FACULTY OF PHARMACEUTICAL SCIENCES

DEPARTMENT PHARMACEUTICS
LABORATORY OF PHARMACEUTICAL TECHNOLOGY

IN-LINE NIR SPECTROSCOPY FOR COMPREHENSIVE PROCESS UNDERSTANDING OF SEMI-CONTINUOUS BLENDING IN THE CONTINUOUS PRODUCTION OF LOW-DOSE FORMULATIONS

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SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Gericke

sentronic

INTRODUCTION

- Growing market of **High Potency Active Pharmaceutical Ingredients** (HPAPIs)[1]
  - ➔ increased need for **low-dose formulations**

- Low-dose formulation: unit dose ≤ 2% w/w API[2]

- Challenges in **continuous manufacturing of low-dose formulations**
  - **Feeder fluctuations** may impact blending performance
  - **Start-up and shutdown losses** limit use for the development of new products
  - **Sensitivity issues** exist for in-line PAT tools used to measure **blend uniformity**
  - **…**

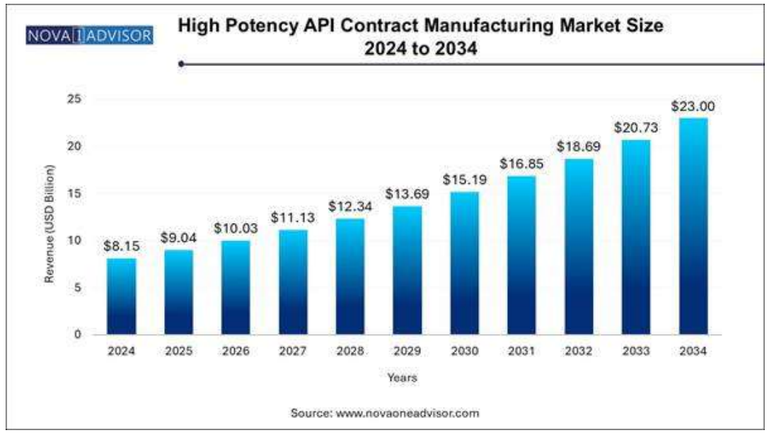

Fig. 1: Predicted future market value of High Potency APIs

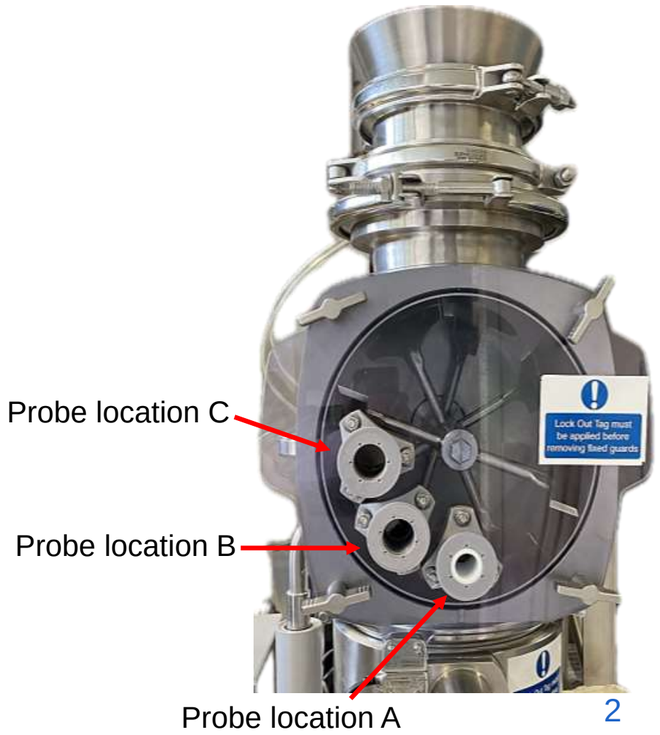

Fig. 2:Semi-continuous blender (GBM 10-P, Gericke AG)

1. P. Van Arnun, Charting API Market Growth and Opportunity, Pharm. Technol. 32 (7), 58–61 (2008)

2. EMA. Guideline on process validation for finished products — Information and data to be provided in regulatory submissions (2016)

INTRODUCTION

- Blending process exists of two blending mechanisms: **macromixing** (convection) and **micromixing** (dispersion)[3]
  - Macromixing: bulk movement of particles in the blender & most impact on blend uniformity
  - Micromixing: delumping of API particles, resulting in a small-scale random motion
    - Macro and micromixing co-occur in most mixers
    - Macromixing results rarely in complete homogeneous mixtures
    - Micromixing is generally slower than macromixing

- End-point of micromixing = end-point blending process

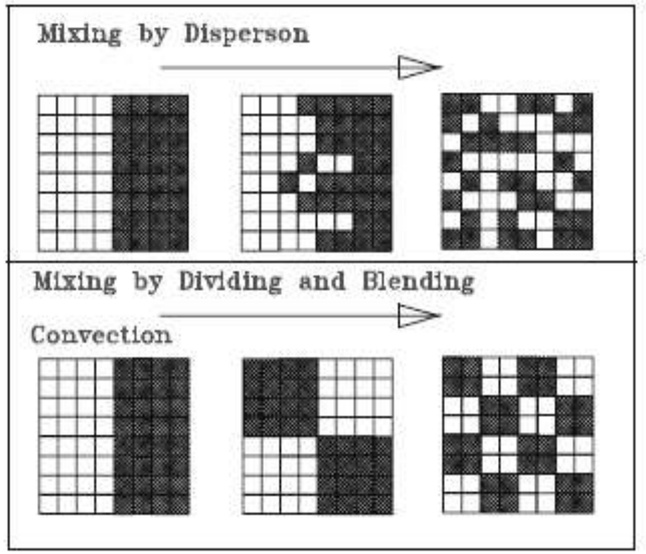

Fig. 3: Schematic overview of dispersive mixing (top) and convective mixing (bottom)

- Objectives of the study:
  1. Direct integration of an **in-line PAT tool** into the GBM 10-P Pharma mini blender (Gericke)
  2. Enhancing **process understanding** of semi-continuous
  3. Evaluating the **impact of process settings** on the blending time required to achieve homogeneity

3. H. G. Merkus and G. M. H. Meesters Editors, “Particle Technology Series Production, Handling and Characterization of Particulate Materials.” [Online]. Available: http://www.springer.com/series/6433

MATERIALS AND METHODS

Formulation	
Caffeine anhydrous powder	2%$_{w/w}$
Lactose (SuperTab 11SD)	98%$_{w/w}$

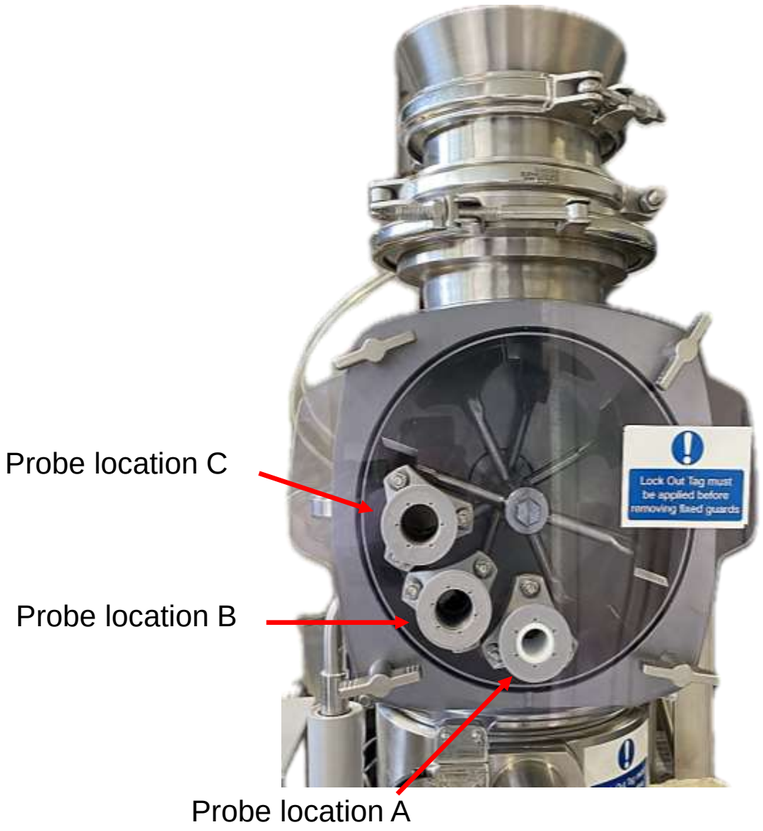

Fig. 2: Semi-continuous blender (GBM 10-P, Gericke AG)

Settings SentroPAT FO	
Integration time	5 ms
Averaging number	40*
Measurement interval	±350 ms

* Without SentroPAT interface lagging

Fig. 4: SentroPAT FO with SentroProbe DR LS (Sentronic)

MATERIALS AND METHODS

- Full factorial screening design
  - 2%$_{w/w}$ drug load
  - Included **factors**:
    - Impeller speed (60 – 100 -140 RPM)
    - Probe location (A – B – C)
    - Fill level (5 – 7.5 – 10L)
  - Defined **responses**:
    - Spectral noise
    - End-point of macromixing and micromixing
  - Spectral analysis methods:
    - Partial Least Squares (PLS)
    - Moving Block Standard Deviation (MBSD)
- A run was blended for 6 minutes while NIR spectra was collected
- 10 powder samples were taken straight from the blender for offline validation

Table 1: Full factorial screening design

Exp. No	Impeller speed (rpm)	Probe location	Fill level (L)
1	60	A	5
2	140	A	5
3	60	B	5
4	140	B	5
5	60	C	5
6	140	C	5
7	60	A	7.5
8	140	A	7.5
9	60	B	7.5
10	140	B	7.5
11	60	C	7.5
12	140	C	7.5
13	60	A	10
14	140	A	10
15	60	B	10
16	140	B	10
17	60	C	10
18	140	C	10
19	100	A	7.5
20	100	A	7.5
21	100	B	7.5
22	100	B	7.5
23	100	C	7.5
24	100	C	7.5

MATERIALS AND METHODS

A. Partial Least Squares (PLS)

- Calibration data:
  - 0.5 – 1.5 – 2.5 – 3.5 – 4.5%$_{w/w}$
  - Blender was running for 6 min ➔ final 2minutes of spectra were used (i.e. homogeneous powder blend)
  - Spectral preprocessing: 2nd Derivative (27 points in each submodel) + SNV

- Model training:
  - Partial Least Squares regression
  - Group Kfold CV (groups = # LCs = 5)
    - *All spectra of one LC (%) are seen as a group during CV*
  - # LVs based upon change in RMSEcv

Table 2: Advantages vs. limitations of PLS modeling

Advantage	**Limitation**
Real-time predictions of API concentration	Equipment process settings may have a significant impact on the predictions ➢ Calibration set required for each blender setting?

MATERIALS AND METHODS

B. Moving block standard deviation (MBSD)

- Calculating the RSD (%) of spectral intensities at 1670nm (i.e. main wavelength of caffeine) across a block of consecutive spectra
  - Block size of 3 spectra

- During each MBSD calculation: a new spectrum is incorporated while the oldest one is discarded

- Over time, MBSD values will stabilize and fall below predetermined threshold
  - Threshold = max. MBSD value calculated during the final two minutes of blending

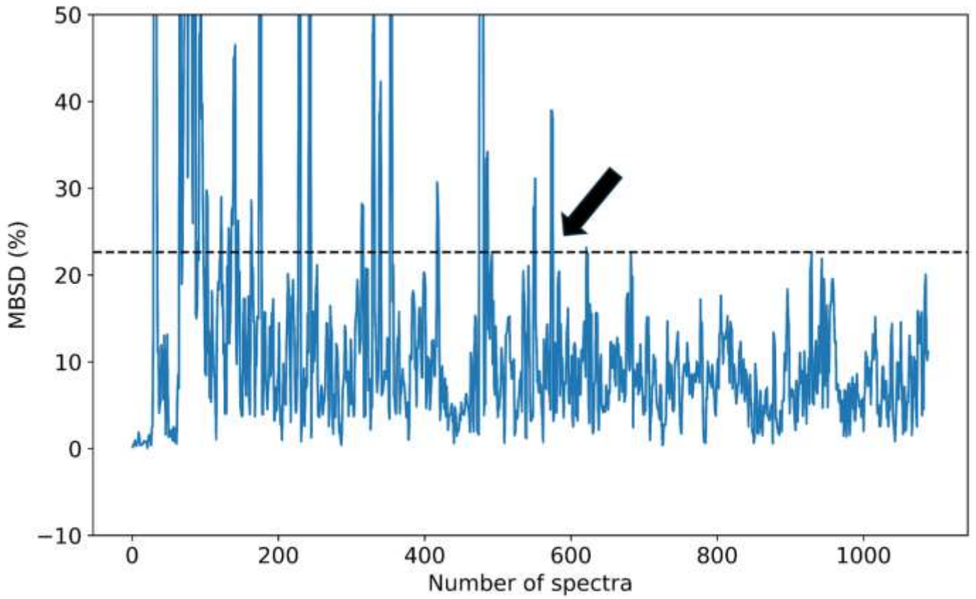

Fig. 5: Endpoint detection via MBSD (7.5L – 60RPM –B)

MATERIALS AND METHODS

Estimating effective sample volume:

- According to the FDA: effective sample size should be comparable to the unit dose of the final drug product[4]

$$M_{spectrum} = \rho H \pi r \left[r + 4(l + r) * \frac{\omega * t_{acq}}{60 * 10^3} \right] * Avg.No.* \frac{3 * \omega * t_{acq}}{sin^{-1}(\frac{r}{l}) * 10^3}$$

  - assumptions:
    - ρ : actual density: between bulk density and tapped density
    - H: 0.28mm (depends on density of the powder)
    - r: radius of the probe spot size
    - l: distance between probe position and center of the blender

Table 3: Effective sample volume calculated for three impeller speeds

Impeller speed (rpm)	Sample volume (mg)	
	Bulk density	Tapped density
60	91	109
100	188	226
140	315	378

4. US Food and Drug Administration . Development and submission of near infrared analytical procedures guidance for industry. Tech. Rep.; U.S.Food and Drug Administration; 2021. URL: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

RESULTS & DISCUSSION

1. SELECTION OF PROCESS SETTINGS FOR PLS MODEL DEVELOPMENT

- Evaluating the impact of blender settings on NIR spectra by **PCA**
  - ➔ Only mean-centering was applied as preprocessing step
  - ➔ Final 2 minutes of each run were included

- **Run 5** (5L; 60 RPM; C), **run 6** (5L; 140RPM; C) and **run 14** (10L; 140RPM; A) are excluded (probe was not fully covered)
- Note: PC1 describes 95% of all variability
- Loadings of PC1 are identical to raw spectra

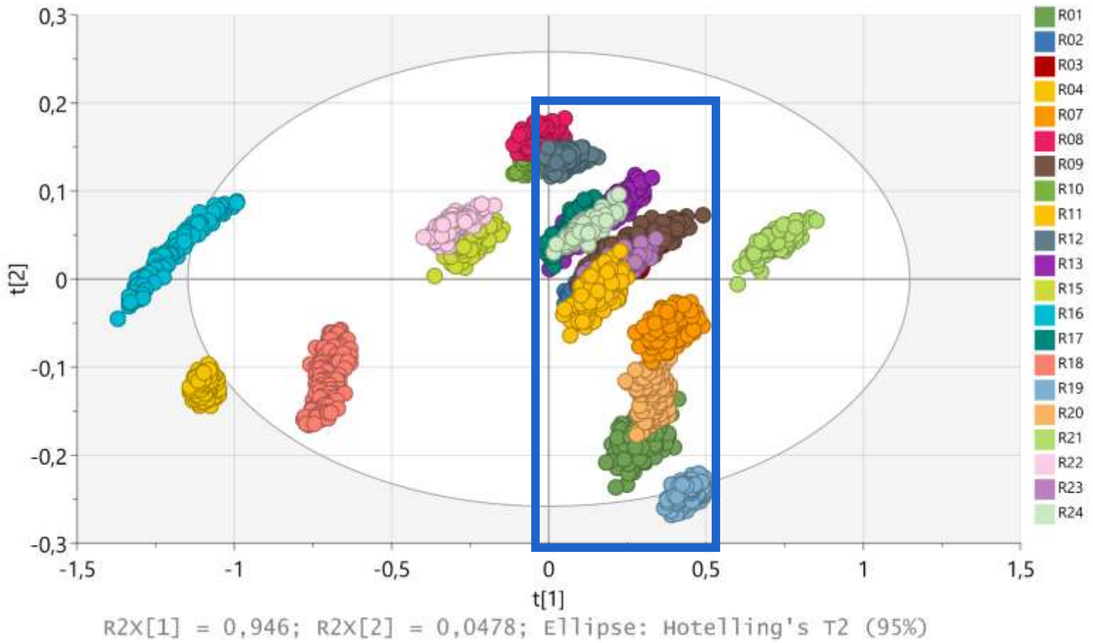

Fig. 6: Score scatter plot of PCA

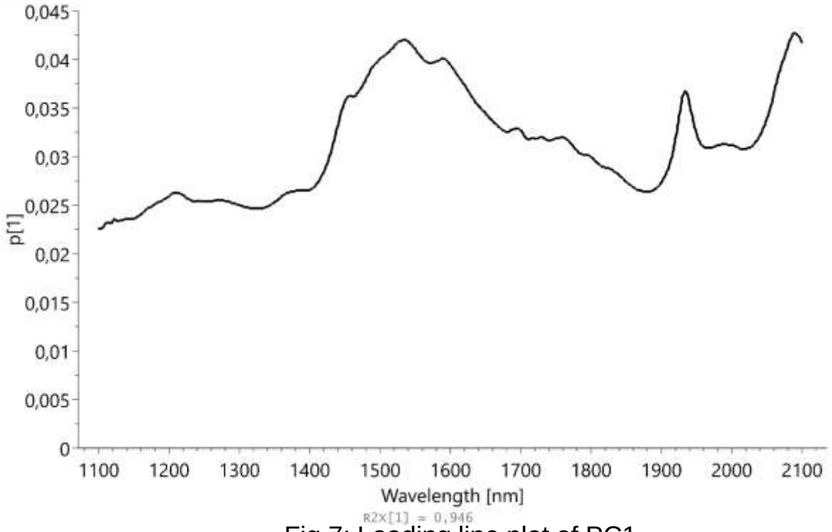

Fig.7: Loading line plot of PC1

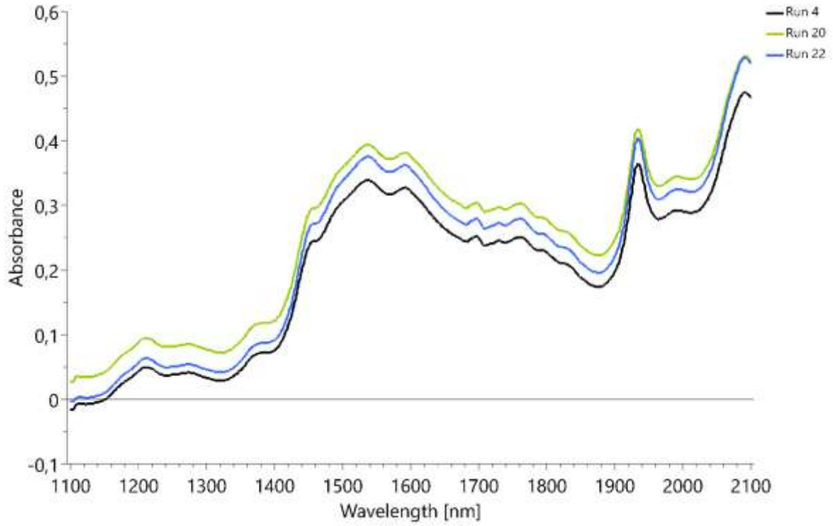

Fig.8: Raw spectrum of run 4, 20 and 22 collected during the final two minutes of blending

RESULTS & DISCUSSION

1. SELECTION OF PROCESS SETTINGS FOR PLS MODEL DEVELOPMENT

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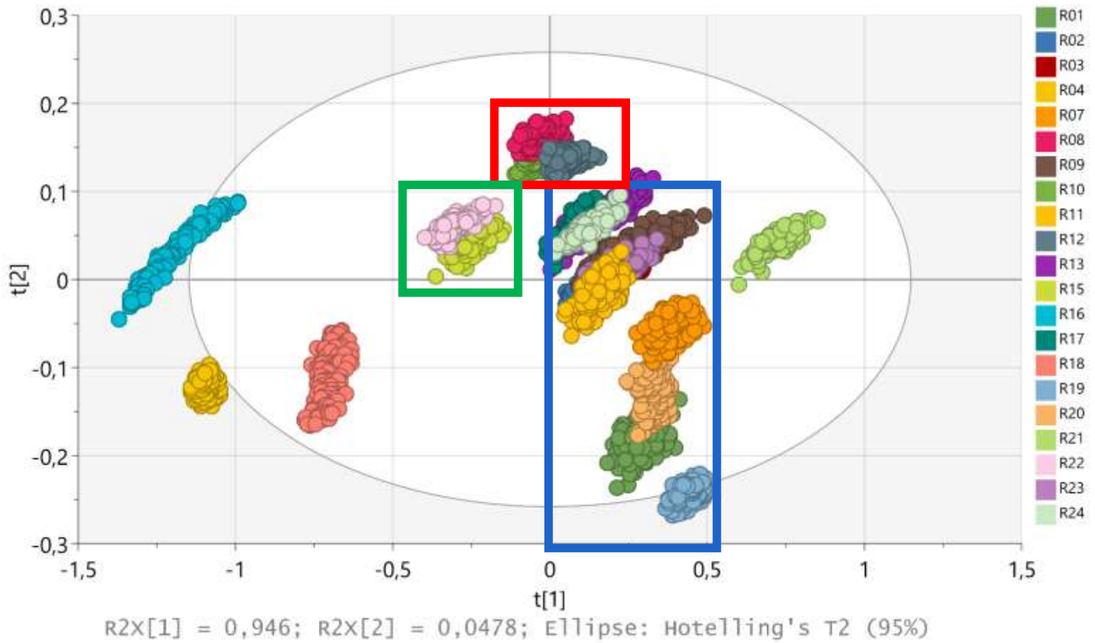
- Note: PC1 describes 95% of all variability
- Loadings of PC1 are identical to raw spectra
- With **3 PLS models: 17 out of 21** DoE runs could be predicted



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5	60	C	5
6	140	C	5
7	60	A	7.5
8	140	A	7.5
9	60	B	7.5
10	140	B	7.5
11	60	C	7.5
12	140	C	7.5
13	60	A	10
14	140	A	10
15	60	B	10
16	140	B	10
17	60	C	10
18	140	C	10
19	100	A	7.5
20	100	A	7.5
21	100	B	7.5
22	100	B	7.5
23	100	C	7.5
24	100	C	7.5

RESULTS AND DISCUSSION

2.1. PLS MODEL USING BLENDER SETTINGS 7.5L-60RPM-B

- Training data
  - Preprocessing: **2nd Derivative (window size: 27 data points) + SNV**
- Model validation
  - $2\%_{w/w}$ blend from t=0 ➔ 360s
  - "When is the blend homogenous?"

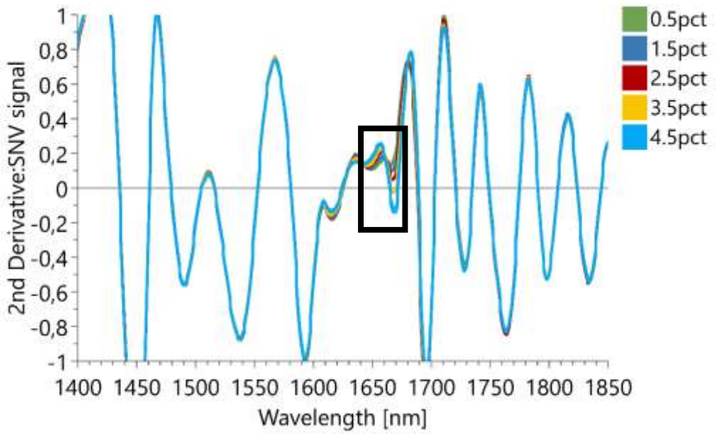

Fig. 9: Preprocessed spectra with 1670nm region indicated

PLS

7.5L-60rpm-B

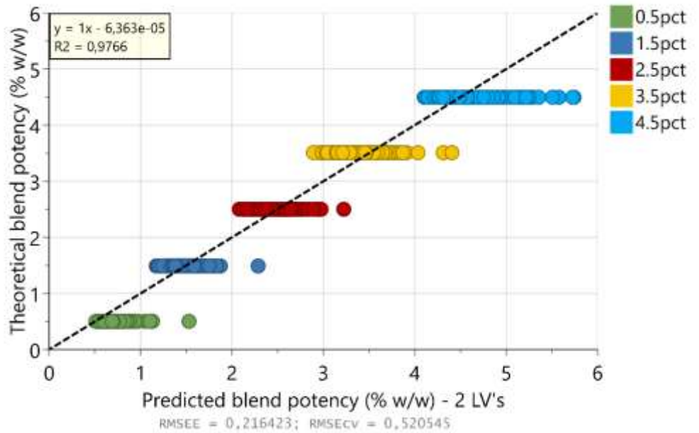

Fig. 10:Observed vs. Predicted of PLS model (7.5L-60rpm-B)

Table 4: Results of the offline analysis

LC(%)	Mean API Content(%)	SD(%)
0.5	95.5	1.56
1.5	96.7	1.61
2.5	97.6	1.61
3.5	97.5	0.85
4.5	97.6	1.46

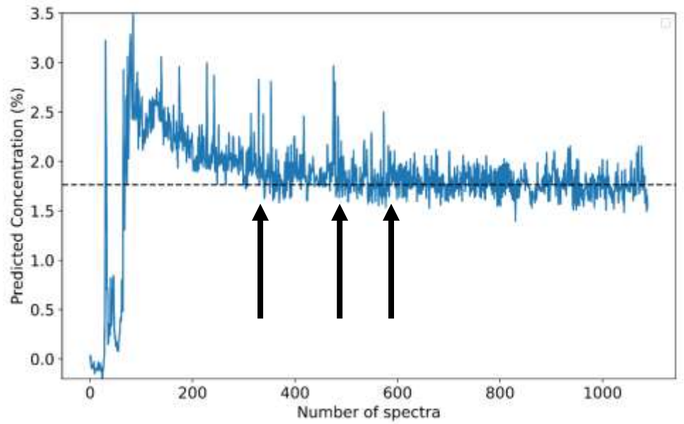

Fig. 11: Predicted blend potency using PLS model: 7.5L-60rpm-B

RESULTS AND DISCUSSION

2.2. THE ENDPOINT OF MICROMIXING USING PLS MODELING

➢ **Score contribution plot**

- To interpret how the X-variables (i.e. wavelength) contribute to the predicted Y-value (i.e. blend potency)
- To distinguish a peak from noise ➔ defining the last peak which is caused by an API agglomerate
- Peak (i.e. black arrow) vs. group of last 2min of spectra (i.e. red colored)
- Assumption: final detected API agglomerate is completely de-lumped and dispersed after the last time it was measured by the NIR probe

PLS prediction

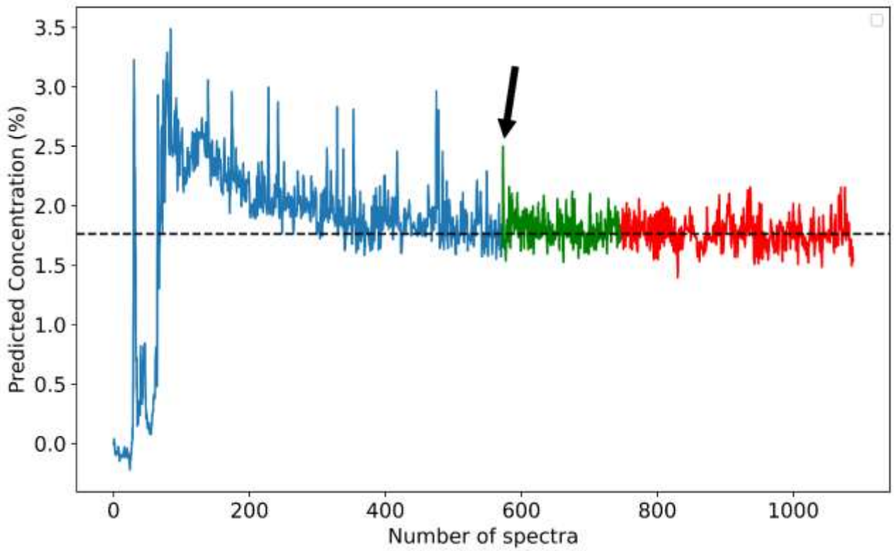

Fig. 12: Validation run of PLS model (7.5L-60RPM-B). Green coloring denotes a homogeneous powder mixture, which continues as red during the final two minutes of blending.

Score contribution plot

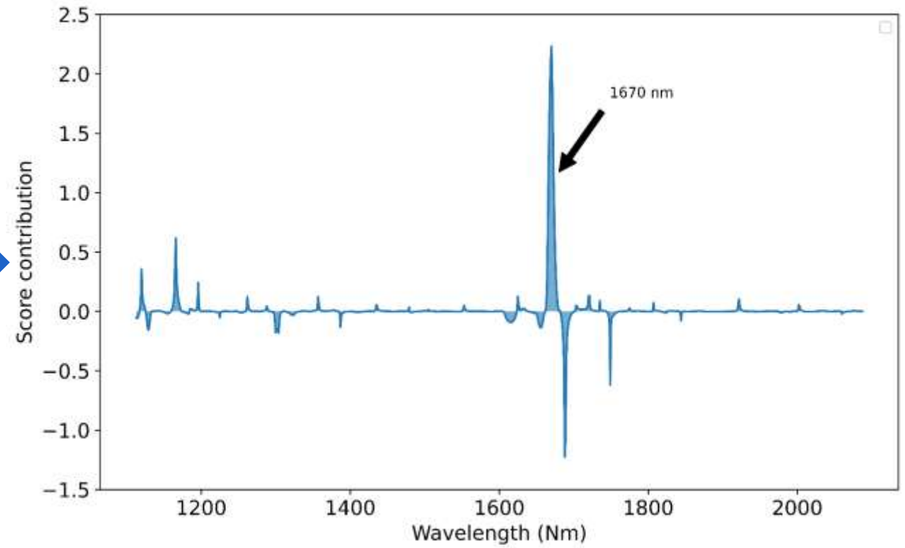

Fig. 12: Score contribution plot.

RESULTS AND DISCUSSION

2.2. THE ENDPOINT OF MICROMIXING USING BLENDER SETTINGS 7.5L-60RPM-B

- Comparison between the endpoint of th PLS prediction (i.e. score contribution) and MBSD
- Both analyzing methods result in similar endpoints

PLS prediction

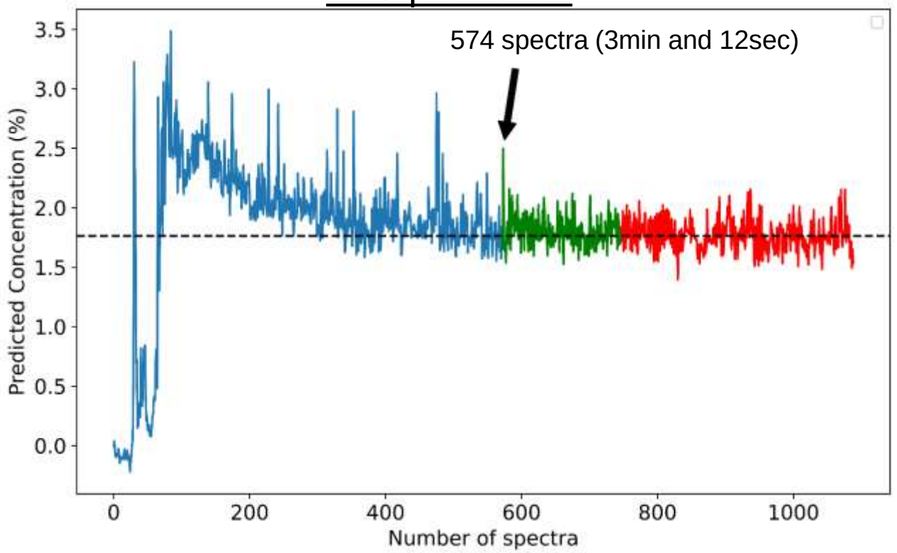

Fig. 12.: Validation run of PLS model (7.5L-60RPM-B). Green coloring denotes a homogeneous powder mixture, which continues as red during the final two minutes of blending.

MBSD

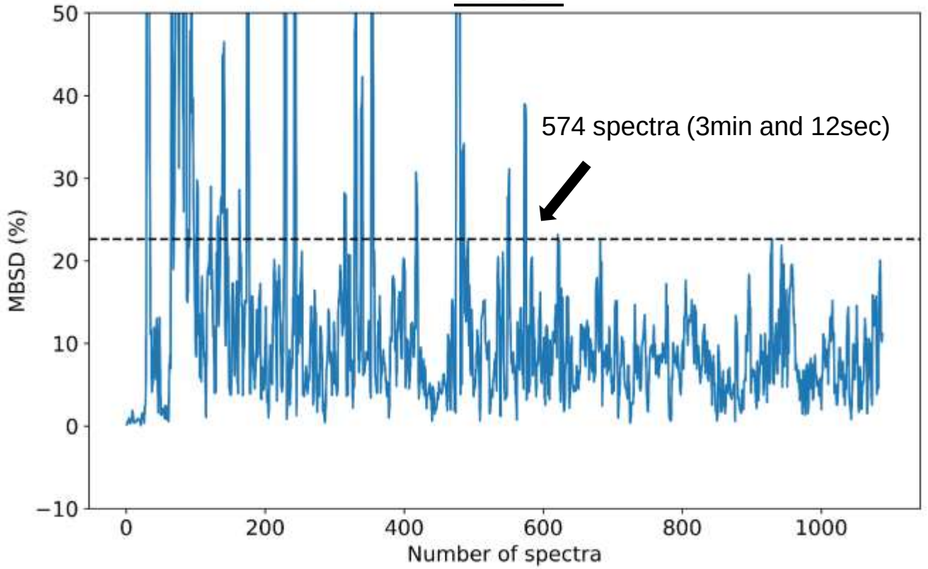

Fig.13 : MBSD of a validation run (i.e. 7.5L-60RPM-B).
(-): Max. MBSD value observed during the final two minutes of blending

RESULTS AND DISCUSSION

4.1. IMPACT OF PROCESS SETTINGS/PROBE LOCATION ON THE ENDPOINT OF MACROMIXING

- **PLS predictions** were used to evaluate the impact of process settings on the end-point of **macromixing**
- Endpoint of macromixing = the moment predicted blend potency values intersect with the average concentration observed during the final two minutes of blending

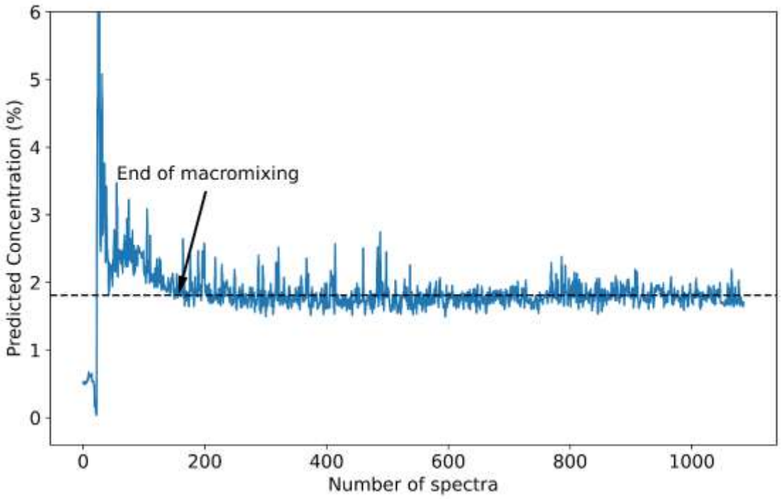

Fig. 20: PLS prediction of 5L – 60RPM –B

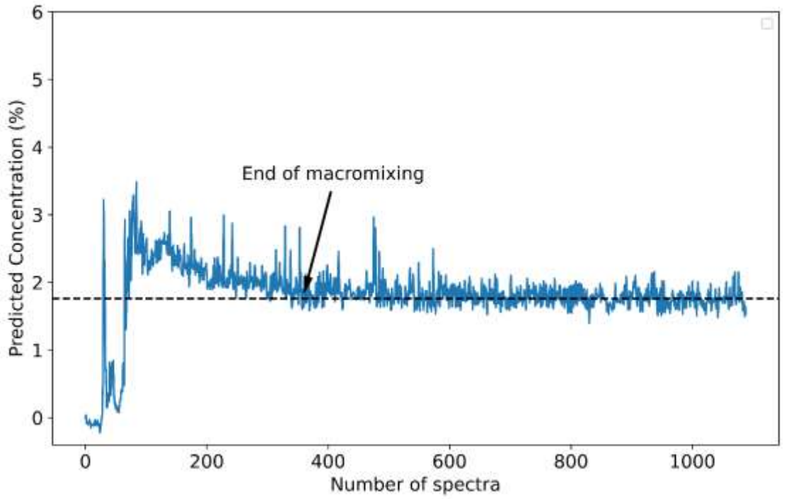

Fig. 21: PLS prediction of 7.5L – 60RPM –B

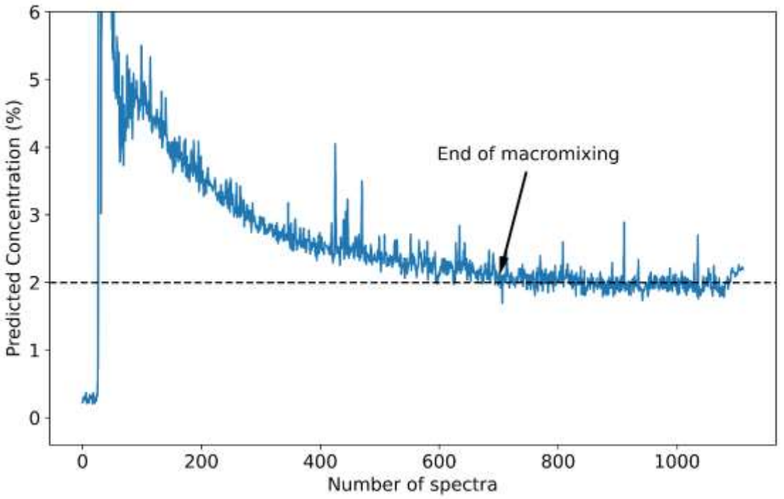

Fig. 22: PLS prediction of 10L – 60RPM –A

RESULTS AND DISCUSSION

4.1. IMPACT OF PROCESS SETTINGS/PROBE LOCATION ON THE ENDPOINT OF MACROMIXING

- **PLS predictions** were used to evaluate the impact of process settings on the end-point of **macromixing**
- Endpoint of macromixing = the moment predicted blend potency values intersect with the average concentration observed during the final two minutes of blending

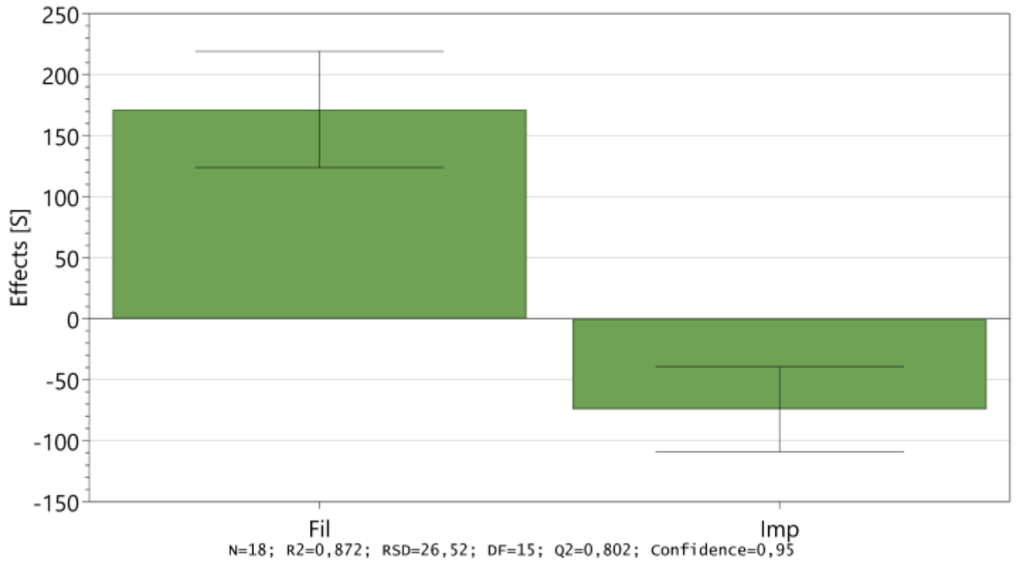

Fig. 23: Effect plot of macromixing. Imp: impeller speed, Fil: fill level

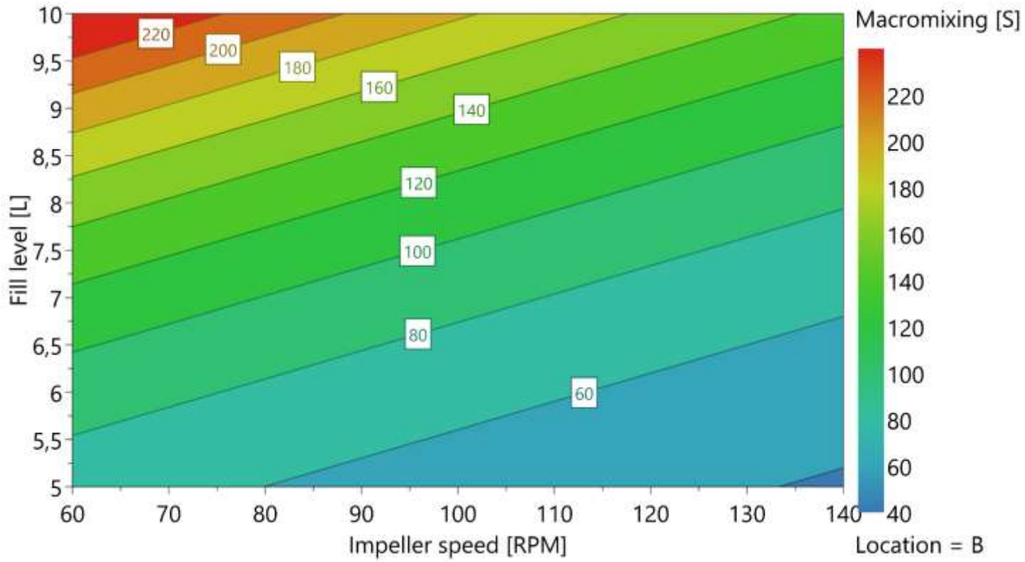

Fig. 24: Contour plot of the endpoint of macromixing

RESULTS OF DOE

4.1. IMPACT OF PROCESS SETTINGS/PROBE LOCATION ON THE ENDPOINT OF MICROMIXING

- Endpoint could be detected by both PLS modeling and MBSD
- To include all 21 DoE runs the MBSD-method was used*

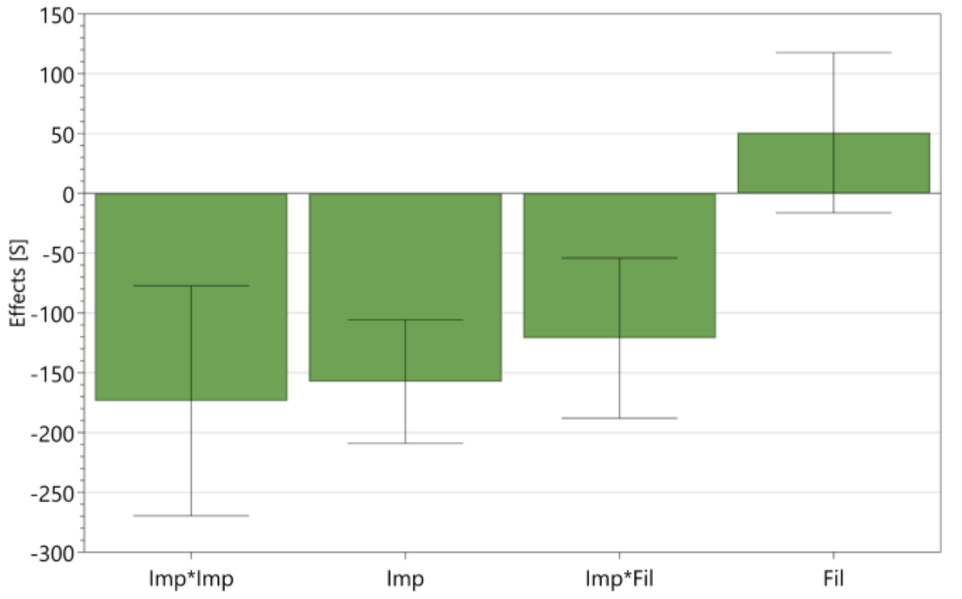

Fig. 25: Effect plot of micromixing. Imp: impeller speed, Fil: fill level

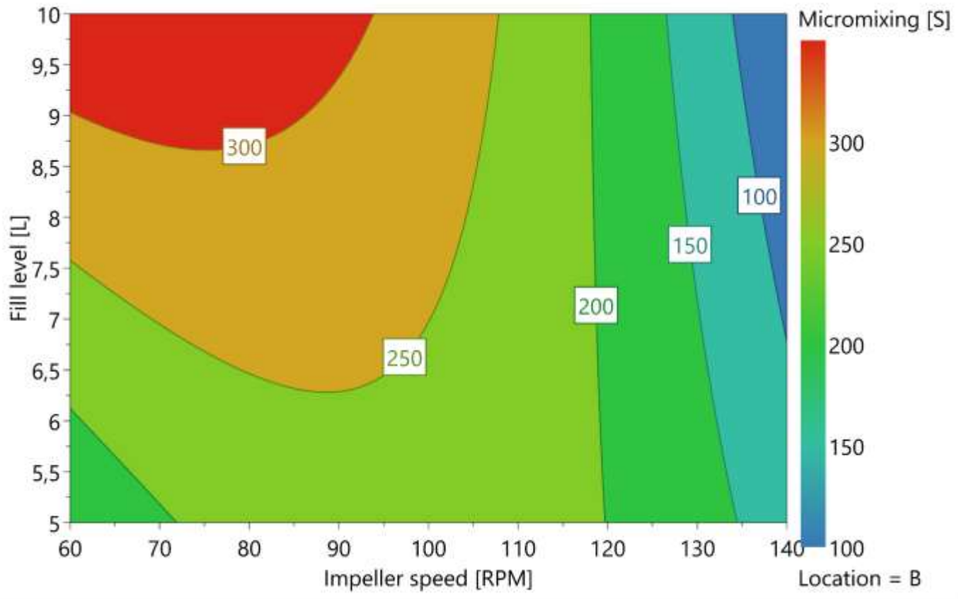

Fig. 26: Contour plot of the endpoint of micromixing

*Run 4/5/14 excluded (probe was not fully covered)

CONCLUSION

- Spectra could be measured in **high quality** and in **real-short time** using a diode arrays spectrometer
  - API signal could always be distinguished from background noise despite the low drug load
  - The effective sample size of one spectrum was comparable to the unit dose of a single tablet

- PLS and MBSD were used as spectral analysis methods:
  - PLS modeling enabled the prediction of both convective and dispersive mixing in 17 out of 21 DoE runs
  - MBSD explained only the endpoint of micromixing, but showed robustness across different blender settings

- Endpoint of macromixing**:**
  - Increasing fill level extended the time required to complete macromixing
  - Impeller speed had the opposite effect

- Endpoint of micromixing (=endpoint of blending process)
  - High shear mixing resulted in shorter blending times compared to low shear blending
  - Fill level only extended the blending time when a low impeller speed was applied

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