Application Note 410000003-A

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

INTRODUCTION

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.

INTRODUCTION

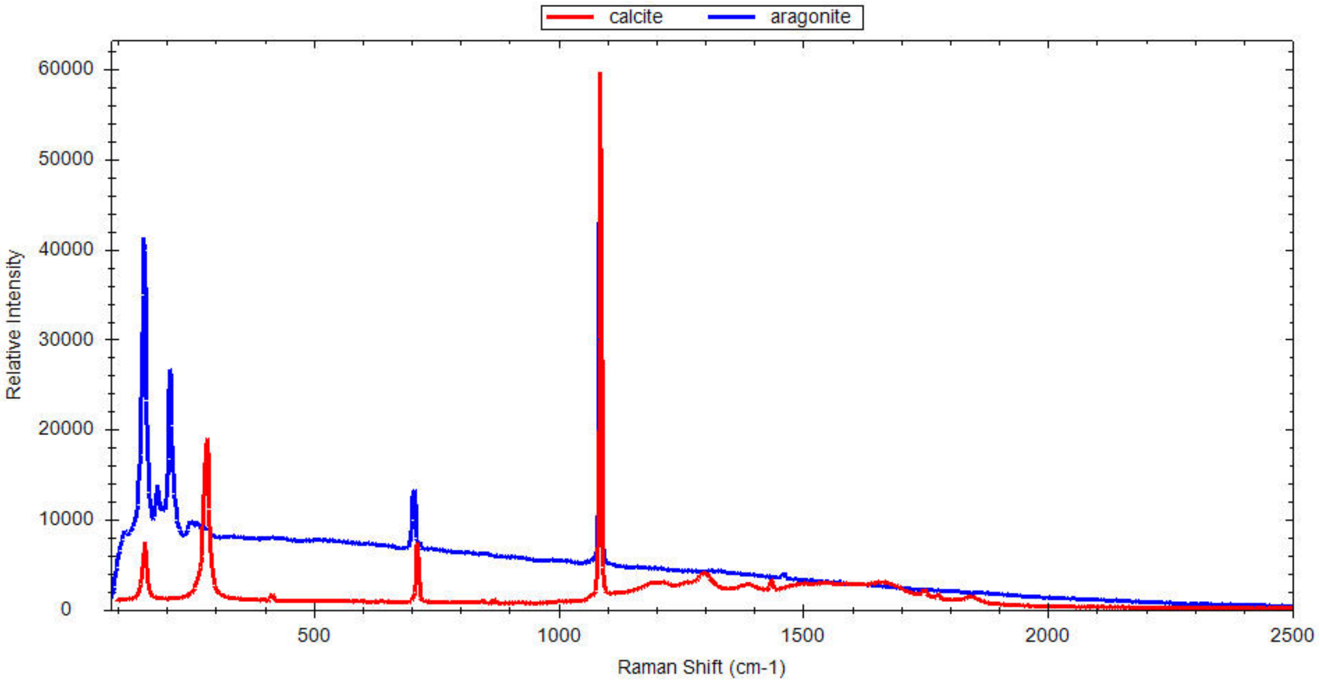

Figure 1. Raman spectra of two polymorphs of calcium carbonate: calcite and aragonite

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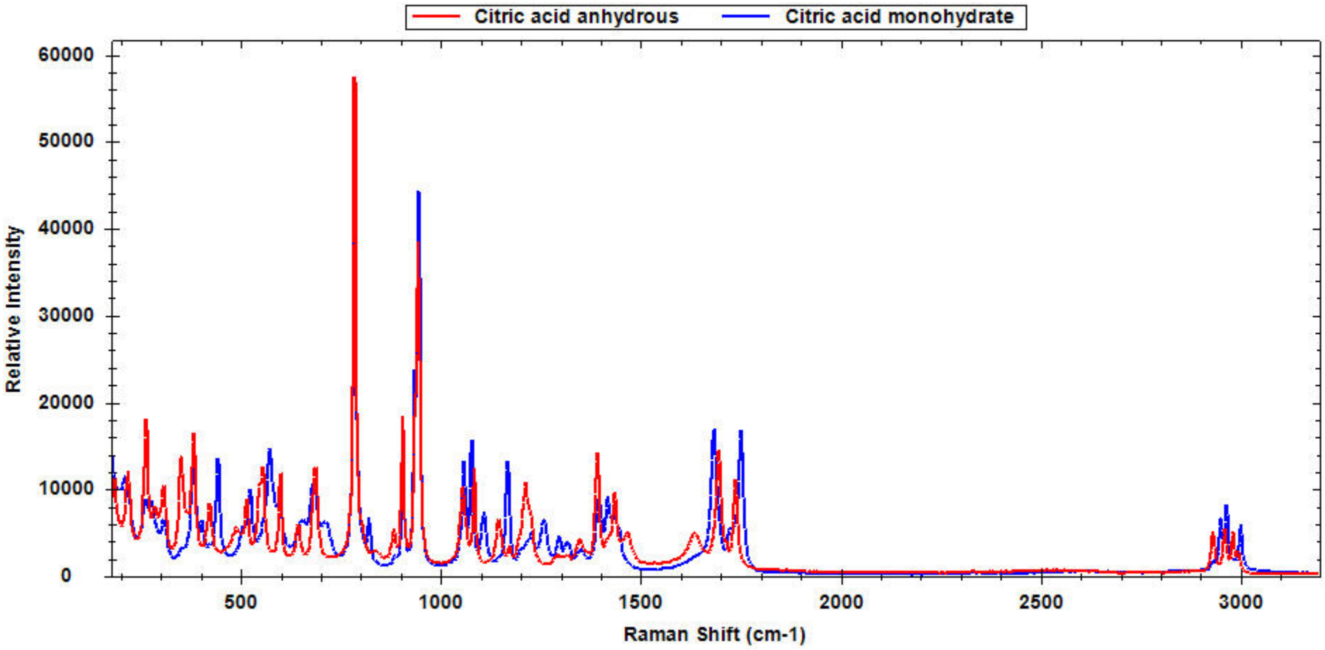

Figure 2. Raman spectra of citric acid polymorphs

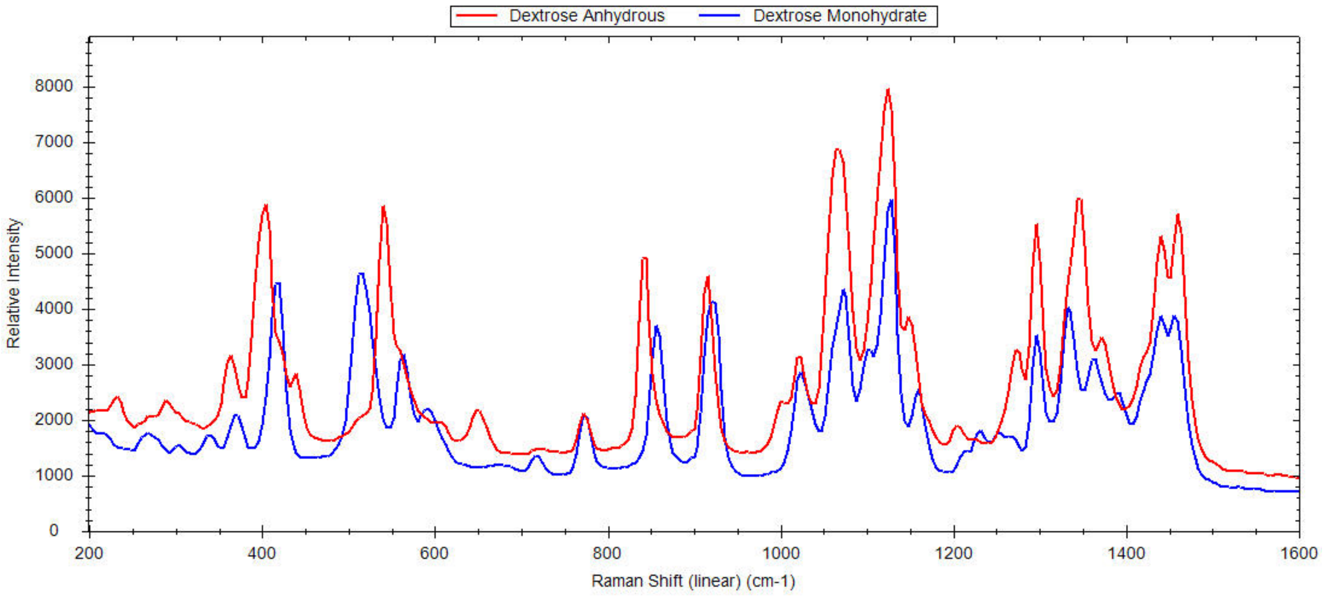

Figure 3. Raman spectra of anhydrous dextrose and dextrose monohydrate

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**.

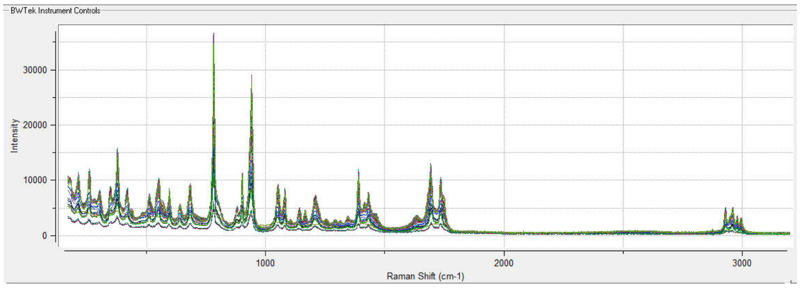

Figure 4. Overlay of Raman spectra collected every 15 seconds during temperature increase to induce monohydrate to anhydrous transition in citric acid

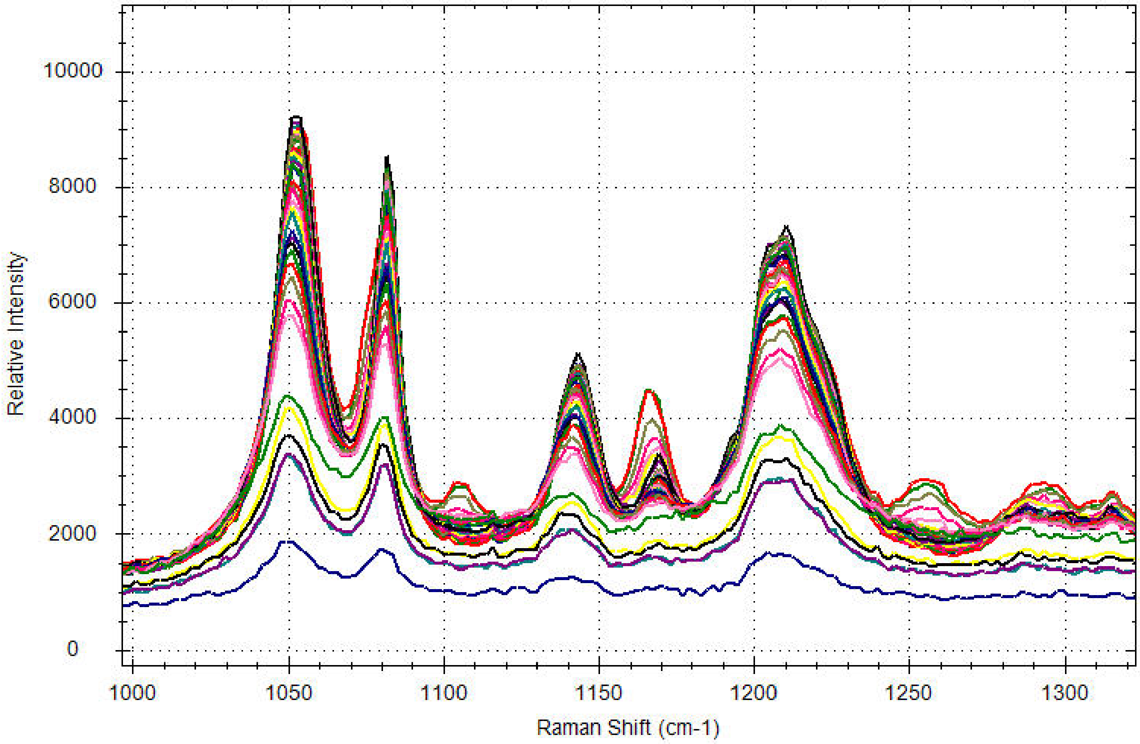

Figure 5. Expanded view of Raman spectra collected during citric acid phase transition

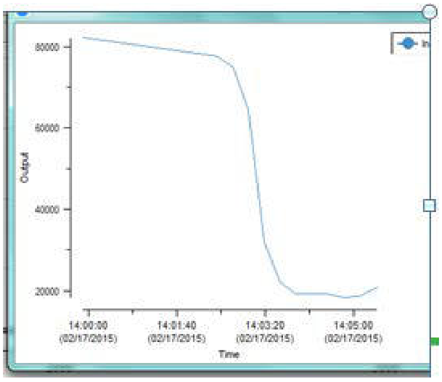

Figure 6. Trend of Raman peak area of 1108 cm-1 citric acid monohydrate, during temperature increase from room temperature to 80 °C

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.

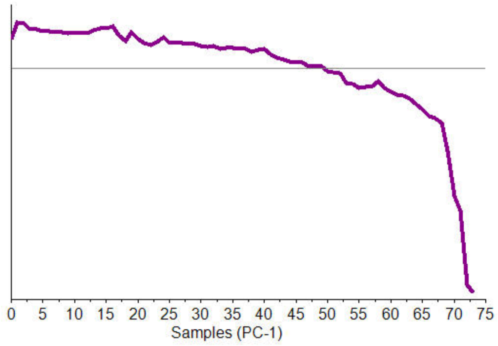

Figure 7. PC-1 score plot from full spectral range PCA analysis of 75 spectra collected during temperature experiment

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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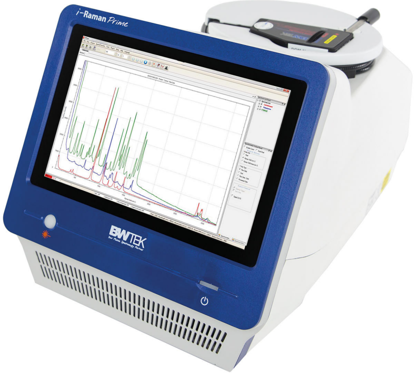
CONFIGURATION

i-Raman Plus 785S

i-Raman® Plus 785Sは、弊社の革新的かつインテリシェントなスヘクトロメーターテクノロシーを備えたi-Ramanホータフル型ラマンスヘクトロメーターの受賞歴のあるシリースの構成要素てす。このホータフル型ラマンスヘクトロメーターは、高い量子効率、TE冷却、ならひに高いタイナミックレンシを備えたCCDアレイ検出器を用い、積分時間てさえ最長30分、低ノイスの傑出した性能を提供します。こうして、弱いラマン信号も測定することかてきます。

i-Raman Plus 785Sは、65 cm^{-1}から3350 cm^{-1}までの測定を可能にするコンフィクレーションを有する幅広いスヘクトル範囲と高分解能のユニークな組み合わせを特徴としています。 システムの小さな底面、軽量構造、そして低消費電力により、とこてもラマン分析を研究レヘルて実施することかてきます。i-Raman Plusには、サンフル採取を簡単にする光ファイハーフローフか装備されており、キュヘットホルター、ヒテオマイクロスコーフ、フローフホルター付きXYZスライトテーフル、ならひに弊社独自の多変量解析ソフトウェアBWIQ®および同定ソフトウェアBWID®と共に使用することかてきます。i-Raman Plusにより、品質分析および定量分析のための高精度のラマンソリューションを常に使用することかてきます。



i-Raman Prime 785S

i-Raman® Prime 785S は、タフレット PC および光ファイハーサンフルフローフ内蔵の、低ノイスかつ高スループットの完全一体型のラマンシステムてす。このホータフル型ラマンスヘクトロメーターは、高い量子効率、TE 冷却 (-25 ° C)、ならひに高いタイナミックレンシを備えた CCD アレイ検出器を使用し、リアルタイムての定量化と同定を含む研究レヘルてのラマン分析を提供します。高スループットにより、傑出した信号対雑音比のラマンスヘクトルを得ることかてきるのて、速いフロセスの測定、および最も弱いラマン信号てさえもか可能となり、サンフルの微細な相違も検出てきます。

i-Raman Prime 785S には、そのホータフル式の構造に加え、幅広いスヘクトル領域と高い分解能というユニークな組み合わせか装備されているため、150 cm^{-1} から 3350 cm^{-1} までの測定か可能てす。i-Raman Prime はハッテリーての稼働か可能なのて、容易に持ち運ひかてきます。そのため、場所を選はす、高精度かつ質的、量的に価値の高いラマン分析を研究レヘルて実施することかてきます。システムは、不透明なハッケーシ越しの分析用の、弊社 STRaman® テクノロシーの使用向けに最適化されました。

532 nmまたは785 nmの励起波長の ラマンフローフBAC100/BAC102のためのオフションとしての浸漬シャフト。ハーフルオロコム製Oリンクて密封された石英カラスウィントウ付き、外径12.0 mmのステンレス316L製76.2 mm長のホティを有しています。空中ての作動距離5.0 mm。-55 ° Cから200 ° Cて使用可。ハッキンは、低圧 (< 1 bar) ては液密てす。