

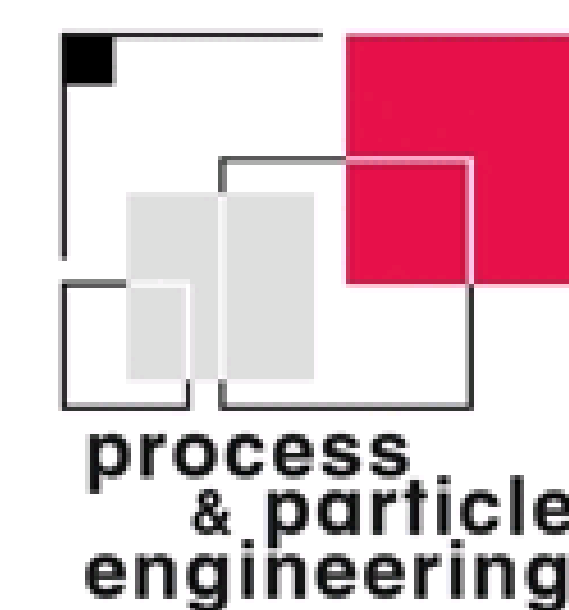
LINKING RHEOLOGICAL KEY PARAMETERS OF PHARMACEUTICAL POWDERS TO MIXING PROPERTIES

O. Scheibelhofer¹, N. Balak¹, D.M. Koller¹, S.D. Fraser¹, T. Freeman², J.G. Khinast^{1,3}

¹ Research Center Pharmaceutical Engineering GmbH, Graz, Austria

² Freeman Technology, Worcestershire, UK

³ Institute for Process and Particle Engineering (IPPE), Graz University of Technology, Graz, Austria



Introduction

Flow and blending of pharmaceutical powders is a complex process, as the behaviour significantly changes with processing history, mixer type and process scale up. Therefore, knowledge of the powder attributes and their influence on the mixing is essential.

In this work, a comprehensive characterization of powders based on Design of Experiments (DoE) was carried out with the FT4 Powder Rheometer. Pure powders and powder blends have been investigated thoroughly, in order to establish Multivariate

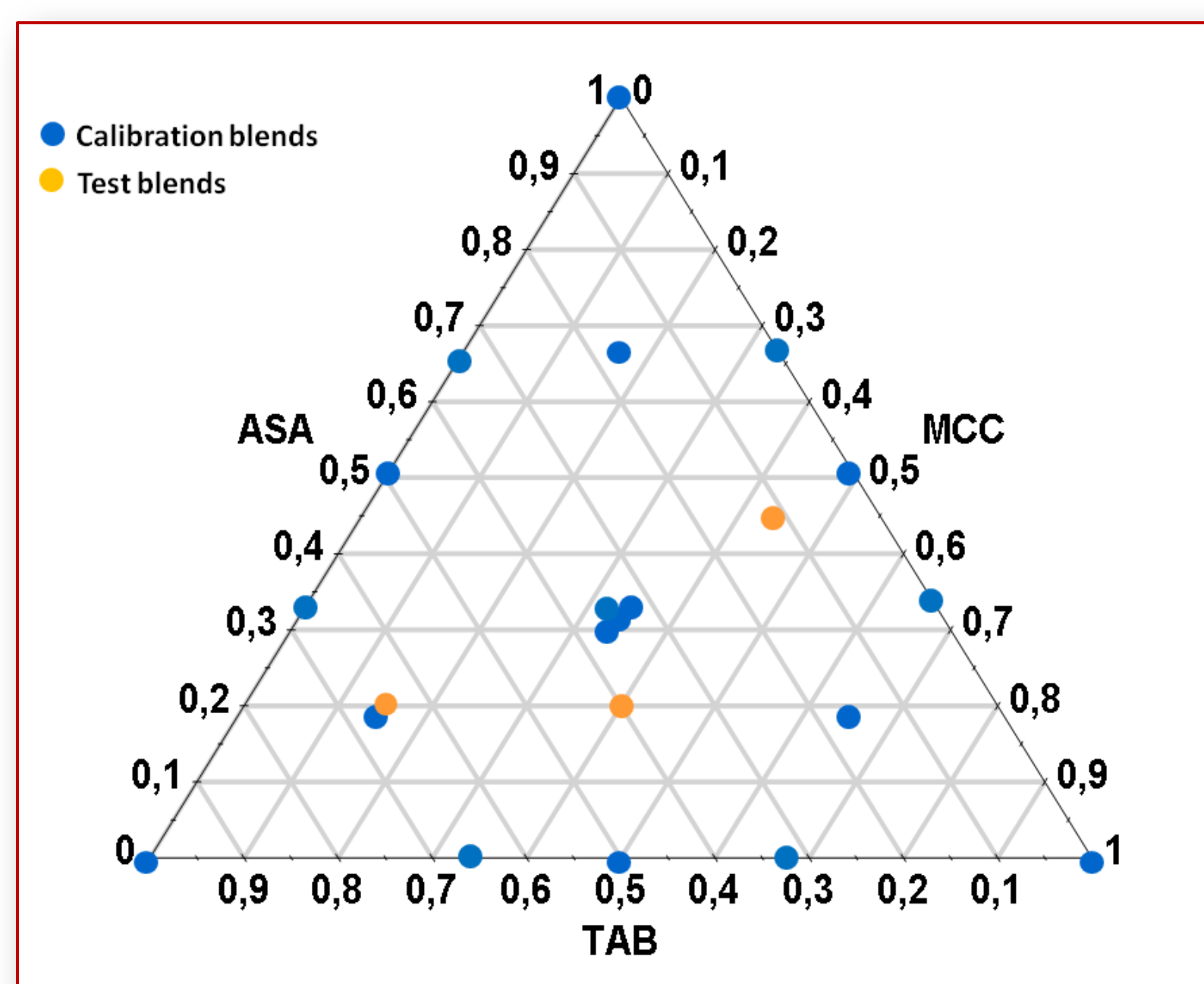
Data Analysis models for different parameters. Using the advantage of the FT4, i.e., higher reproducibility than traditional methods like shear cell tests and flow through a funnel, sound models were developed and examined.

Overview

1. Design of Experiments (DoE) to get statistical significant data and reduce the amount of necessary experiments.
2. Preparing mixtures and pure powders according to the DoE, in a Turbula® mixer.
3. Conditioning of the powder blends in the FT4.
4. Characterization of the powders in a standardized and repeatable way with the FT4.
5. Multivariate Data Analysis (MVDA) based on the DoE to explore correlations between powder fractions in the mixture and FT4 parameters.
6. Comparison of measured and predicted properties for unknown blends.

Design of Experiments

DoE applied to reduce the experimental effort based on statistically representative experiments for identifying latent correlations between powder blend properties and the measured FT4 parameters.



A simplex design was created using MODDE (Umetrics) for three powders, Acetylsalicylic acid (ASA) as the API and granulated Lactose (TAB) and Microcrystalline Cellulose (MCC) as excipients. Every point in the mixture diagram above represents a certain blend, as proposed by DoE. To get equal starting conditions for all experiments, the powders were preprocessed in a Turbula® Mixer.

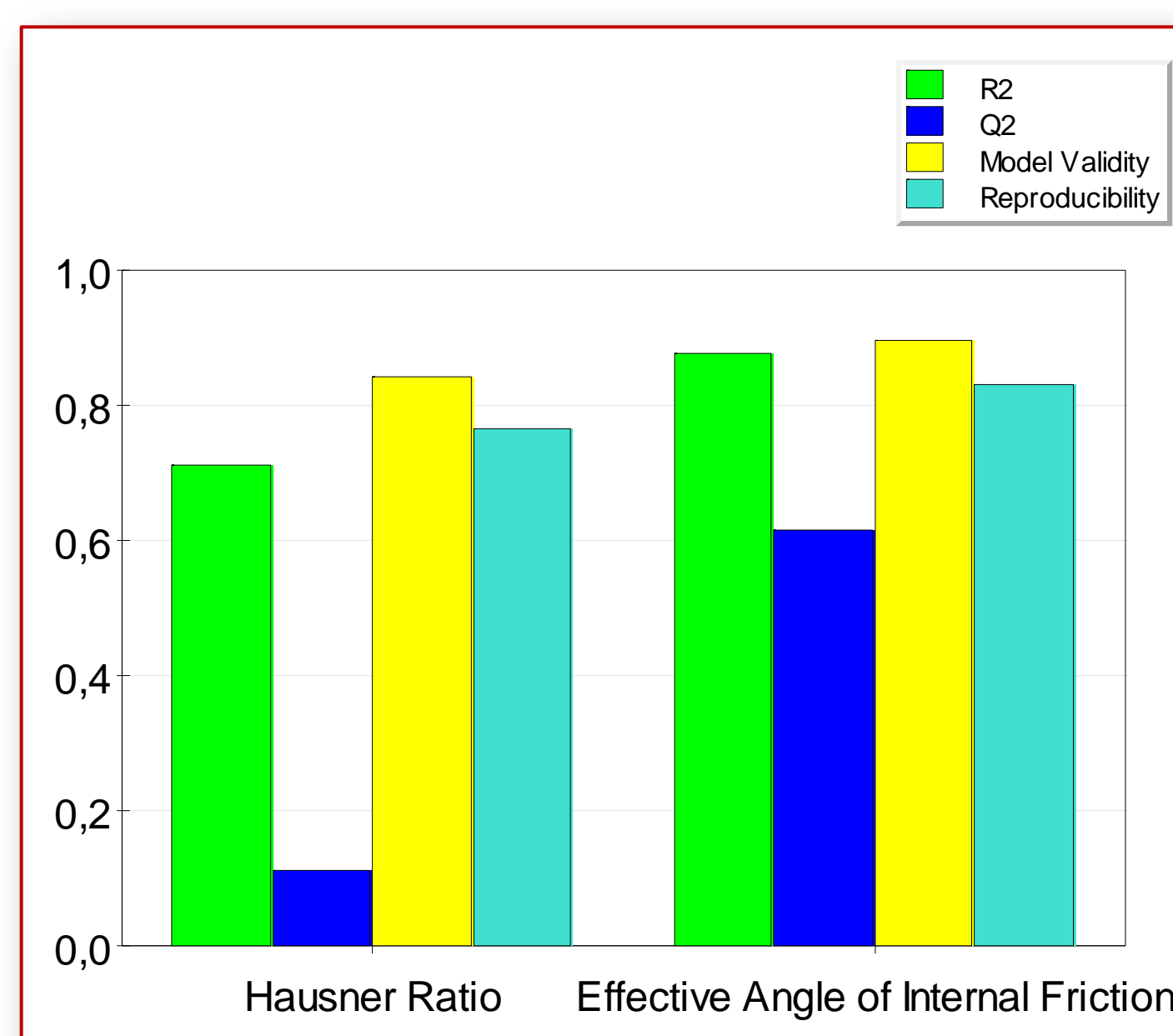
FT4 measurements

The FT4 Powder Rheometer (Freeman Technology) was applied to determine powder properties, such as shear properties, permeability, cohesion, compressibility, Hausner ratio, etc. in standardized routines.



Model Building

A partial least squares regression (PLS) model was developed for selected FT4 parameters as response for all tested powder blends of the DoE.



The obtained models can be evaluated regarding:

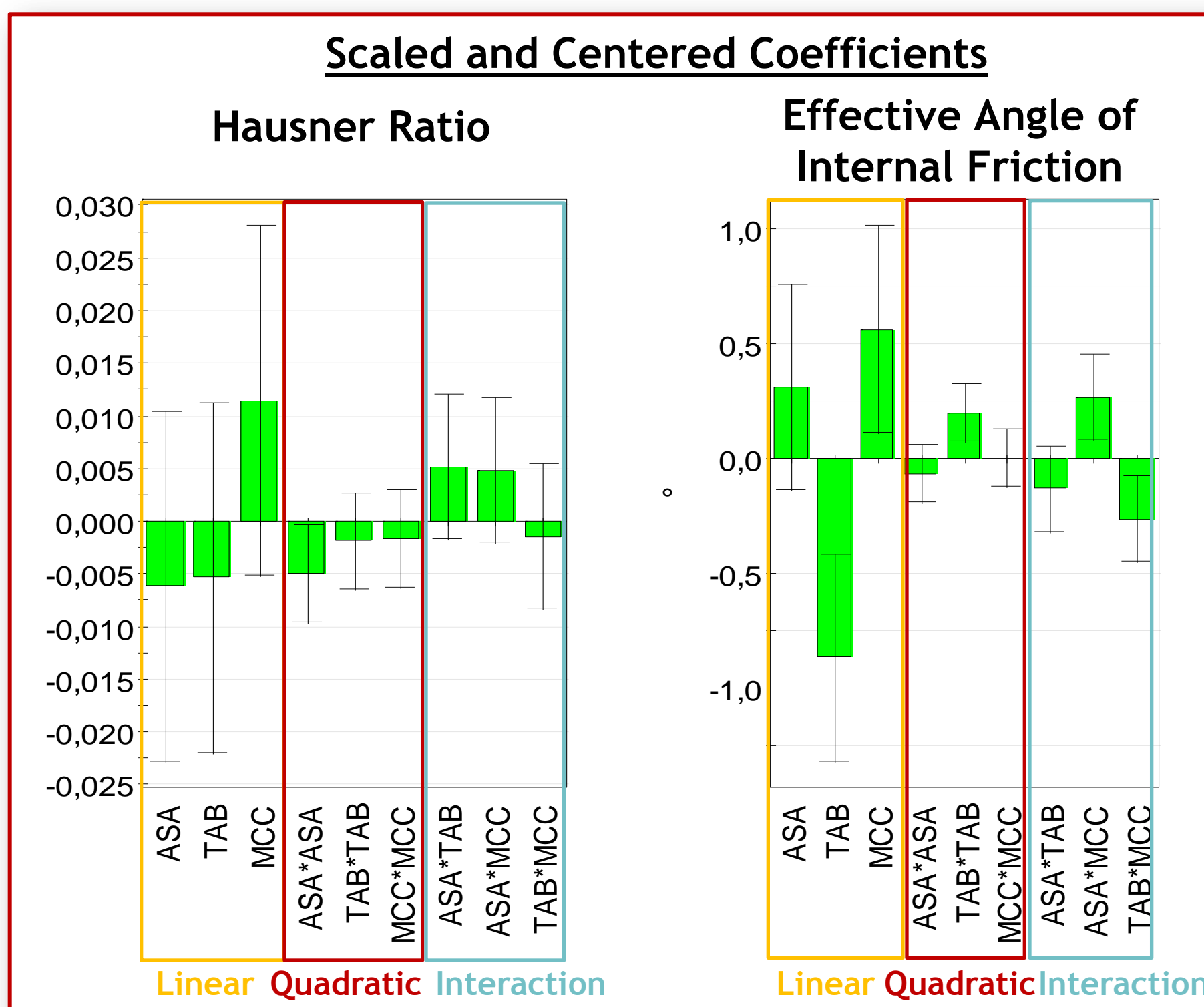
- R2: How well is the measured data explained?
- Q2: How good can new blends be predicted?
- Validity: How large is the error of the model?
- Reproducibility: How repeatable are the measurements?

Exemplarily two different FT4 parameters are shown here:

- The Hausner Ratio (HR) (with 250 tappings)
- The Effective Angle of Internal Friction (AIFE)

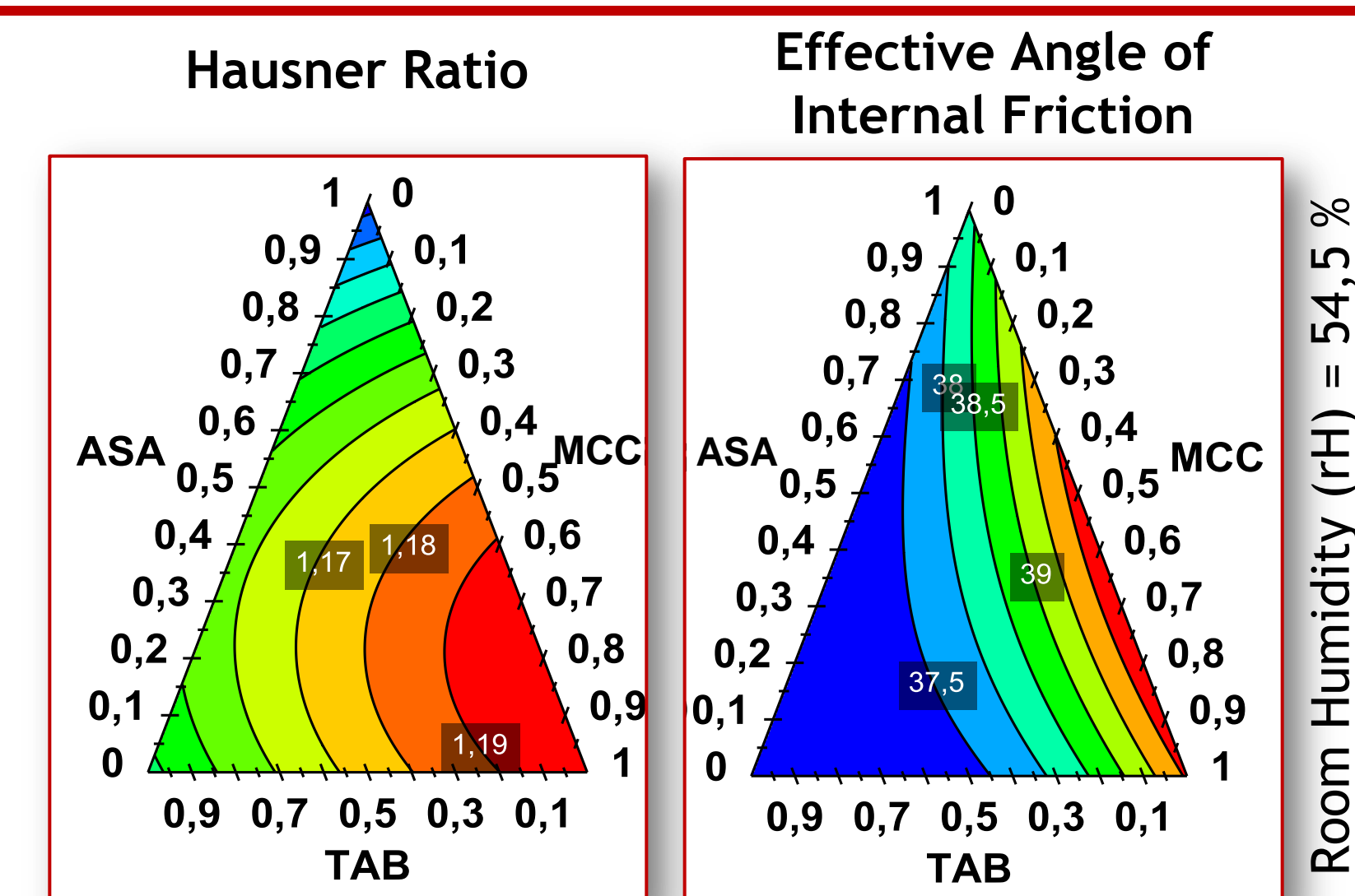
The comparison shows, that for both responses, the reproducibility and the model error are feasible. However, the Hausner Ratio has a lack of predictive ability.

PLS establishes a model by estimating regression coefficients for the influential parameters (in this case powder fractions). Therefore, linear and quadratic influences, as well as interaction terms can be assessed for their importance for a certain response. The regression coefficients, scaled and centered are displayed below.



For the Hausner Ratio (left) the fraction of MCC is important, but further terms show all equal importance. The lack of significant terms, prevents a clear statement. The model for the Effective Angle of Internal Friction (right), is dominated by linear terms and the interaction between Multicrystalline Cellulose and both other components.

Predictions



Plotting the predicted response over the whole mixture triangle results in a "Response Surface". Above, contour plots for the Hausner Ratio (HR) and Effective Angle of Internal Friction (AIFE) are shown.

The values increase from blue to red. It can be seen clearly, that for certain compositions extreme values are reached. Comparison of both FT4 responses shows, that the AIFE is much more influenced by the amount of TAB than the HR. Only for low fractions of TAB, the other powder components alter the overall behavior of AIFE.

Further optimization with additional experiments or new DoEs may be done on basis of the gained knowledge.

With an established model, responses can be predicted for yet unknown blends, which were compared to experimental measurements. The mean of three measurements for one mixture (20% ASA, 40% TAB, 40% MCC, 53% rH) is shown exemplary here:

	HR	AIFE
Lower	1,17	37,46
Expected	1,18	37,85
Upper	1,19	38,24
Measured	1,16	37,97

The upper and lower limits are given by a 95% confidence interval. The measured value for AIFE fits the model, while the value for HR is just outside the confidence interval.

Conclusion

- Powder blends have been studied to establish predictive models for their flow properties. Blend properties determined with the FT4, were modelled using DoE and MVDA.
- It has been shown, that some properties are not suitable for a model, while for others models can be developed allowing predictions for unknown blends.
- Hence, a whole formulation instead of single powders can be characterized and optimized.
- Finally these knowledge can be carried over to mixing experiments for the same blends. An example would be the Basic Flow Energy determined with the FT4, which is an indicator for the energy, which is needed for powder agitation.
- Different mixing properties like powder segregation, mixing time until blend uniformity, etc. can be monitored with Process Analytical Technology (PAT) tools as near-infrared spectroscopy and correlated with the FT4 key parameters.