Method transfer of solid dosage forms

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The use of near-infrared (NIR) spectroscopy in the pharmaceutical industry has been rapidly increasing over the past decade, with the success of applications such as moisture content of lyophilized materials, blending uniformity studies and active ingredient quantitation.

Traditionally, these types of analyses were accomplished with Karl Fischer titration or high performance liquid chromatography (HPLC) which are relatively slow and laborious. These techniques also waste raw materials and require the skills of a chemist. NIR has the ability to sample through containers rapidly and non-destructively while maintaining a high degree of accuracy and precision making it an excellent tool for quality analysis and quality control processes. The analysis of solid dosage forms, such as tablets or capsules, is of particular interest due to their widespread use and need for rapid, non-destructive analysis with strict QA/QC standards. The development of NIR applications for tablets has met with a good deal of success, however the technology to implement these applications has yet to be extensively developed.

As tablet applications gain wider acceptance, an important performance requirement will be the ability to transfer calibration methods from one spectrometer to another. The ability to transfer quantitative and qualitative analysis methods without re-running calibration standards is of paramount importance in NIR spectroscopy, with the impact of initiatives like Process Analytical Technology (PAT). Analytical techniques developed in a laboratory would undergo rapid migration to the process room floor, saving the time and expense of implementing new process protocols. NIR analytical methods, typically developed in research or QC labs, can, under favourable circumstances, be readily migrated out to multiple production sites. If the methods do not transfer, i.e. give the same predicted numbers from one spectrometer to another, time-consuming re-collection of standards may be required for each instrument where the method is implemented. Working methods may contain hundreds or even thousands of NIR standards, making re-scanning of all standards in a method so time consuming that it quickly becomes prohibitive. For this reason, method transfer has been an active area of research for many years.

To succeed with method transfer there are many factors to consider. The hardware configuration of a spectrometer has a significant impact on the success of a method transfer. Optical components must be manufactured reproducibly and aligned to tight tolerances. Component matching and production controls are also essential in maintaining instrument sameness. An internal laser for frequency calibration can provide stability along the x-axis to ensure that spectral data does not shift. Other factors that influence the transfer of methods, whether model-to-model or cross-platform, are data spacing changes between wavelength domain and frequency domain, y-axis stability, software and quantitative analysis packages.

Numerous methods effecting NIR calibration transfer have been described. These methods involve either application of algorithms to 'match' instrumentation (spectral correction) or difference compensation between the primary and target instruments (method correction). Ideally, NIR users could take methods developed on a primary instrument and transfer them directly to a target instrument without the need for secondary algorithms to correct for optical path differences in instrumentation. Such a convenience would avoid both diagnosing and solving instrument mismatch problems, as well as save the effort of recollecting standards. Additional complications arising from poor transfer exist for highly regulated industries such as the pharmaceutical industry, where compliance with regulations and guidelines requiring method validation (USP, EP, CFR 21 Chapter 11 etc.) is of paramount importance.

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In the current study, we use clinical tablets and released tablet products to demonstrate the potential for method transfer from a primary FT-NIR instrument to a target FT-NIR instrument. Large and small tablets with varying amounts of active ingredient were analysed for active ingredient content in milligrams. Differing tablet sizes were used to show overall applicability of a method transfer as well as to compare the performance of transmission and reflection.

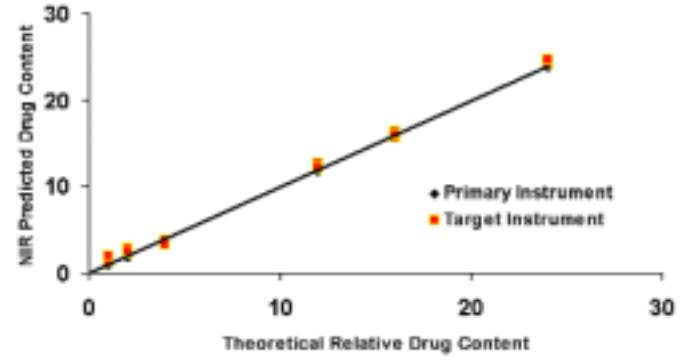

Figure 1 – Calibration curve for transmission analysis of smaller tablets

Experimental

Diffuse reflectance and transmission spectra were acquired on a Nicolet™ Antaris™ FT-NIR Method Development Sampling System from Thermo Electron Corporation. Tablets were analysed in transmission using the Tablet Analyzer module. The data were collected non-destructively in transmission and reflectance modes for both types of tablets. All reflection measurements were made with the scored side of the tablet facing up. The tablets were analysed using the same set of collection parameters for both the primary and target instruments. Reflection spectra were acquired using the Integrating Sphere module. Sampling parameters were 50 scans per tablet at 8cm^{-1} resolution from 4000 to 10000cm^{-1} in reflection mode. Transmission parameters were 100 scans per tablet at 8cm^{-1} resolution from 6000 to 12000cm^{-1}. Two sets of tablets were used as models for this investigation. One set consisted of small, thin, round tablets with less than 10% of weight due to the active component. The smaller tablets were measured using transmission mode. A second set consisted of larger, thicker oval tablets with greater than 40% of weight due to active component. The larger tablets were measured using reflectance mode.

The quantitative analysis methods were developed using Thermo Electron's TQ Analyst Quantitative Analysis software (Version 6.2). The method used for the larger tablets was Partial Least Squares (PLS) analysis with 3 factors. Data pretreatment included a second derivative and a Norris smoothing function using an 11 point segment with no gap. The analysis range used for the method was 4181-9169cm^{-1}. The smaller tablet method was also a PLS analysis with 4 factors using a second-derivative pretreatment and a Norris 25 point segment also with no gap. The analysis range for the transmission method was 8924-11209cm^{-1}. All tablet pathlengths were assumed to be constant. In the transmission method, a mean-centering correction was added to the pretreatments.

Results and discussion

For the smaller set of tablets, transmission provided better results based on comparison of the method errors. This is typical for smaller, more transmissive tablets with lower percentages of active ingredient. The calibration plot for the small tablet model is shown in Figure 1 and the error residual for the calibration plot is shown in Figure 1a. The correlation coefficient was .9996 while the Root Mean Squared Error of Calibration (RMSEC) was .247 mg/tab. The method was transferred to the target instrument where the primary prediction model was applied to spectra taken from the same set of tablets using the target instrument. Predictions from the target instrument are shown against the calibration curve from the primary instrument in Figures 1 and 1a. The Root Mean Squared Error of Prediction (RMSEP) for tablets run on the target instruments was 0.486 mg/tab. The residual shows a

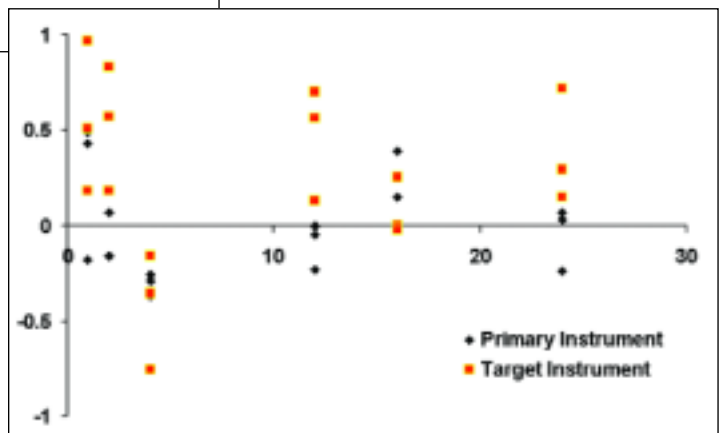

Figure 1a – Residual plot for transmission analysis of smaller tablets

homogeneous distribution of error in predicted value for the target spectra as well as for the primary calibration. No bias was found upon analysis of the data on the second instrument. In addition, the curve fit and error residual for prediction on the target instrument are comparable to the primary instrument for all levels of active ingredient found in the tablets.

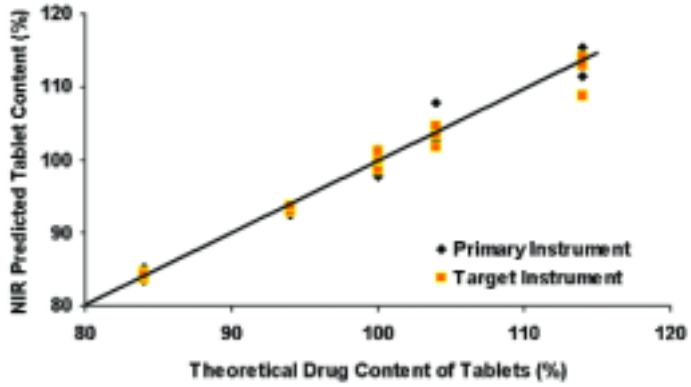

Figure 2 – Calibration results for tablet reflectance on the large set of tablets

For the set of larger tablets, reflectance proved a better technique. This is often the case for less transmissive tablets with a high percentage of active ingredient. The results are shown in Figure 2 with the residual in Figure 2a. The correlation coefficient in this case was 0.9864 and the RMSEC was 1.65%.

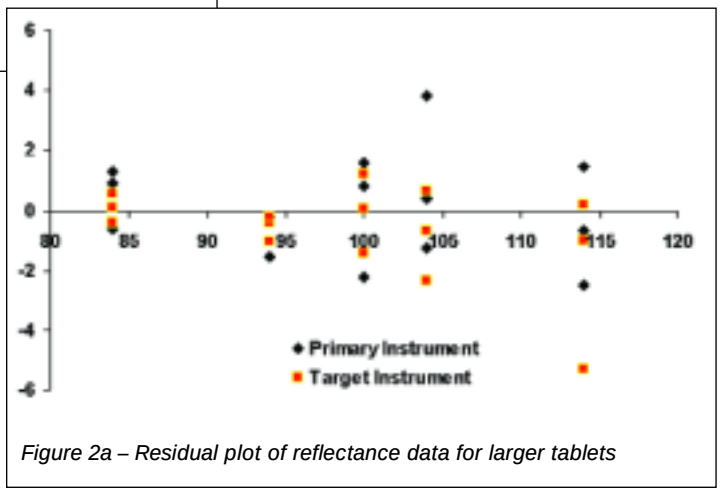

Figure 2a – Residual plot of reflectance data for larger tablets

The model was again transferred to the target instrument and the larger tablets analysed. The RMSEP for spectra from the target instrument was 1.64%. All of the data reported for these tablets were collected on the unscored side. The side-to-side bias for the reflectance measurements was found to be 3.5%. This is an important caveat when employing reflectance measurements for tablet samples.

Table 1 shows the data comparing the analysis of the exact same tablets on the primary and target instruments. Examination of this table shows the similarity of the data obtained from the two instruments.

Conclusion

Quantitative methods for two sets of physically different tablets with varying amounts of active ingredient were developed on an FT-NIR analyzer. These methods were then transferred to a target FT-NIR instrument where the same samples were run and quantified against the primary method. It was found that for both methods, transmission for small tablets and reflection for large tablets, the predictive capacity of the method was not significantly degraded when the method was transferred to the target FT-NIR instrument. A significant side-to-side tablet variation was also found (3.5%) for reflection measurements demonstrating the necessity of good sampling practices. ■

Table 1 – Performance of primary and target instruments on larger tablets

Drug Content (% Label Claim)	Primary Instrument	Target Instrument	% Difference from Primary
84	85.7	85.4	–0.35
94	93.2	93.6	0.43
100	100.1	99.8	–0.30
104	104.7	102.8	–1.81
114	112.5	111.0	–1.33

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