Multivariate Calibration Transfer between Near-Infrared Tablet Analyzers

Challenge

Successfully validate the calibration transfer without requiring reference values for prediction of an Active Pharmaceutical Ingredient (API) in tablets

Solution

Perform calibration transfer & develop PLS models. Results of backward and forward calibration in term provides reliable real-time predictions

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A calibration transfer method is evaluated by transferring multivariate models between two equivalent near-infrared (NIR) analyzers for the prediction of an Active Pharmaceutical Ingredient (API) in tablets. The method includes selecting a few representative samples, building a transformation relation, and standardizing spectra. *Backward* and *forward* transfer approaches are compared. A practical approach is proposed to maintain multivariate models and to validate successfully the calibration transfer without requiring reference values.

"Direct Standardization is an effective approach for calibration transfer of multivariate models for the tablet API prediction."

Introduction

The ability to use a calibration developed on one instrument on another instrument is referred to as calibration transfer. Since the setup of a calibration model from scratch requires considerable costs and time, mainly from reference analysis, a calibration transfer method which preserves the existing calibration model will give substantial savings. The approach presented here consists in Adjusting Spectra from one analyzer to the other. A reference analysis is not required, and outlier diagnostics are kept. Few selected samples scanned on both instruments side by side are used for estimating an additive absorbance correction b vector, and a transfer matrix **F**, to handle wavelength and multiplicative absorbance shifts. Then a spectrum **x** of one instrument is adjusted to $\mathbf{x}^a$ by Eq.1, and $\mathbf{x}^a$ is used with or within the calibration model on the other instrument:

$$x^a = b + x\,F$$

There are two directions for spectral adjustments as shown in Fig. 1

1) *Backward* where the slave instrument's spectra are adjusted to be like spectra on the master instrument

2) *Forward* where the calibration spectra from a master instrument are transformed to look like the spectra on a slave instrument. The latter is preferred when the two instruments are of different types, or when real-time prediction is required.

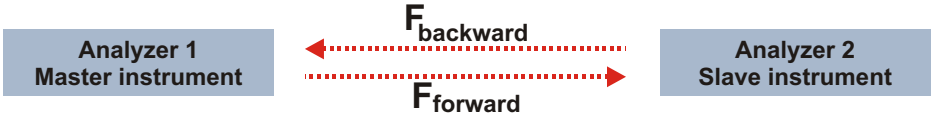

Figure 1. Scheme of backward and forward methods of calibration transfer. A calibration is developed on a master instrument (Analyzer 1), while predictions will occur on spectra from a slave instrument (Analyzer 2). Fbackward and Fforward are the transfer matrices for each direction respectively.

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Materials and Methods

Public source data from the IDRC Shootout 2002 were deployed for this study. Pharmaceutical tablets data from two Multitab spectrometers (Foss NIRSystems) have been split into two calibration sets (155 tablets, CALIBRA1 and CALIBRA2) and two validation sets (460 tablets, TEST1 and TEST2). API references were measured by HPLC with a nominal value of 200 mg per tablet. Calibration transfer was performed within the spectral region 1100-1700 nm using the Accessory Pack for Spectroscopy (CAMO Software AS, Oslo, Norway). The Unscrambler® 9.7 (CAMO Software AS) was used to develop PLS regression models, apply predictions and validate results.

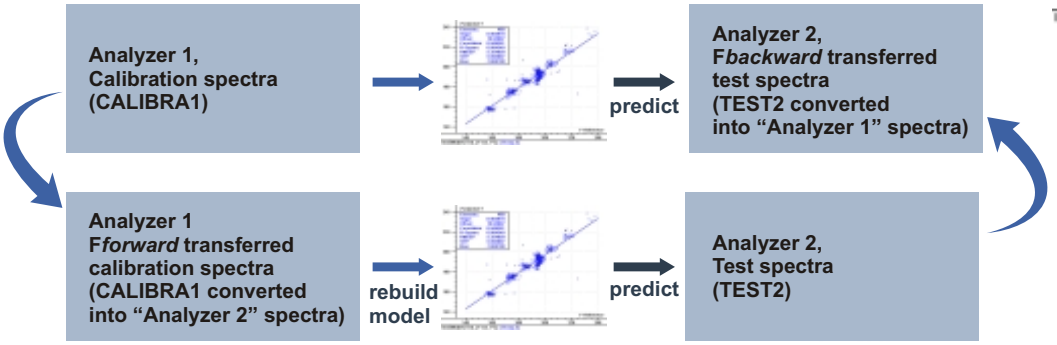

Figure 2. Top: Backward calibration transfer: TEST2 data from Analyzer 2 are adjusted so that they can be predicted with the model built on the CALIBRA1 data from Analyzer 1. Bottom: Forward calibration transfer: CALIBRA1 data from Analyzer 1 are first transformed so that their calibration model can predict the TEST2 data from Analyzer 2 directly.

Results and discussion

A PLS1 model was built on calibration set CALIBRA1 from Analyzer 1. This model was then applied for prediction on both test sets TEST1 (from Analyzer 1) and TEST2 (from Analyzer 2). Fig. 3 shows the histogram plots of y-Deviations from these respective predictions. The much larger y-Deviations observed for TEST2 (Fig.3 B) compared to TEST1 (Fig.3 A) suggest that the model is not directly suited to predict data from Analyzer 2: in order to obtain comparable accuracies for data from different instruments, the model needs to be transferred.

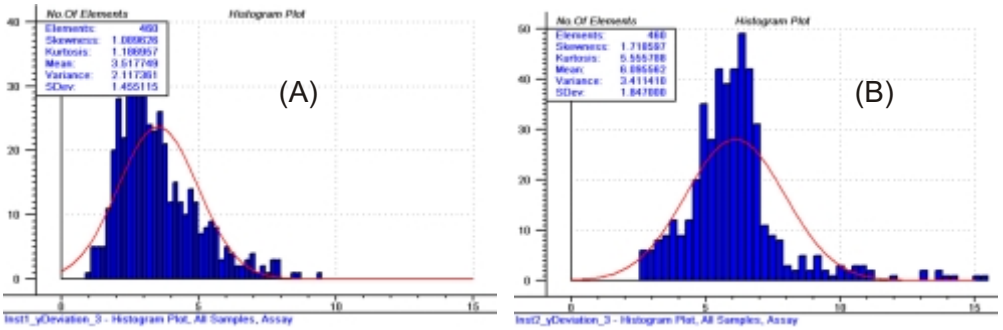

Figure 3. *Histogram plots of y-Deviations of (A) TEST1 (center ~ 3.5) and (B) TEST2 (center ~ 6.1).*

For the *Backward* calibration transfer, 10 samples were selected by applying the Accessory Pack for Spectroscopy's (APS) *StdSelect* functionality to CALIBRA1. Then the APS's *StdGenerate* functionality was used to calculate a transformation matrix between analyzers 1 and 2 for the 10 pairs of spectra (CALIBRA1 and CALIBRA2 spectra). TEST2 spectra were then standardized with this transformation matrix using the APS's *StdApply* functionality, and the PLS1 model above was used to predict the transformed TEST2 data.

For the *Forward* calibration transfer, the same 10 selected samples were used but switching the roles of Analyzer1 and Analyzer2 for the transformation matrix estimation: this time the transform matrix will convert instrument 1 spectra into instrument 2 spectra. Thereupon CALIBRA1 was standardized by the new transformation matrix. A new PLS1 model was built by using exactly the same settings as in the previous model, and TEST2 data were predicted (see Fig.4).

Table 1 compares modeling and validation results for the prediction of TEST2 data in the three cases: with *backward*, *forward* or without calibration transfer. The results show that with an appropriate calibration transfer, it is fully possible to predict Analyzer 2 spectra with a calibration model built on Analyzer 1 data.

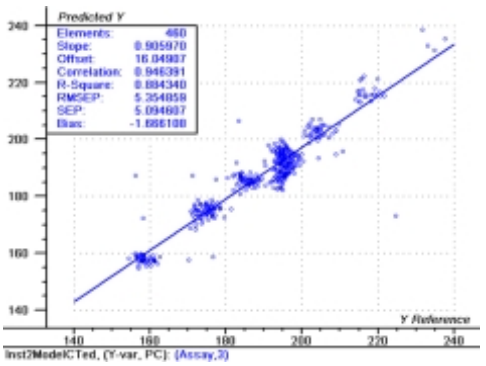

Figure 4. *Predicted vs. Reference API in the Forward calibration transfer*

	R-Square	RMSEP	Comments
No transfer	0.548	10.584	Low modeling power; high estimated error in prediction.
Backward	0.867	5.740	High modeling power; estimated error in prediction reduced by almost 50%
Forward	0.884	5.355	

Table 1. Prediction results comparison for backward, forward, and no calibration transfer

Conclusions

Direct Standardization is an effective approach for calibration transfer of multivariate models for the tablet API prediction. After a successful calibration transfer, the data from the slave NIR analyzer can be predicted with a model built from the master analyzer. Results of *Backward* and *Forward* calibration transfers were comparable, and the *Forward* approach can provide convenient and reliable ways for real-time prediction. Guidance from regulation authorities for success criteria of a calibration transfer is expected in the near future.

Application note overview

Methods	PLS regression, Calibration transfer (Direct Standardization)
Data type	NIR transmission spectra of pharmaceutical tablets
Industry	Pharmaceutical, Spectroscopy
Added Value	Transfer of calibration models without additional reference analysis, leading to costs and time savings, yet maintaining accuracy level and outlier diagnostics.
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