Design of experiments methodology in studying critical factors influencing Near-Infrared diffuse transmission spectra of tablets

Branko Vranic
BÜCHI Labortechnik AG, Switzerland – NIR Division, Flawil 9230, Switzerland
* Corresponding author: vranic.b@buchi.com

Introduction

Current approach in NIR method development and monitoring is mainly empirical. Design of Experiments (DoE) methodology is a science-based alternative in spotting the critical factors influencing NIR calibration model performance. DoE was applied in this work for determining the critical factors influencing NIR diffuse transmission spectra of tablets and prediction accuracy of the developed quantitative models.

Materials and Methods

Direct compression tableting was done on a Presster™ – tablet press simulator (Metropolitan Computing Corporation, East Hanover, New Jersey).

The adjustments were the following:
- 10 mm flat face punch
- 200 mg tablets
- 1.8 mm punch gap (~3.5 kN)
- Simulating Korsch PH336 rotary punch with 36 stations and 10800 TBH

The following tablet formulation was used:
- Caffeine, USP, 20 – 30 % m/m
- Micro-crystalline cellulose
- Cross-linked carboxymethylcellulose sodium (Ac-Di-Sol)
- Magnesium Stearat

NIRFlex N-500 FT-NIR spectrometer (BÜCHI Labortechnik AG, Switzerland) with solids transmittance measurement cell was used for spectra acquisition.

BUCHI NIRCal 5.4 chemometric software was used for generating the PLS calibration models. Beckman DU530 UV/Vis spectrometer was used for reference analysis of the tablets. MODDE 9.0 – software was used for design of experiments.

Results and Discussion

Three most relevant tableting parameters, compression pressure, pre-compression pressure and tableting speed were studied in terms of the effect on near-infrared spectra and consequently, predictions made by the developed calibration models. The range of the studied factors was chosen based on the screening experiments. The responses studied were Standard Error of Prediction (RMSEP) of the test set which was composed of 20 tablets obtained from each experimental run designed by the software MODDE 9.0 and Average Euclidean Distance of the spectra obtained as an average distance of the 20 tablets of each experimental run, from the reference spectrum (mean of the 20 spectra obtained with the central value of the each of 3 process parameters; compression pressure, pre-compression pressure and tableting speed. Raw diffuse transmission spectra were pretreated using Standard Normal Variate (SNV) to reduce the scattering effects. The factors were studied using response surface modeling. D-optimal design, quadratic model with 17 runs was chosen to model and optimize the effect of the 3 tableting factors on 2 studied responses.

Multiple Linear Regression (MLR) was used for model fitting. Obtained model for standard error of prediction had 9 terms. Compression pressure (c.p.), tableting speed (t.s.) and squared compression pressure (c.p.2) were significant. C.p. and t.s. showed significant effect on the Average Euclidean Distance. The fitted models showed high degree of prediction performance and validity, for response standard error; R2 = 0.99, Q2 = 0.94 (model predictability), Model Validity 0.76 and Reproducibility 0.99.

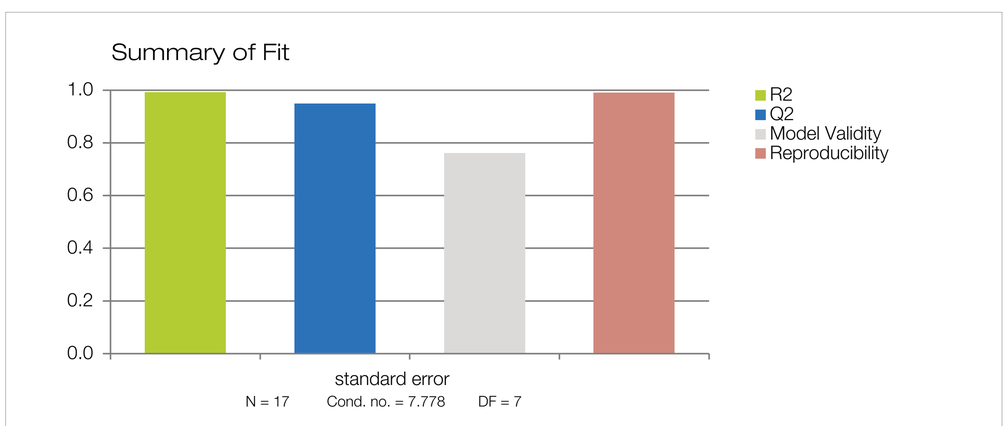

Figure 2: Summary of fit for response standard error

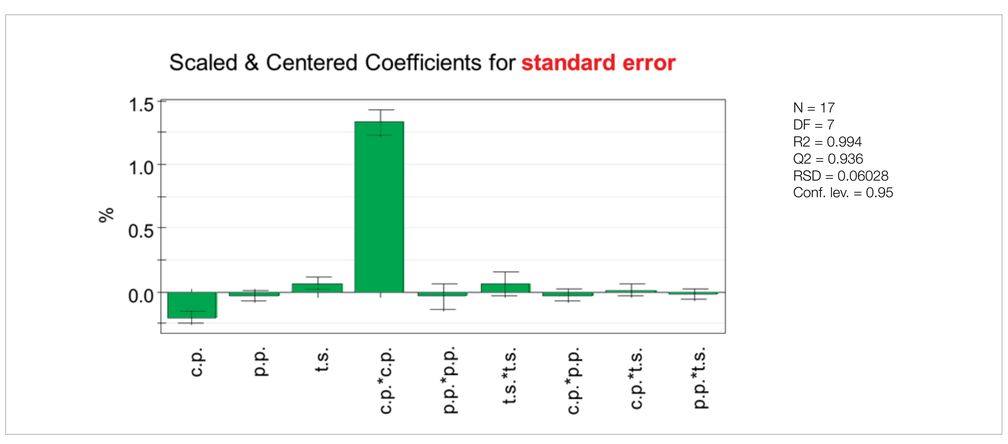

Figure 3: Scaled and centered coefficients of the model for the response standard error

Model for the response Average Euclidean Distance was characterized by R2 = 0.99, Q2 = 0.97 (model predictability), Model Validity 0.94 and Reproducibility 0.99.

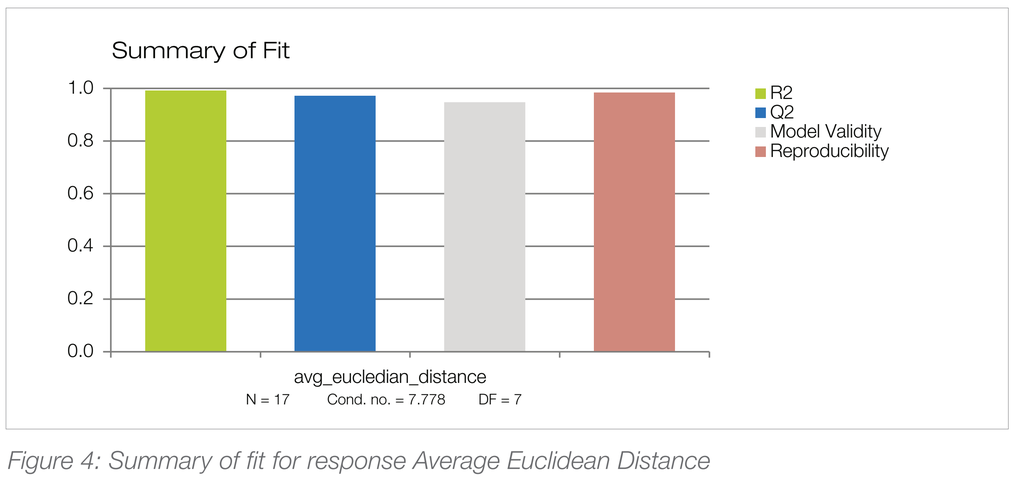

Figure 4: Summary of fit for response Average Euclidean Distance

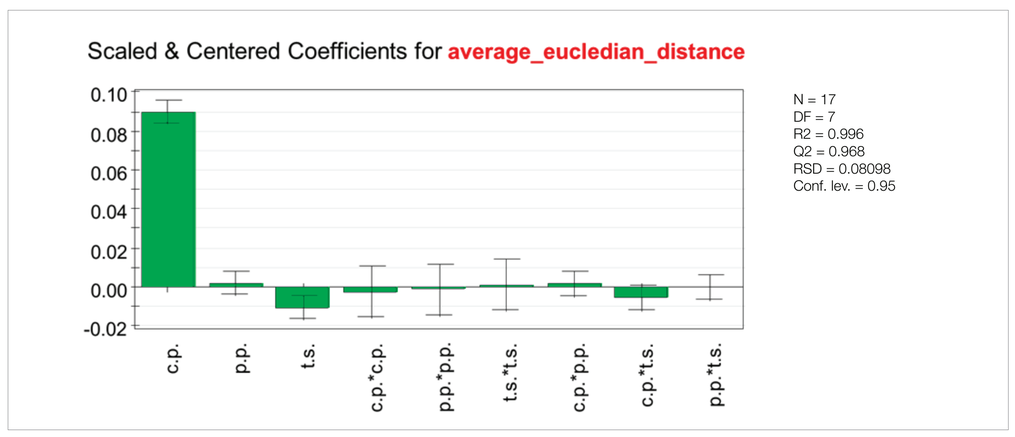

Figure 5: Scaled and centered coefficients of the model for the response Average Euclidean Distance

Conclusions

Systematic and science-based approach in studying the critical factors of the tableting process affecting NIR spectra and calibration model performance was proposed in this work. Design of Experiments was used to spot the most influencing parameters. Compression pressure, tableting speed and squared effect of compression pressure showed significant effect on standard error of prediction. Compression pressure and tableting speed showed significant effect on Average Euclidean Distance. Parameters shown to have significant effect were included in the developed global calibration model.

Figure 1: NIRFlex N-500 FT-NIR spectrometer with solids transmittance module.