Combining a Compact Process Analytical Technology (PAT) Analyzer, Analytics, and Applications in a Quality by Design (QbD) Environment

Technological advances in analytical instrumentation and computing systems have allowed many industries to better monitor and control business critical processes. This has enabled proactive, not reactive approaches to real-time quality assurance and product release. Until the advent of QbD and subsequent PAT initiatives, pharmaceutical and related industries were not fully equipped with the right guidance and supporting architecture to gain the benefits of modern, state-of-the-art quality control and assurance systems.

QbD is not a single approach to the development and maintenance of a product's lifecycle, but the utilization of many analysis and analytical tools and a modern approach to quality by subject matter experts. For many years, near infrared (NIR) spectroscopy has been the PAT tool of choice for process monitoring due to its adaptability and analytical precision. There are many applications where NIR has been utilized for process monitoring in a wide number of industrial sectors and many publications exist in the literature for the interested reader to obtain.

The MicroNIR™ spectrometer from Viavi Solutions™ (formerly JDSU Optical Security and Performance) has revolutionized miniaturization of analytical instrumentation and has allowed the installation of such devices into process environments where larger, less robust instrumentation of the past has not been able to be utilized. At the time of the original PAT framework document release, NIR instrumentation was bulky, wireless technology was only in its infancy, and the lack of computerized quality-management systems capable of handling the large amounts of data that PAT-based instruments can generate were all obstacles to effective implementation. In today's environment, these obstacles are no longer a problem and there are many guidance documents available for implementing PAT and QbD in a pragmatic way.

So, why is there still resistance to change? Maybe there is still a belief that the implementation of PAT for unit operations alone cannot be justified and that in order to gain the most out of a QbD approach, the whole process must be changed all at once. This is fundamentally an unrealistic approach since the project can get very big, very fast and the "trees cannot be seen for the forest." Under the philosophy of design of experiments (DoE), the best insights are gained when the problem is broken down into smaller parts. In this case, deeper insights into process behavior and its relationship to formulation can be better understood. Information with PAT-generated data can provide a chemical probe into the system allowing subject matter experts to

justify at the physical, chemical, or biological level any conclusions drawn from the data. In a QbD environment, this is absolutely critical as its purpose is to allow a manufacturer to demonstrate enhanced process knowledge and understanding to the regulatory bodies and not the other way around.

To turn this knowledge into a real-time quality assurance system, control models are required. This has primarily been the domain of multivariate analysis (MVA), sometimes known as chemometrics when applied to chemical data. NIR spectra by definition are multivariate in nature and the specific absorbance bands relate to chemical phenomena occurring as the sample changes during processing. In product blending operations, these changes in spectra are being associated with blend uniformity or consistency. The NIR spectrometer can be attached to any blender configuration (dynamic or static) and when a new sample is scanned, it provides a snapshot of the state of uniformity of the product in the blender without having to physically sample (and avoid the introduction of additional sampling errors).

Utilizing wireless communication protocols, real time assessment of blend uniformity can be made allowing the process to be stopped at a "desired state." It is believed that this point will result in fewer processing issues in unit operations downstream. When NIR is implemented for such processes in a continuous manufacturing (CM) environment, results obtained are used to determine whether the samples measured go on to further processing or are ejected off the process.

The purpose of this paper is to provide a practical example of how a scientist or engineer may approach the development of a monitoring or control strategy for powder blending operations, a common process used in many industries. Solid blending processes are one of the least understood of all industrial processes and smaller, more portable NIR analyzers have allowed greater insights into the mechanics of powder mixing. When combined with a DoE and MVA approach, QbD systems are possible that continuously verify that every batch is produced consistently based on the best knowledge management tools under a Pharmaceutical Quality Management System (PQMS).

Experimental System and Equipment

No matter the industry, powder blending operations have the same objective: to ensure components are mixed together consistently such that the product's performance is assured. The main difference between the industrial applications is the risk to be taken regarding the final state of uniformity. For example, if the blending of a washing powder is compared to the blending of a drug substance with a high therapeutic index (TI), then a small change in consistency of the washing powder is insignificant to the end user compared to under or overdosing a drug product. Risk should be used in all cases to assess business and customer safety, but also should be used pragmatically: it should not take up so much time that it stifles the main objective of the technical implementation.

The system chosen for this study is a blend of coffee, sugar and creamer blended in proportions defined using a design of experiment known as a mixture design. The system was chosen based on the following criteria:

- Coffee granules purchased commercially are usually consistent in nature and possess a large particle size with respect to the sugar and the creamer used. Also, coffee granules are highly friable (they break down easily under mechanical influence, such as attrition caused by the blending process itself, and this should be seen as a physical change in the NIR spectrum).
- The formulation of an acceptable coffee mixture does not include 100% of one component. In this case, a target formulation was chosen and the mixture components varied in a small but deliberate manner in order to induce a response when analysed by DoE or MVA.
- All components are readily available and are representative of materials used in many industrial applications. In the case of this system, the risk is that the final formulation does not satisfy the taste requirements of the coffee drinker. This is highly subjective, therefore it is a business risk more than a consumer risk as the product is not deemed acceptable. It is the job of the company to position the right formulation into the right market.

Now that risk has been mitigated through pragmatic means, a technology for assuring uniformity must be chosen. For this application, the MicroNIR PAT (Viavi Solutions, Santa Rosa, CA, USA) system was chosen. It is a solid-state spectrometer system utilizing a linear variable filter (LVF) for collecting spectra over the wavelength range 950 – 1650 nm. The MicroNIR PAT system is equipped with internal Wi-Fi connectivity sending spectral data to the main controlling software at predefined intervals. The MicroNIR PAT system was connected to a 5 kg V-cone blender rotating at 25 rpm. An internal accelerometer is utilized to collect spectra at optimized points during the blender rotation and these spectra are stored in order to develop blend uniformity models or to assess a new blend against an existing model.

To develop the test blend formulations, the Design Expert™ software package (Version 9.04, Statease Inc., Minneapolis, MN, USA) was used. The test system was based on the following component constraints (in % of total formulation).

$$18.8 \leq \text{Coffee} \leq 25.0$$

$$12.5 \leq \text{Sugar} \leq 18.8$$

$$56.3 \leq \text{Creamer} \leq 62.5$$

The task of the formulation scientist in this case is to define a target formulation, in this case

$$\text{Coffee} = 23\%$$

$$\text{Sugar} = 17\%$$

$$\text{Creamer} = 60\%$$

From there, a suitable variability around the target is defined to determine if there is a more preferred formulation in terms of sensory appeal or if there is a point where blending of components is physically optimized. Note in the design, the blend components are standardized such that there is not 100% of one component in the blend; there is no point in making a blend of 100% sugar. This is why the constrained mixture design was used.

A total of 7 experimental blends were generated using a simplex centroid design. Table 1 provides the formulation details for the experiment.

Table 1. Coffee blend formulation components for NIR blending study

Blend	Coffee (%)	Sugar (%)	Creamer (%)
Design 1	19	19	62
Design 2	25	13	62
Design 3	25	19	56
Design 4	22	16	62
Design 5	22	19	59
Design 6	25	16	59
Target	23	17	60

Each formulation was weighed out and placed into the blender using the standardised order: coffee, sugar, and creamer. Dark current and white reference, using a Spectralon standard, were collected before mounting the MicroNIR PAT onto the V-cone blender using a sanitary fitting. Figure 1 shows the position of the blender where the MicroNIR PAT was mounted for the purposes of this experiment.

Figure 1. Mounting of the MicroNIR PAT system into the V-cone blender

Once loaded, MicroNIR PAT started collection of spectra when the blender was set into operation, and the process was allowed to continue for 300 revolutions before stopping. The stored spectral data were sent to The Unscrambler® X (Version 10.3. CAMO Software, Oslo, Norway) for visualization, pre-processing, and data analysis.

Results and Interpretation

According to ICH Q2(R1) on analytical method development, the analytical method under investigation must be assessed for specificity and selectivity. Specificity relates to the method's ability to isolate the component in question in the presence of other components or interferents. Selectivity is the method's ability to detect concentration changes in the blend components. Both criteria must be established in order to develop a method for use in pharmaceutical or related industries.

The easiest way to establish specificity and selectivity in NIR spectroscopy is to scan the raw material components and compare the data using a suitable pre-processing method. This is typically achieved using a derivative function. Figure 2 compares the blend components using a second derivative (Savitzky-Golay, 5 point smooth, 2nd order polynomial) transform.

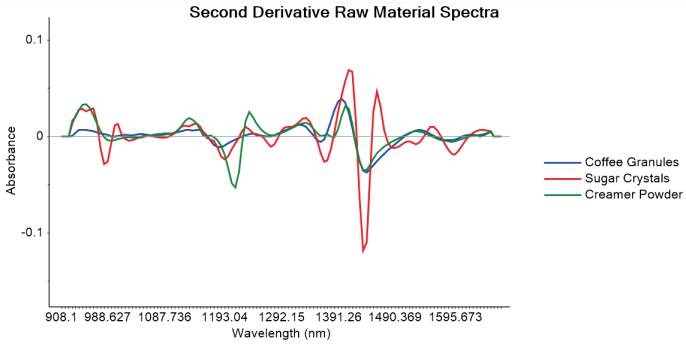

Figure 2. Second derivative transformed raw material spectra for coffee blends

There are three distinct spectral regions for monitoring sugar uniformity at 980, 1365, and 1600 nm (corresponding to carbohydrate absorptions) and one region at 1210 nm for the creamer related to –CHx absorptions. In this case, coffee does not provide a distinct absorption band and an assumption has to be made that the blend is uniform if sugar and creamer are uniform.

Each formulation listed in Table 1 was prepared and blended. Figure 3 shows the pre-treated spectra of the target formulation blend study. This figure shows that the 4 wavelength regions isolated in Figure 2 all show variations expected in a blending process. The greatest variations occur in the wavelength region between 1100 – 1500 nm. This was the region used to perform moving block analysis for blend uniformity studies.

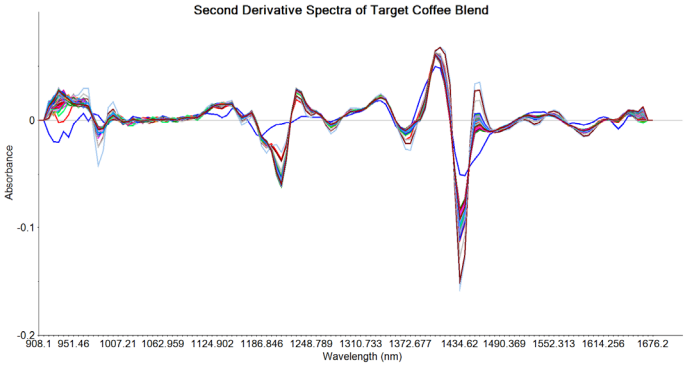

Figure 3. Spectral variations observed for target coffee blend analysis by NIR spectroscopy

Figure 4 provides the results of applying a moving block standard deviation (MBSD) and moving block mean (MBM) to the data using a block size of 5 (step size of 1) in the region 1100 – 1500 nm for the target coffee blend.

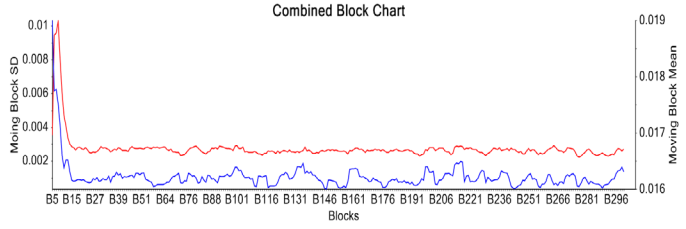

Figure 4. Moving block standard deviation and mean charts for target coffee blend

The MBSD chart is an indication of the spectral variability in the data set. A minimum value close to zero is ideal as this represents a state where the spectra in the chosen block are similar to each other. The MBM is a secondary measure of uniformity. This plot is used to determine that the spectral profile is remaining the same within the block. The two criteria of minimum MBSD and constant MBM are an indication of chemical and physical uniformity of the system.

For each formulation defined in Table 1, the optimal number of rotations was determined by isolating the minimum MBSD and the point where MBM is stable. Stability in an MBM plot must be defined based on the mean particle size distribution of the materials being blended. Experience with the product being formulated will allow a process engineer to define upper and lower bounds on the mean spectrum and once a blend simultaneously reaches this point and the MBSD is minimized, this is a good indication that the blend has reached uniformity. In practice, MBM is used to ensure that the blend does not suffer from attrition to the point where the particle size is too fine. This could lead to process issues further downstream. The ratio of MBSD and MBM leads to a plot of % relative standard deviation (%RSD) for the blending process. Typically, %RSD values of 5% or lower are a good indication of uniformity.

The process of defining optimal blend rotations is empirical initially. However, once a better understanding of the system is made through the use of some repeated experiments on the optimal formulations, a control strategy can be implemented. Where a lower limit on MBSD can be used as a first endpoint criteria followed by either an analysis of moving slope on the MBM curve or a criteria such that if X points out of Y observations lie within the upper and lower bounds of MBM, then the blending operation can be considered complete.

Figure 5 shows the response surface for the formulations studied based on their optimal blend rotations. This figure provides a map for which to better understand the blending properties between the components and to isolate the best blend and its optimal end point for process monitoring.

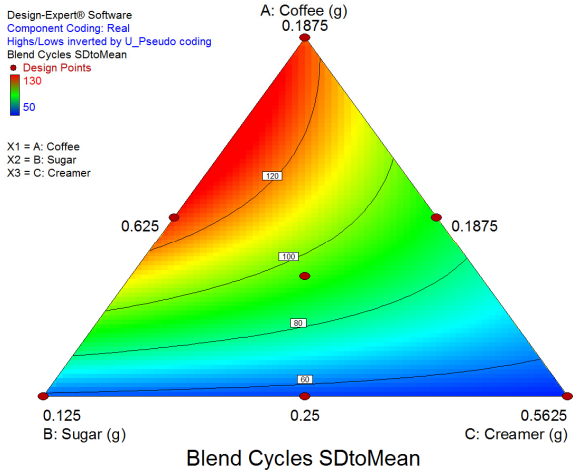

Figure 5. Response surface for optimal blend time for coffee blends study

The response surface in Figure 5 shows that there is a small quadratic behavior in the blending that is mainly a synergistic relationship between coffee and sugar at higher levels of creamer content. It takes longer for coffee and sugar to blend when there are higher quantities of creamer in the blend.

This behavior becomes more linear when there are higher levels of coffee and sugar, therefore, the creamer content may be viewed as a critical component to control, or consider, when developing such formulations.

Figure 6 shows the response surface for preference of the blends scored as an average over a number of taste testers on a scale from 1 to 9. This data is used by marketing professionals to determine where the majority of a population would purchase such a product were it on the market.

There are now two criteria that must be jointly optimized: preference and blend optimization. A company may wish to target a preference value greater than 7, while keeping blend rotations lower than 100 to ensure the product appearance does not become too fine-powdery. Figure 7 shows joint optimization results for preference and blend rotations.

The joint optimization shows that there does exist a region, sometimes referred to as a design space, where both optimization criteria are met simultaneously. Since preference would be the most important factor to optimize, it is the formulator's task to choose a blend in the yellow region of the plot that minimizes the cost of the formulation components, while maximizing the preference.

The methodology used for the coffee blend analysis is a typical procedure used in the pharmaceutical or other industries for better understanding and controlling of powder blending operations which ultimately lead to more consistent product and higher quality.

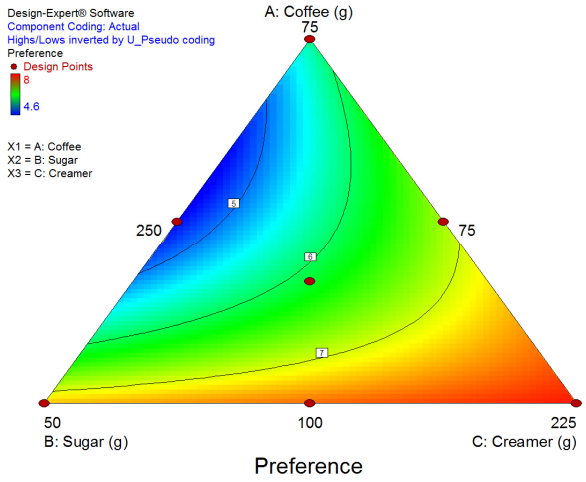

Figure 6. Preference response surface for coffee blend study

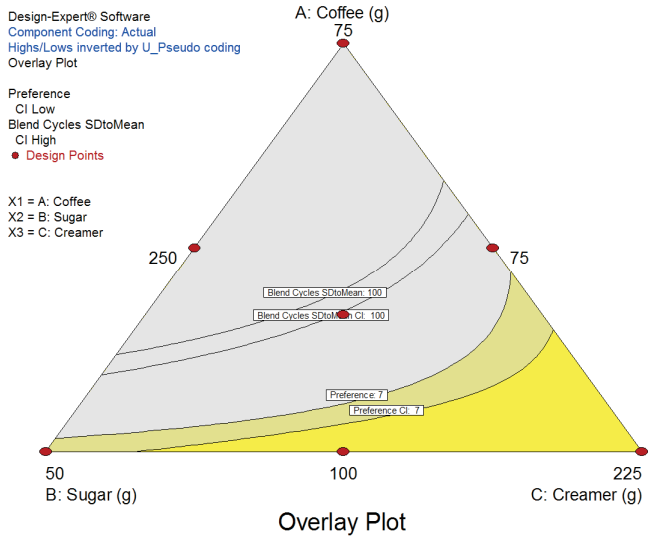

Figure 7. Joint optimization of product preference and blend optimization

Conclusion

The aim of this study was to determine the suitability of a portable NIR spectrometer to monitor the blend uniformity of three components used to make an instant coffee formulation. The MicroNIR PAT spectrometer proved to be robust and reliable for this application and the use of a designed experiment and multivariate analysis provided insights into the mechanism of the way the ingredients blended with each other.

The design was extended to include a measure of preference for the coffee blends resulting in a second response surface showing which formulations would be most acceptable. The joint optimization allows both the formulator and the process engineer to optimize the product and the process used to manufacture it.

This is exactly the goal of QbD in the pharmaceutical industry. Extending this study to a hypothetical drug product, the formulator would design a range of formulations to test for blend uniformity. After understanding how the components blend with each other using NIR spectroscopy, better product and process understanding is gained. The new formulation would then be tested for performance characteristics such as dissolution and friability and the optimal formulation would be chosen for manufacturing. Using the in-line NIR spectrometer, blend uniformity would be assessed in a continuous verification manner.

Americas +1 800 254 3684
Europe +33 1 30 81 50 41
Asia Pacific +86 512 6956 7895
E-mail ospcustomerservice@viavisolutions.com

pat-an-osp-ae
30179570 000 1015