NIR Modeling for Potency of a NTI Drug Product

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NIR Modeling PAT Project - Objectives

- Assess feasibility of NIR as alternate content uniformity method in tablets (9 potencies)
- Eliminate the need to analyze each drum of tablets via HPLC
- Replace HPLC assay method with NIR method
- Realization of an at-line real time PAT technique
A Bruker Optics FT-NIR MPA (Multi Purpose Analyzer) was evaluated for determination of API content in tablets of a NTI drug product.

Two Bruker units were purchased (one for lab modeling; one for the manufacturing lab).

An experimental plan was devised to develop NIR calibration model.

NIR spectra of 1,300 tablets (1 mg to 10 mg potencies) were collected.
Experimental - Samples
- 9 different potencies of API - namely 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg
- 4 different expired finished stock lots of each potency
- Tablets at target thickness but varying hardness
- Tablets at target hardness but varying thickness
- Placebo tablets
- Tablets containing ± 15% of theoretical values for 1, 6, and 10 mg potencies
- 2 rejected lots (32 drums each)
- Tablets representing current formula/new formula
- Tablets made using current process/new process

NIR Modeling PAT Project – Materials and Methods

Experimental – NIR Analysis
- Between 10 (for lots containing ≤ 100 tablets) and 30 (for lots containing > 100 tablets) tablets were scanned using the Bruker FT-NIR analyzer
- The 30 position auto-sampling wheel was used
- Each tablet was scanned in duplicate in transmission mode
- Scanning range between 8350 and 12500 cm⁻¹
- Thickness of each tablet was measured before scanning with NIR

Experimental – HPLC
- Scanned tablets sent to manufacturing lab for content uniformity analysis of API content
- HPLC analysis performed on individual tablets
NIR Modeling PAT Project – Materials and Methods

- Experimental – Data Analysis *
  - Partial Least Squares (PLS) modeling using Bruker dedicated “OPUS” chemometrics software
  - Mean centering and vector normalization
  - Spectral range between 8632 and 8864 cm\(^{-1}\)
  - Cross validation
  - 160 samples in calibration set and 70 in validation set

* All results reported are for 230 samples for which HPLC data is available

NIR Modeling PAT Project – Results

Reflectance Spectra of API and Excipients

Expanded boxed area from graph on left

Absorbance Units

Wavenumber cm\(^{-1}\)
Reflectance Spectra of API and Drug Product Blends (1, 5 and 10 mg)

Enlarged boxed area from graph on the left

API
10 mg blend
5 mg blend
1 mg blend

Wavenumber cm$^{-1}$

Absorbance Units

NIR Modeling PAT Project – Results

Vector normalized Transmission spectra
Drug product potencies: 1, 2, 3, 4, 5, 7.5 and 10 mg

Absorbance Units

Wavenumber cm$^{-1}$
NIR Modeling PAT Project – Results

**Enlarged boxed area from previous slide**

- Transmission spectra of tablets
- Absorbance Units
- Wavenumber cm⁻¹
- Measured API Content (mg)
- NIR Predicted API content (mg)

**Results**

- RMSECV = 0.118
- \( R^2 = 99.81 \)
- No. of Factors = 5
- Cross Validation
NIR Modeling PAT Project – Results

- RMSEP = 0.091
- $R^2 = 99.89$
- No. of Factors = 2
- Test set Validation

NIR Modeling PAT Project – Next Steps

- HPLC analysis of NIR scanned tablets ongoing in manufacturing lab.
- Calibration model being expanded as HPLC data becomes available
- Headquarters and manufacturing site functions preparing for tech transfer activities
- Plan being developed for real time NIR monitoring of tablets at manufacturing site