Abstract

Calibration model transfer, update and maintenance for on-line application – a comparison of the three existing approaches

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Introduction

In order for NIR spectroscopy to be an integral part of the QbD approach, the main challenge is robustness to new sources of variability (e.g. transfer between production lines). A strategy for calibration model transfer, update and maintenance needs to be in place prior to implementing a spectroscopic method for real-time quality measurements. This paper deals with the most common case, when neither a standardisation set nor a small experimental design is available for model transfer. The principle is to use a few in-process control (IPC) samples to update the model. The 3 existing methods are BS (Bias/Slope correction), MRD (Model Redevelopment) and Dynamic Orthogonal Projections (DOP). NIR data collected from a pharmaceutical application were used for this study. The drying process is very critical.

Materials and Methods

NIR spectroscopy was chosen to monitor the solvent level in real-time in order to determine the drying endpoint. NIR equipment used was an ABB Bomem FTPA2000 spectrometer connected to a diffuse reflectance probe (Precision Sensing Device). The data were collected from two similar production lines (L1 & L2) with different NIR instruments (I1 & I2) and two drug products (DP1 & DP2) differing in their particle size distribution (PSD). Off-line IPC samples were taken following a sampling plan in order to build NIR models. The overall data collected were the NIR spectral data and the IPC samples for off-line laboratory measurements of the residual solvent content in the drug product. A PLS model was built and optimised by leave-one-batch-out cross-validation on data from calibration batches (DP1, L1, I1). This calibration model was applied on different test sets containing sources of variability: batch difference effect (TEST1) over time and PSD difference effect combined with batch and line effects (TEST2). The prediction results were compared before and after correction with BS, MRD and DOP using the same 2 IPC samples for corrections. The performance criteria were the RMSEP, bias and R^2.

Results and Discussion

Strong biases were observed for the prediction of the test batches using the calibration model. The prediction performance was poorer when dealing with batch, line and product effects respectively. BS correction was successful in correcting most of the effects. However, BS-corrected models are no longer accurate when the effect disturbing the spectra disappears. The MRD method did not show satisfactory results for correction of strong effects when only very few IPC samples are available. On the contrary, the DOP correction showed the best results, even when the new source of variation disappeared.

Conclusion

The study showed advantages of using the DOP method over the BS and MRD methods for calibration model transfer and update during its on-line implementation and routine use, using only a few reference control points to update the model. It showed a successful transfer between production line and NIR instruments as well as an update against particle size changes and maintenance over batch effect. This method could also be used to reduce cost associated with model robustness improvement. Attention has to be paid to the selection of the samples (IPC) to beused for correction.

Reference paper as:
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