parameters. First step to deep dive into data in case of clusters/trends.



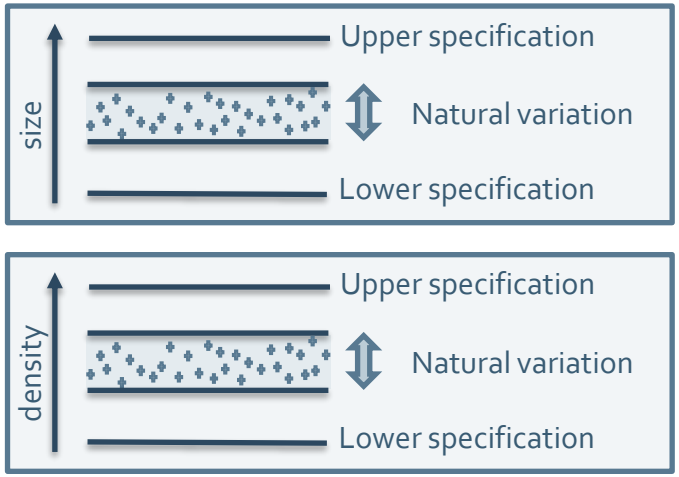
Typical evaluation can be evaluated for each parameter independently



N=2 testing required:

- Maximum size
- Minimum size

Typical evaluation can be evaluated for each parameter independently



N=4 testing required:

- Maximum size, maximum density
- Minimum size, maximum density
- Maximum size, minimum density
- Minimum size, minimum density

Typical evaluation can be evaluated for each parameter independently

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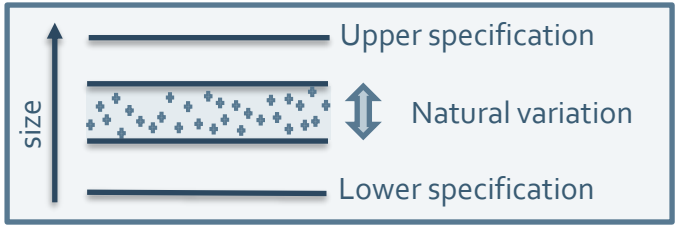
Full factorial testing of X parameters:

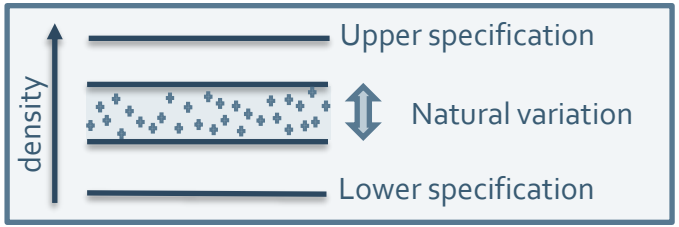
- 2^X tests required

Time + Resources

Not all combinations of parameters are relevant

What is purposeful variation?





N=4 testing required?

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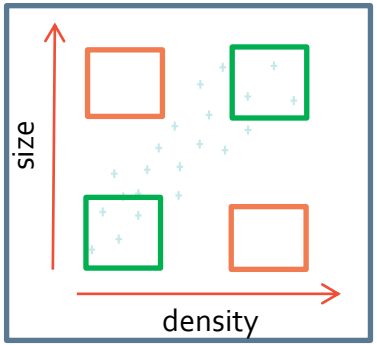
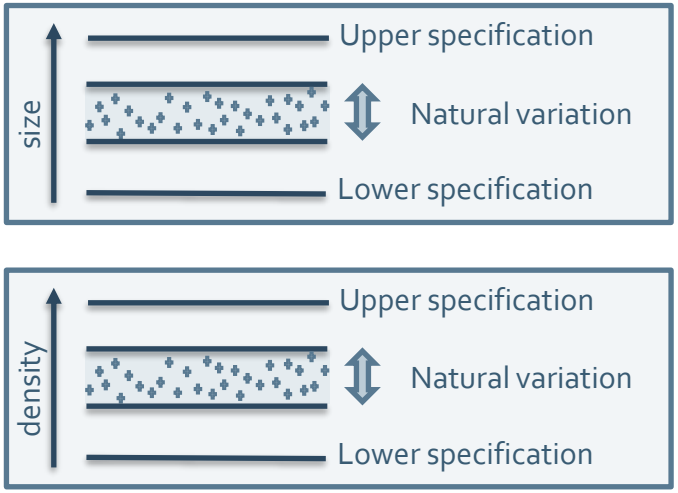
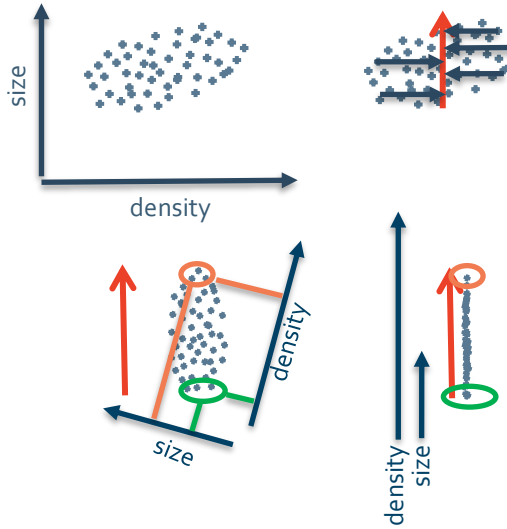


PCA can be used to reduce the number of parameters

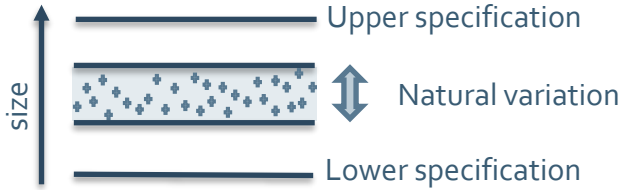


Reduction of parameters – from 2 to 1
Which direction has the most variance?

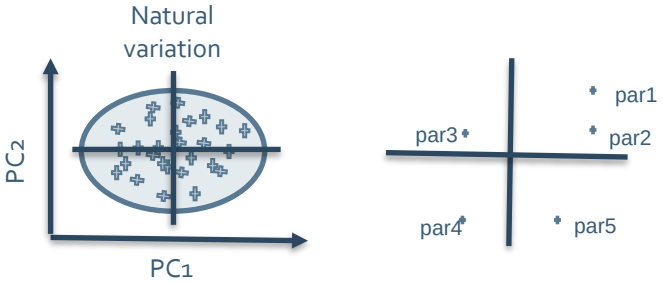


Direction with most variance:
0.5 *x* size + 0.87 *x* density

PCA can be used to reduce the number of parameters



Reduction of parameters – from N=5 to 2
Which directions have the most variance?

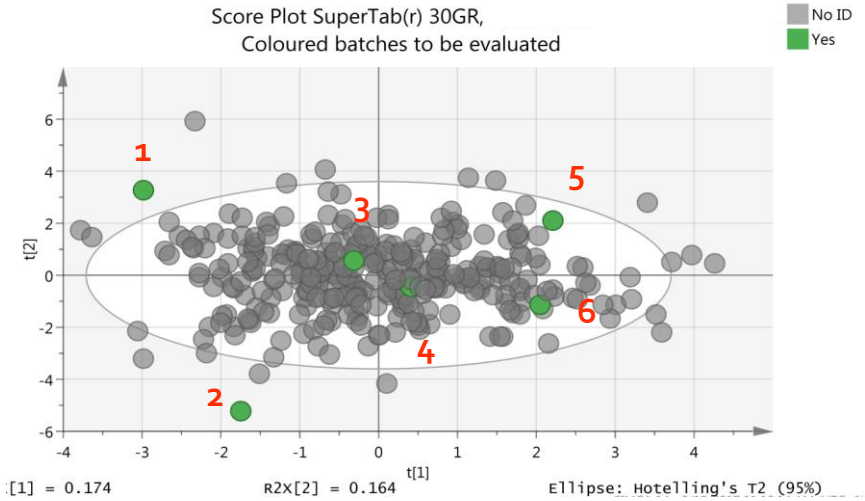


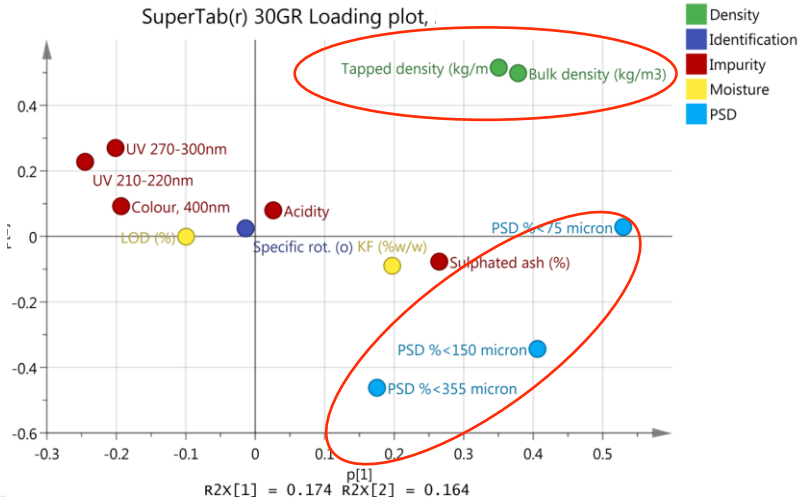
An eightfold reduction of parameters:

- **From 32 (2^5) to 4 (2^2)!**

Case study: six batches that cover the knowledge base are selected

- The consistency of SuperTab® 30GR is tested
- Six batches that cover a large portion of the knowledge space are tested

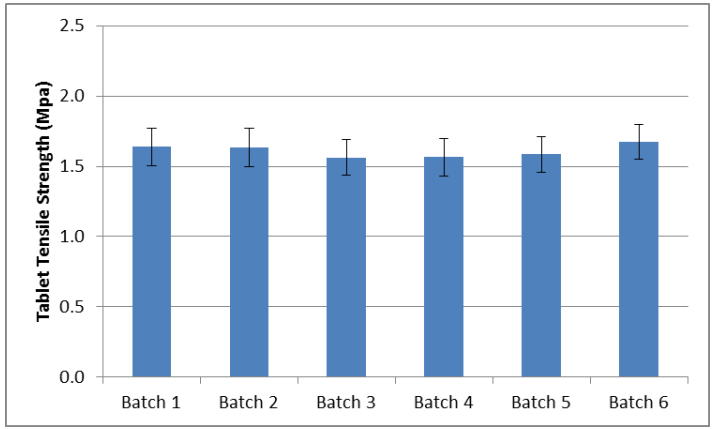


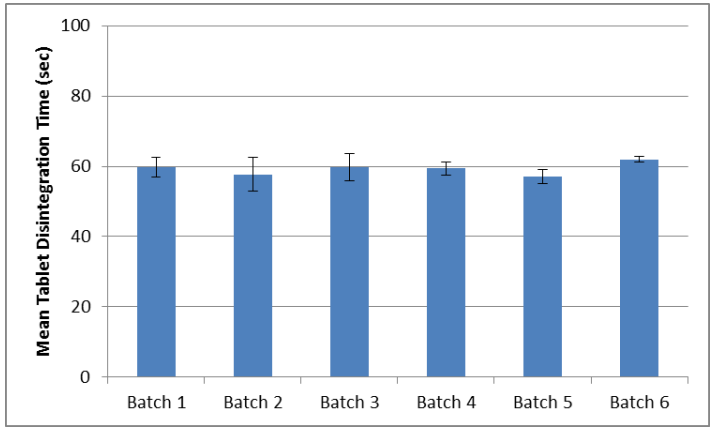


A huge reduction in testing was obtained

Reducing time + resources (in theory) from 8192 (=2^{13}) to 6 batches for testing

- Consistent tablet tensile strength and consistent tablet disintegration times are observed
- The process can therefore be considered as robust for variation in physical properties of SuperTab® 30GR





*RoTab tableting equipment. Compression at 10kN, 9 mm flat beveled tooling. Tablet weight target 250mg. Formulation: 97.5% w/w SuperTab® 30GR, 2% w/w Primojel®, 0.5% w/w MgSt. SoTax HT100 automated tablet testing N=20. Erweka Disintegration tester N=6. TTS = 2 x Hardness / π x d x t.

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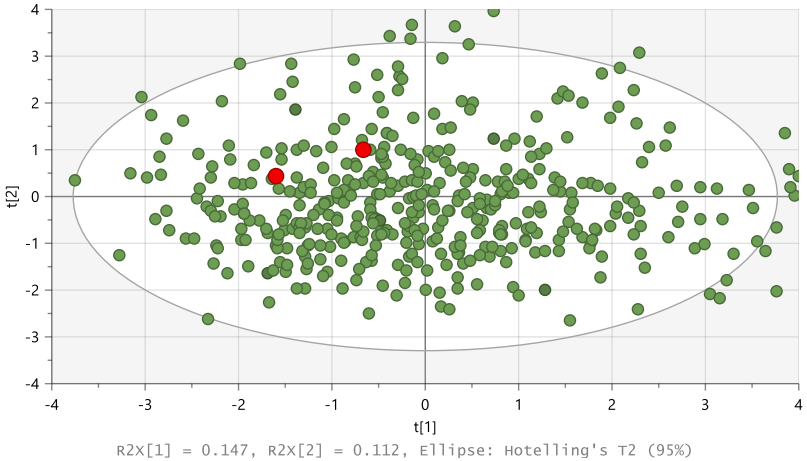
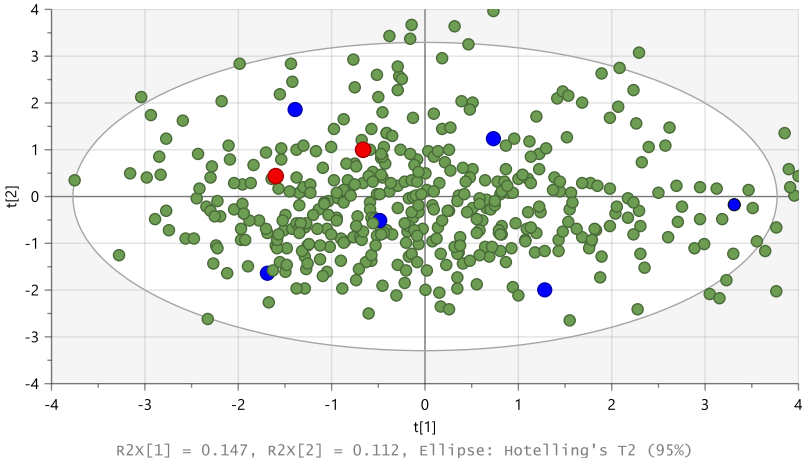
PCA can show how batches compare to each other

Historical product space provides insights in variation of used batches



● = batches used by customer

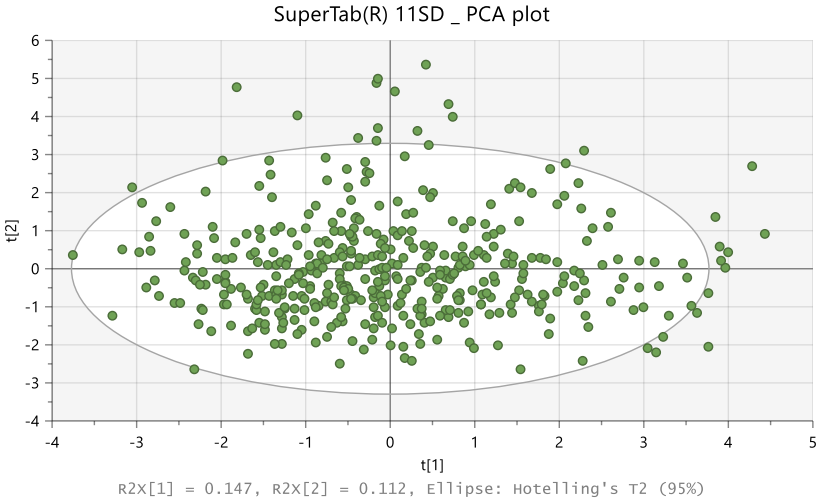
Historical product space provides insights in availability of batches that represent the variation

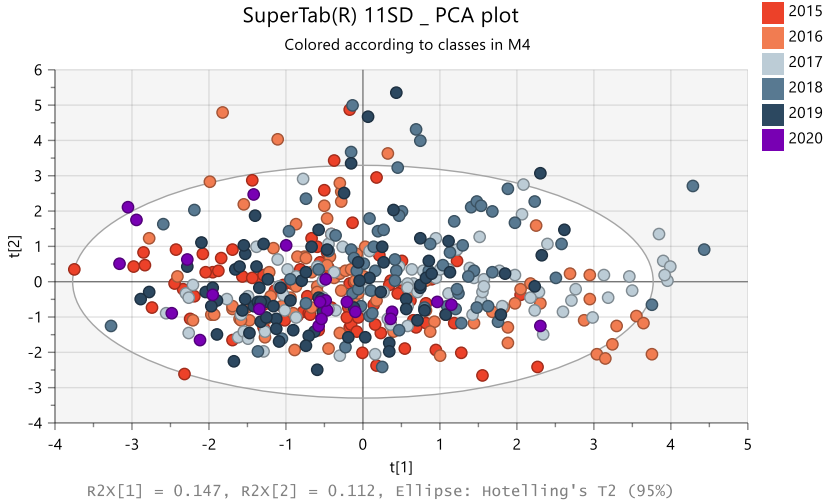


● = batches used by customer
● = batches on stock

PCA can show the year-to-year consistency

- Batches are colored according to production year
- A lack of clusters in the dataset is observed, indicating the absence of trends
- Year-after-year consistency showed by multivariate analyses





Communication between suppliers and users is key!

Currently

Known to User

No

Yes

Unspecified Attributes & True Variability

Excipient Interaction with Product Criticality

Certificate of Analysis

Excipient Impact

Known to Supplier

Yes

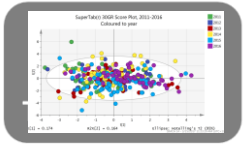
No

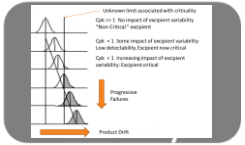
Future?

Known to User

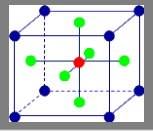
No

Yes





Certificate of Analysis



Known to Supplier

Yes

No

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OUR SOLUTIONS.

MOVING TO A HEALTHIER WORLD.