Application note

Using the Thermo Scientific MarqMetrix All-In-One Process Raman Analyzer in real-time monitoring of the Crystallization Process

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Summary

Crystallization plays a vital role in product quality by influencing particle size, purity, and product yield. Strict crystallization process control is essential in pharmaceutical industries to meet the desired specifications of active pharmaceutical ingredients (APIs). The crystallization quality also impacts other process aspects, such as drying, flowability, and scalability. For instance, a wide particle size distribution resulting from the crystallization process can lead to slow filtration and inefficient drying, causing bottlenecks in the manufacturing process.

This application note demonstrates the Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer, combined with chemometric analysis, as a powerful in-line process analytical technology (PAT) tool for monitoring the crystallization process for a crucial API. After optimizing the analysis conditions and identifying peaks corresponding to the API and solvent background, a Principal Component Analysis (PCA) model was developed to track the crystallization kinetics and determine the exact completion time for the process.

This real-time, in-line PAT tool provides users with assurance regarding the quality of their API crystallization process. By enabling continuous monitoring and analysis, it facilitates better process control, optimization, and the production of high-quality crystalline materials, ultimately contributing to improved product quality in various industries, including pharmaceuticals.

Background

Crystallization is one of the crucial steps in separating and purifying APIs during pharmaceutical manufacturing. The process requires specific attention to the product crystals' yield, size, shape, distribution, and purity. These critical quality attributes (CQA) can significantly impact downstream processes such as filtration, washing, and drying, as well as the physiochemical properties such as solubility, the formation of polymorphs, rate of dissolution, and permeability. Therefore, crystallization may have significant direct and indirect effects on the quality of a final drug product. The introduction of PAT into the manufacturing process enables real-time monitoring of changes during the process to achieve desirable quality products. Raman spectroscopy is an important optical spectroscopic PAT tool that has attracted significant attention due to its capability to monitor processes in real time and provide actionable information.

Raman spectroscopy offers distinct advantages over other analytical methods like infrared (IR) and near-infrared (NIR) spectroscopy, as Raman spectra are unaffected by interference from water molecule vibrations. This makes Raman spectroscopy particularly useful for monitoring water-based (aqueous) samples, which are commonly encountered in small molecule drug production crystallization processes.

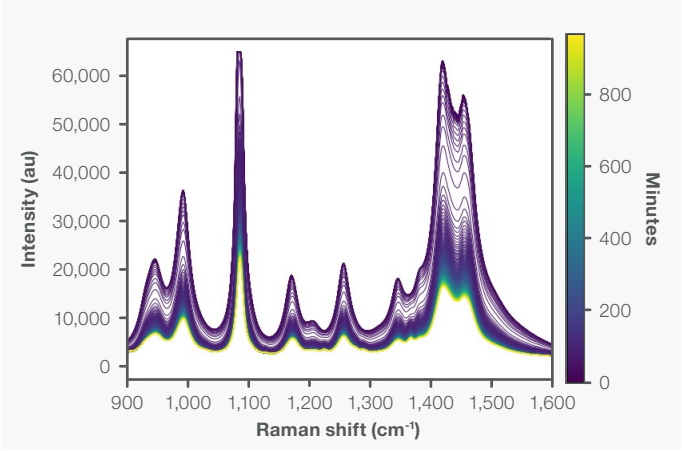

Figure 1. The Kinetic Raman Spectroscopy data was collected using the MarqMetrix All-In-One Process Raman Analyzer. The data was recorded at one-minute intervals throughout the entire crystallization process. The plotted spectra in the analysis focus on the region between 900 and 1600 cm^{-1}, as this range contains predominant features from both the solvent and the API. This specific spectral region provides valuable information about the chemical composition and structural changes occurring during the crystallization process.

Experiments and results

In the crystallization process described in this note, crystallization was initiated by gradually adding the API as an aqueous solution to the organic antisolvent while maintaining a specific temperature stirring constantly. The Thermo Scientific™ MarqMetrix™ Process BallProbe™ was inserted into the vessel through a standard PG13.5 connection to monitor the entire process in real time. Spectra acquisition parameters, such as laser power, number of averages, and integration time, were optimized to achieve the best signal-to-noise ratio (SNR). These parameter settings were customized based on the specific application.

Figure 1 displays the raw Raman spectra collected at one-minute intervals throughout the entire crystallization process, with the dark background automatically subtracted. While the predominant Raman shifts are from the solvent, a Raman shift peak at around 1370 cm^{-1} (shown in Figure 2, zoomed in on the spectra region between 1300 and 1400 cm^{-1}) is believed to originate from the API, as it is not present in the pure solvent spectra (shown in red). It is evident that the intensity of the API peak increases with the progress of the crystallization process.

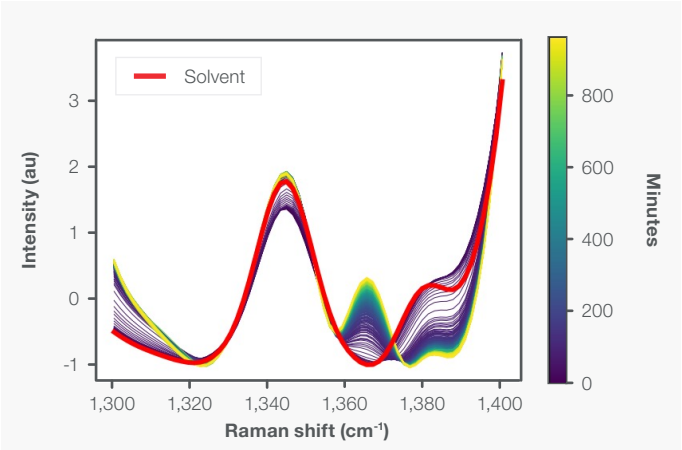

Figure 2. The observed increase in the intensity of the characteristic peak at around 1370 cm^{-1}, attributed to the crystallized API, demonstrates the ability to monitor the crystallization process in real time. This is supported by the fact that the solvent spectra in the region do not exhibit any Raman peak. The increasing intensity of the API peak suggests the growth and accumulation of the crystalline API substance over time. This information provides valuable insights into the kinetics and dynamics of the crystallization process.

A chemometric PCA model was built in Python to analyze the raw data further. The raw spectra were pre-processed using standard normalization variant (SNV), first derivative, and mean centering techniques. The PC1 score plot, shown in Figure 3, indicates that the process completes at approximately 200 minutes, with a maximum conversion rate of around 60 minutes. This detailed kinetic information can only be obtained through in-line monitoring, enabling a deeper understanding of the process and facilitating better process control and accurate real-time monitoring.

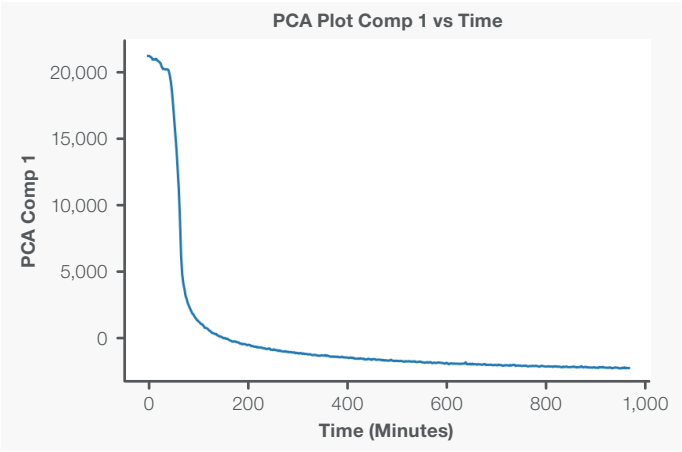

Figure 3. The chemometric PCA analysis, specifically the PC1 score plot, illustrates the ability to monitor the crystallization process in real time. The PC1 score plot shows a clear trend, indicating the progression of the process over time.

By analyzing the PC1 score plot, it is possible to identify the maximum turning point, which occurs at around 50 minutes, and the completion time, which is approximately 200 minutes. This information is crucial for in-line process monitoring, as it allows for real-time determination of the key stages of the crystallization process. The use of in-line process monitoring, aided by chemometric techniques like PCA, provides valuable insights into the crystallization kinetics, thereby enabling optimization of the process parameters to maximize throughput. Production time can be optimized by accurately determining the critical time points, leading to increased efficiency and cost savings.

Conclusion and impact

Raman spectroscopy enables real-time, continuous, *in situ* monitoring of a chemical process and has been widely used in various industries, including pharmaceutical, chemical, and food industries. Implementing real-time monitoring of the crystallization process using PAT tools like the MarqMetrix All-In-One Process Raman Analyzer offers several advantages, including the ability to perform real-time process monitoring, which allows for the determination of the completion time of crystallization.

This information can be crucial in optimizing production line occupancy time and improving process efficiency. By monitoring the process in real time, manufacturers can make rapid in-process changes as needed to build quality into the workstream. This flexibility can lead to significant reductions in cycle time (for example, shortening a given process from around 10 hours to 3-4 hours), resulting in higher throughput and faster workflows. This reduction in time can potentially lead to significant cost savings, estimated at approximately 20,000 euros per batch in a typical case.

Furthermore, inline monitoring using Raman spectroscopy allows manufacturers to understand processes in greater detail and act quickly to respond to any anomalous behaviour in the process. This increased understanding of processing details facilitates more efficient design and control of processes in manufacturing and development settings.

Overall, the implementation of real-time monitoring, supported by technologies like Raman spectroscopy, improves process efficiency and aligns with regulatory initiatives such as the FDA's PAT and Quality by Design (QbD) programs. This facilitates regulatory approvals of processing strategies and promotes a more comprehensive understanding of processing details, leading to enhanced control and optimization of processes.

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