Quantitative Analysis of APIs in Blending Mixtures and Tablets

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Introduction

Pharmaceutical tablets consist of an Active Pharmaceutical Ingredient (API) with excipients including fillers, binders, and lubricants. In tablet manufacturing, blending is the process where APIs and various excipients are blended together to form a homogenous mixture. The blending process control is very important for final tablet quality, and yet blending process control can still be very challenging when it comes to detection or characterization of raw material variations and final blend homogeneity. The USFDA guidance on pharmaceutical manufacturing process control indicates that each batch incorporated into a blend should meet established purity specifications when involving APIs; also, blending validation should show homogeneity of the blended batch for dry blended APIs.

Experiment

In this study, Raman spectroscopy, along with chemometrics, was used to establish the analytical method to quantify the API Naltrexone HCl in blended powder mixtures as well as in the final product 3mg tablets.

Table 1. Samples

Sample	Naltrexone HCl (mg/tablet)	
1	100% Naltrexone HCl powder	feasibility evaluation
2	2.70 (mg/tablet) powder	chemometric model
3	2.85 (mg/tablet) powder	
4	3.00 (mg/tablet) powder	
5	3.06 (mg/tablet) powder	
6	3.14 (mg/tablet) powder	
7	3mgT1	prediction
8	3mgT2	

An i-Raman Plus® with a 785nm laser excitation and fiber optic probe were used. A probe holder was used to provide stability for sampling and data collection, which is very important in the accuracy of the chemometric model.

Spectra were collected at three different locations from each sample through plastic bags. All measurements were taken at 100% laser power (~300mW) with a 6s integration time.

The software BWIQ was used for chemometric analysis.

Chemometric Analysis

Figure 1 compares the Raman spectra for samples with different concentrations of the API to 100%. The distinctive Raman peaks belonging to Naltrexone HCl are apparent in the Raman spectra of the samples used to build the chemometric model.

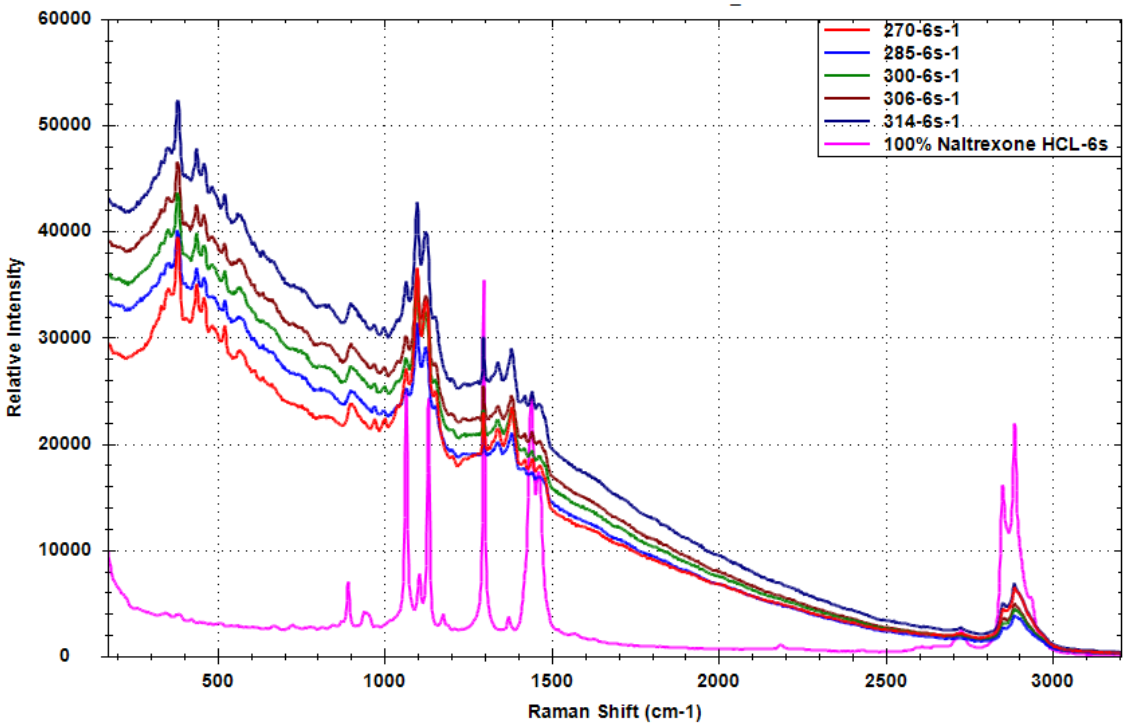

Figure 1. Raman spectra of samples with different Naltrexone HCl concentration compared to pure Naltrexone HCl

By collecting multiple spectra from different locations on a sample, the API uniformity within the blending mixtures is taken into account, and a more complete representation of the mixtures is built into the chemometric model.

In order to remove fluorescence variability, the data was baseline–corrected using an adaptive iteratively reweighted Penalized Least Squares (airPLS) algorithm provided in BWIQ.

Figure 2 illustrates the background removal for one spectrum.

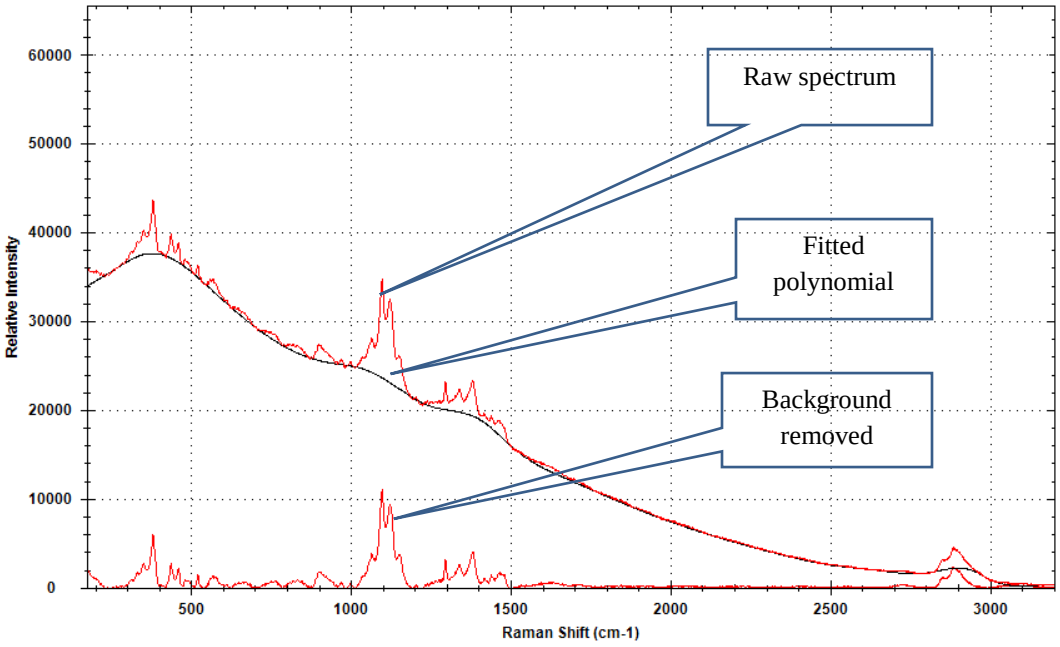

Figure 2. Raman Spectral background removal using airPLS

With the concentration of Naltrexone HCl (mg/tablet) set as the response, the Partial Least Squares (PLS) regression was used for building the model. Since the Raman bands for Naltrexone HCl are within the range of 800 – 3000 cm^{-1}, the PLS regression was performed on the same range. The model gives a good linear fit to the data (R2=0.9922, RMSEC = 0.01384), as shown in Figure 3.

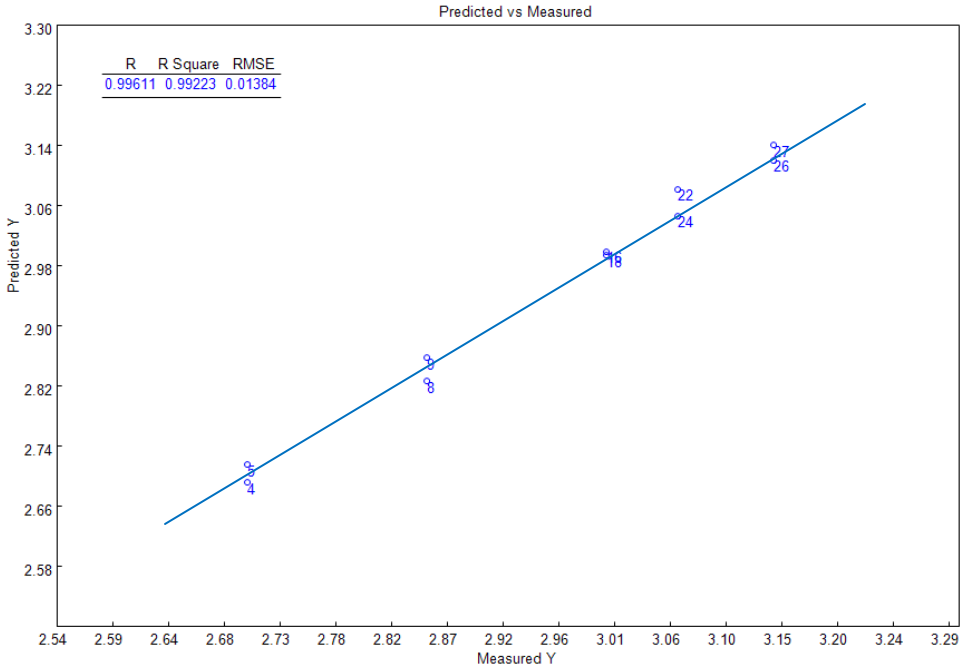

Figure 3. PLS model: measured vs. predicted curve

Some sample spectra were reserved for cross-validation. The model gives a linear fit to the validation data (R^2=0.76866, RMSECV= 0.05287).

The predicted results on the two (3mg) tablets are shown in Table 2. Two spectra from each sample were collected.

Table 2. Predicted results

Prediction Tablet	Predicted Naltrexone HCl (mg/tablet)
3mgT1-1	2.9668
3mgT1-2	2.9244
3mgT2-1	2.9038
3mgT2-2	2.9296

Conclusions

Raman spectroscopy with chemometrics can be used to develop a quantitative method to measure the concentration of APIs such as Naltrexone HCl in blending mixtures and final product tablets. The method provides quick predictions of API concentrations in blending mixtures, allowing for use in on-line monitoring for blending processes. The high sensitivity, high resolution, and stability of the i-Raman Plus instrument conform to the requirements in developing reliable quantitative Raman analysis methods.

The physical non-uniformity within a sample (powder or tablet) could directly affect the accuracy of the model. Multiple measurements at different locations within a sample are needed for collection of calibration spectra. That being said, an estimation of the sample API uniformity can also be assessed when the actual API concentrations of the prediction samples are known.

Good practices require that standard samples with known API concentrations are used to verify the stability of the method as well as the hardware on a regular basis.

