Use of tolerance intervals in the development of near infrared spectroscopic methods: An innovative way to select the most appropriate calibration model

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1   Introduction

FDA's Process Analytical Technology (PAT) aims at "improving the pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, process analysis and process control" [1]. Regarding its non-invasive, non-destructive character and fast data acquisition, near infrared spectroscopy is more and more integrated in the PAT system. However, the implementation of NIR quantitative method is performed using an iterative heuristic approach that will ultimately build a model allowing the prediction of the compound of interest according to the product specifications [2].

In this context, an innovative approach based on the tolerance intervals and desirability indexes was developed to select the most appropriate predictive model from models plurality instead of using conventional criteria devoid of objective decision rules such as R^2, RMSEC, RMSECV and RMSEP [3-4].

2   Material and methods

Pilot and industrial batches of pharmaceutical pellets were manufactured by a pharmaceutical industry. Samples were analysed by reflexion mode using a multipurpose analyzer Fourier transform near infrared spectrometer (MPA, Bruker Optics, Ettlingen, Germany). As reference method, a HPLC method was used to determine the amount of active pharmaceutical ingredient (API) in the samples.

Variability sources such as production campaigns, batches and operators were introduced in the calibration and validation sets. Partial least square (PLS) regression on the calibration set was performed to build calibration models of which the ability to quantify accurately was tested with the validation set. Regarding the product specifications, the acceptance limits were set at 5% for the API determination.

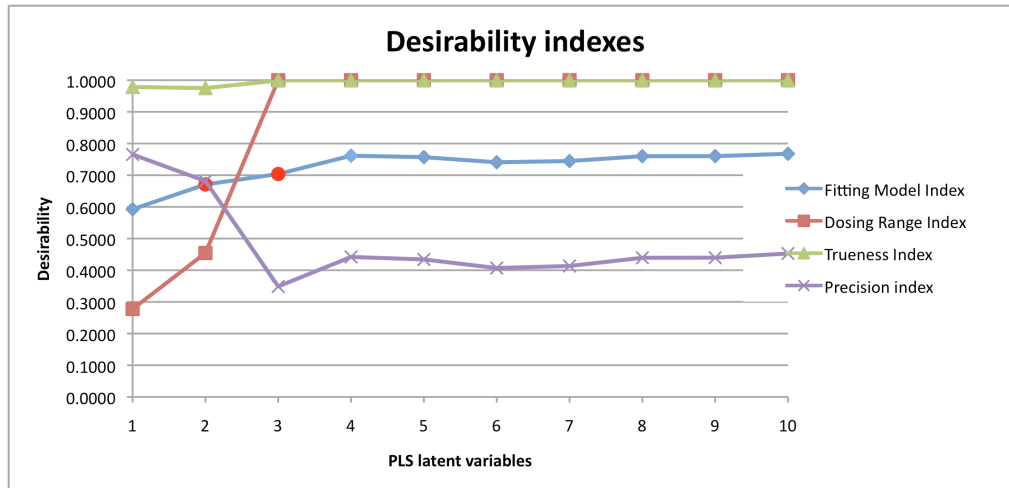# 3   Results and discussion

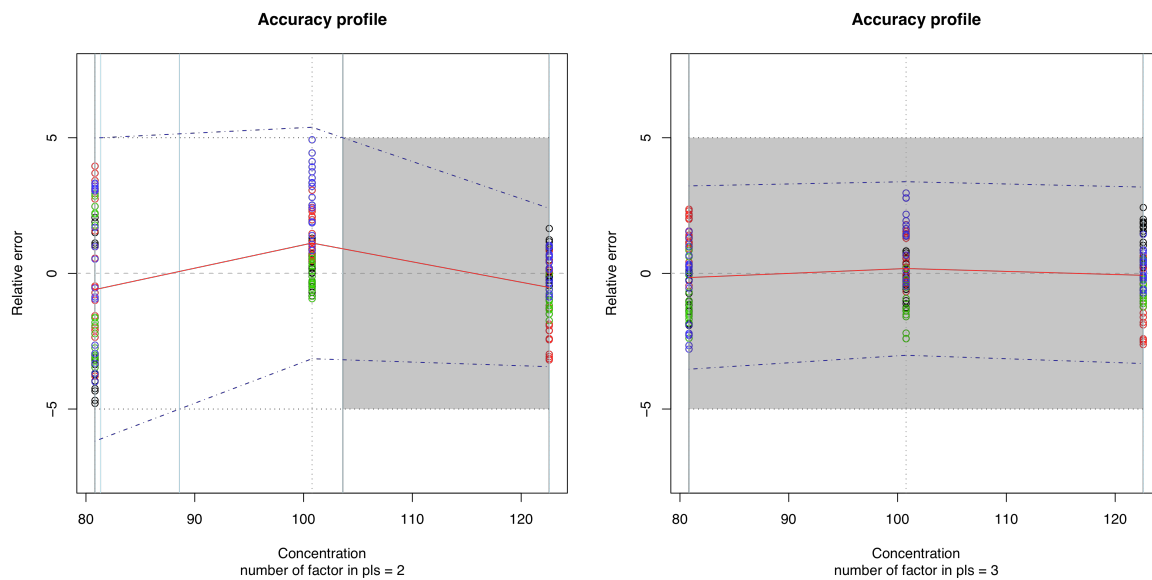Figure 1 – Desirability indexes of a calibration model according to the number of PLS latent variables.

Figure 2 – Accuracy profiles of a calibration model according to the number of PLS latent variables:

a) 2 PLS latent variables (left), b) 3 PLS latent variables (right).

As can be seen on Figure 1, the Fitting Model Index (FMI) reaches a plate after 3 PLS latent variables. Regarding the Figure 2, only predictive model using 3 PLS latent variables meets the product specifications.

4   Conclusion

The innovative approach can be applied on the development of a NIR quantitative method, which requires a time-consuming reference method and an iterative heuristic approach, to build a model allowing the prediction of the compound of interest according to the product specification.

This new approach, which increases significantly the objectivity of the decision process, allows to reduce dramatically the development and validation steps and thus could ease the implementation of NIR spectroscopy in pharmaceutical industry.

5   References

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