Quantification of a degradant in an intact pharmaceutical tablet

Benefits at a glance
- Non-destructive tablet analysis
- Quantification of degradant
- Elimination of subsampling and focus effects

Introduction

Patients typically prefer to have pharmaceuticals administered as orally ingestible tablets. Solid dosage forms (tablets and capsules) represent 70% of marketed pharmaceutical products worldwide.

With any pharmaceutical formulation, degradation is a key issue. The propensity for the active ingredient to degrade is investigated using stability studies. During such studies, the active is measured in samples that have been exposed to various conditions for specified periods of time. One issue with stability protocols is that degradation behavior must be assessed statistically. Typically, samples are analyzed destructively. A non-destructive method that would allow the same dosage unit to be followed throughout the duration of a study would enhance the accuracy and convenience of the evaluation.

Interest in Raman spectroscopy for quantitative analysis has increased greatly in recent years. However, the use of Raman for quantification in quality control applications has suffered from two major drawbacks: unrepresentative sampling (sub-sampling), and inconsistent sample focus. Traditional Raman measurements are made using small incident laser spot sizes. This creates problems for static solids measurements because there is no surety that the measurement is representative of the entire sample.

Many solutions have been proposed to minimize subsampling. The most common is automation, but a solution that allows superior sample interrogation without moving the sample would be preferable because inconsistency of sample placement can reduce Raman signal intensity.

A solution that also reduces the sensitivity of the measurement to sample focus would be desirable.

A Raman analyzer equipped with a large volumetric probe represents a novel solution to both of these drawbacks. In this note, the application of Raman for the quantitation of a degradant in a tablet formulation is discussed.

Experimental

The samples were commercial uncoated furosemide tablets. The degradant ranged from 0% to 1.56% of the tablet weight. The range of degradant level was achieved by storing different batches of tablets under different conditions for different periods of time. The nominal degradation level in each batch was determined by HPLC, and the average value for each batch was used as the reference value for quantitative analysis.

A Raman analyzer, operating at 785nm and equipped with a non-contact probe with a 3mm spot size, was used to non-invasively measure samples. Each spectrum was acquired using 1 scan of 30 seconds and approximately 150 mW.

Chemometric treatment of the data was accomplished using Pirouette® (Infometrix, Bothell, WA). Principal components analysis (PCA) was used to screen the data. Quantitative analysis was accomplished using partial least squares (PLS) regression.

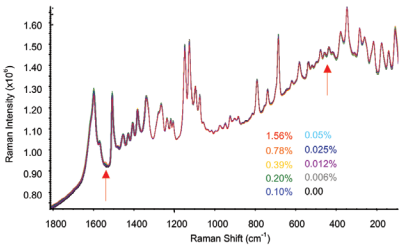

Figure 1: Raman spectra of furosemide tablets with various degradant content

ⓘ All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

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Results

The spectra for the furosemide tablets are shown in Figure 1. The arrows in the figure indicate regions in which the spectral signature of the degradant could be visualized.

Figure 2 shows an expanded overlay of the second-derivatives of the spectra in Figure 1. After this mathematical manipulation, the peak maxima become minima. The second derivative also normalizes the baseline for easier spectral comparison. This treatment makes apparent where the spectral features of the degradant begin to appear.

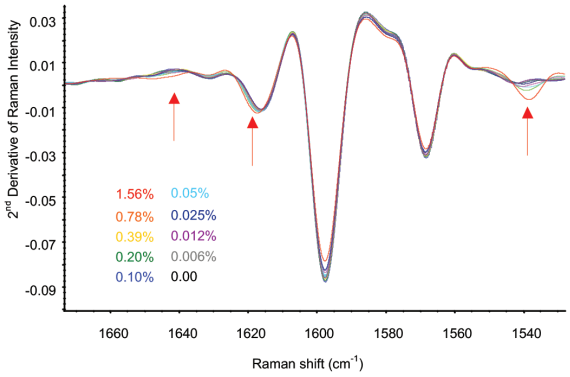

Figure 2: Second-derivative treatment of the tablet spectra

The quantitative analysis of the data was accomplished with a four-factor PLS model (Figure 3). The correlation coefficient was 0.9980 and the root mean squared error of calibration (RMSEC) was 0.030%. The cross validation indicated some non-linearity at the extremes when those samples were left out. The root mean squared error of cross validation (RMSECV) was 0.17%. More samples in the calibration would increase the robustness of the method; however, these results demonstrate that the degradant level can be modeled.

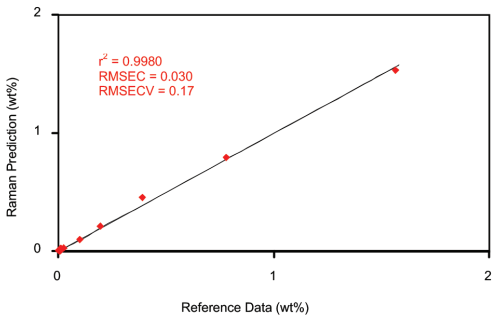

Figure 3: Results of a four-factor PLS model

Figure 4 shows an expanded second-derivative spectrum featuring a band in the fingerprint region representing the degradant. These spectra suggest that the data are linear to a level less than 0.1% of the tablet weight, possibly as low as 0.05%.

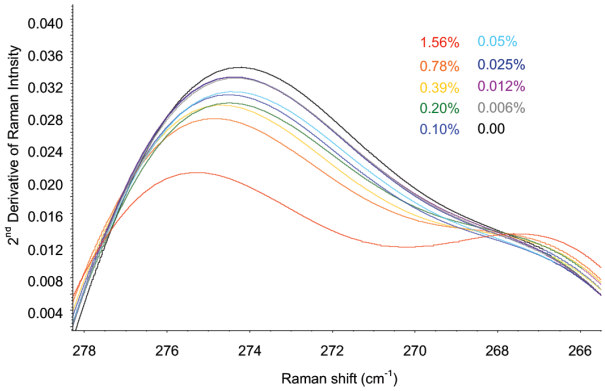

Figure 4: Demonstration of the linearity of the second-derivative spectra.

Conclusions

This study demonstrates that quantification of components in solid samples is achievable through the use of a Raman probe. The use of quantitative Raman in the laboratory on static samples has historically been hampered by inconsistent sample focus and lack of representative sampling. Using a novel design approach that offers both a large depth of field and a large spot size (an order of magnitude greater than that in typical Raman measurements—less than 200 µm), the non-contact probe solves both of these issues.

The non-destructive quantification of a degradant of furosemide in whole tablets, ranging from 0% to 1.56% of the tablet weight, proved the technique to be successful for analyte contents greater than or equal to 0.1%. Employing a large spot size for the incident excitation radiation provides superior representative sampling, leading to more reliable measurements. The results shown here indicate that the non-contact probe is well-suited for quantitative analysis of tablet formulations using Raman spectroscopy.

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