Near Infrared Spectroscopy (NIRS) has been used in many forms in the past to monitor the endpoint of powder blending processes in many types of mixers used in the pharmaceutical, food and consumer product sectors.

MicroNIR PAT-W is an ideal choice of spectral sensing system for monitoring the endpoint of powder blending processes in the various forms of tumble blender available for the following reasons,

1. It has no moving parts, making it robust for process conditions.
2. It has built in WiFi connectivity and an internal battery that allows it to be easily interfaced with tumble blenders.
3. It measures high quality spectra rapidly allowing these spectra to be collected during each rotation of the blender.
4. It has an intuitive user interface and OPC connectivity that allows results to be sent to a control system for real time feedback and process control.
5. The high signal to noise ratio of the spectrum measured by MicroNIR PAT-W is suitable for most of the applications commonly encountered in blend monitoring.

These features alone allow traditional methods, such as thief sampling to be eliminated as they require the process to be physically opened to the environment and sampled in a non-representative way and they also require samples to be sent to a QC laboratory, thus reducing the Overall Equipment Efficiency (OEE) and keeping a product in a state of Work in Progress (WIP) until a result for uniformity is obtained.

NIRS can be used in a Quality by Design (QbD) manner where the blending process is continued until the desired state of the product has been reached. This desired state of blend uniformity lies within the design space established for the process. In this way, a 21st Century approach to pharmaceutical quality can be implemented, allowing 100% quality assurance for each and every batch, in-line, which also allows an organization to move into a continuous verification quality paradigm.

The following white paper describes how MicroNIR PAT-W was integrated into a commercial manufacturing environment for the purposes on monitoring the endpoint of a granulated product in real time.

Equipment and Process Description

For the purposes of this example, a 500 Kg double cone blender was utilized. The rotation speed was set to 15 rpm, resulting in 1 rotation every 4 seconds. MicroNIR PAT-W was interfaced to the material addition port end of the blender using a Viavi Solutions standard PAT lid mounting kit. The mounting kit has a sapphire window inserted so that it is flush to the lid of the blender and makes no protrusion into the process itself. The complete blender/instrument interface is shown in figure 1 below.
The MicroNIR PAT-W instrument was auto-integrated against a white spectralon reference material and the scanning conditions in table 1 were used to collect data on the process.

<table>
<thead>
<tr>
<th>Acquisition Mode</th>
<th>Diffuse Reflectance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration Time (ms)</td>
<td>8.9</td>
</tr>
<tr>
<td>Scan Count</td>
<td>100</td>
</tr>
<tr>
<td>Scan Mode</td>
<td>Autonomous (Gravity)</td>
</tr>
<tr>
<td>Delay Time (ms)</td>
<td>333</td>
</tr>
</tbody>
</table>

Table 1: Optimized scanning conditions for NIRS blend endpoint monitoring.

The standard validated blending time for the chosen process was 15 mins. The product consisted of an active material (40%) and 4 other excipients. After the validated endpoint time was reached, magnesium stearate (0.5 w/w%) was added in a staged process with a final blending time of 1 minute before the blend was sampled using traditional methods. The MicroNIR PAT-W was configured to scan both main blending and lubricant addition and the raw spectra of the entire set for one batch is shown in figure 2.

Assessment of figure 3 shows that the real endpoint of the process occurs around the 150 rotation point compared to the traditional approach which rotates the blend 430 times. The NIRS method has the advantage of reducing blend time, but more importantly, not exposing the blend to overprocessing, which may lead to the production of fines and result in issues during compression.

Validation Against a Second Blend

The MicroNIR Pro software environment allows the application of developed models to new data in both routine analysis methods and in a test environment. Figure 4 shows the application of the method to a new batch of material.

A second derivative pre-treatment was applied to the data using 5 smoothing points and the method of Moving Block Standard Deviation (MBSD) was used to assess the endpoint. A block size of 30 was chosen for the analysis based on prior knowledge obtained from the uniformity of test blends and the MBSD chart for the data are shown in figure 3.

Assessment of figure 3 shows that a similar endpoint was also achieved for the second batch of material. The process would continue for every batch produced in a continuous verification environment. It would typically take 5-10 batches to fully refine the endpoint criteria and with the new features in MicroNIR Pro software, advanced control scripts can be developed based on multiple criteria.

Figure 1: Interface of the MicroNIR PAT-W into the lid of a double cone blender.

Figure 2: Raw NIR spectra obtained for a blend uniformity analysis.

Figure 3: Moving Block Standard Deviation (MBSD) Chart for blend uniformity analysis.

Figure 4: Application of the Moving Block Standard Deviation (MBSD) model to a validation batch.
Assessing Lubricant Mixing

Lubricants such as magnesium stearate are only added to blends in small proportions (0.5-2% w/w% is typical). Even though the lubricant only makes up a small component of the blend, its affect on the blend structure and NIR spectra are observable. Figure 5 shows the MBSD chart for the blending of magnesium stearate into the final blend using a block size of 5.

Figure 5: Monitoring lubricant blending using MicroNIR PAT-W

Figure 5 shows that after the 1 minute of blending time, the blending curve reaches a minimum point. Figure 6 shows the application of this model to the second batch of data, where a similar trend to a minimum point was observed after 1 minute of blending.

Summary

This application showed for the particular product and blender combination, MicroNIR PAT-W and the MicroNIR Pro software suite were able to produce models that detected the endpoints of the main blending process and the lubrication step. MicroNIR Pro software provides many tools for the development of endpoint models and this example highlights one of many possible applications.