Introduction:
Cellulose is a naturally-derived, highly common raw material found within the pharmaceutical world, providing the underlying foundation for a diverse array of applications. For pharmaceutical applications cellulose is used as an excipient in drug formulations, creams, gauze, cotton, sunscreens and has numerous utilizations. Despite the prevalence of cellulose and its derivatives in pharmaceutical products, traditional handheld Raman utilizing a 785 nm laser is limited in its ability to accurately identify and verify cellulose, as the fluorescence generated is often too overwhelming (red spectrum, Fig. 1). The NanoRam®-1064 from B&W Tek minimizes fluorescence of cellulose materials (blue spectrum, Fig. 1), allowing handheld Raman to verify them easily in a pharmaceutical setting.

The NanoRam-1064 is fully compliant with the Raman chapters of all major pharmacopeias. The NanoRam-1064 and its records management software is FDA 21 CFR Part 11 compliant with a complete audit trail.

Methodology:
A NanoRam-1064 with a point and shoot adaptor was used to analyze five different types of cellulose sealed in Whirl-Pak® sample bags. Laser power was set at 90% of the maximum power (~380 mW). The Identification mode of NanoRam-1064 was selected for a more robust analysis based on a multivariate method. Individual methods were created for cellulose, methyl cellulose, sodium (Na) carboxy-methyl cellulose, cellulose acetate, and ethyl cellulose. Each method was created by scanning five different spots on each sample to create a multivariate model. After each method was enabled for use, all samples were then evaluated against each method to assess the validity of the model.

Results:
For the methods to be valid, each method needs to prove its “specificity” by passing the correct sample and failing all other samples. Whether the sample passes or fails the method is based on statistical significance (p-value). The default threshold is \( p = 0.05 \), corresponding to the significance level set for these methods. Calculated p-values over \( p = 0.05 \) will result in a “Pass” result, and p-values calculated below \( p = 0.05 \) will result in a “Fail” result. Table 1 shows a specificity matrix, where each pass/fail result is listed. The table indicates that the cellulose methods are specific for each material.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Samples</th>
<th>cellulose</th>
<th>methyl cellulose</th>
<th>Na carboxy-methyl cellulose</th>
<th>cellulose acetate</th>
<th>ethyl cellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cellulose</td>
<td>PASS ( p=1 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
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<tr>
<td></td>
<td>methyl cellulose</td>
<td>FAIL ( p=0 )</td>
<td>PASS ( p=0.999982 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
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<tr>
<td></td>
<td>Na carboxy-methyl cellulose</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>PASS ( p=0.99777 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
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<tr>
<td></td>
<td>cellulose acetate</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>PASS ( p=0.99998 )</td>
<td>FAIL ( p=0 )</td>
</tr>
<tr>
<td></td>
<td>ethyl cellulose</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>FAIL ( p=0 )</td>
<td>PASS ( p=1 )</td>
</tr>
</tbody>
</table>

Figure 1. Raman spectra of cellulose powder collected with 785nm and 1064 nm laser excitations. Spectra manually offset for clarification.

Table 1. Specificity matrix for cellulose and cellulose derivatives
Figure 2a shows the “Pass” result for the cellulose sample against a cellulose method. Figure 2b shows the “Fail” result for the methyl cellulose against the cellulose method.

**Figure 2.** (a) “Pass” result for cellulose sample against a cellulose method ($p=1$) and (b) “Fail” result for methyl cellulose sample against the cellulose method ($p=0$)

**Conclusion:** The NanoRam-1064 is effective for minimizing fluorescence in naturally-derived materials, allowing easy verification of crucial pharmaceutical material such as cellulose with multivariate analysis and handheld Raman spectroscopy.

**Authors:**
Vanessa Mayle  
Technical Content Specialist  
B&W Tek, LLC

Kristen Frano  
Applications Manager  
B&W Tek, LLC