tornado spectral systems

Tracking Polymorph & Crystal morphology with High Throughput Raman for Process Understanding & Control

INTRODUCTION

Crystallization is a commonly used process for solid-dose manufacturing. To improve the biological performance and economic benefits of a crystallization process, proper process control is necessary. However, crystallization can be difficult to control due to the complex relationship between thermodynamic and kinetic factors and processes such as nucleation, growth, and agglomeration. A thorough understanding of the process is required, which can be done through modeling, design of experiment stress testing and the use of process analytical technologies (PAT).

Raman Spectroscopy has been shown to be a ubiquitous PAT technology ranging in application from the large molecule to monitor the small molecule space. By coupling the HyperFlux™ Pro Plus Process Raman Spectrometer to a high-quality complementary tool such as the Crystalline® Parallel Crystallizer from Technobis Crystallization Systems, it is possible monitor your crystallization process and accelerate the development of drug products to market.

EXPERIMENT

Proof of Concept

Mefenamic acid was used for a proof-of-concept study. Mefenamic acid has three polymorphs, with Form I being the stable form. Using Raman spectroscopy, it is possible to track the rapid conversion of polymorph Form II to Form I using the carbonyl band located at 1676 cm^{-1}.

For this experiment, 50 mg of mefenamic acid Form II was suspended in 5 ml EtOH and stirred using an overhead hook impeller (700 rpm) at 25 °C in the Crystalline®. The Crystalline® was interfaced to a Tornado Hyperflux™ PRO Plus Raman spectrometer equipped with a Hudson™ Probe adapted to the Crystalline sampling port (see Figure 1). Exposure time was set to 160 ms with 30 spectral averages, yielding a spectrum every 5 seconds.

Figure 1

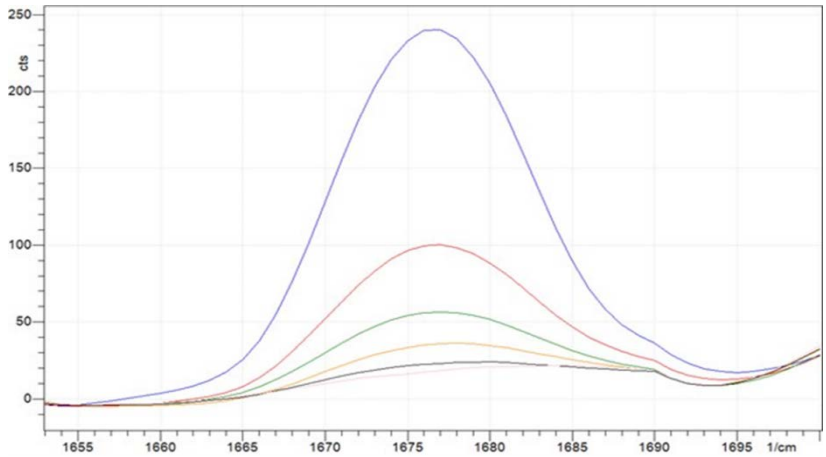

Figure 2

Figure 2 shows the decrease in intensity of the peak of interest allowing the tracking of complete conversion to the thermodynamically stable Form I. This experiment highlights how coupling the Hyperflux™ Pro Plus to a tool such as the Crystalline® facilitates the understanding and monitoring of polymorph conversions in real time. This combination of technologies allows true understanding of your process, leading to better control and increased productivity and profitability.

Case Study

For this work, carbamazepine was used due to the fact that it is well recognized as a benchmark material in the field of crystallization. For this compound, there are 4 known anhydrous polymorphs and a dihydrate form, with Form 3 being the stable polymorph and Forms 1, 2 and 4 being metastable but readily obtainable through various crystallization procedures. It is possible to differentiate between Forms 2 and 3 using Raman spectroscopy as well as optical microscopy, as the two polymorphs show different morphologies: Form 2 needles and Form 3 blocks, respectively (Figure 3).

This experiment also employed the coupling of the Crystalline® with the Hyperflux™ Pro Plus. Exposure time was set to 150 ms and spectral averaging was increased to 100 averages, yielding a spectrum every 15 seconds.

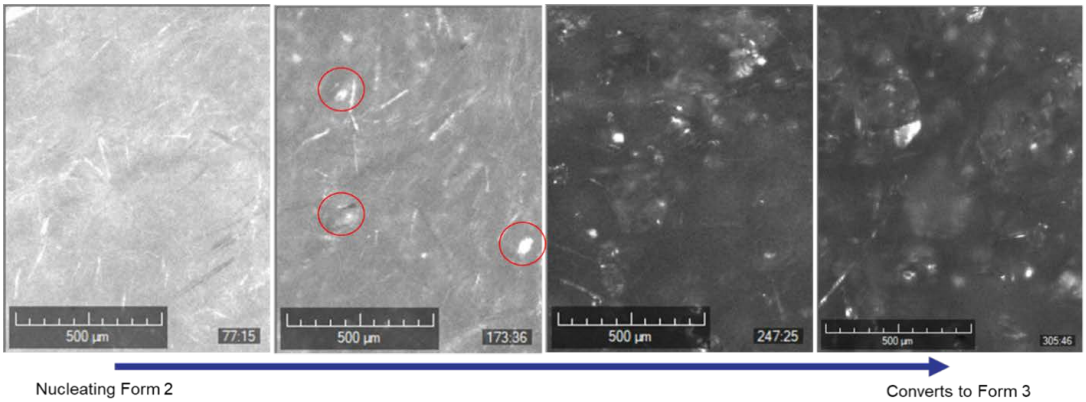

Figure 3: Morphology transformation of carbamazepine Form 2 (needles) to Form 3 (Blocks) captured using the Crystalline®

Carbamazepine (199 mg) was suspended in isopropyl alcohol (5 ml). The sample was then heated to 70 °C and held with stirring (700 rpm) until a clear solution was obtained. The solution was then crash cooled to 20 °C at 20 °C/min to induce crystallization and held at that temperature with constant stirring for several hours. After several minutes large amounts of fine needle-shaped crystals could be seen with the camera and a peak was observed at 262.5 cm^{-1} indicating the formation of the kinetic metastable Form 2. After ~100 mins a few block-shaped crystals of Form 3 appeared, together with the emergence of peaks at 248 and 271 cm^{-1} in the Raman spectra. Over the course of the next 130 mins the amount of Form 3 increased as the metastable Form 2 converted. This can be seen in the increase in the number of block shaped crystals on the particle viewer and the decrease in needle-like crystals. Furthermore, the peak at 262.5 cm^{-1} associated with Form 2 decreased until it was no longer visible at the end of the experiment, and the peaks of Form 3 grew in intensity showing that the thermodynamic form was now the majority (Figure 4).

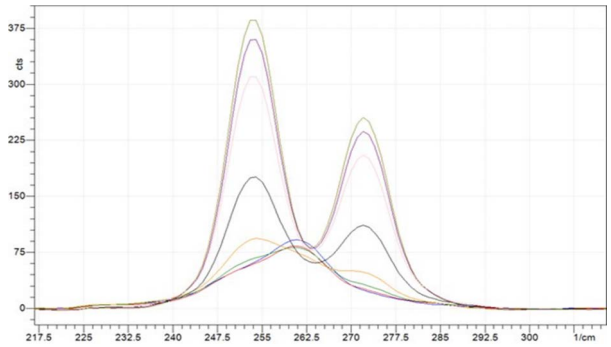

Figure 4: Raman spectrum transformation for carbamazepine captured using the Tornado Hyperflux™ integrated with the Crystalline®

CONCLUSION

By coupling the Crystalline® device with a HyperFlux™ PRO Plus Raman spectrometer, it is possible to monitor and track polymorphism and morphology. It allows deeper process understanding during process and product development and facilitates superior process control when deployed in production. Because of the sensitivity of the PRO Plus monitoring can be achieved even at the low working volumes required by the Crystalline®. By using these reduced volumes, the material required for crystallization development can be significantly reduced. Solid form selection and research can be undertaken earlier in API development, therefore increasing the speed in which regulatory approval can be gained. Beneficial therapeutic entities therefore reach manufacturing quicker and are released to the market with fewer delays. These benefits can be realized because Tornado's HTVS™ technology facilitates insightful ***Measurements-You-Can-Trust***.

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