In situ monitoring of polymorphic transformation of active pharmaceutical ingredients

Benefits at a glance
- *In situ* crystallization and slurry monitoring
- API operation understanding
- Raman-based PAT enables rapid process optimization and scale-up

Introduction

The pharmaceutical industry is frequently confronted with the presence of multiple polymorphs. The presence of multiple polymorphs of the active pharmaceutical ingredient (API) is particularly challenging with solid, oral dosage drug products. The properties of these solid forms can sometimes be quite similar, but more often the physical and chemical properties of the forms can vary dramatically. These variations have great impact on pharmacokinetics, ease of manufacturing, and dosage form stability. Physical properties that can differ among the solid forms include color, solubility, crystal shape, water sorption and desorption properties, particle size, hardness, drying characteristics, flow and filterability, compressibility, and density. Different solid forms can also have different melting points, spectral properties, and thermodynamic stability.

In a drug substance, these variations in properties can lead to differences in dissolution rate, oral absorption, bioavailability, toxicology results, and clinical trial results. Ultimately, both safety and efficacy can be impacted by differences in solid forms. Furthermore, stability presents a special concern, since it is easy to inadvertently generate the wrong form during the development process. In addition, interconversion can occur during routine API manufacturing operations and during drug product formulation, storage, and use. For this reason, manufacturers often select a polymorphic form that has the desirable characteristics that will aid in the manufacture of the drug product formulation. Therefore, it becomes critical to have a robust crystallization process that consistently produces the desired form of the bulk API.

The FDA's process analytical technology (PAT) initiative encourages the industry to move away from empirical analyses and embrace a science-based approach to manufacturing. The industry is evaluating appropriate process analyzers, PAT tools, to yield knowledge. Raman spectroscopy has been identified as one of these useful tools within the PAT toolbox. A successful PAT approach results in process knowledge, resulting in optimized operations with control systems that ensure quality outcomes.

In this study, *in situ* Raman was used to monitor the solvent-mediated polymorphic transformation of flufenamic acid (FFA), an anti-inflammatory drug, from Form I to Form III under various process conditions.

Experimental

A Raman analyzer with a Rxn-10 probe fitted with an immersion optic was used in these experiments.

Spectra were acquired within seconds using 100 mW of laser power. The crystallization and slurry transformation were studied under various process conditions within a cGMP environment.

Results

Raman spectra of the two most common forms of FFA (Forms I and III) are shown in Figure 1.

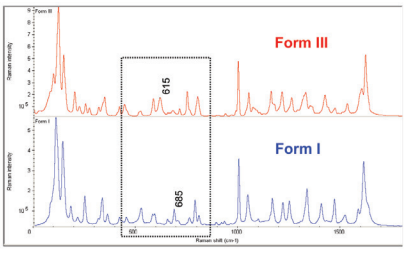

Figure 1: Raman spectra of FFA solid forms I and III showing characteristic peaks

ⓘ All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

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The high information content of the Raman spectrum allowed characteristic peaks for the two polymorphic forms to be identified and monitored: Form III – 615 cm^{-1} and Form I – 685 cm^{-1}.

Figure 2 shows the Raman intensity profiles for Forms I and III during a seeded batch-cooling crystalization of FFA from ethanol/water (70/30 v/v) solution. Results suggest that Form I crystallized upon Form III seed addition. Subsequently, Form I crystal nucleated as the temperature of the solution was lowered from 50 °C (Form I is the stable form at 50 °C). The Form I crystals were subsequently

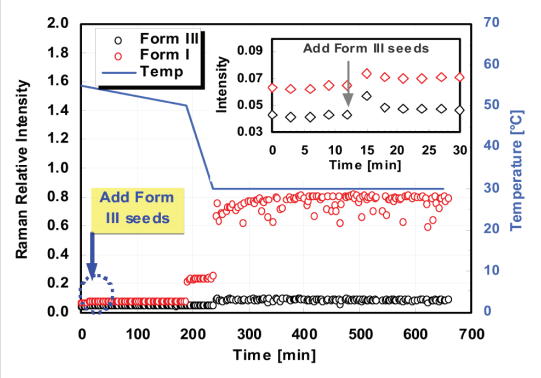

Figure 2: Raman relative intensities for Form III and Form I, and slurry temperature as a function of time during seeded cooled crystallization. Inset indicates changes in the relative Raman intensity profiles upon seed addition (seed particles: 482.4mg Form III).

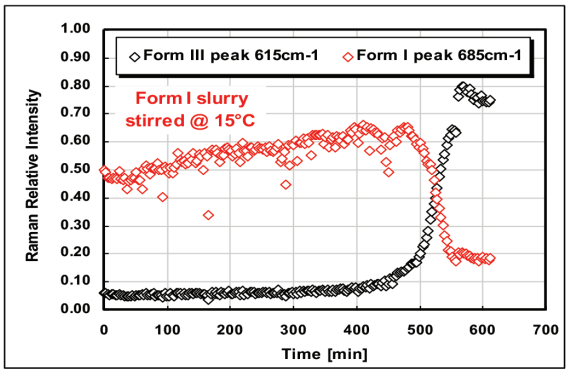

Figure 3: Profiles of Form III and Form I during slurry conversion experiment

stirred at 30 °C for 8 hours and no conversion to Form III was found (Form I becomes the metastable form at 30 °C).

Form I particles were slurries in ethanol/water (70/30 v/v) mixture at 15 °C (Figure 3). It can be seen that Form I transforms to Form III (the stable form at 15 °C) at a relatively slow rate (approx. 10 hours). However, with the addition of a small amount of Form III the solvent-mediated conversion process was accelerated (Figure 4). Figure 4 shows that Form I completely converted to Form III in less than 5 hours.

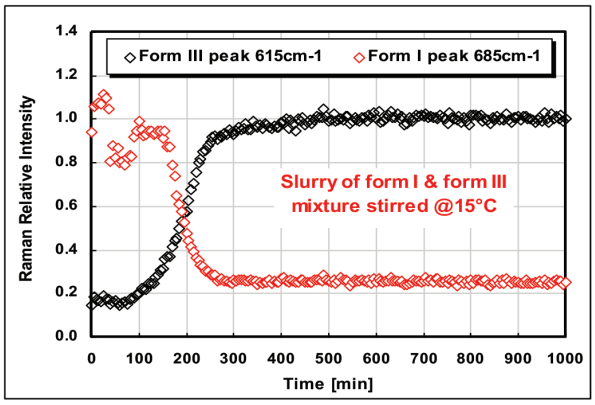

Figure 4: Profiles of Form III and Form I during slurry conversion experiment where the Form I (≈95%) and Form III (≈5%) FFA particles were stirred at 15°C in 80ml ethanol/water (70/30 v/v).

Conclusions

In situ Raman spectroscopy is capable of accurately following the enantiotropic polymorphic interconversion of FFA using univariate methods. Conversion kinetics were found to be dependent on process temperature and the presence of the stable form. Monitoring permitted the rate of polymorphic transformation to be predicted over a wide range of process temperatures.

The high information content of the Raman spectrum provided a means of characterizing and optimizing the API crystallization and slurrying processes *in situ* and offers the potential for control of polymorphic forms during scale-up and manufacturing. This application confirms the utility of Raman spectroscopy as a PAT tool within the API life cycle.

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