Application Note: 50875

The Use of FT-Raman Spectroscopy and Chemometric Procedures in the Analysis of Pharmaceuticals

Key Words

- FT-Raman
- Pharmaceuticals
- QA/QC
- Quantitative Analysis

Introduction

The FT-Raman technique has many benefits in the analytical laboratory, including speed, easy sample preparation and spectral information that is interpreted in the same way as FT-IR spectra. Functional groups such as carbon double bonds produce strong FT-Raman vibrations, whereas functional groups with strong dipoles, such as water, are often weak in FT-Raman spectra. Therefore, aqueous solutions or samples in glass bottles can be measured directly. In addition, the active ingredients present in pharmaceutical tablets often show a very strong FT-Raman spectra while their excipients have much weaker vibrations.

FT-Raman allows most samples to be analyzed in their original form, which is a major advantage when the sample structure is subject to change with heat or pressure. Combined with the fact that samples can be measured directly in the sample bottle or packaging, the minimal sample preparation makes FT-Raman spectroscopy an ideal technique for QA/QC analysis methods.

Vitamin E Gel Capsules

An example is the analysis of vitamin E gel capsules. The gel produces a relatively weak FT-Raman spectrum, allowing the strong scattering of the active ingredients to be clearly analyzed through the wall of the capsule. In this application, gel capsules that appeared cloudy were identified. Clouding occurs as a consequence of oxidation processes. Therefore when a capsule appeared cloudy, the sample was identified as 'bad', and its spectrum was compared against the 'good' reference spectra from clear capsules.

The FT-Raman spectra in Figure 1 demonstrate the relative weakness of the FT-Raman spectrum of the isolated gel and the small spectral differences between a 'good' and a 'bad' tablet. The difference spectrum of the good spectrum from the bad spectrum (Figure 2) shows the differences

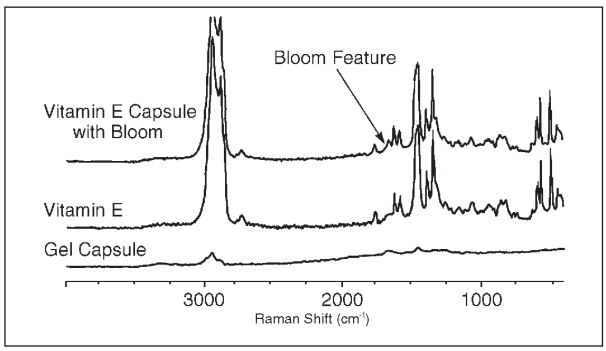

Figure 1: FT-Raman spectra of good and cloudy vitamin E gel capsules, and of the gel capsule itself

attributed to the clouding of the material. Although this is a small contribution to the overall measurement, it was possible to identify the chemical compound causing the clouding as Gelatin Bloom (CAS#:9000708), also shown in Figure 2. Gelatin Bloom is a common contaminant that arises during the oxidation processes. This analysis was performed by searching the difference spectrum against the 4 cm^{-1} resolution Aldrich FT-Raman spectral library containing spectra of over 14,000 compounds. The entire search procedure took only about 7 seconds.

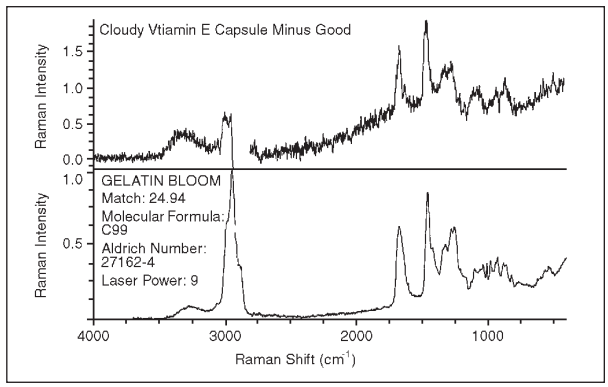

Figure 2: FT-Raman difference spectrum of cloudy minus good vitamin E capsule

For this QA/QC method, the challenge was to quickly determine whether the amount of clouding, i.e. Bloom, was acceptable or whether the capsule should be rejected. This was achieved using the Similarity Match feature in TQ Analyst™ spectral analysis software package (Figure 3).

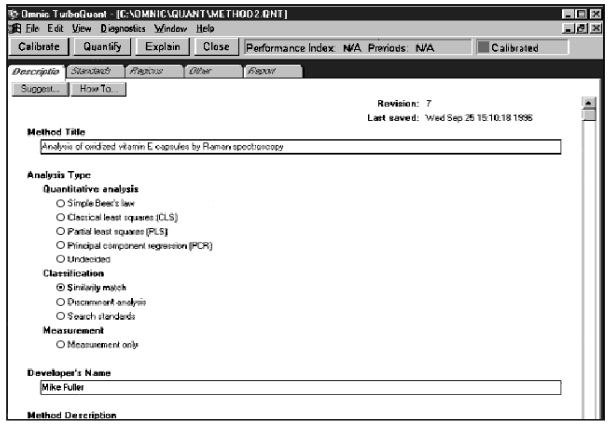

Figure 3: TQ Analyst software method description window

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The Similarity Match algorithm is typically used for quality control applications. In these applications, the desired composition of the samples is known and the analyst is interested in verifying the samples or identifying when impurities are present. Similarity Match is a spectral classification technique that indicates how closely an unknown material matches a known material. Multiple standards may be used to describe the known material. Multiple regions of the spectrum may be used in the comparison.

A Similarity Match method compares the spectral information in the specified region or regions of an unknown sample spectrum with that of a known set of standard spectra to determine how closely the sample matches the standards. The result of this comparison is called a Match Value. The Similarity Match method in this experiment focused on the region between 1850 and 1525 cm^{-1} because the most intense bands of Bloom were present in this region. The Match Value was compared against a Limit Value which was calculated by comparison of the Match Values of the FT-Raman spectra of 'good' and 'bad' capsules. From the results, it appeared that the clear capsules had a match value lower than 20, whereas the cloudy capsules exceeded this value. The method was calibrated to alert the operator when the Match Value for a sample spectrum exceeded 20. This allowed the lab to identify capsules that fell outside of the acceptable range using a very easy, quick and reliable procedure which could be run directly from the OMNIC™ software during data collection (Figure 4).

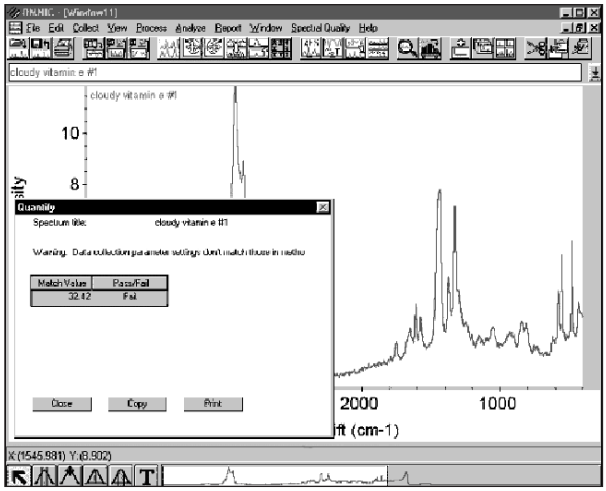


Figure 4: Similarity Match method ran directly from OMNIC software

Composition of Effervescent Cold Tablets

Effervescent cold tablets typically contain aspirin, phenylpropanolamine bitartrate, chlorpheniramine maleate, sodium bicarbonate, citric acid and aspartame. The tablets not only differ slightly in composition from tablet to tablet, but also from manufacturer to manufacturer and from one strength to another.

Figure 5 shows a typical FT-Raman spectrum of an effervescent cold tablet. This spectrum was searched against the Aldrich FT-Raman library in order to determine the nature of the components present in the tablet. The best match from the Aldrich library is sodium hydrogen carbonate, due to the strong band just above 1000 cm^{-1}.

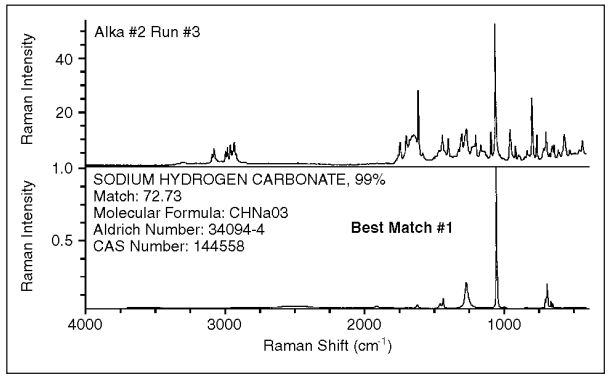


Figure 5: FT-Raman spectrum of effervescent cold tablet, and first library search hit

When this spectrum is subtracted from the original spectrum, a second search can be performed resulting in acetylsalicylic acid (Figure 6). When this procedure is repeated, the third hit is citric acid, shown in Figure 7. Finally, the search result shows that ascorbic acid is present in the tablet (Figure 8). Note that each subtraction was performed using spectra from the Aldrich 4 cm^{-1} resolution FT-Raman library. This was done because a high resolution spectrum contains a greater amount of spectral information and thus provides greater accuracy when doing subtraction. Figure 9 shows the residual spectrum showing that essentially all of the Raman spectral information has been accounted for.

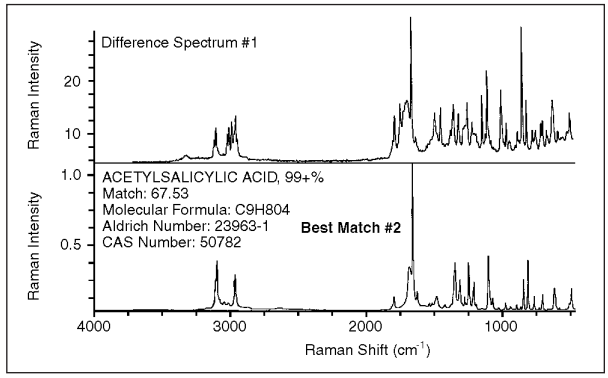


Figure 6: FT-Raman difference spectrum of effervescent cold tablet, and secondary library search hit

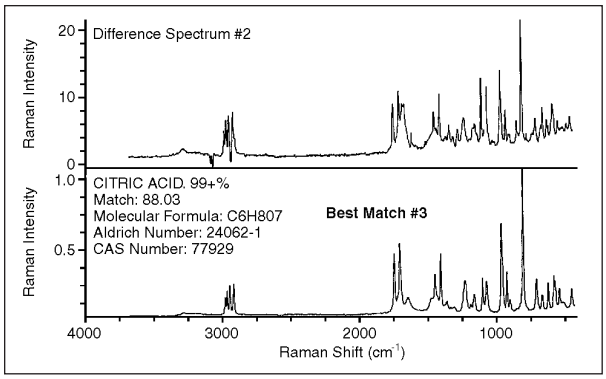


Figure 7: FT-Raman difference spectrum of effervescent cold tablet, and third library search hit

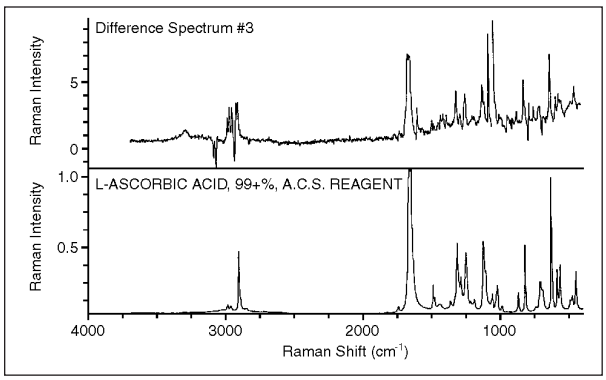


Figure 8: FT-Raman difference spectrum of effervescent cold tablet, and final library search hit

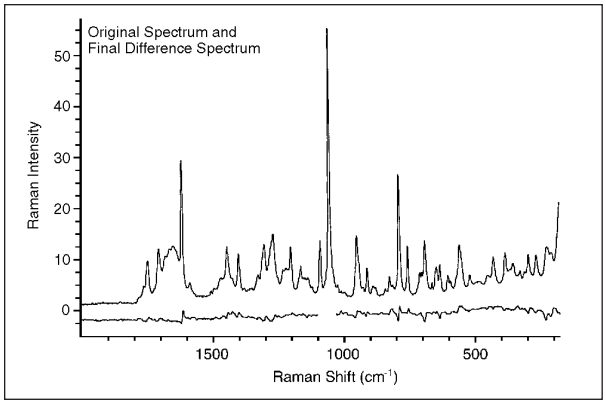


Figure 9: Comparison of FT-Raman spectrum of effervescent cold tablet, and final difference spectrum

This analysis was applied to easily distinguish between three types of effervescent cold tablets. In the FT-Raman spectra of the three cold tablets (Figures 10a and 10b), differences from tablet to tablet within the same batch are observed as well. Therefore, a method was built to cover both the differences within the spectra of one type, as well as the differences from batch to batch.

Discriminant Analysis is a spectral classification technique that determines the class of an unknown material which is most similar to different classes of known materials. The Discriminant Analysis algorithm can be used to screen a variety of materials.

In these applications, the analyst is interested in identifying which known material each sample is most like. A Discriminant Analysis method applies the spectral

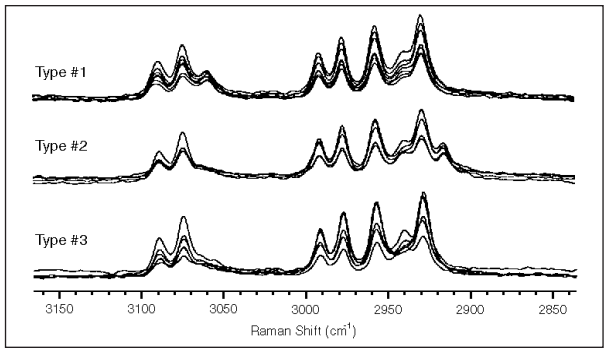


Figure 10a: FT-Raman spectra of different types of effervescent cold tablets

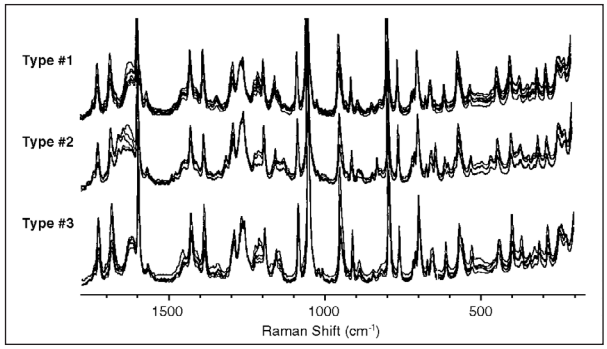
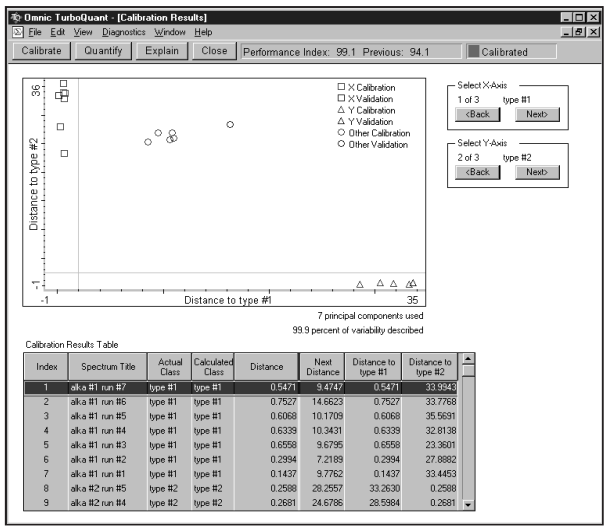


Figure 10b: FT-Raman spectra of different types of effervescent cold tablets

information in the specified region or regions of an unknown sample spectrum to a stored calibration model to determine which class of standards is most similar to the unknown. The result of a discriminant analysis is the name of the class that is most similar to the unknown sample spectrum and a measurement of the distance between the unknown sample and each reported class. The closer each distance value is to zero, the better is the match. Figure 11 shows the discriminant analysis output of the FT-Raman spectra of the effervescent cold tablets and it can be observed that the spectra group in 3 different clusters each describes a different class. With the aid of this model, a QA/QC method was built that could quickly distinguish between the different tablets, even when the samples were measured directly in the blister packaging.



Index	Spectrum Title	Actual Class	Calculated Class	Distance	Next Distance	Distance to type #1	Distance to type #2
1	alka #1 run #7	type #1	type #1	0.5471	9.4747	0.5471	33.9945
2	alka #1 run #6	type #1	type #1	0.7527	14.6623	0.7527	33.7768
3	alka #1 run #5	type #1	type #1	0.6068	10.1709	0.6068	35.5691
4	alka #1 run #4	type #1	type #1	0.6339	10.3431	0.6339	32.8138
5	alka #1 run #3	type #1	type #1	0.6558	9.6795	0.6558	23.3601
6	alka #1 run #2	type #1	type #1	0.2994	7.2189	0.2994	27.8882
7	alka #1 run #1	type #1	type #1	0.1437	9.7762	0.1437	33.4453
8	alka #2 run #5	type #2	type #2	0.2588	28.2557	33.2630	0.2588
9	alka #2 run #4	type #2	type #2	0.2681	24.6786	28.5984	0.2681

Figure 11: Discriminant analysis output of different types of Effervescent cold tablets

Conclusions

FT-Raman spectroscopy is an important tool in the modern laboratory and its unique advantages make it very useful in QA/QC environments. The Aldrich FT-Raman library adds a very powerful analytical method for identifying unknown compounds and the data analysis tools, such as the classification procedures, in TQ Analyst software maximize the utility of FT-Raman measurements in a QA/QC environment.

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