

## Fit-for-Purpose MicroNIR™ Spectrometer Facilitates Quality-by-Design (QbD) Adoption

In recent years, the FDA has emphasized applying QbD principles to the development and manufacture of pharmaceuticals. Implementing QbD methodologies along with on-line, at-line, and in-line process analytical technology (PAT) tools leads to a greater understanding of both the process and the product. This enhanced understanding enables systematic and scientific process-control strategies and real-time process feedback, as well as perpetual knowledge building of the process itself. The benefits are considerable: higher-quality products, improved product consistency, reduced product development cost, reduced manufacturing cost, and faster regulatory approvals.

Near-infrared (NIR) spectroscopy is one of the PAT tools that can be used at various stages of process manufacturing, from raw material verification, moisture content monitoring in drying processes, and end-point monitoring in blending to active-ingredient tablet assay. Conventional NIR spectrometers are typically expensive and bulky systems designed with Czerny Turner grating-based systems or Fourier-transform technologies. Fourier-transform infrared technologies in particular require high precision and costly mechanical components.

However, many process-monitoring and control tools are designed for multipurpose solutions, and exceed the needs of a specific application. This excess capability increases capital investment costs. In these situations, the MicroNIR spectrometer from JDSU is particularly appropriate. Weighing less than 60 g and measuring less than 50 mm in diameter (see Figures 1 and 2), it is more practical to cost-effectively implement as an on-line and at-line tool for process development, process transfer, and manufacturing process monitoring and control.



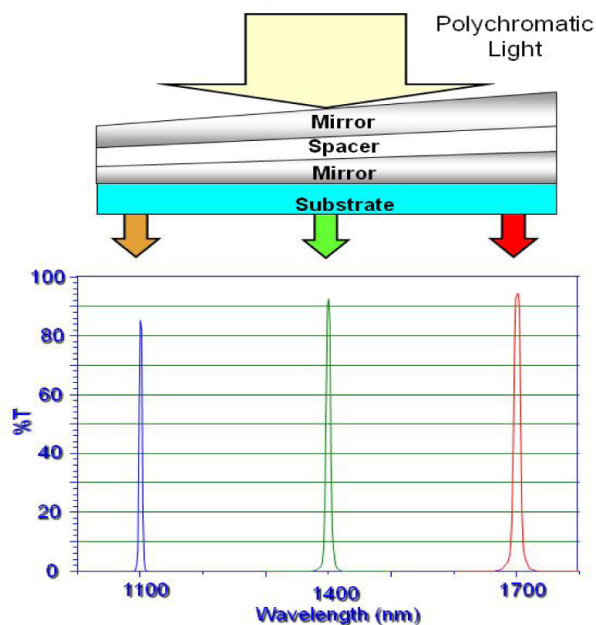
**Figure 1. The MicroNIR spectrometer**

Not only suitable for use on batch processes, the MicroNIR enables newly-developed continuous manufacturing processes that use multiple NIR sensors across the entire process flow—MicroNIR spectrometers can be installed as simply and as ubiquitously as temperature sensors.



**Figure 2. The MicroNIR enclosed in a stainless-steel housing suitable for PAT applications**

The MicroNIR uses a linear variable filter (LVF) component mounted over a diode array detector that separates incoming light into individual wavelengths. The working principle of the LVF is provided in Figure 3. The spectrometer integrates the light source and readout electronics inside a small construction. It can be mounted directly on the window of a blender, a fluid bed dryer, or any other process without the need for costly fiber optic probes. It can also operate in a wireless configuration, allowing use on rotating blenders for end-point monitoring.



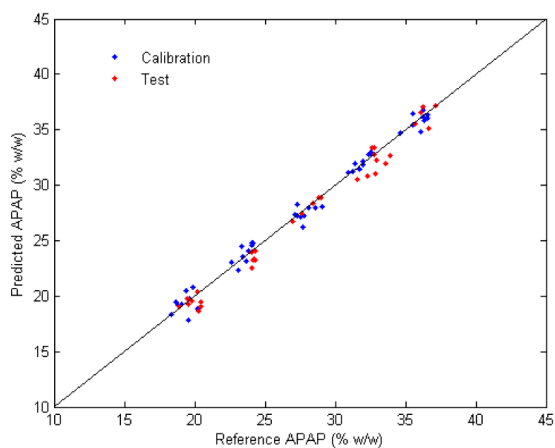
**Figure 3. Working principle of an LVF component—the wedge in the thickness is applied to all layers comprising the bandpass filter design**

### At-Line Non-Destructive API Tablet Assay

The MicroNIR spectrometer was recently evaluated as part of a study related to NIR calibration life-cycle management conducted at Duquesne University, Center for Pharmaceutical Technology. A calibration model was developed for the acetaminophen content of tablets using the spectrometer.

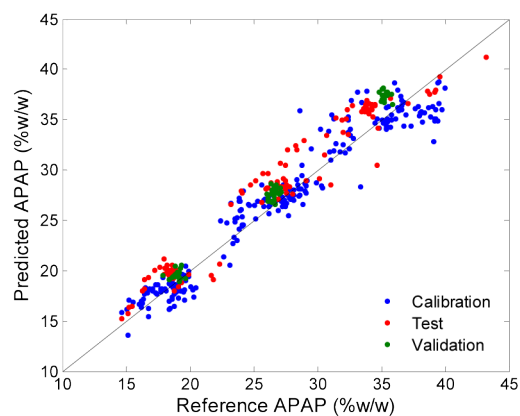
Tablets made of acetaminophen, lactose, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate were created at laboratory and pilot scales. A total of 165 samples were available for calibration, 100 for test, and 60 for validation. The data had seasonal variability (high and low humidity), batch variability (different granulations), and manufacturing variability (lab and pilot scales). The active content of each tablet was measured by high-performance liquid chromatography (HPLC) and an average standard error of 0.83% was determined for all tests.

In controlled laboratory conditions, 45 calibration and 35 test tablets produced with the same granulation and with limited environmental changes, the RMSEP value using the MicroNIR spectrometer was 0.87%, w/w. PLS results are shown in Figure 4.



**Figure 4. PLS results of calibration and test of acetaminophen content in tablets prepared and tested under controlled laboratory conditions**

In the presence of significant environmental variability described earlier, which is more characteristic of typical manufacturing conditions, the RMSEP was 1.54%, w/w. Results are shown in Figure 5.



RMSEC	RMSEP <sub>Test</sub>	RMSEP <sub>Val</sub>	R <sup>2</sup> Cal	R <sup>2</sup> Test	R <sup>2</sup> Val
1.84	2.22	1.54	0.93	0.95	0.99

(%, w/w)

**Figure 5. PLS results of calibration, test, and validation of acetaminophen content in tablets prepared and tested under variable environmental conditions; statistical differences are due to variability differences included in each set**

## Conclusion

The study results show great promise towards the successful implementation of affordable NIR spectrometers as fast and non-destructive analytical tools for tablet analysis that are essential for making timely business-critical decisions.

Not only is the MicroNIR spectrometer useful as an at-line and on-line tool for monitoring batch manufacturing processes, it will be an essential on-line tool in the new and emerging continuous manufacturing processes that require continuous monitoring and real-time process control.