APPLICATION NOTE

FT-NIR Spectroscopy

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A Comparison of Two FT-NIR Sampling Techniques for SIMCA Classification of Spectroscopically Similar Pharmaceutical Raw Materials

Introduction

NIR Spectroscopy is a useful technique throughout various stages of the manufacturing process but is particularly useful for raw materials identification and verification. If the materials to be identified are spectroscopically dissimilar, it is often only necessary to use a simple distance measure such as a spectral difference for identification. If the spectra are similar, on the other hand, it may be necessary to use more sophisticated techniques which take into consideration both the intra- and inter-material spectral variation for identification and classification. The SIMCA (Soft Independent Modelling of Class Analogy) algorithm, a Principal Component Analysis (PCA) method, provides such an example.

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This application note compares two different sampling approaches used in FT-NIR spectroscopy to discriminate between six spectroscopically similar raw materials used in the pharmaceutical industry. These materials were sampled using a Spectrum Two N™ FT-NIR spectrometer with a hand-held diffuse reflectance fiber optic probe, also known as the Remote Sampling Module (RSM), and a Near-Infrared Reflectance Module (NIRM).

Polyvinylpyrrolidone Products

Polyvinylpyrrolidone (PVP) products, also referred to as povidone or polyvidone, are used in the pharmaceutical industry as a synthetic polymer auxillary for dispersing and suspending drugs. They also act as disintegrants and tablet binders. In this application note, six povidone products have been studied (PVP K12, PVP K25, PVP K30, PVP K90, copovidone, and crospovidone).

Soluble polyvinylpyrrolidone (povidone) is one of the most widely used pharmaceutical auxiliaries. It is a linear polymer with different degrees of polymerization, which results in polymers of a wide range of molecular weights. The average molecular weight is expressed in terms of the 'K-Value'.

Vinylpyrrolidone-vinyl acetate copolymer (copovidone) is a water-soluble povidone product which contains the two components in a 3:2 ratio. Copovidone is somewhat more hydrophobic than povidone and produces less brittle films, owing to the vinyl acetate component.

Crospovidone, an insoluble povidone, is a cross-linked polymer and is considered one of the 'superdisintegrants' for tablets.[1]

NIRM vs. RSM

The Spectrum Two N FT-NIR spectrometer can be used with a Remote Sampling Module (RSM) or Near-Infrared Reflectance Module (NIRM), as shown in Figure 1. These sampling accessories can be used for a variety of applications and each provide their own benefits.

NIR fiber optic systems offer the potential to take the measurement directly to the sample and can provide real sampling advantages in situations where it is impractical or inconvenient to take sample aliquots and transfer to the lab for analysis. As an example, in raw materials testing of powder materials in the warehouse, it is possible to collect the spectrum from the test sample by measuring directly through the sample bag in its container, or through the sample vial container to avoid cross-contamination risk between samples. Spectra may also be collected by placing the fiber probe tip either directly onto the sample, or slightly above at a fixed distance. Additionally, the probe may incorporate electronic control of the instrument and display information at the probe itself, so operators can control the measurement and analysis from the probe handle.

The NIRM accommodates disposable glass vials and petri dishes. Petri dishes can be placed onto a magnetically detachable spinner to provide a larger surface area for sampling, resulting in more repeatable measurements for inhomogeneous samples.

Figure 1. Spectrum Two N FT-NIR spectrometer with RSM (top) and NIRM with vial holder (bottom) accessories.

Additionally, alternate measurements of the sample and an internal reference material are taken throughout the sample scan to eliminate the effect of drift. The NIRM is ideal for applications in which removing the sample from the container is not an issue.

The RSM and NIRM can both be used in conjunction with Spectrum Touch™ software, a workflow-oriented interface, allowing users of any background to analyse materials.

Experimental

Six different povidone products used in pharmaceutical formulations were supplied (Copovidone, crospovidone, PVP K12, PVP K25, PVP K30 and PVP K90). The NIR spectra of all products were recorded using a PerkinElmer Spectrum Two N FT-NIR Spectrometer fitted with the NIRM and RSM, using the instrument parameter settings shown in Table 1. For each material, and for each data collection method, 15 spectra were collected using Spectrum™ 10 software. In total, 90 spectra were collected for each data collection method.

The analysis was initially performed using the NIRM, and then repeated using the RSM to compare their discriminatory abilities. When using the NIRM, samples were placed into 10 mm diameter glass vials, which were then secured in a vial holder. Replicates were generated by scanning different portions of each product in different vials. When using the RSM, the probe was simply immersed into the sample in its sample container. RSM replicates were generated by immersing the probe into different areas of the sample and the probe tip was cleaned with tissue and isopropyl alcohol between materials. Alternatively, to avoid cleaning of the probe tip, the probe can be placed at a fixed distance over the sample.

Table 1. Spectrum Two N instrument parameter settings.

Spectrum Two N Instrument Parameter Settings	
Scan Range	10,000 – 4,000 cm^{-1}
Resolution	16 cm^{-1}
Number of Scans	64

PerkinElmer AssureID™ software was used, with a SIMCA algorithm, to create PCA models for the two data sets collected by the different sampling techniques. The spectra for each povidone product were randomly split into calibration and validation datasets, in which 80 % of spectra were used for building the SIMCA model and the remaining 20 % used for independent validation. All spectra were pre-processed using MSC, first derivative (13 point) baseline correction, and the spectral range adjusted to 9,000 – 4,200 cm^{-1} (Figure 2).

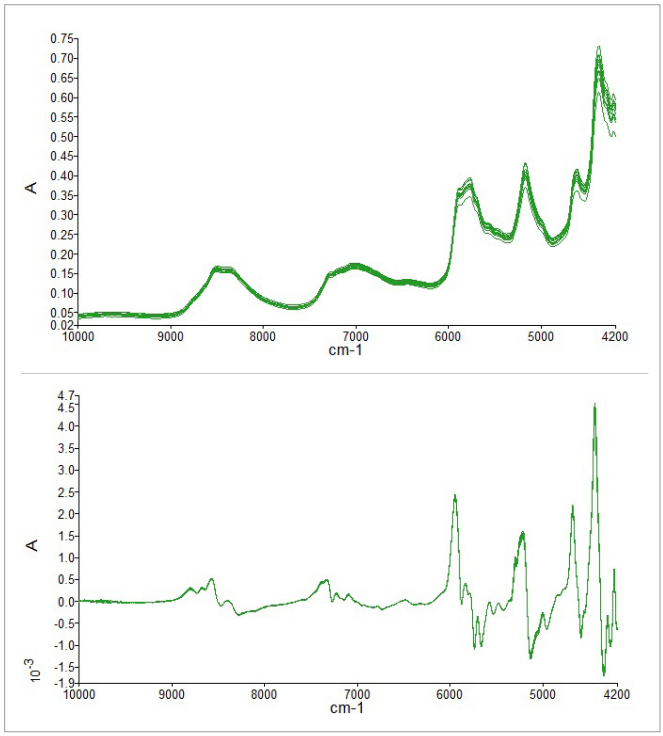

Figure 2. Example raw (top) and pre-processed (bottom) spectra of PVP K25 taken using the NIRM.

Results

Model Creation

Representative spectra of the products recorded on the NIRM are illustrated in Figure 3. The curves have been offset for clarity, however, some of the spectra are visually very similar.

The global PCA models, using the NIRM and RSM, are demonstrated in Figure 4, with each of the hyperspheres representing the six different materials. Each hypersphere encapsulates an area of 99 % reliability surrounding a material population. This means that there will be a 1 % probability of a sample being misclassified with respect to that material. The global PCA plots provide an overview of the complete model and are useful to help understand relationships between material types. Using both sampling techniques, the model clusters for PVP K90 are not as tight as the rest of the materials. This can be explained by the more crystalline nature of the sample. In general, the spectra for the samples collected on the NIRM are more tightly clustered than those collected on the RSM due to slight differences in sampling repeatability. Figure 5 demonstrates the mean and standard deviation of Co PVP spectra taken using the NIRM and RSM.

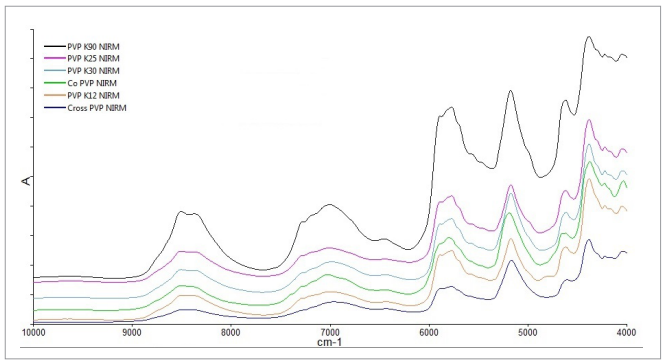

Figure 3. Example spectra of six different povidone products scanned using the NIRM.

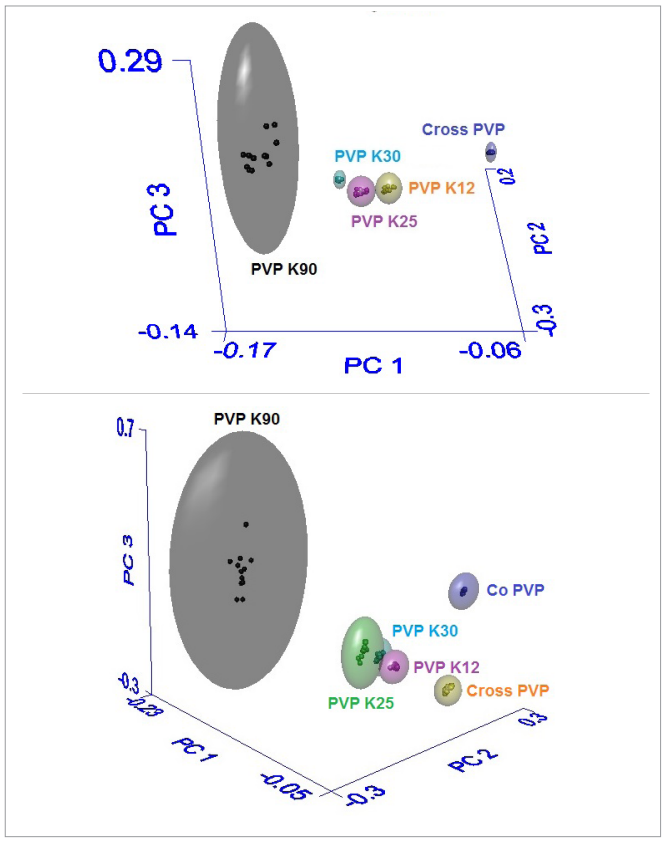

Figure 4. Povidone SIMCA models using the NIRM (top) and RSM (bottom).

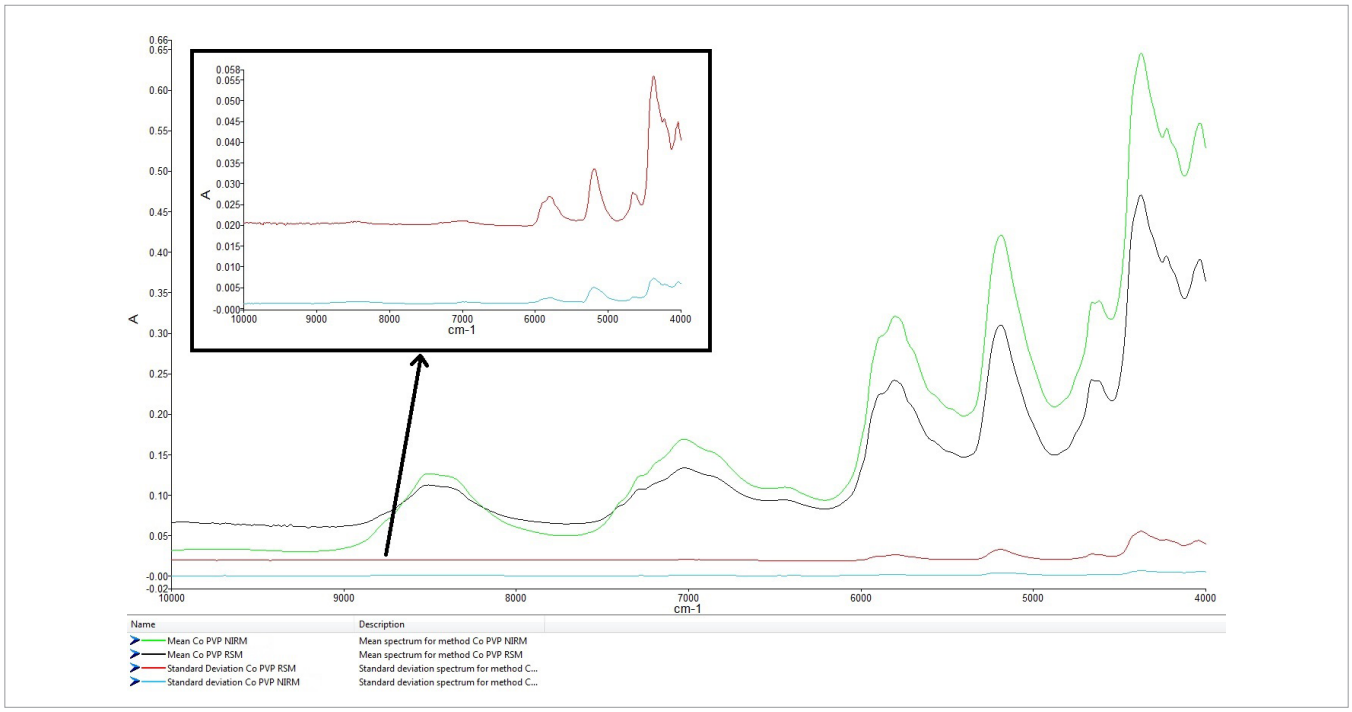

Figure 5. Mean and standard deviation spectra (n = 12) of Co PVP using the NIRM and RSM.

The models were evaluated using SIMCA diagnostics to ensure that none of the batches of spectra overlapped. The diagnostic report provides the inter-material distances which is an arbitrary measure and estimate of the separation between two materials relative to the spread within each material. Tables 2 and 3 show the inter-material distances for the six different povidone products on the NIRM and RSM, respectively. Both sampling techniques demonstrated good material separation. However, sampling using the NIRM provided the best separation between materials as indicated by the larger inter-material distances.

The built-in model diagnostics provides a classification performance report which shows the recognition and rejection rates (%) for each material. During this process, each standard spectrum is checked to ensure that the ones from a single class fit that class (recognition), and standards from other classes are rejected (rejection). The two rate columns should ideally report 100 % for each material type. For both NIRM and RSM data sets, the two rate columns reported 100 % recognition (12/12 standards) and 100 % rejection (60/60 standards) for all materials, indicating good separation of each class of compound.

A Coomans plot, as shown in Figure 6, shows the model distances between two classes of material – in this case, PVP K25 and PVP K30 exhibit clear separation using the RSM. In both NIRM and RSM models, there are no overlaps between the materials, meaning there is a low chance of misclassification.

Table 2. Inter-material distances of the six povidone SIMCA models using the NIRM.

Material	Co PVP	Cross PVP	PVP K12	PVP K25	PVP K30	PVP K90
Co PVP	-	36.90	44.40	43.30	40.70	9.72
Cross PVP	-	-	14.90	16.60	15.90	9.21
PVP K12	-	-	-	9.94	10.20	6.89
PVP K25	-	-	-	-	6.33	5.41
PVP K30	-	-	-	-	-	6.95

Table 3. Inter-material distances of the six povidone SIMCA models using the RSM.

Material	Co PVP	Cross PVP	PVP K12	PVP K25	PVP K30	PVP K90
Co PVP	-	15.40	15.10	14.70	14.50	10.20
Cross PVP	-	-	10.40	12.50	8.99	9.84
PVP K12	-	-	-	4.28	4.59	3.88
PVP K25	-	-	-	-	5.04	2.45
PVP K30	-	-	-	-	-	3.85

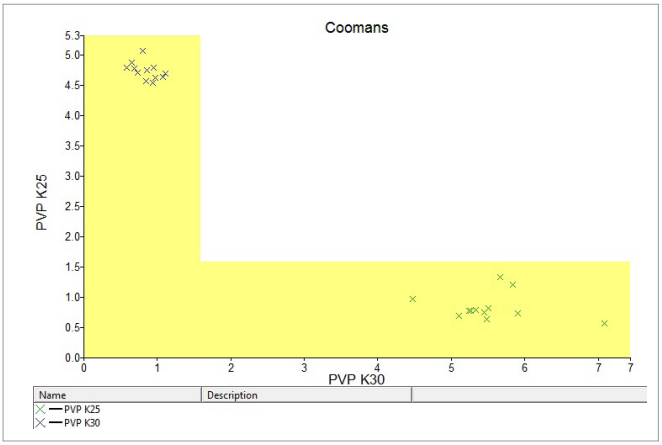

Figure 6. Coomans plot showing separation of PVP K25 and PVP K30.

Validation

Using both sampling techniques, the SIMCA models were tested using independent validation sample sets. Tables 4 and 5 demonstrate the SIMCA algorithm correctly identifying 100 % of the validation standards for the NIRM and RSM, respectively. The 'Specified Material Total Distance Ratio' gives an indicator as to whether the sample has passed or failed the model. This value is the ratio of the total distance (distance from the centre of the model) against the critical distance (distance from the edge of the calculated hypersphere), with a sample only being classified within the model if the ratio is less than 1.0000. In each case, all validation samples were within the Specified Material Distance Ratio Limit and, therefore, passed.

Simplifying the Measurement Process Using PerkinElmer's Spectrum Touch Software

Qualitative results can be achieved using a Spectrum Touch method specifically designed to perform raw material identification analysis. Spectrum Touch methods are aimed at routine operators to achieve rapid results and encompass a simple interface with step-by-step instructions. This eliminates the need for costly and time-consuming training. AssureID methods are incorporated directly into the Touch method and the user simply follows the steps in the guided Spectrum Touch workflow.

Examples of the workflow and results output for the povidone method using Spectrum Touch are shown in Figures 7 and 8, respectively. Within the workflow, the user can be prompted to specify the expected sample material. The result will be a pass or fail against that material. Alternatively, the user can select 'unspecified' and the results will simply state which class the sample belongs to.

Table 4. Average (n = 3) validation results using the NIRM.

Average Validation Results (n = 3)			
	Pass (%)	Specified Material Distance Ratio	Specified Material Distance Ratio Limit
Co PVP	100	0.6870 ± 0.0789[a]	1.0000
Cross PVP	100	0.5339 ± 0.0812	1.0000
PVP K12	100	0.6625 ± 0.0314	1.0000
PVP K25	100	0.6811 ± 0.0634	1.0000
PVP K30	100	0.5932 ± 0.0665	1.0000
PVP K90	100	0.5346 ± 0.1214	1.0000

[a] Mean ± standard deviation.

Table 5. Average (n = 3) validation results using the RSM.

Average Validation Results (n = 3)			
	Pass (%)	Specified Material Distance Ratio	Specified Material Distance Ratio Limit
Co PVP	100	0.5522 ± 0.0691[a]	1.0000
Cross PVP	100	0.5524 ± 0.0168	1.0000
PVP K12	100	0.5049 ± 0.0528	1.0000
PVP K25	100	0.5863 ± 0.1280	1.0000
PVP K30	100	0.7670 ± 0.1466	1.0000
PVP K90	100	0.6324 ± 0.0627	1.0000

[a] Mean ± standard deviation.

Figure 7. Spectrum Touch workflow example for povidone analysis. Top: Details on the purpose of the application. Bottom: Sample naming and material selection.

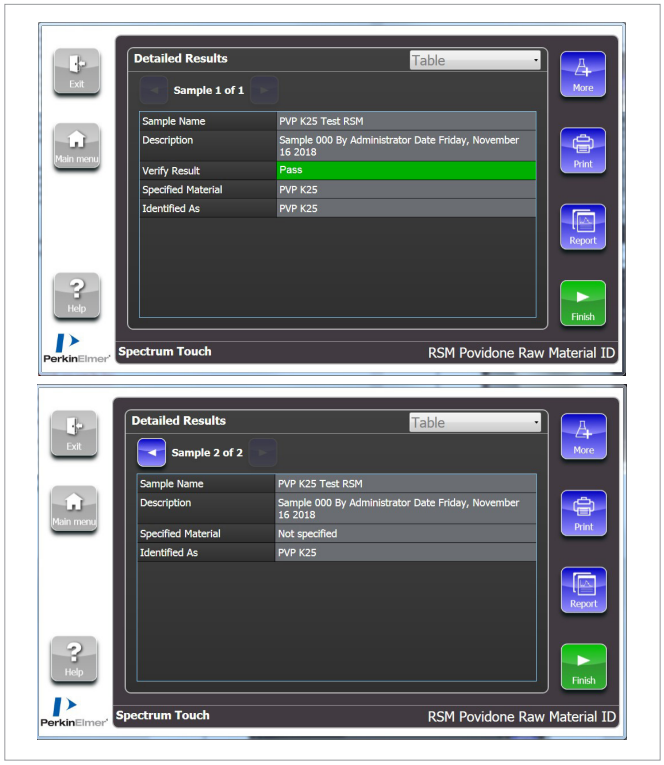

Figure 8. Spectrum Touch results output examples when selecting a sample as a specific material (top) and selecting a sample as 'Unspecified' (bottom).

Conclusion

SIMCA is a powerful tool for classifying spectroscopically similar pharmaceutical products. This example showed successful separation and classification of various povidone products which are chemically similar, differing largely in their physical properties. The NIRM sampling accessory provides a rapid and convenient means of sampling, with improved discrimination using SIMCA when compared with the RSM. The RSM, however, provides good separation between materials and has versatility in sampling, being able to take the measurement to the sample. Operators can also control the measurement and analysis from the probe handle.

Additionally, SIMCA models may be implemented into Spectrum Touch Enhanced Security™ (ES) software to achieve a simple, workflow-based approach to the identification of raw materials whilst adhering to 21 CFR Part 11 compliance.

Reference

1. V. Bühler, Polyvinylpyrrolidone Excipients for Pharmaceuticals. Springer Science & Business Media, 2005.

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