Monitoring a pharmaceutical crystal transformation *in situ*

Benefits at a glance
- Crystallization monitoring in real time with no disruption of process conditions
- Representative sampling in slurries
- Identification of polymorphic solid forms using precision instrumentation

Introduction

Many organic compounds can crystallize in several different forms called polymorphs. Biologically active polymorphs have different solubility and stability; hence, they have different bioavailability. The effectiveness of a drug compound depends critically on its particular polymorph.

There are two types of polymorphic systems: monotropic and enantiotropic. In monotropic systems, one polymorph is more stable than the other at all temperatures below the melting point. In enantiotropic systems, one polymorph is more stable than the other above a certain temperature, and the other polymorph is more stable below this temperature. In addition, some systems include hydrates and solvates. Hydrates include water in the crystal lattice, and solvates include other solvent molecules. Hydrates and solvates are not true polymorphs because they differ by more than just the three-dimensional arrangement of the crystal lattice. Yet, they do occur along with polymorphs in real systems, so they are important to consider in the same context.

Polymorph analysis

Traditionally, polymorphs have been identified by off-line techniques such as powder x-ray diffraction (PXRD), solid state NMR, and DSC. However, these techniques are unsuitable for process monitoring because they are slow and require invasive preparation of the sample, which might change the sample's polymorphic form before it is analyzed.

Online techniques offer the following advantages:

- Fast sampling to observe polymorphic transitions in real time
- No preparation nor destruction of the sample
- No disruption of process conditions

On-line techniques that have been used recently include focused-beam reflectance measurement, FTIR, near-infrared (NIR), and Raman spectroscopy.[1,2] Of these, only Raman has been reported to give quantitative data on polymorphic transitions *in situ* without the need for grab sampling. This note describes the use of *in situ* Raman spectroscopy to probe the kinetics of a hemihydrate, transforming to an anhydrous polymorph and then to a different polymorph.

Experimental

The compound described in this note is a proprietary material developed at the Merck Research Laboratory (Rahway, NJ).[1] It exhibits four different anhydrous polymorphs, plus a hemihydrate, a dihydrate, and a solvate. The polymorphs are referred to as forms A, B, C, and D. This note describes the transformations of the hemihydrate to form C and form C to form A. Forms A and C are enantiotropic, with form A more stable above 21 °C. All transitions took place in isopropyl acetate suspension.

A Raman spectrometer interfaced with a sapphire-window-sealed immersion probe was used to collect spectra at 785 nm with 12 accumulations per spectrum. The total collection time for each sample was 1 minute.

Hemihydrate → form C transition

A Raman waterfall plot showing the transformation from the hemihydrate to form C is shown in Figure 1.

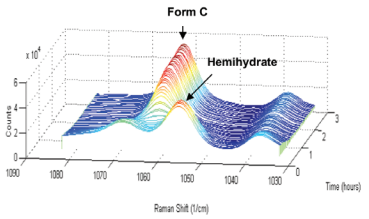

Figure 1: Raman waterfall plot of hemihydrate–form C transition. (Reprinted, with permission, from Ref. 1. Copyright 2002 American Chemical Society.)

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

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Figure 2 shows profiles of the hemihydrate–form C transition at 15 and at 25 °C. The kinetic data were derived from the intensity of the 1062 cm^{-1} peak for form C and the 1055 cm^{-1} peak for the hemihydrate via a second-derivative pretreatment and PCA. As expected, the transition is faster at the higher temperature.

The rates are found in Table 1.

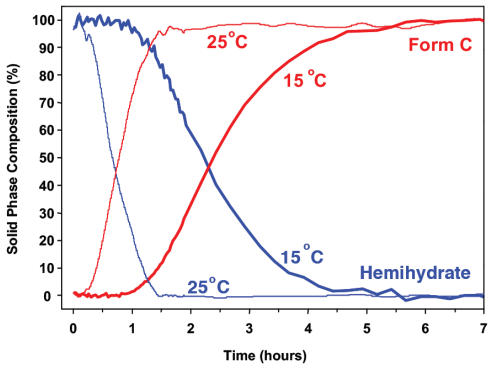

Figure 2: Profile of hemihydrate–form C transition. (Re-printed, with permission, from Ref. 1. Copyright 2002 American Chemical Society.)

Form C → form A transition

After the transformation from the hemihydrate to form C, another transformation occurs, turning form C to form A. This transformation is monitored by observing the shift of the 1062 cm^{-1} peak to 1060 cm^{-1}, demonstrating the excellent wavelength-axis stability provided by Raman instruments. A calibration curve calculated by PLS regression for quantifying a mixture of form C and form A is found in Figure 3. The rates for this transformation are also found in Table 1.

	Rate (mmol L^{-1} min^{-1})	
Temp (°C)	Hemihydrate → C	C → A
15	2.5	
21.5		0
25	6.1	1.9
35		2.7
65		31.5 ± 1.7 (*N* = 7)

Table 1. Kinetic Data. (Reproduced, with permission, from Ref. 1. Copyright 2002 American Chemical Society.)

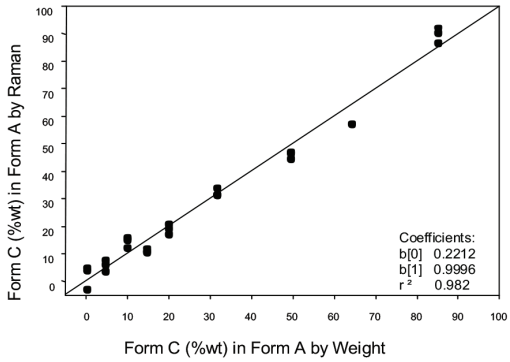

Figure 3: Calibration plot of mixtures of polymorphic forms A and C. (Reprinted, with permission, from Ref. 1. Copyright 2002 American Chemical Society.)

Conclusions

Raman spectroscopy is sensitive to both true polymorphic transformations and transitions involving hydrates and solvates. The quantitative results provided by Raman can be used to generate robust kinetic data and construct efficient process cycles.

Raman measurements can be performed easily in the industrial process line. Because Raman is a scattering rather than absorbance technique, it is compatible with opaque slurries. The results are consistent with those from off-line PXRD, even though they were obtained without sample preparation and in a fraction of the time required for PXRD. Raman provides several advantages over NIR and FTIR including low water signal and highly specific composition information. Moreover, Raman can access the low wavenumber spectral region that provides information on molecular structure and can collect measurements directly in aqueous environments. For these reasons, Raman is now the preferred method for inline polymorph measurements.

References

1. Starbuck, C.; Spartalis, A.; Wai, L.; Wang, J.; Fernandez, P.; Lindemann, C.M.; Zhou, G.X.; Ge, Z. Process Optimization of a Complex Pharmaceutical System via *In Situ* Raman Spectroscopy. *Crystal Growth & Design*, Vol. 2, **2002**, 515, and references therein.
2. Zhou, G.; Wang, J.; Ge, Z.; Sun, Y. Ensuring Robust Polymorph Isolation using *in situ* Raman Spectroscopy. *American Pharmaceutical Review*, **Winter 2002**.