REVERSE ENGINEERING PHARMACEUTICAL FORMULATION USING THE MORPHOLOGI G3-ID.

PARTICLE SIZE

PARTICLE SHAPE

CHEMICAL IDENTIFICATION

Introduction

According to the definition established by the FDA, a generic drug is "a drug product which is comparable to a reference listed drug (RLD) product in dosage form, strength, route of administration, quality, performance characteristics, and intended use". Rigorous rules and regulations pertaining to abbreviated new drug application (ANDA) submissions are complex and the generic drug industry strives to meet these regulations to obtain FDA's approval. And being the "first to file" is the most fundamental principle in the generics business because several companies compete to create generics of successful products going off patent. Therefore, generics companies must be highly skilled and disciplined in product development and achieving bioequivalence—the most critical development area.

Though generics companies commonly use reverse engineering techniques, the topic and, more importantly, the tools needed to carry out the process are rarely discussed in the public domain. In this application note we discuss one such tool that can be used for oral solid dose formulations.

Case Study

Two cold remedy formulations were analysed on the Morphologi G3-ID: one was a commercial brand and the other a generic one. Individual components within the formulations were identified by comparing their Raman spectra with those in a commercial database. Once the components were identified the particle size distributions of individual components in each formulation were compared, as was the overall composition of the two formulations.

Methodology

The cold remedies were dry powder formulations that were automatically dispersed and analysed using the Morphologi G3-ID. 13 mm3 of sample was dispersed using the instrument's integrated dry powder dispersion unit using the low pressure dispersion option.

Figure 1 shows an example image of one of the dispersed samples. The samples were morphologically analysed using the 5 x objective. Particles with a circular equivalent diameter (CED) larger than 25 µm were targeted for the Raman chemical identification. In this case the acquisition time was 10 seconds for each particle and spectra from a few thousand particles from each sample were gathered in an overnight analysis.

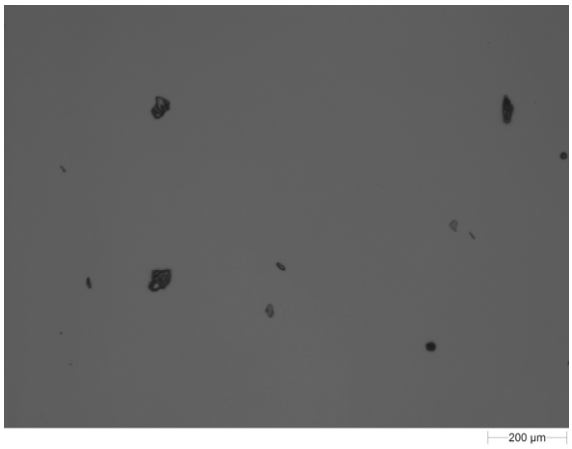

Figure 1: Example image of dispersed sample (5x magnification).

Results and discussion

Figure 2 presents the overlays of the Circular Equivalent Diameter (CED) particle size distributions of the two cold remedies by number and volume respectively. The commercial brand contains more particles in the 30 to 200 µm range than the generic brand. The number based distribution indicates the commercial brand also contains more fine particles less than 20 µm in size.

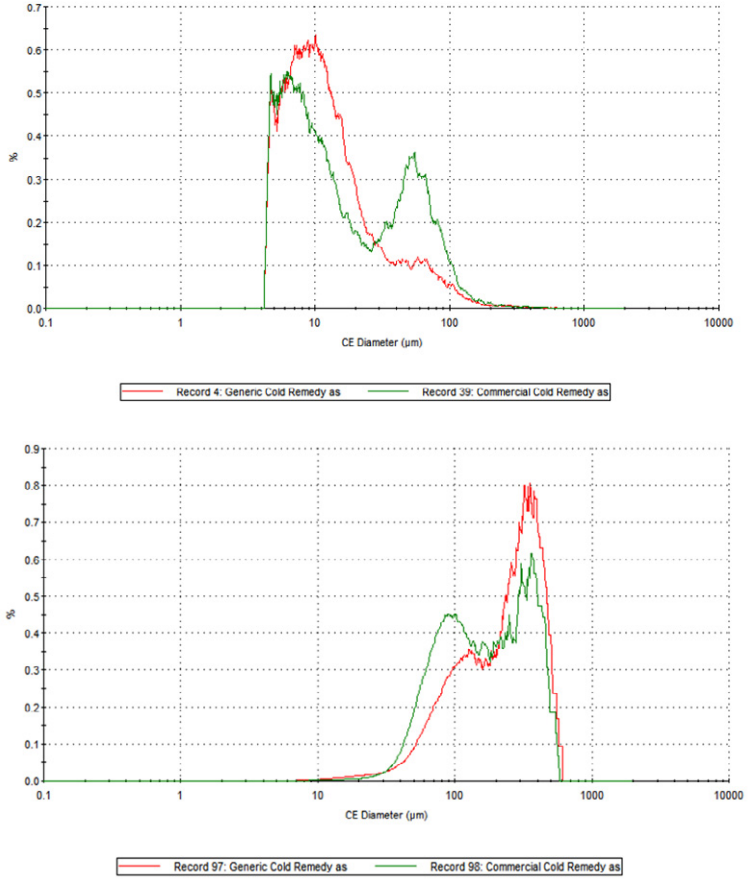

Figure 2: Overlay of the number based (top) and volume based (bottom) CED distributions.

Component identification

Both of the cold remedies are made of more than ten components, including the two active pharmaceutical ingredients (APIs) Paracetamol and Phenylephrine. Since pure materials were not available from which to create reference libraries, Raman spectra acquired by the Morphologi G3-ID from 11 different components were identified and these were used as reference library spectra. As examples, the reference spectra for the components 1, 2 and 11 are displayed in figure 3.

Figure 3: Raman spectra collected for components 1, 2 and 11.

Based on the reference spectra, it is possible to classify individual particles as being one of the formulation components. During this classification process a correlation calculation is performed between each particle's spectrum and the reference spectra and a correlation score generated. A score close to 1 indicates a good match whereas a score close to zero indicates no match. Chemical classifications based on these correlation scores were applied to the results to identify the proportion of each component present in the two formulations.

The results of the volume based classifications and are presented in figure 4. The three most common components in both formulations were components 1, 2 and 11. The commercial product contains more of component 1 than the generic product whereas the generic product was found to contain more of component 2.

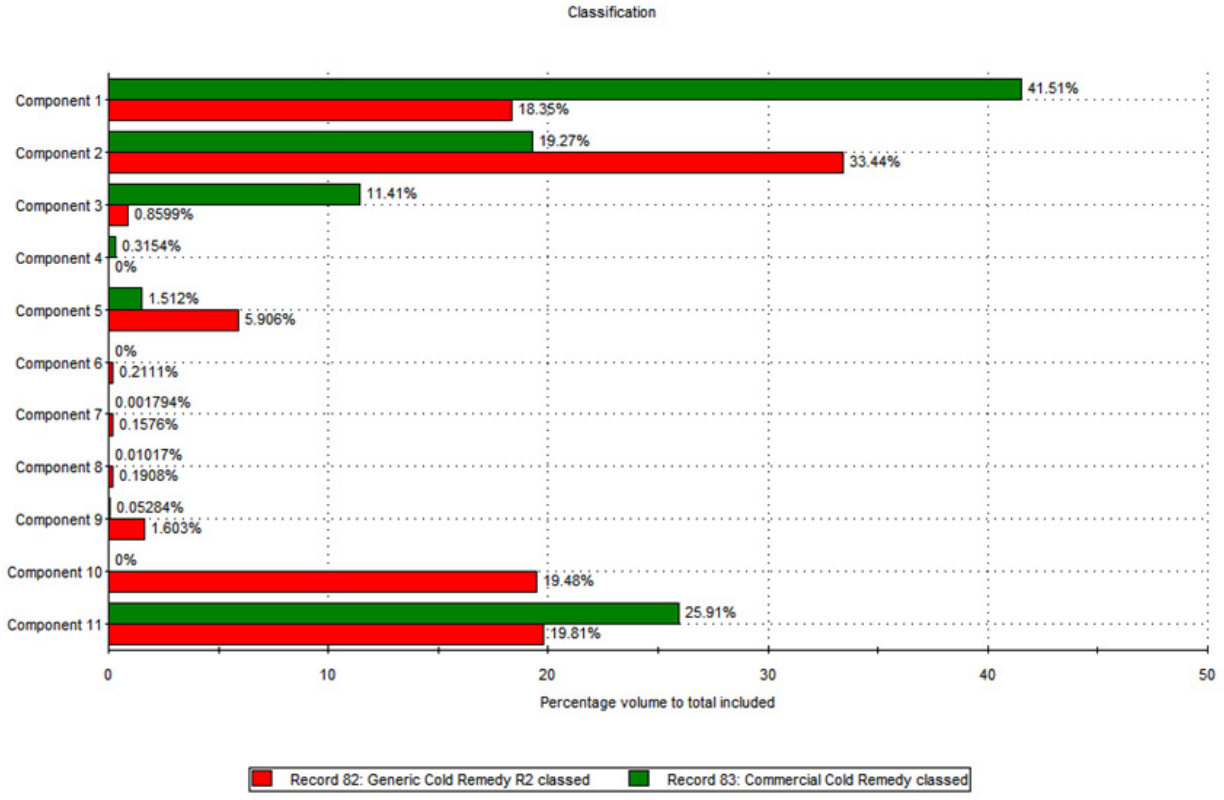

Figure 4: Volume based chemical classification results

Some of the components were identified by performing an advanced spectrum search using Thermo Scientific's online database 'ftirsearch.com.' Figure 5 shows the result for the identification of Components 1, 2 and 11. Component 2 was found to be the API Acetaminophen (Paracetamol). Components 1 and 11 were found to be different forms of sucrose.

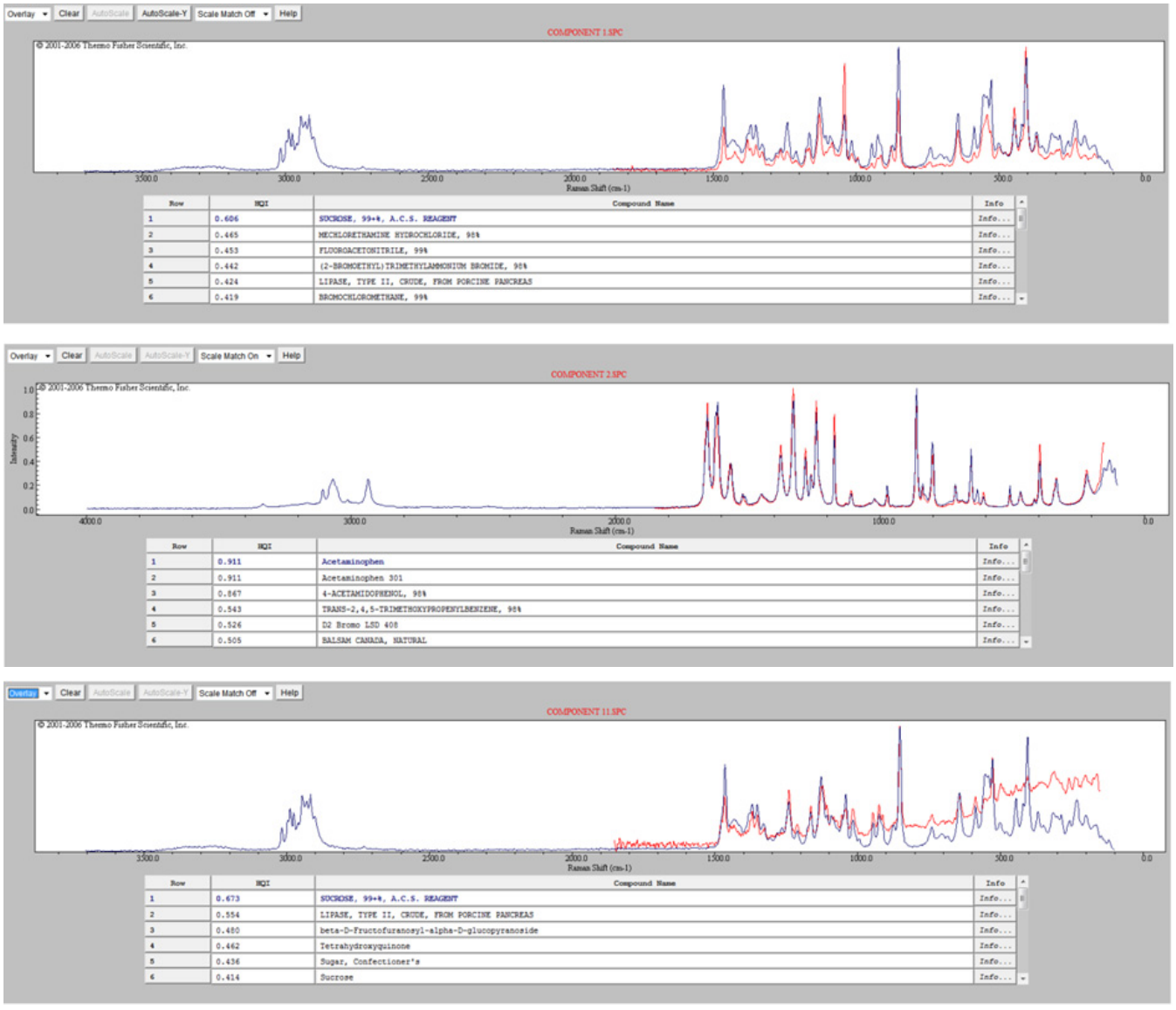

Figure 5: Result of an Advanced Spectrum Search for components 1, 2 and 11 respectively using Thermo Scientific's online database 'ftirsearch.com.'

Individual component size distributions

Figure 6 presents the overlay of the volume based CED size distributions for the particles that were classed as Paracetamol in each sample along with example particle images. The generic product contains larger particles of Paracetamol than the commercial product.

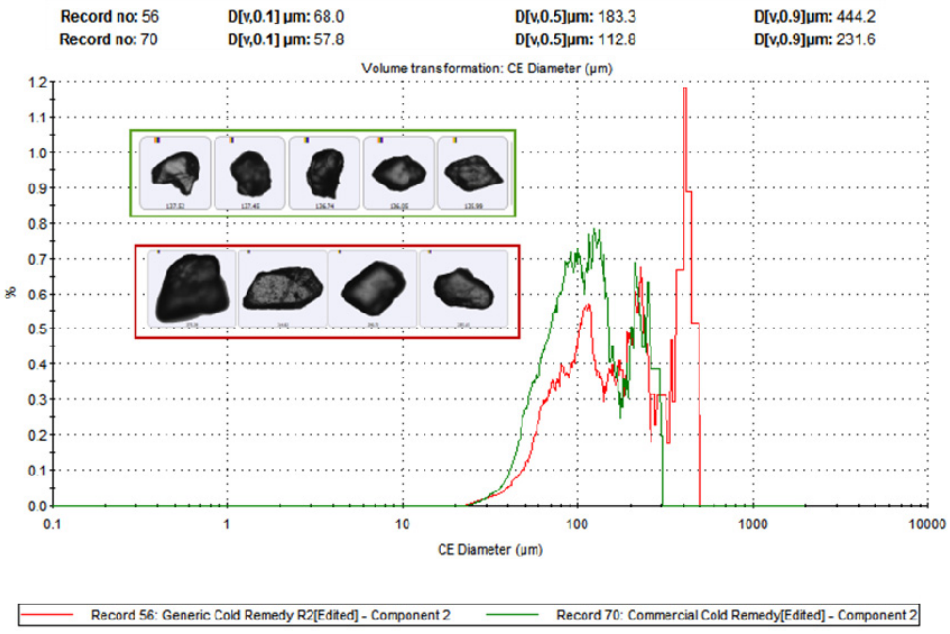

Figure 6: Overlay of the CED particle size distribution for the Paracetamol particles.

Whilst component 7 was not found to be very abundant in either sample, on comparing the particle shape of the various components, it was found to be considerably more elongated (needle-like) than the others. Figure 7 presents the scattergram of correlation score to component 7 vs. elongation. It shows that all particles with a high correlation score to reference component 7 do have a high elongation. The particle images shown in the top left of the figure also confirm this.

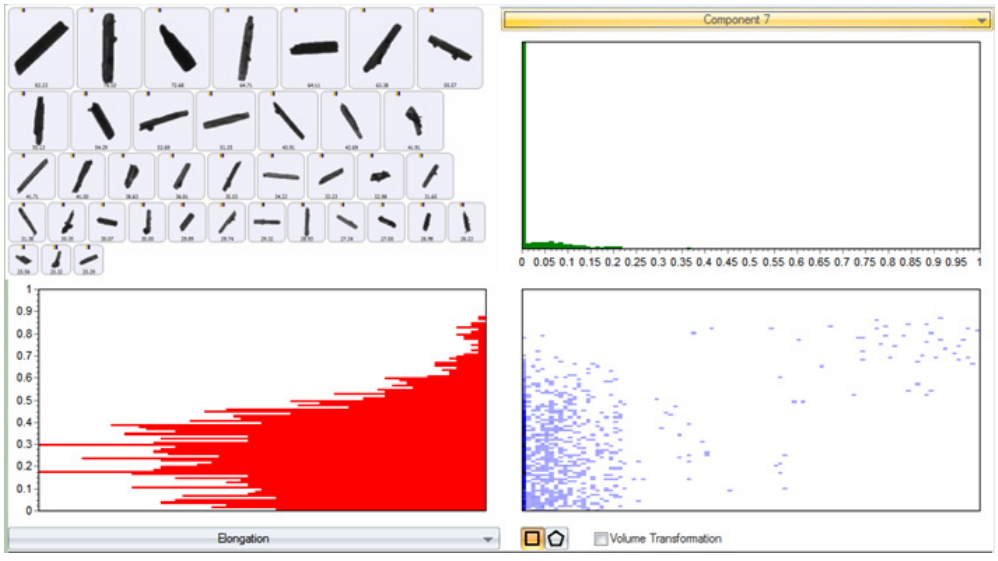

Figure 7: Scattergram of correlation score to component 7 vs. elongation.

An advanced spectrum search was performed on the reference spectrum for component 7 and it was found to be Aspartame, another form of sweetener (figure 8). The generic product contained significantly more Aspartame while the commercial product contained significantly more Sucrose. This may suggest the generic product uses more artificial sweetener to reduce cost, while the commercial product contains more natural sweetener which may give an improved taste.

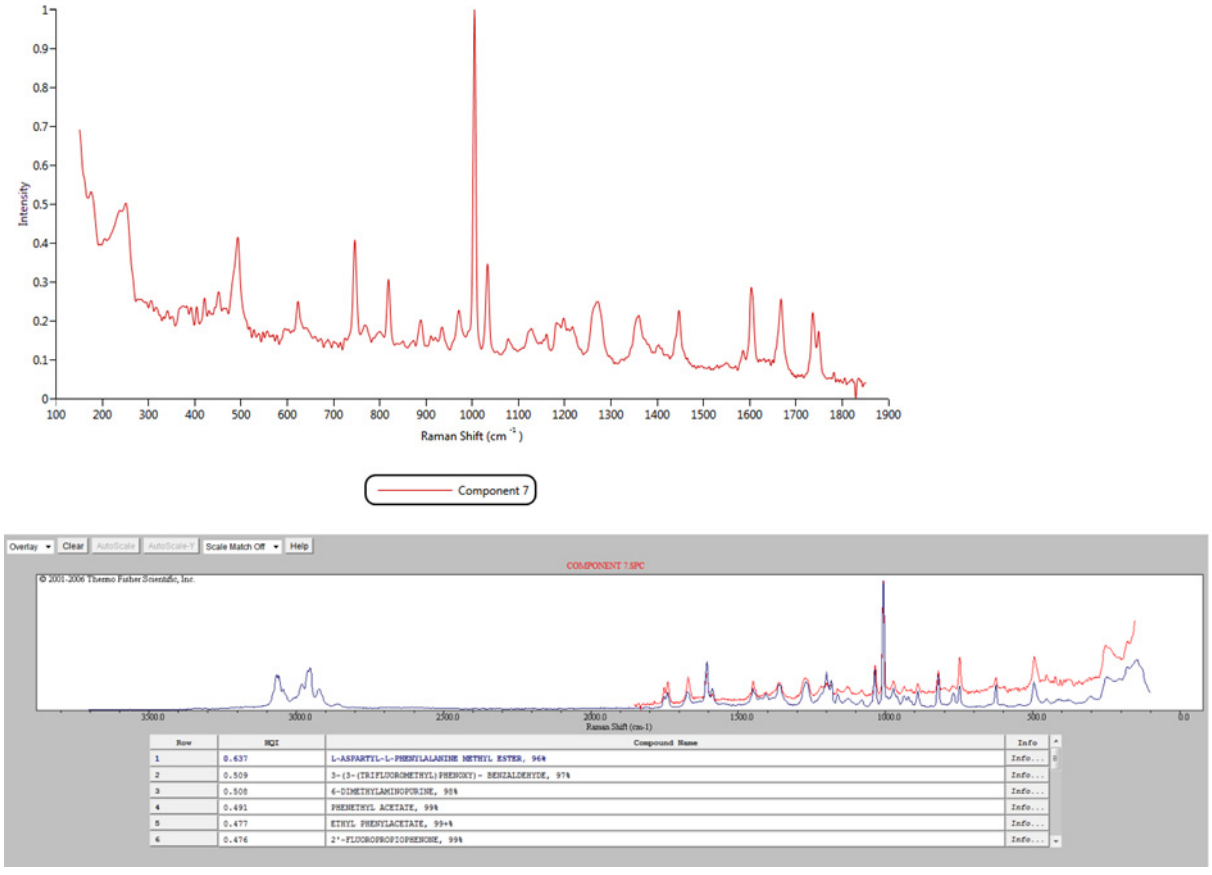

Figure 8: Result of an Advanced Spectrum Search for component 7 using Thermo Scientific's online database 'ftirsearch.com.'

Conclusion

Two different cold and flu remedy formulations were analysed on the Morphologi G3-ID. Eleven different chemical components were identified and characterised. The most abundant in both formulations were found to be forms of sucrose and the API Paracetamol. The commercial formulation was found to contain more Paracetamol by volume and presented a larger particle size distribution.

Whilst not very abundant in either formulation, Aspartame was also identified in both formulations and was found to have a more needle-like particle shape relative other components. The commercial formulation contained more natural sugar in comparison to the generic product.

In the case of the cold and flu remedies the particle size and shape affects the dissolution rate for each component; this may influence the effectiveness of the remedy and may also affect mouth feel and perceived quality. The composition of the formulations may affect taste, and therefore perceived quality, but may also contribute to their effectiveness in relieving cold and flu like symptoms. For an over-the counter cold and flu remedy these differences may be trivial but for formulations requiring submission to the FDA these differences would be critical therefore the ability to identify and characterise different components within a formulation can be critical when reverse engineering a product.

Malvern Instruments Ltd

Enigma Business Park • Grovewood Road
Malvern • Worcestershire • UK • WR14 1XZ

Tel: +44 (0)1684 892456
Fax: +44 (0)1684 892789

Malvern Instruments Worldwide

Sales and service centers in over 50 countries
for details visit www.malvern.com/contact

more information at www.malvern.com