
CrystalBreeder


Crystal16


Crystalline

IN-SITU CRYSTALLIZATION MONITORING WITH CRYSTALLINE AND RAMAN SPECTROSCOPY

Crystalline & RAMAN Advantages

The ***Crystalline*** instrument with through the vial analytical capabilities gives the user access to real time Raman spectroscopy in combination with an accurate temperature controlled parallel crystallizer with transmissivity measurement. The independent Raman probes are integrated in an ergonomically designed, pre-aligned, robust and sealed module. The user does not have to insert any probes into the reaction vessel eliminating cross contamination.

Learn here how to identify polymorphic transformation by using Raman and the Crystalline instrument

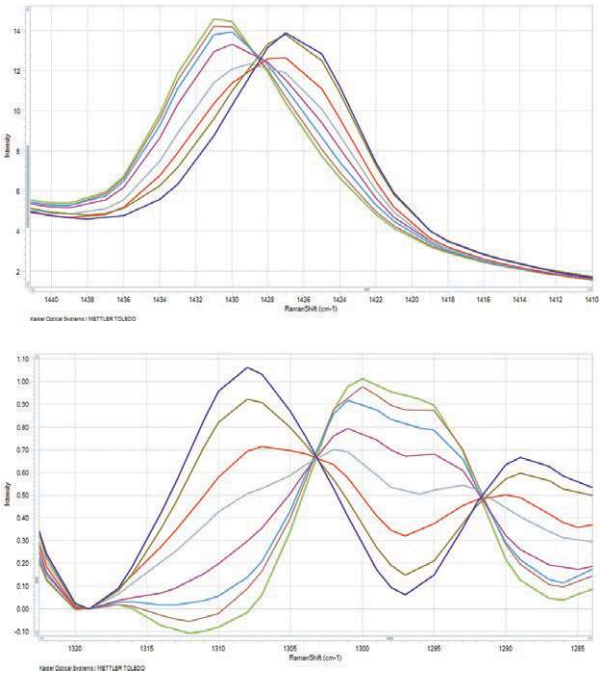
The following case study shows both significant and small changes in the crystal structure of an active ingredient. The research was performed at Boehringer Ingelheim laboratories.

All in one!

***Crystalline*, your development solution:**

- Multiple reactor systems
- Temperature control
- Small volume
- Raman spectroscopy
- Transmissivity
- In-situ probes

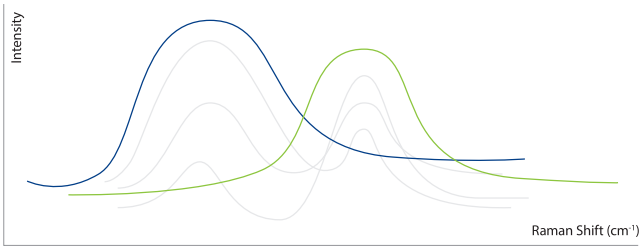
Crystalline & RAMAN Advantages



***Small changes (top)** vs **Significant changes (bottom)** in the crystal structure identified with Crystalline and Raman spectrometry.*

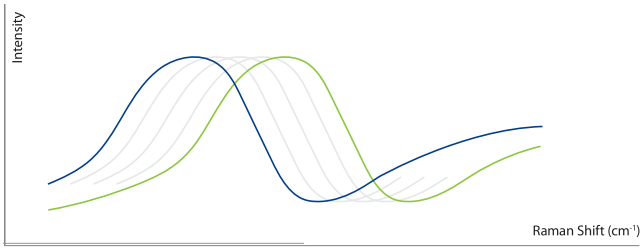
Molecular materials and each phase/polymorph of those materials produce unique Raman spectra. The typical Raman spectrum consists of sharp well-resolved peaks, whose intensity is dependent on concentration. ***Crystalline*** with Raman integration can provide compositional information about the content of the reaction vessel. Raman spectroscopy is a type of vibrational spectroscopy, producing similar information as FTIR (Fourier transform infrared spectroscopy). Raman however is well suited to monitor the solid phase in slurries, including those containing water. While FTIR is essentially blinded by water's strong IR absorption, water produces only a weak Raman signal.

Typical RAMAN shifts indicating polymorphic

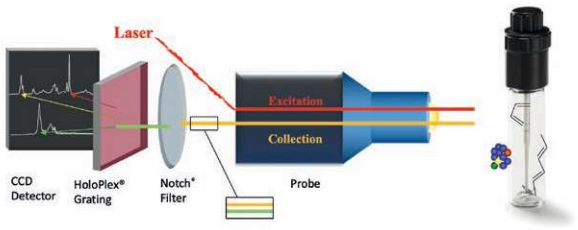


transformations

A. Raman spectroscopy may resolve the smallest differences in energies of the crystal lattice vibrational modes, which are affected by changes in molecular interactions arising from different unit cell structures or configurations of the molecules, or formula units within the unit cell, hence indication of polymorphism.



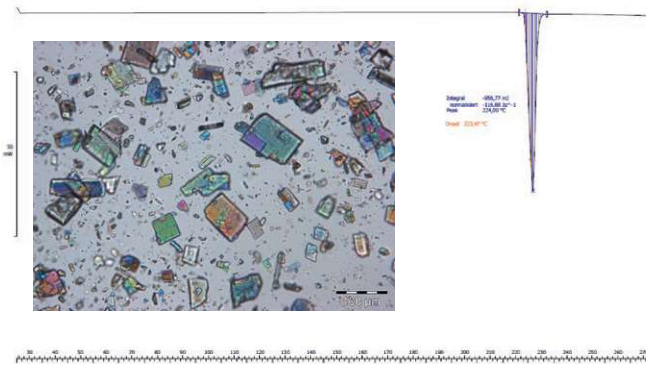
B. The Raman spectra of crystals with small differences in bond lengths or crystal spacing will also manifest small differences in the Raman peak positions.



Boehringer Ingelheim Case Study

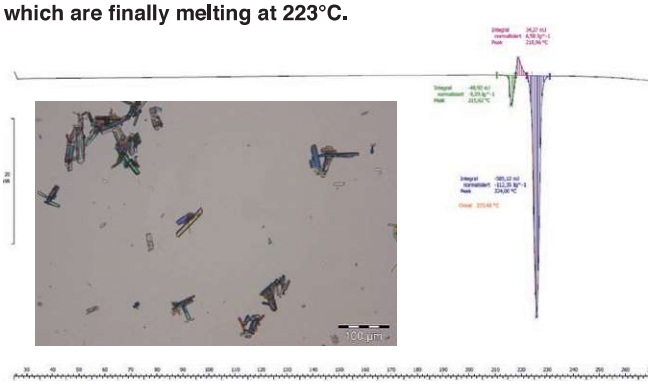
The active ingredient under investigation has two known anhydrous forms, hereunder designated as Form I and Form II.

Crystals of Form I are plates and melting at 223°C.



DSC curve of Form I showing a melting endothermic event at 223°C. Microscope image of Form I.

Crystals of Form II have a rod-like shape. Form II is first melting at 215°C. The melt is recrystallizing in crystals of Form I at 218°C, which are finally melting at 223°C.



DSC curve of Form II showing a melting endothermic event at 215°C followed by exothermic recrystallization event to Form I at 218°C and its endothermic melt event at 223°C . Microscope image of Form II.

Preliminary experiments showed that Form II is the more stable form at room temperature. According to Burger and Ramberger[1,2], these two forms have an enantiotropic relationship. The transition temperature was now determined at BI laboratories to be around 70°-75°C through bracketing experiments with slurry of both forms at different temperatures, using ***Crystal16*** and ***Crystalline*** instruments.

In order to better understand the crystallization and the stability of these two forms, suspensions of each form were measured by using the ***Crystalline*** instrument (sampling parameters: excitation time: 3 minutes, accumulations: 1) and Raman spectroscopy (Kaiser Optical Systems Rxn2, 785nm). After comparison of the two