APPLICATION NOTE

No. RB 3892904

Discrimination of Povidone and Crospovidone Using a Handheld Raman Analyzer with On-board Chemometrics

Pharmaceutical oral solid dosage forms are cost effective, patient friendly, easy to manufacture, and remain the most common dosage form on the market. When choosing excipients in solid dosage formulation, pharmaceutical manufacturers consider such factors as the API's chemical and physical properties, release profile (e.g. immediate release, sustained release, enteric release), and manufacturing process (e.g. direct compression, wet granulation, roller compaction).

Povidone and crospovidone are excipients routinely used in pharmaceutical drug formulation. Povidone (Polyvinylpyrrolidone, PVP), a water-soluble polymer, is used as a binder giving cohesiveness to the various powders within a tablet and necessary strength to form a compact tablet under compression. Crospovidone (Polyvinylpolypyrrolidone, PVPP), a highly cross-linked povidone analog, is a hygroscopic disintegrant providing dispersion of the tablet in the gastrointestinal tract. Both free-flowing white to off-white powders, povidone and crospovidone appear visually identical and as structural analogs discrimination between them is challenging.

Standard laboratory-based material identity verification for povidone and crospovidone uses wet chemistry and Fourier transform infrared (FT-IR) spectroscopy which requires opening secondary packaging, sampling materials, transporting samples to the lab and quarantining remaining raw materials, laboratory space and instrumentation, sampling and testing consumables, and expert sample preparation and analysis of monograph test results. Conventional testing can take hours or days trapping valuable inventory in quarantine and slowing production.

Handheld Raman instruments, capable of non-contact analysis through packaging, allow for quick material identity testing anywhere within the manufacturing plant at any stage of production. The Thermo Scientific™ TruScan™ RM handheld Raman analyzer is designed to meet stringent good manufacturing practices (GMP) and 21 CFR Part 11 compliant environments.

TruScan RM's built-in multivariate residual analysis decision engine can verify most pharmaceutical materials directly. When characterizing structural analogs as similar as povidone and crospovidone, building individualized chemometric models to further enhance specificity is necessary. Thermo Scientific TruTools™ is embedded chemometrics software which runs on TruScan RM and expands its analytical capabilities. TruTools offers advanced preprocessing of spectra, qualitative discrimination, quantitative component analysis, and customized chemometric models including PCA, PLS, and PLSDA. For daily operators, TruTools methods are selected through standard TruScan RM menus without requiring chemometric or method development expertise.

In this application povidone and crospovidone analyzed by TruScan RM show good Raman features but the difference between the spectra is relatively small. Figure 1 displays the mean of 25 spectra of povidone and crospovidone each as measured through polyethylene bags. The rich detail and good intensity in the spectra's fingerprint region make these materials reasonable candidates for spectroscopic qualitative identification. The cross-linking differentiating crospovidone from povidone is a chemical bond that links one polymer chain to another with increased frequency. Fine structure within the spectra exhibit indications of the differences in cross-linking; additionally, the relative intensity of bands between the spectra prove important.

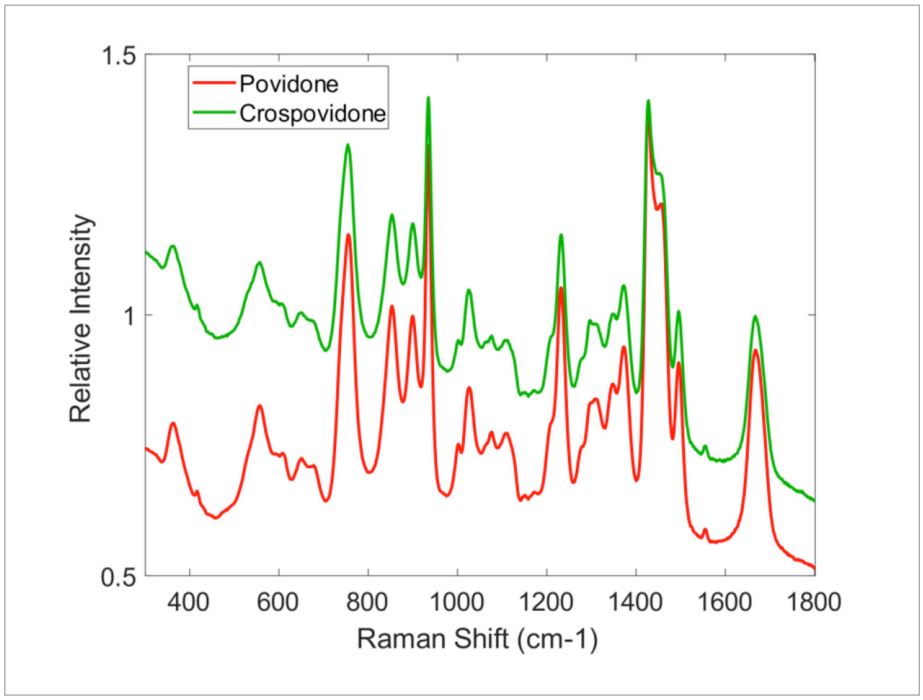

Figure 1. Raw Raman spectra collected from TruScan RM (mean of 25 spectra each)

Before chemometric analysis in TruTools, the raw spectra were pre-processed employing first-derivative filtering and then mean centering (Figure 2). The first-derivative filtering helps to remove the fluorescence baseline aspects of the spectra. Mean centering is a standard pre-processing technique which translates the spectra properly to the new Principal Component Analysis (PCA) origin, enhancing the differences in the data. It is easier to see within this plot the relative intensity differences of certain bands than in the raw Raman spectra.

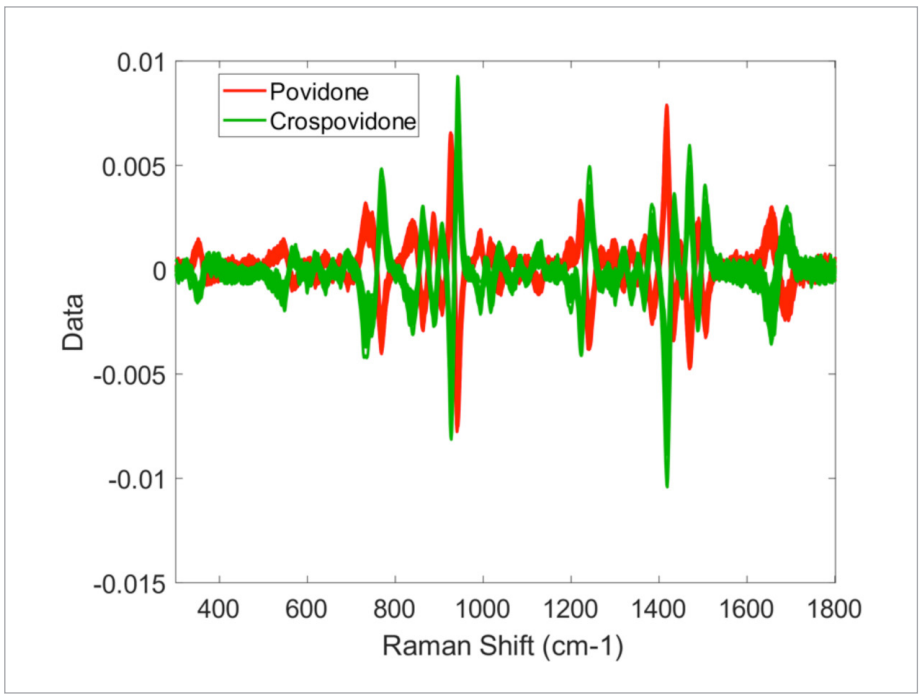

Figure 2. Pre-processed spectra utilizing first derivative filtering and mean centering

Using these data in an exploratory PCA model, good separation between povidone and crospovidone is observed without any supervision of the data identity. The scores-scores plot shown (Figure 3) exhibits excellent separation of the two materials about the first principal component with over 94% of the spectral variance answered by PC 1. The second principal component, PC 2, includes only 2% of the variance and is presented primarily to show the 95% confidence limits for this data set—the addition of more reference spectra could further contract the povidone and crospovidone ellipses.

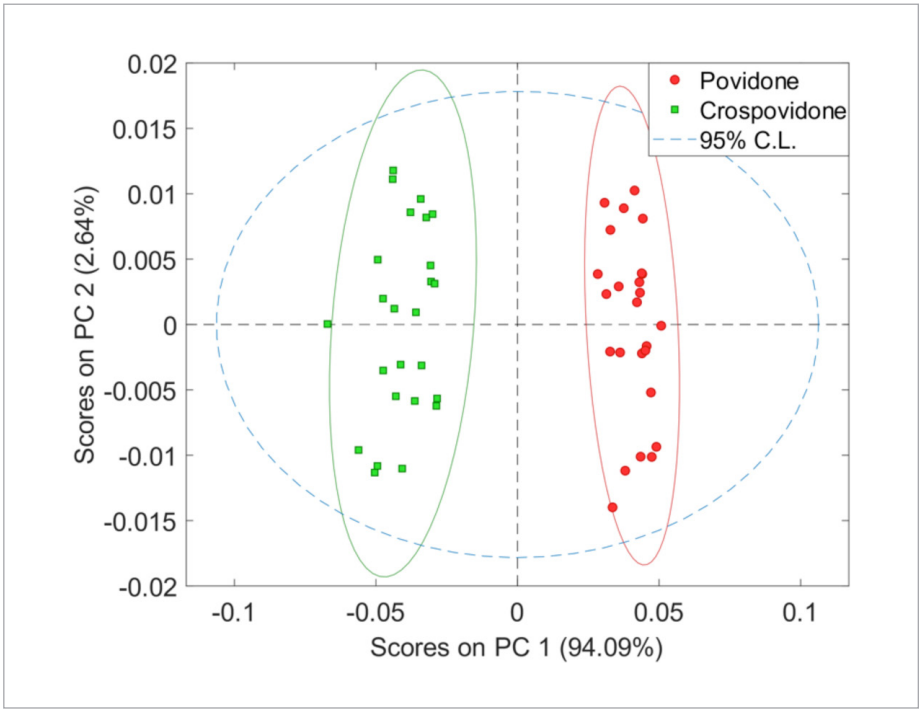

Figure 3. PCA analysis shows good separation between povidone and crospovidone

As an extension of the PCA results, a PLSDA model (Figure 4) was developed to take advantage of the known identity (i.e. supervised classification) of the two excipients and performed well identifying povidone and crospovidone as distinct classes. The dashed red line reveals a distinct discriminant threshold between the two class sets. The povidone class is recognized in this example to have a cross validated distribution about 1 while the crospovidone class groups about 0. These results are the first step to ensuring a robust model once deployed on the TruScan RM.

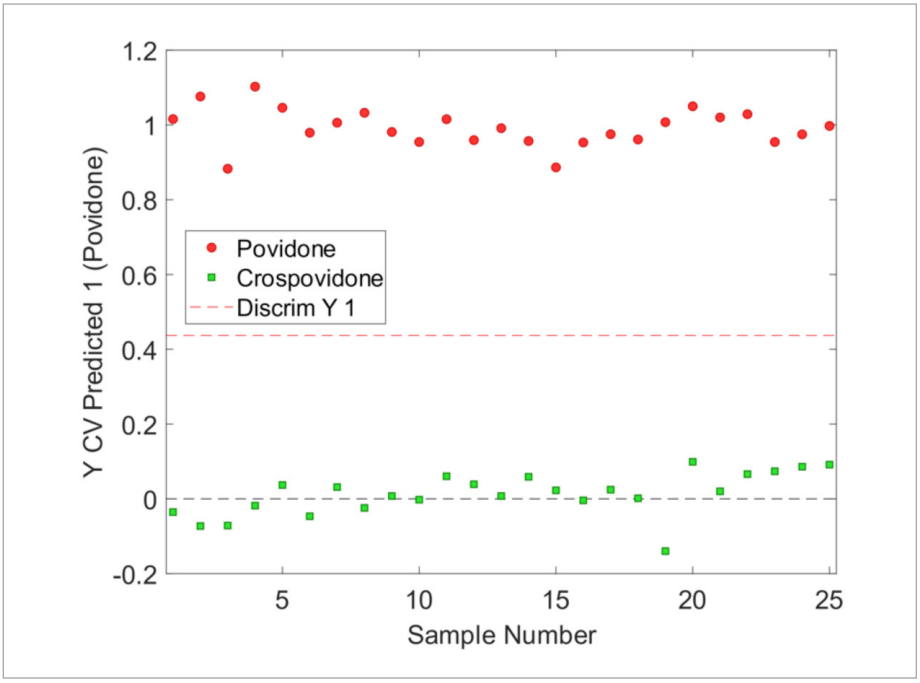

Figure 4. PLSDA model used to further separate the different classes

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Figure 5 exhibits the practical testing of the povidone versus crospovidone PLSDA model onboard the TruScan RM with TruTools. TruTools allows the end user to deploy the model and review results on the handheld device in real time without needing to synchronize the data and reprocess it through additional software on a secondary computer. Clear results are shown onboard the analyzer identifying povidone with a probability equal to 100% when run against a sample of itself. A comparative match is shown on a second screen comparing the likelihood of the sample being povidone or crospovidone. The very strong povidone result lends credibility to the robustness of the PLSDA model. Although not observed in this

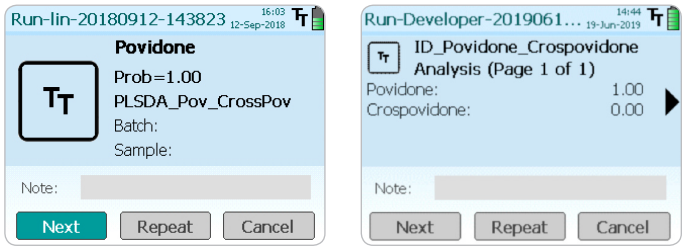

Figure 5. TruTools PLSDA model run on a TruScan RM shows definitive results

study, further model development and sample collection may be required to account for raw material variability, supplier variability, packaging effects, or product age to ensure optimal PLSDA model robustness.

Conclusion

Outlined here are the steps used to evaluate and pre-process spectra on TruScan RM with TruTools and then build an unsupervised exploratory model (PCA) which is subsequently formalized as a supervised classification model (PLSDA). A Raman material identification method was developed and tested to illustrate how a method developer would generally implement a classification model onboard the analyzer as well as how the output will appear to the end user. This use case scenario provides method developers, QA/QC managers, and materials managers an overview of method development efforts with replicate runs and underscores the necessity of validation protocols for long-term method robustness. Once fully implemented the data are synchronized via the standard TruScan RM SyncServer, reports can be generated in similar fashion as those classically provided by the TruScan RM with further details of the measurement for 21 CFR Part 11 compliance.

TruScan RM with TruTools extends the breadth of materials that can be classified and quantified onboard the analyzer. Here a previously unmet need to differentiate povidone from crospovidone is answered with the addition of specialized models to fully contrast one class of material from another. This conventional chemometric approach complements the standard multivariate residual analysis p-value algorithm for materials with such exceeding spectroscopic similarity that TruScan RM will not ensure specificity at the fidelity (e.g. signal-to-noise ratio) and data collection speed of the native algorithm.

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