Robotic-Assisted NIR Spectroscopy for Optimised Calibration of Chemometric Models and Enhanced Predictive Power for Blend Homogeneity

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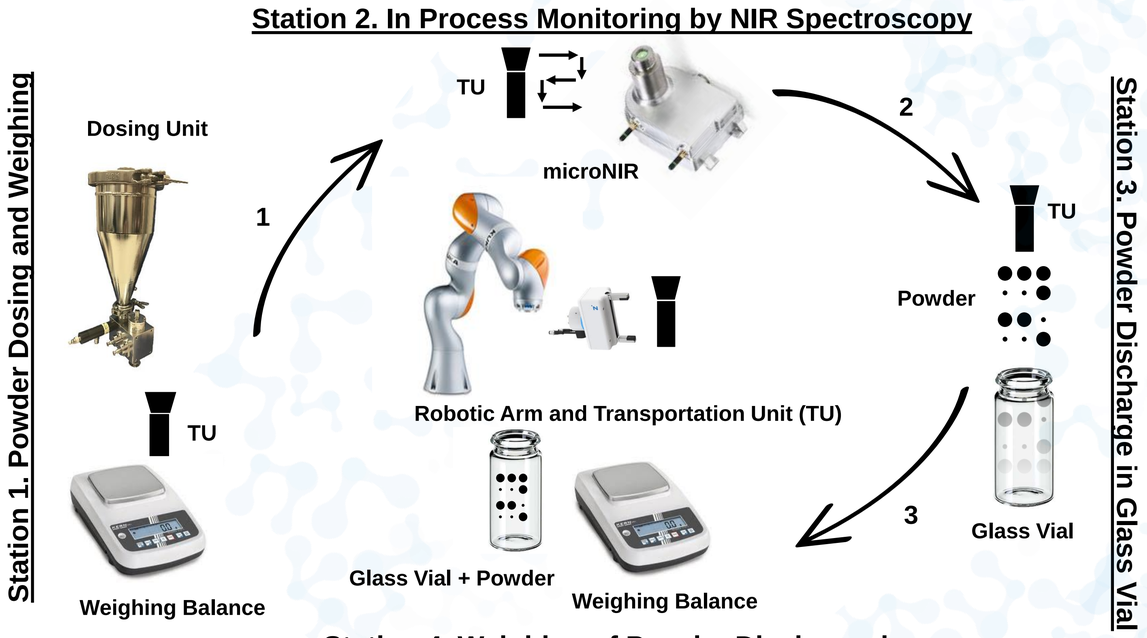
Background

Our research focuses on autonomous microscale manufacturing for the pharmaceutical R&D industry, which enables high-speed, precise, and resource-efficient experiments. This technology accelerates drug development research and reduces costs by providing better control over crucial process parameters for optimal formulation and process enhancement.

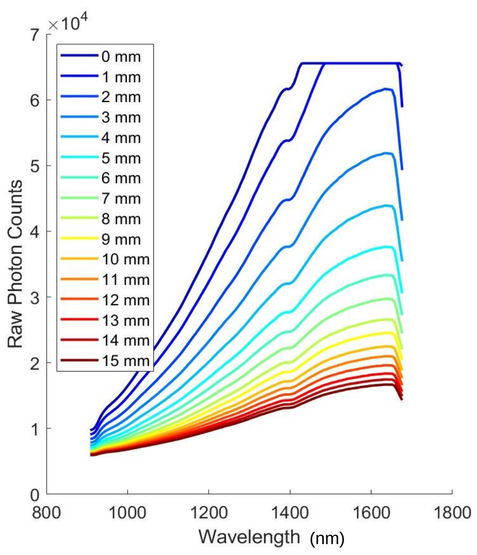
We strive towards a Quality by Control (QbC) approach for assured product quality, aligning seamlessly with our microscale tableting process to maintain consistency. Incorporation of Process Analytical Technology (PAT) tools further optimizes our QbC approach. PAT enables real-time process monitoring, thereby enhancing understanding, reliability, and overall quality of pharmaceutical manufacturing.

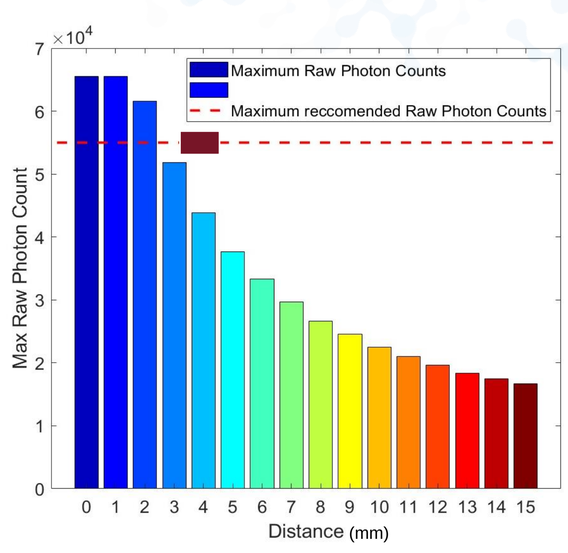
DM² Autonomous Microscale Manufacturing Platform

Pre-Compaction Workflow



Effective Sampling Distance

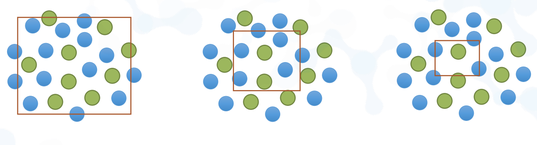




(a) line plots showing Raw Photon Counts vs. Wavelength (nm) acquired by assessing a white 99% reflectance panel at various distances (0-15 mm) from the spectrometer's glass window, and (b) bar plots indicating the Maximum Raw Photon Counts at each sampling distance (mm) derived from descriptive statistics. The red dashed line (---) at 55,000 represents the manufacturer's recommended maximum raw photon counts limit.

Effective Sampling Size

Evaluation of relevance of a single point or multiple point measurement to assess the properties of mass of material dosed (spot size, scale of scrutiny).



Procedural Flow Diagram

Performed for **paracetamol/lactose (w/ and without MgSt)** binary blends of **5,10,15 & 20 % w/w in triplicate**.

High-Performance Liquid Chromatography (HPLC)

- MPA: 90% H_2O
- MPB: 10% Acetonitrile
- Diluent: 90/10 H_2O/Acetonitrile
- Flow Rate = 1 mL/min
- Run Time = 8 minutes
- Temperature = 30
- Injection Volume = 20 µL

Agilent Zorbax Eclipse Plus C18, 250 mm x 4.6 mm x 5 µm

Robotic Assisted Raster Scanning

Supervisory Control System

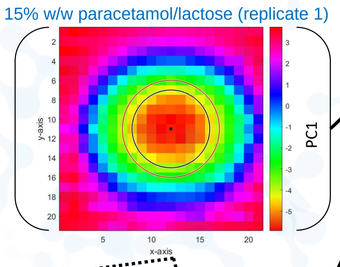
LabVIEW

PCA

microNIR

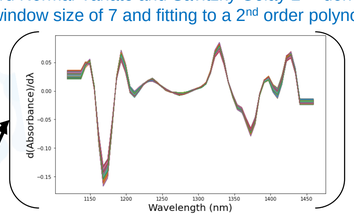
False Color Image of PC1 scores

15% w/w paracetamol/lactose (replicate 1)

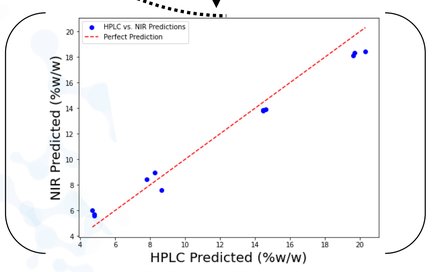


Sample NIR Pre-Processed Spectra obtained from Raster Scan

Applied Standard Normal Variate and Savitzky Golay 2nd derivative, smoothing at window size of 7 and fitting to a 2nd order polynomial

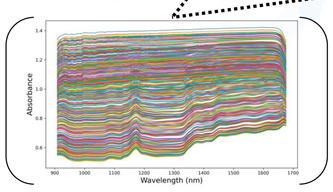


Partial Least Squares
PLS
Components = 2 or 3



PLS Regression Model

- Calibration Set = NIR spectra for blends analysed not containing MgSt
- Training set varied (see below)
- Test Set = NIR spectra for each blend containing MgSt
- Reference data from HPLC assay



Sample NIR Raw Spectra obtained from Raster Scan

Each sample was subjected to a 21x21 raster scan, resulting in 441 NIR spectra per blend/replicate.

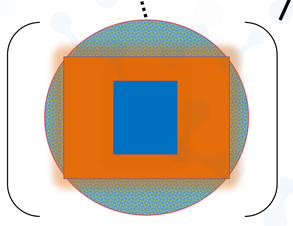


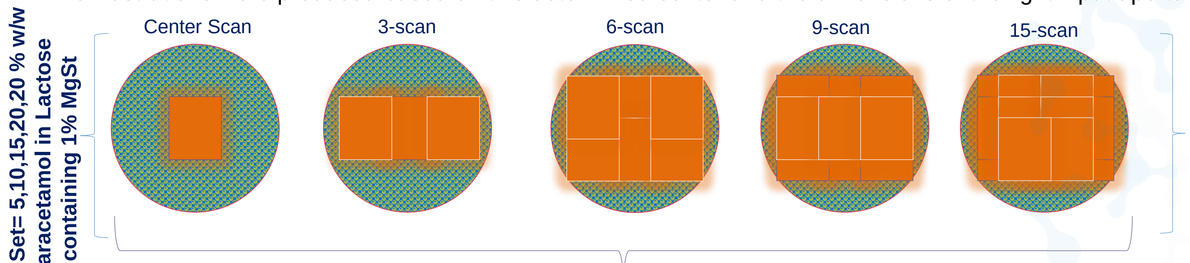
Illustration ofSample size & Scan Dimensions

Light Input Aperture Dimensions = 2.5 x 3 mm
Sapphire Glass Diameter = 8 mm
Sample Area: Multiple NIR scans (15) extracted

Effective Sampling Size

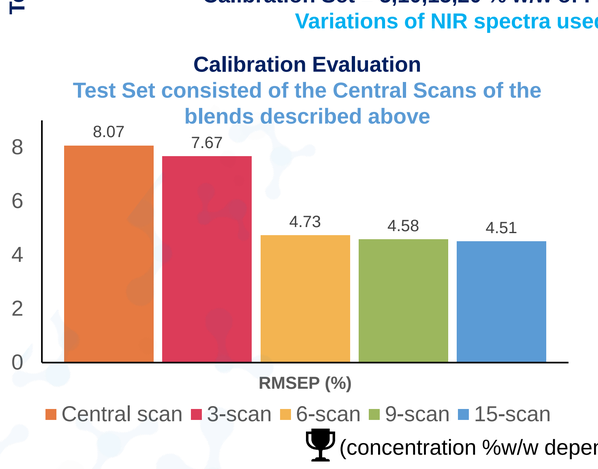
Illustration of single central point measurement and variations of multiple measurements

- The analytical center was determined through the production and evaluation of NIR false colour images for different blends.
- The lowest PC1 scores in the images represent the sample area.
- For each blend replicate, the fifteen lowest PC1 scores were extracted.
- The illustrations were produced based on this determined center and the dimensions of the light input aperture.



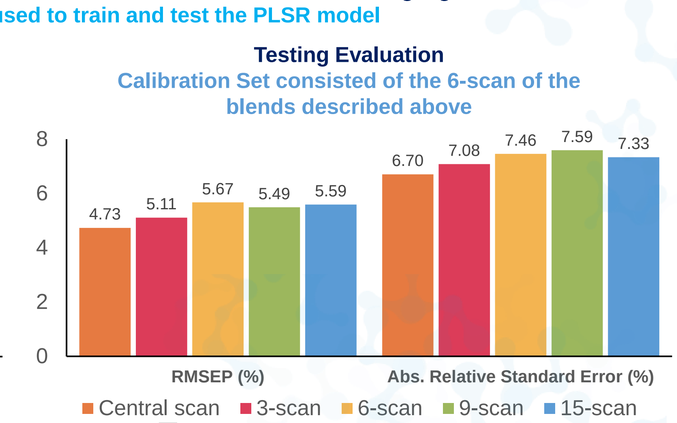
Calibration Evaluation

Test Set consisted of the Central Scans of the blends described above



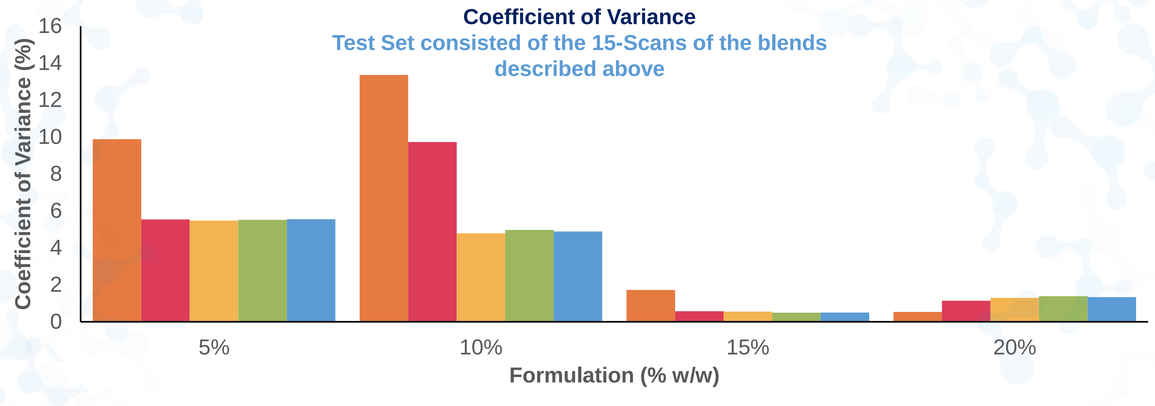
Testing Evaluation

Calibration Set consisted of the 6-scan of the blends described above



Coefficient of Variance

Test Set consisted of the 15-Scans of the blends described above

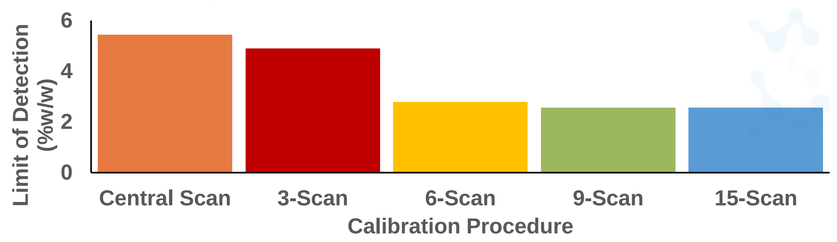


Limit of Detection (LoD)

Test Set consisted of the 15-Scans of the blends described above

$$LOD_{ICH} = \frac{3.3\sigma}{b} \quad (1)$$

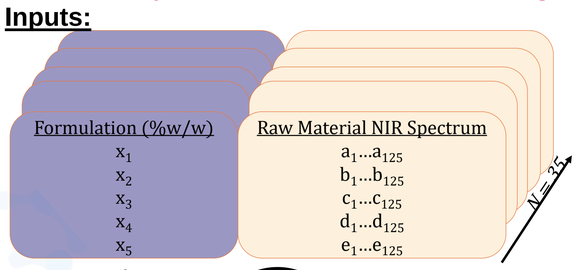
where σ is the residual standard deviation and b is the slope of the regression line for the plot of predicted (NIR) vs. true (HPLC).



NIR Spectroscopy Data Driven Model

Using machine learning regression models to predict the NIR spectrum of powder mixtures, considering the % w/w composition of each formulation and the NIR spectra of each component. Aimed for use in the production of predictive models for blend homogeneity assessment.

Inputs:

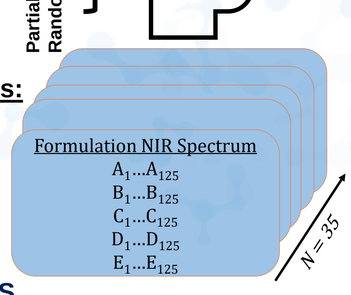


Raw Materials

sp1 (Paracetamol)
la1 (Lactose)
ma1 (Mannitol)
cc1 (Croscarmellose Sodium)
dc1 (Dicalcium Phosphate)
mc1 (Microcrystalline Cellulose)
ms1 (Magnesium Stearate)

Partial Least Squares
Random Forest

Outputs:

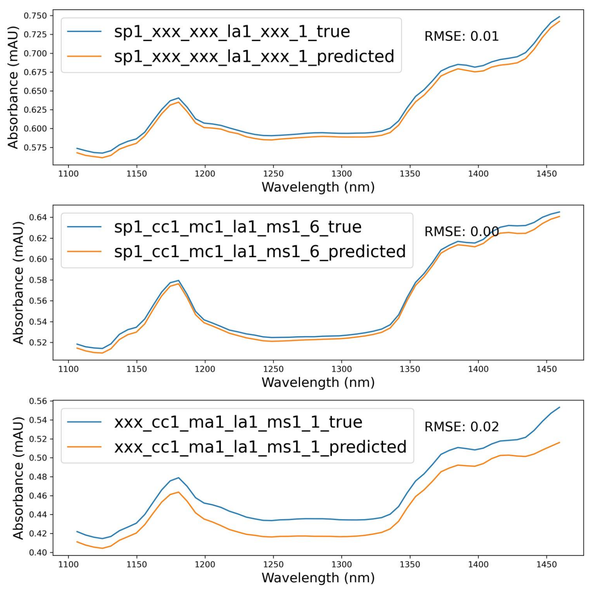


Formulations

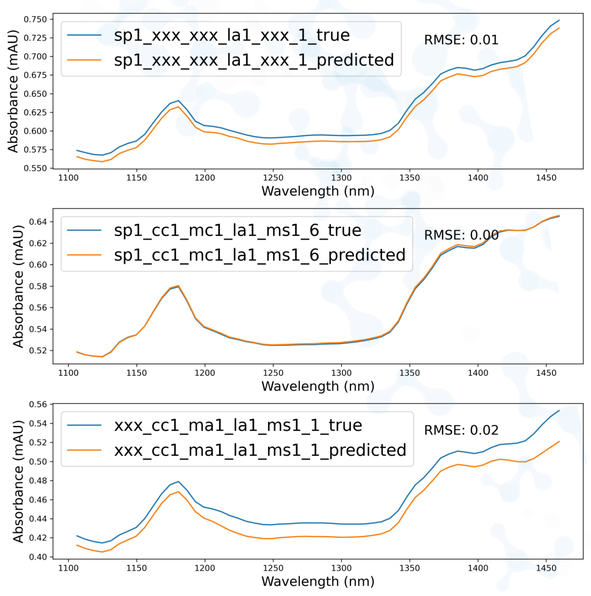
sp1_xxx_xxx_la1_xxx	sp1_cc1_mc1_ma1_ms1
sp1_xxx_xxx_la1_ms1	sp1_cc1_la1_dc1_ms1
sp1_cc1_mc1_la1_ms1	xxx_cc1_ma1_dc1_ms1
sp1_cc1_mc1_xxx_ms1	xxx_ccc1_ma1_la1_ms1
sp1_cc1_mc1_dc1_ms1	xxx_cc1_ma1_la1_ms1

Various combinations (%w/w)

e.g., PLS



e.g., Random Forest



UK Research and Innovation

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DM² website

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