Crystalline
CrystalBreeder
Crystal16

APPLICATION NOTE

In-situ Crystallization Monitoring with CrystallineRR and Raman Spectroscopy

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CrystallineRR & RAMAN Advantages

The ***CrystallineRR*** 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.

Do you have a Raman Spectrometer? Connect it now to the *Crystalline* instrument! Controlling your crystallization process was never so easy!

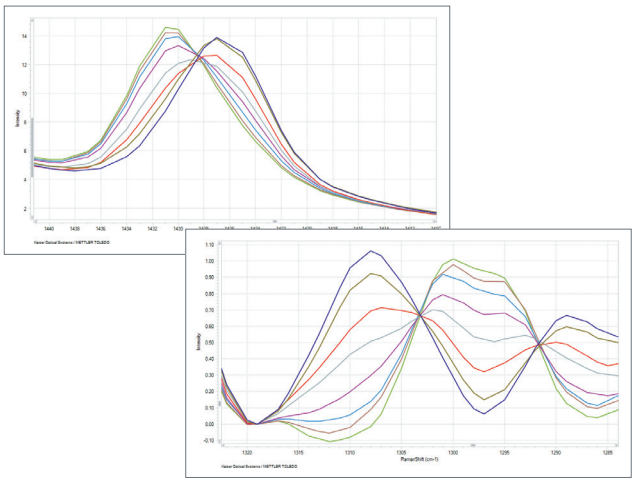
Learn here how to identify polymorphic transformation by using Raman and the Crystalline instrument

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!

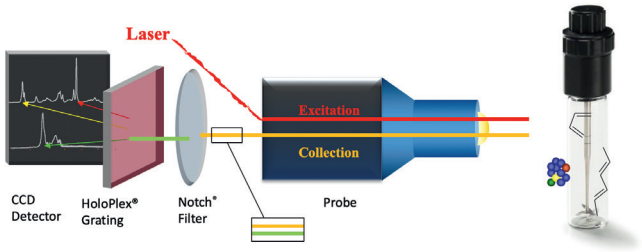
***CrystallineRR*, your development solution:**

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



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

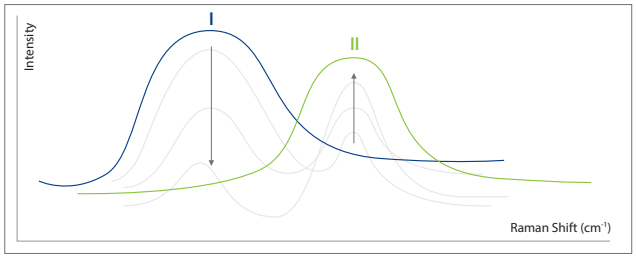
Technobis
crystallization systems



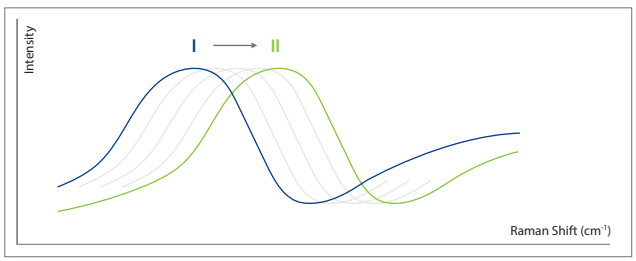
CrystallineRR & RAMAN Advantages

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. ***CrystallineRR*** 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.

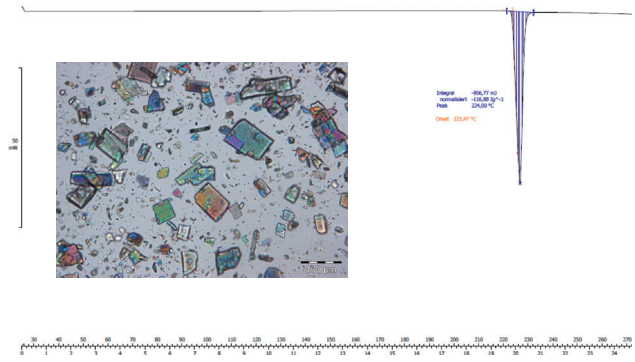


B. The Raman spectra of crystals with small differences in bond lengths or crystal spacing will also manifest small differences in the Raman peak positions.

Boehringer Ingelheim Case Study

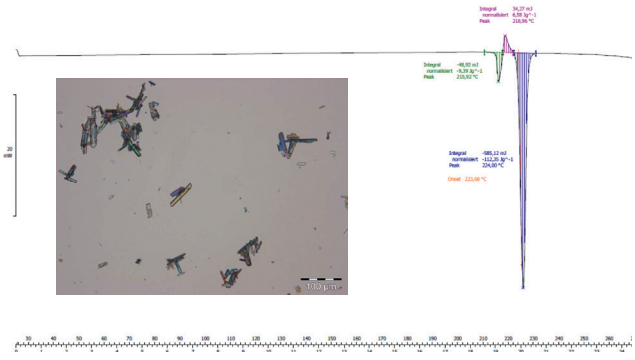
The active ingredient under investigation has two known anhydrous forms, hereunder designated as Form I and Form II.

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 spectra, the peaks of interest were selected and are shown below (in this case amide III bands).

A given amount of the metastable form (Form I) was suspended in a saturated solution of the compound and 10% of the stable form (Form II) was added.

The polymorphic transformation from Form I (blue spectrum) to Form II (yellow spectrum) using either the peak height of appearing/disappearing peaks (left) or the shift of a peak maximum (right) was successfully monitored by Raman spectroscopy. The spectra have been normalized on a peak of the solvent, close to the area of interest.

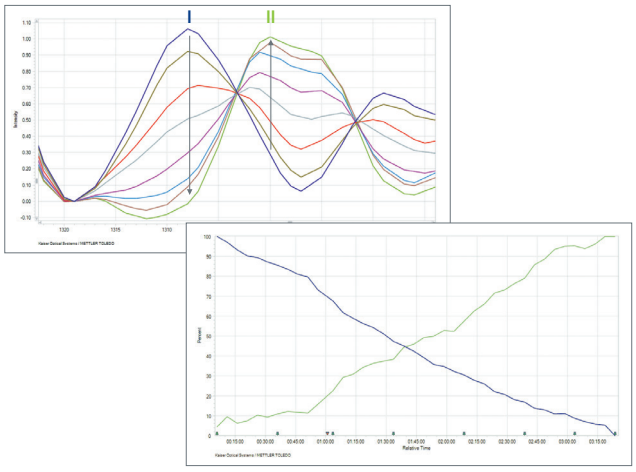
The kinetic transformations were observed at different temperatures as follows:

- At 60°C (graphs below) a full conversion to the stable form was observed after 200 minutes.
- At 20°C, 600 minutes were required to achieve the same result.

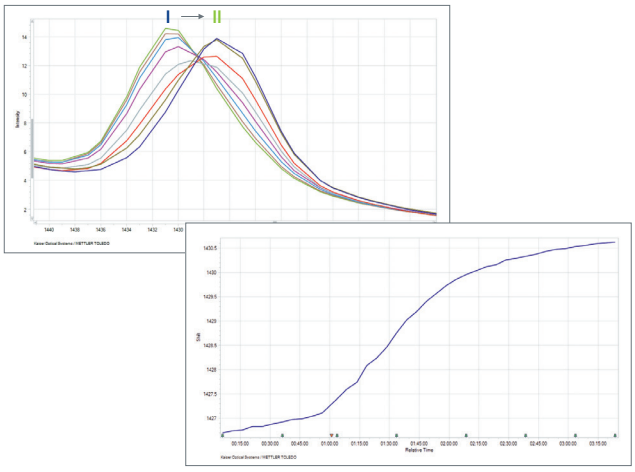
In this particular example, Raman provided valuable information about the crystallization behavior of the two polymorphs at the lab scale. Moreover, this information is now being used to optimize the crystallization process of the preferred polymorph at larger scale.

1. A.Burger, R. Ramberger, On the polymorphism of pharmaceuticals and other molecular crystals. I, Microchimica Acta, 1979, Volume 72, pp 259-271
2. A.Burger, R. Ramberger, On the polymorphism of pharmaceuticals and other molecular crystals. II, Microchimica Acta, 1979, Volume 72, pp 273-316

Controlling your crystallization process was never so easy! Connect now your Raman Spectrometer to the *Crystalline* instrument!



Peak height of appearing/disappearing peaks *(left) indicating transformation from Form I (blue spectrum) to Form II (yellow spectrum). The spectra have been normalized on a peak of the solvent, close to the area of interest (right).*



Shift of a peak maximum *(left) indicating transformation from Form I (blue spectrum) to Form II (yellow spectrum). The spectra have been normalized on a peak of the solvent, close to the area of interest (right).*

REAL TIME RAMAN during crystallization experiments

The ***CrystallineRR*** gives the user access to **real time Raman spectroscopy**, in combination with a sophisticated **parallel crystallizer** with turbidity 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. **No cleaning of the analytics! No inconsistency in your data! No cross contamination!**

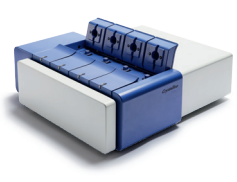
CrystallineRR

- 8 Reactors with a working volume of **2.5 - 5 mL**
- **8 Independently controlled temperature zones**
- Temperature range **-25°C to 145°C** in 4 reactors*
- Temperature range -20°C to 145°C in 8 reactors*
- Linear and non-linear temperature profiles supported
- **0° - 20°C/min** heating/cooling rate
- Temperature control accuracy: 0.1°C
- Variable overhead stirring in each reactor
- Variable magnetic stirring in each reactor
- Stirrer speed: 0 - 1250 rpm
- Transmissivity measurement in each reactor
- Reflux, slow evaporation, anti-solvent and seeding capabilities
- **Parallel real time Raman probes**
- **Correlation of Raman spectra with temperature profiles and transmissivity signals**
- Software interface for spectroscopic analysis
- Compatible with most of the RAMAN Spectrometers

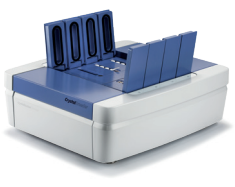
** When ambient temperature is 21°C ± 2°C and chiller cooling capacity at 18°C is about 1180 watt.*

Also part of Technobis Crystallization Systems portfolio

Crystal16



CrystallinePV



CrystalBreeder

More information in less time

- **Multiple reactor systems**
- **No cleaning analytics**
- **Small volume**
- **Clear correlation between results**
- **Data consistency**
- **Quartz reactors easily available**
- **Little training required**

Technobis
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