Quantification of Tablets Containing Multiple APIs Using Transmission Raman

The ability to predict multiple constituents of a final dosage form in one fast, non-destructive measurement can reduce analysis time. This is especially important when quantification of multiple APIs is required for tests such as content uniformity, assay and ID.

This example, based on a common cold and flu product, demonstrates the quantification of 5 components (3 APIs and 2 excipients) using a 9 second measurement. Nominal concentration ranged from 1 to 85 % w/w.

Introduction

Typical solid dose forms of a drug product are often complex and contain at least one active pharmaceutical ingredient (API) and a range of excipients at varying levels. The most widely-used means of quantitative analysis is high performance liquid chromatography (HPLC), which is slow, laborious, prone to manual errors and expensive. Transmission Raman spectroscopy (TRS) is a regulatory-acceptable alternative technique for content uniformity, assay and drug product ID, enabling fast, non-destructive analysis of tablets and capsules without chemical preparation or skilled analytical chemists.

Usually only APIs are quantified, but monitoring excipients as well as API’s may be advantageous. For example, if a particular batch of drug product differs in terms of one of its excipients, it may affect one of the quality critical attributes such as dissolution. This extra information comes with almost no extra cost or complexity from transmission Raman methods.

Experimental

The drug product in this example, a common cold and flu formulation, contained 5 constituents (3 API’s and 2 Excipients) at the nominal concentrations shown below. This product is expensive to analyse by HPLC as multiple separations are required to measure all 3 APIs, taking several days to complete.

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Caffeine</th>
<th>Paracetamol</th>
<th>Mag Stearate</th>
<th>Tabletose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>4%</td>
<td>85%</td>
<td>1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

In order to use transmission Raman spectroscopy to quantify multiple components a thorough calibration set is required. The calibration design in this example included an orthogonal 5 level design consisting of 20 samples. In order to validate the models, 5 independent validation samples with varying concentrations were tested.

Powdered materials were weighed, ground, mixed and compressed into tablets. Samples were loaded into a sample tray and then into the TRS100 instrument for automated analysis. Two tablets per sample were scanned using 1.0 W laser power (830 nm) for 9 seconds. Spectra shown in Figure 1 indicates regions of variation due to constituents.

Figure 1: Calibration spectra, baselined and normalised to show spectra variation.
Results and Analysis

Calibration spectra were used to build predictive models for each constituent of the mixture (Fig. 2).

The results indicate that PLS models can be built for all constituents, with good model parameters for the APIs. Of all constituents magnesium stearate is the worst performing model. This is due to the poor Raman scattering ability of the constituent and the low concentration at 1% w/w. Of greatest importance is the success of the phenylephrine model, which gives acceptable model performance in a single measurement, even though the spectra are dominated by the acetaminophen component.

Validation of the model, and prediction of independent samples, are shown in Figure 3. Results indicate that all substances are predicted well with higher performance for the stronger Raman scatterers (the APIs and caffeine, as the highest content excipient).

Summary

It was demonstrated that multiple APIs in a single intact tablet can be quantified easily by transmission Raman spectroscopy. The time taken for CU, assay and ID was reduced from approximately 2 days (by chromatographic methods) to <5 minutes for a batch of 10 tablets, and does not require skilled analytical resource for routine testing.

With little extra effort the concentrations of excipients are also determined in the method, which can provide useful attributes for process monitoring applications.

Transmission Raman is an effective and powerful tool for quantifying multiple actives quickly and effectively, even for low concentration components.

References: