

Portable Raman Spectroscopy for the Study of Polymorphs and Monitoring Polymorphic Transitions

Materials can exist in different polymorphic forms, meaning that their crystal structure can vary, even though they have the same chemical composition. Polymorphs exist in organic as well as inorganic materials, including metal oxides and silica (quartz). Different polymorphs have different stabilities and may be formed preferentially based on the crystallization process. Polymorphism is important in pharmaceutical products because the efficacy of a drug can be impacted substantially based on the solubility of the different crystal forms.

Raman spectroscopy is used for material characterization by analyzing molecular or crystal symmetrical vibrations and rotations that are excited by a laser, and exhibit vibrations specific to the molecular bonds and crystal arrangements in the molecules. Due to its excellent spectral specificity, Raman technology is a valuable tool in distinguishing different polymorphs, and can also be used in the study of solvate forms, as well as the kinetics of

polymorphic transitions and crystallization processes[1-4].

Raman can be used for in situ measurements as a PAT (process analytical technology) tool for online continuous monitoring of chemical reactions as well as polymorph transformations. Portable Raman systems are an excellent tool in the rapid identification of polymorphs that exhibit distinct spectral differences due to the different arrangement of molecules in the crystal. Portable Raman is especially beneficial in process development where polymorphic screening, stability and formation are determined because of its small compact scale and ease of installation and use.

The Raman spectra of several polymorphs are shown in **Figures 1-3** to illustrate how distinct the Raman spectra are for these polymorphic pairs: calcium carbonate (aragonite and calcite), citric acid, and dextrose.

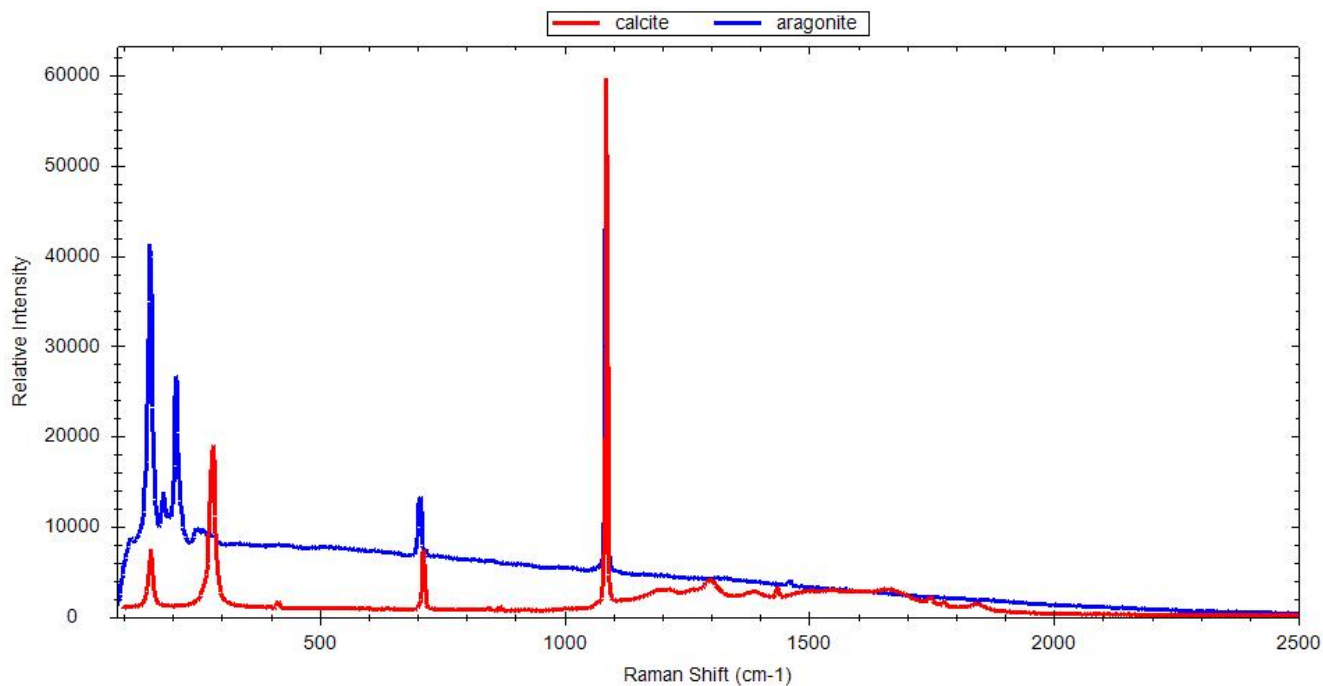


Figure 1. Raman spectra of two polymorphs of calcium carbonate: calcite and aragonite

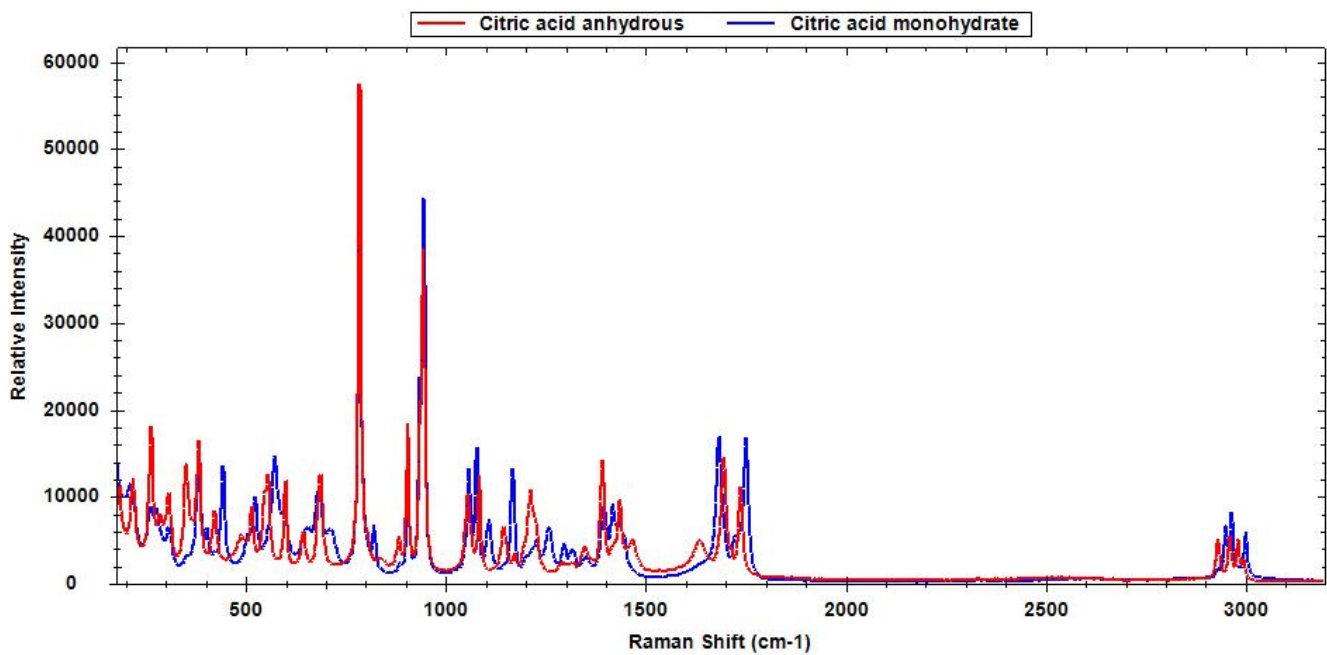


Figure 2. Raman spectra of citric acid polymorphs

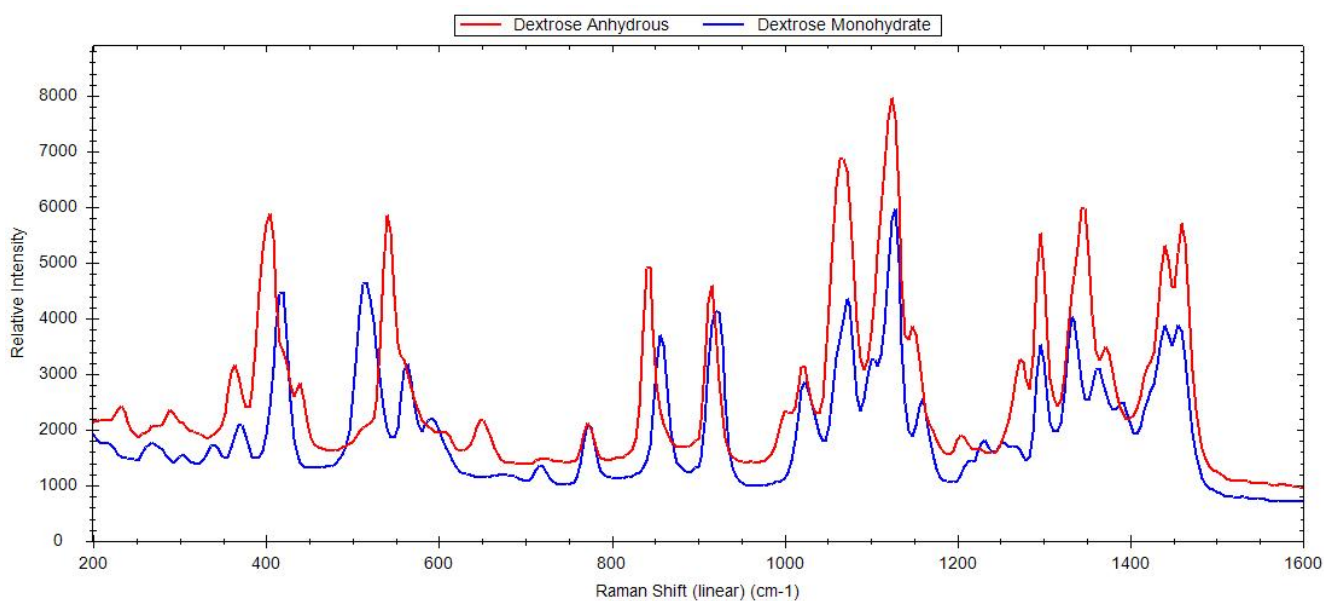


Figure 3. Raman spectra of anhydrous dextrose and dextrose monohydrate

EXPERIMENT

In this work the capability of portable Raman as a process monitoring tool is shown based on the use of B&W Tek's i-Raman Plus. Measurements were performed using portable i-Raman Plus equipped with a sensitive TE-cooled back-thinned CCD as well as a patented CleanLaze® laser excited at 785 nm with 300 mW maximum power output, covering the spectral range from 175-3200 cm^{-1} . A long shaft lab grade Raman probe is positioned above the sample surface, at a working distance of 5 mm such that the laser is well focused as a spot. Data were collected with an acquisition time of 15-30 seconds with 300 mW laser power.

Citric acid, a well-known food additive, is selected here as a model system to study polymorphism based on two of its solid crystal phases: monohydrate and anhydrous, which crystallize from water at different temperatures[4]. Citric acid monohydrate and citric acid anhydrous were purchased from Sigma-Aldrich. The transition of the monohydrate form to the anhydrous was performed by heating the solid powder from room temperature to 80 °C. Real-time monitoring and trending of the

polymorphic transition of citric acid was done using B&W Tek's BWSP-21pt11 software. This allows for continuous data collection and trending based on evolving PCA scores, chemometric models, or data trends. As the interest here is in following the transition (not quantitating the amount of the forms in the system during this process) we used the trend of the disappearance of monohydrate peak at 1108 cm^{-1} and formation of the anhydrous form with the change in intensity of the new peak at 1146 cm^{-1} . There are other peaks specific to the monohydrate form including at 442, 820, 1167, 1260 and 2950 cm^{-1} and for the anhydrous form at 1635, 2932 and 2982 cm^{-1} that could be readily used to trend the transition. An overlay of spectra collected continuously as the temperature is increased to 80 °C is given in **Figure 4**. In the expanded view of the spectral region used for peak trending, the spectral changes on phase transition are evident in **Figure 5**. The trend of the monohydrate peak disappearance that was generated in real-time during data collection is given in **Figure 6**.

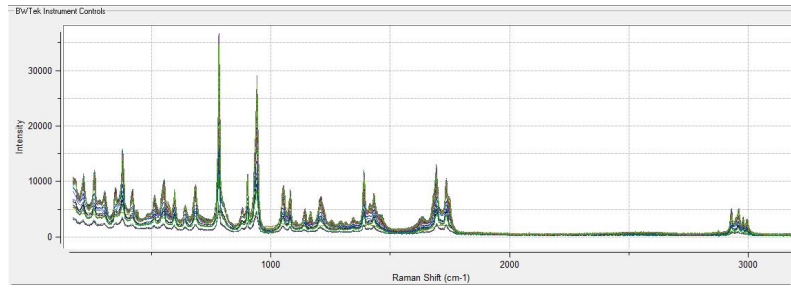


Figure 4. Overlay of Raman spectra collected every 15 seconds during temperature increase to induce monohydrate to anhydrous transition in citric acid

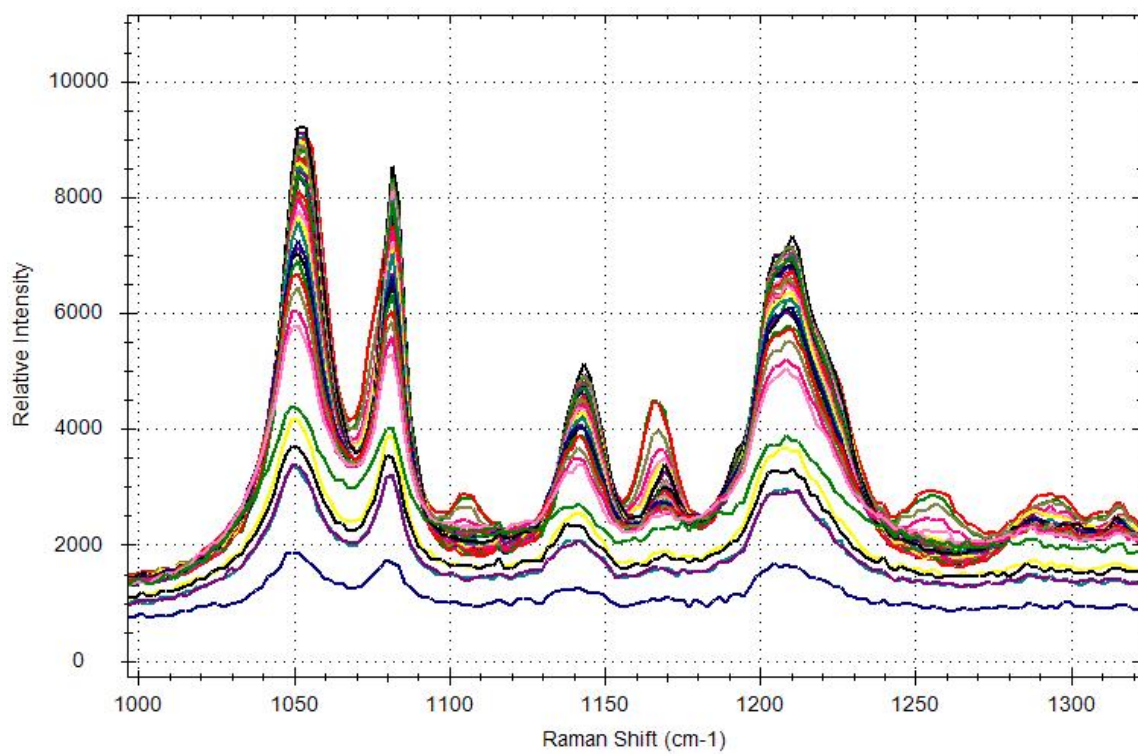


Figure 5. Expanded view of Raman spectra collected during citric acid phase transition

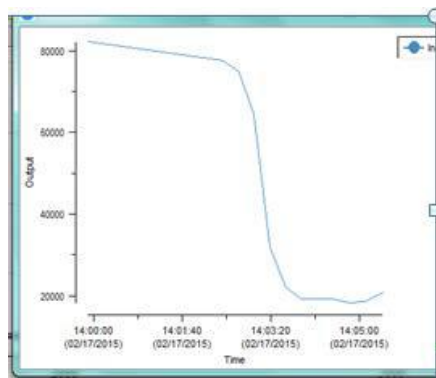


Figure 6. Trend of Raman peak area of 1108 cm^{-1} citric acid monohydrate, during temperature increase from room temperature to 80 °C

CONCLUSIONS

Because the spectral changes related to the change from the monohydrate to the anhydrous citric acid are not limited to discrete changes, a more holistic approach using multivariate data analysis, reflecting the systematic spectral changes with the increase in temperature can be captured using Principal component analysis (PCA). Using PCA analysis over the full spectral range, it is found that the first

principal component explains 90% of the data variance over the course of the 75 spectra collected. A line plot of the score of PC-1 vs. sample spectrum shows the same trend as seen by following a single peak, and reflects changes across the Raman spectrum with the conversion for the monohydrate to anhydrous form. **Figure 7** shows the plot of the PC-1 scores.

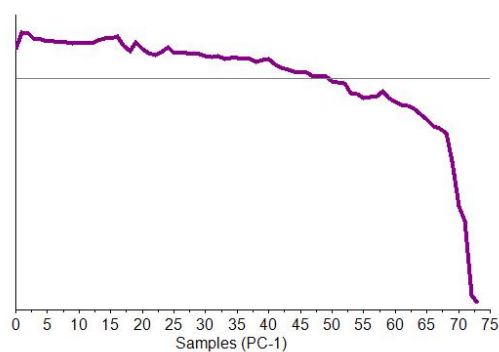


Figure 7. PC-1 score plot from full spectral range PCA analysis of 75 spectra collected during temperature experiment

Here we show some examples of the value of Raman spectroscopy to monitor and identify different polymorphs. We used the portable i-Raman Plus with BWSP-21pt11 software for continuous monitoring

and trending of the monohydrate to anhydrous transition of citric acid, with spectra collected every 15 seconds as the temperature was increased.

REFERENCES

1. E. Smith and G. Dent, Modern Raman Spectroscopy - A Practical Approach, John Wiley and Sons, Hoboken, NJ, 2005.
2. J. Huang and M. Dali, J. Pharm. and Biomedical Anal. 86(2013) 92-99.
3. M. Steindl et al, Chem. Eng. and Processing 44(2005) 471-475.
4. A. Caillet, F. Puell, G. Fevotte, Chem. Eng. and Processing 47(2008) 377-382.

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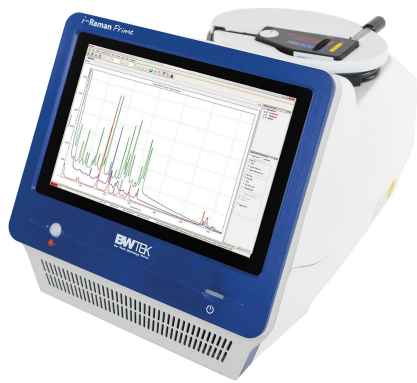
CONFIGURATION



i-Raman Plus 785S Portable Raman Spectrometer

The i-Raman[®] Plus 785S is part of our award-winning series of i-Raman portable Raman spectrometers powered by our innovative intelligent spectrometer technology. Using a high-quantum-efficiency CCD array detector with TE cooling and high dynamic range, this portable Raman spectrometer delivers excellent performance with low noise, even at integration times of up to 30 minutes, making it possible to measure weak Raman signals.

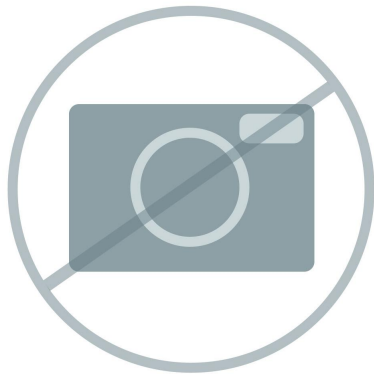
The i-Raman Plus 785S features the unique combination of wide spectral range and high resolution with configurations which allow measurements from 65 cm^{-1} to $3,350\text{ cm}^{-1}$. The system's small footprint, lightweight design, and low power consumption ensure research-grade Raman analysis capabilities at any location. The i-Raman Plus is equipped with a fiber probe for easy sampling, and can be used with a cuvette holder, a video microscope, an XYZ positioning stage with a probe holder, as well as our proprietary BWIQ[®] multivariate analysis software and BWID[®] identification software. With the i-Raman Plus, you always have a high precision Raman solution for qualitative and quantitative analysis.



i-Raman Prime 785S Portable Raman Spectrometer

The i-Raman[®] Prime 785S is a low-noise, high-throughput, and fully integrated Raman system with an embedded tablet computer and a fiber-optic sampling probe. Using a high-quantum-efficiency CCD array detector with TE deep cooling (-25 °C) and high dynamic range, this portable Raman spectrometer delivers research-grade Raman analysis capabilities, including real-time quantitation and identification. The high throughput gives Raman spectra with excellent signal-to-noise ratio, making it possible to measure rapid processes and to measure even the slightest Raman signals, detecting subtle sample differences.

In addition to its portable construction, the i-Raman Prime 785S features the unique combination of wide spectral coverage and high resolution, thus enabling measurements from 150 cm⁻¹ to 3,350 cm⁻¹. The i-Raman Prime can be battery-operated for easy portability, providing research-grade Raman analysis capabilities for high-precision qualitative and quantitative work wherever needed. The system is optimized for use with our STRaman[®] technology for analyses through non-transparent packaging.



Immersion shaft for portable Raman instruments

Optional immersion shaft for BAC100/BAC102 Raman probes with an excitation wavelength of 532 nm or 785 nm. Equipped with a 76.2 mm long body made of 316L stainless steel with an outer diameter of 12.0 mm and a silica window that is sealed with an O-ring made of perfluoro rubber. Operating distance 5.0 mm in air. Can be used at -55 °C to 200 °C. The seal is liquid-tight at low pressure (< 1 bar).