Application note

Measuring content uniformity in low-dose tablets using near-infrared transmission analysis

Authors

Scot Randle, Tyco Healthcare/ Mallinckrodt
St. Louis, MO, USA
Jeffrey Hirsch, Thermo Fisher Scientific
Madison, WI, USA

Keywords

Antaris, content uniformity, FT-NIR, low-dose, tablets, transmission

Abstract

This study examines the ability of FT-NIR spectroscopy to predict API concentration in low-dose tablets using the Thermo Scientific™ Antaris™ Fourier Transform Near-Infrared (FT-NIR) Analyzer.

Introduction

Tablets are the most commonly produced pharmaceutical dosage form for a variety of reasons. They are cost-effective to produce, simple to dispense, and can be safely administered by patients. Tablets are versatile in that they are a simple, solid matrix for drug dispersion that can be changed or altered to suit a particular need, like changing release profiles. Solid tablets provide a stable environment for the suspension of Active Pharmaceutical Ingredients (APIs), resulting in long shelf life. Yet, despite these advantages and a century of manufacturing knowledge, tablet fabrication is still poorly understood.

Tablet analysis is a crucial component of the manufacturing process, ensuring quality and integrity across batches. Multiple chemical and physical characteristics can be of interest in any one tablet, and significant effort is expended on analytical techniques toward this end. Titrimetric and chromatographic analyses are performed on a large scale in order to guarantee the integrity of a tablet batch. Properties like hardness, dissolution profile, and chemical concentration are all regularly quantified. The single most critical and commonly analyzed parameter for QA and QC of tablets, however, is the concentration of API from tablet to tablet across an entire batch (defined as content uniformity).

Quantification of tablet API is essential to pharmaceutical cGMP and established validation protocols. The USP includes a permanent chapter dedicated to content uniformity measurements in tablets, Chapter 905. Although the USP is not a regulatory body, their recommendations for testing protocols are readily adopted by pharmaceutical companies. In the case of content uniformity in compressed tablets, the criteria for acceptance testing are:

1. The actual % API in 10 tablets tested must be between 85.0% and 115.0% of the label claim.
2. The Relative Standard Deviation (RSD) is no greater than 6.0%.

If 1 in 10 tablets does not meet the specification for % label claim (outside 85.0% to 115.0% but not outside 75.0% to 125.0%) or RSD, then an additional twenty (20) tablets must be tested. If the RSD for the set of now 30 tablets is less than or equal to 7.8% with not more than 1 unit outside the range of 85.0% to 115.0% label claim (but still not outside 75.0% to 125.0%), then the criteria are met.

The USP-derived protocol is generally accepted for QA and QC analysis of compressed tablets; however, the current methodology for determining % API is cumbersome. Typical measurements include titration and HPLC (High-Performance Liquid Chromatography). Each of these techniques carries the risks of operator error and poor reproducibility. In addition, both methodologies use solvents and require a significant amount of training. Fourier Transform Near IR Spectroscopy (FT-NIR) has been shown to be an efficient, rapid method for quantifying physical and chemical properties in tablets. In many cases, Near IR is preferred to other techniques because training time is minimal and high-resolution FT-NIR analysis is a robust, proven technology. The USP has also written a chapter on Near IR analysis, Chapter 1119, meaning it is a generally accepted technique for pharmaceutical analysis and can readily be part of any modern validation protocol.

NIR spectroscopy has the advantage of being able to run two different measurements on tablets, reflection and/or transmission. Each measurement type gives distinct and useful data to understand the chemical and physical nature of the tablet. The two techniques are complementary; reflection gives information about the outside or coating of the tablet, while transmission passes light through the body of the tablet giving information about the whole dosage form.

Transmission measurements for content uniformity in tablets are, in general, more accurate and precise than reflection. Although reflection enjoys higher signal to noise than tablet transmission, the sampling is localized. The only part of the tablet being analyzed in reflection is the first 500 microns or so of the surface. Even though the wavelength coverage and signal to noise in reflection are better than in transmission, the integrity of any content uniformity analysis relies on interrogating the entire tablet volume. Reflection can prove useful when an API only has peaks in the wavelength range between 4000 cm^{-1} and 7000 cm^{-1}. In this range, transmission analysis is problematic due to high absorbance. This is, however, the exception rather than the rule, so the ability of transmission to see the entire tablet becomes the dominant factor leading to a better analysis. For coating-only analysis, reflection becomes the method of choice due to its high signal-to-noise versus transmission. The Antaris analyzers are capable of measuring both transmission and reflection at the same time on tablets allowing both pieces of data to be collected in half the normal NIR analysis time.

In building a calibration curve for Near IR content uniformity analysis, the main goal is to predict unknown samples accurately and precisely. The challenge for content uniformity is that the %API is, by definition, always somewhere around 100% label claim. In order to build a calibration for this type of analysis, multiple API dosage strengths must be created synthetically to extend the calibration curve above and below 100%. This will have the effect of significantly lowering prediction error, making the analysis more robust. To further this point, if one is using USP Chapter 905 on content uniformity, the calibration curve would have to include values allowing for quantification at levels of 75% to 125% label claim. This means that synthetic samples ranging from approximately 68% to 137% label claim (75% to 125% plus and minus 10%) are required for NIR analysis adhering to USP <905>. In the current experiment, low-dose tablets (<2.0% w/w, ~5 mg active) were analyzed using transmission analysis on an Antaris FT-NIR analyzer. Synthetic calibration samples were created to span the range from 50% to 150% label claim, and production samples were culled to be included with the validation set. The primary method, in this case, was an already-validated HPLC determination, ensuring the traceability of the NIR analysis.

Results and discussion

Method accuracy was determined with a set of 149 calibration standards, some synthetic and some from production batches. This training set was validated with 49 validation standards spanning the same original range. The API ranged from ~50% to ~150% label claim (from approximately 2.5 mg active to 7.2 mg active). Label claim, in this case, was approximately 5.0 mg active, making this a low-dose tablet at approximately 2% w/w API for a 250 mg uncoated tablet.

The method, in this case, used a Partial Least Squares (PLS) algorithm with a constant pathlength treatment (no scattering correction). The data were pretreated as a second derivative with a Norris smoothing filter. The Segment Length was 11, and the Gap was set to 10. The spectral region was approximately 8650 cm^{-1} to 8880 cm^{-1}.

The calibration curve is shown in Figure 1a, and the residual is shown in Figure 1b. The correlation coefficient (Pearson's coefficient) in this case is 0.9816, which shows a strong correlation between the HPLC measurements and the NIR predictions. In addition, a Root Mean Square Error of Calibration (RMSEC) and Root Mean Square Error of Prediction (RMSEP) of, respectively, 0.168 and 0.149 also demonstrate the high degree of correlation in this method. For this method, the RMSEC expressed as a % of label claim is 3.3%, and the RMSEP is 2.9%. The Predicted Error Sum of Squares (PRESS) plot is shown in Figure 2. The shape of the PRESS, in this case, is indicative of a reasonable correlation with the HPLC data. The number of factors chosen in this case was 4 as there is no noise factored into the Principal Component spectra up to the 4th factor. There were also no spectral outliers found in this calculation as done by the Chauvenet method.

Method repeatability was also determined in this experiment by analyzing the same tablet 6 times without changing its presentation to the instrument. Altering tablet presentation, especially with the presence of embossing or stamping, can significantly alter the NIR predictions. This issue must be addressed either via sampling (presenting the sample to the instrument the same way every time) or by factoring this variability into the method. The former will result in a more robust, more precise method, whereas the latter allows operators to orient the tablet in any fashion. The repeatability test was run on 5 separate tablets and resulted in an RSD of <1.0%.

Conclusion

The Antaris FT-NIR analyzer has been shown to be an accurate and rapid method for analyzing content uniformity in low-dose tablets. The validation batch in question, it has been determined, falls within the acceptable criteria for USP <905>.

The data were collected using an older model instrument Antaris FT-NIR. Currently, Thermo Scientific offers an improved model, the Antaris II FT-NIR, which offers superior speed and performance over its predecessor model.

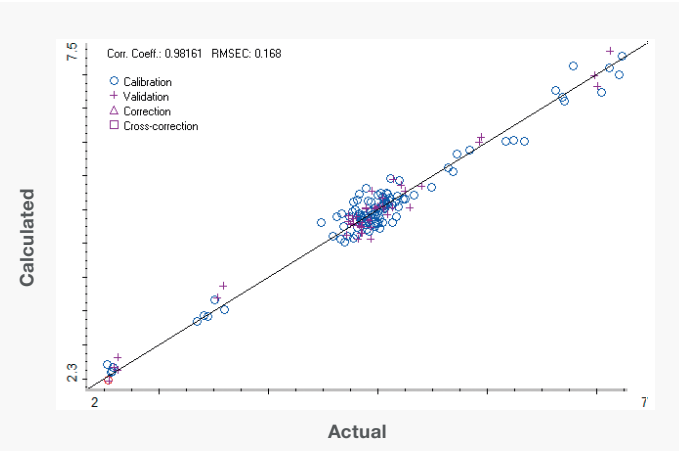

Figure 1a. Calibration curve for API in low-dose tablets.

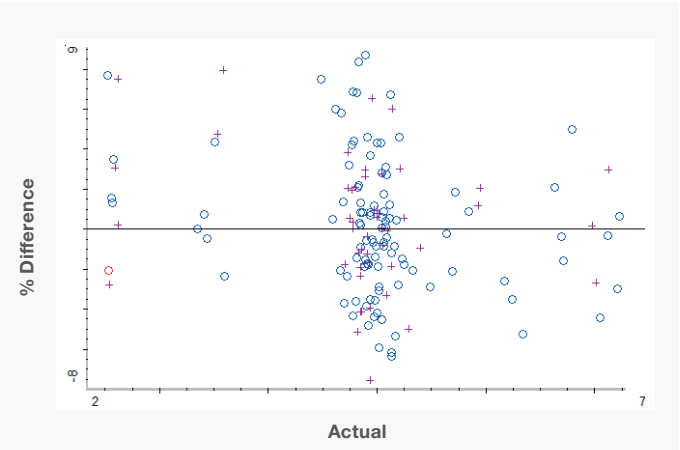

Figure 1b. Residual for calibration in Figure 1a.

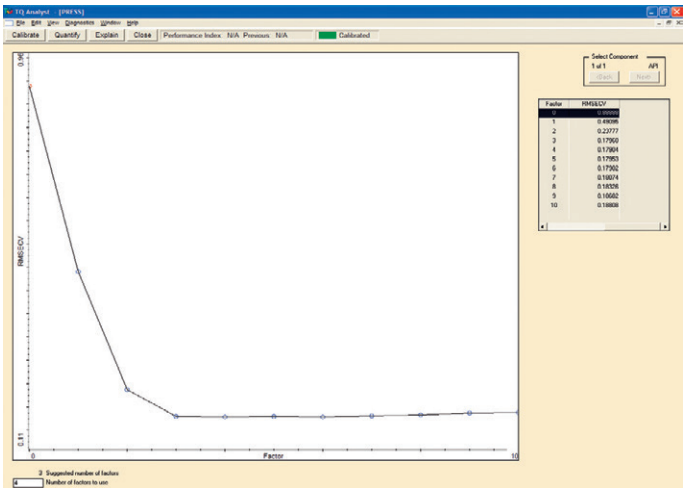

Figure 2. PRESS plot for PLS API method.

Learn more at **thermofisher.com/brighteroutcomes**

thermo scientific