Application Note AN R525

Raman Microscopy – a Valuable Technique for Polymorph Investigations

Polymorphism

Polymorph studies have developed into an important domain in pharmaceutical research. Raman spectroscopy can provide fundamental insights with comparatively little time and effort.

Polymorphs (greek: poly= many; morph = form) have an identical chemical formula but different crystal structure forms. The difference can be due to changes in the arrangement or conformation. If changes in the crystal structure are induced by solvent molecules, this effect is called pseudomorphism (see "hydrates").

Polymorphs can have significantly diverse physical and chemical properties e.g. stability, solubility, dissolution rate. This affects the general quality of a product and especially its bioavailability.

Different polymorphs can be a purposeful result of a synthesis. However, transitions can occur in many processes involved in pharmaceutical technology e.g. crystallisation, grinding, tablet pressing etc.

It is therefore essential to produce the correct polymorphic form and control its identity during formulation, storage and application.

Keywords	Instrumentation and software
Polymorph differentiation	SENTERRA II
Pharmaceuticals	OPUS spectroscopic software
Contactless analysis	Linkam microscopic sampling
Pressure and temperature variation	OPUS/PRO temperature ramping software

Raman spectroscopy in polymorph investigations

Raman scattering as a contact free analytical method is an efficient method in polymorphic investigations due to its substantial sensitivity to the crystalline structure of molecular compounds. As Raman spectroscopy also covers the spectral region below 400 cm^{-1}, it is in particular sensitive to molecular skeleton deformations, which are directly related to the polymorphic forms.

The following figure shows classical polymorphism of acetazolamide due to changes in spatial molecular arrangement.

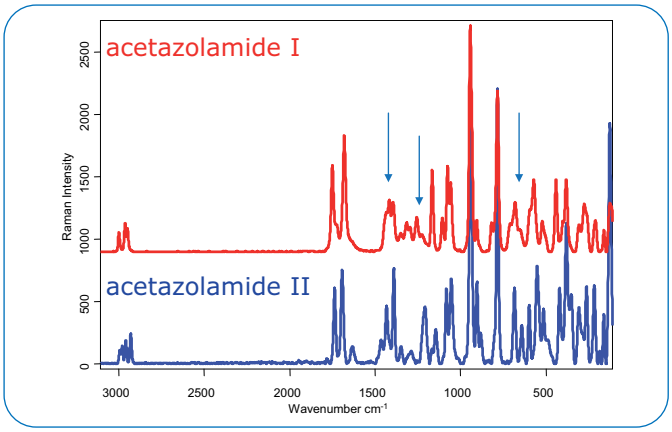

Figure 1: Acetazolamide, ("Diamox"), is a carbonic anhydrase inhibitor.

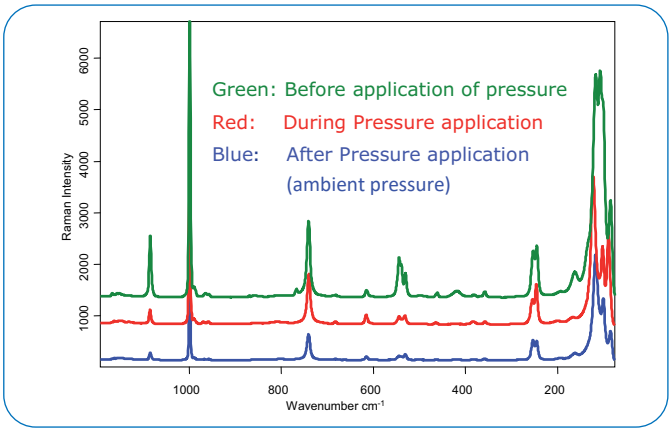

Figure 2: Pressure induced polymorphism of Resorcin.

Compared to other applicable analytical techniques like IR, NIR, x-Ray diffraction, solid state NMR, Raman has the following advantages

- No sample preparation
- Contact-free measurement
- Measurement directly in glass vial or multi-well plate
- Applicable for pure polymorphic forms and formulations
- High information content, high specificity due to sharp and isolated Raman peaks
- Identification and quantification

Bruker Optics dispersive Raman microscope SENTERRA II provides an excellent tool for polymorphism investigations due to its

- compact and robust design
- high wavenumber accuracy and permanet wavenumber calibration (Surecal [1])
- true confocal and high throughput performance (FlexFocus [2])
- automated fluorescence removal options (AFR, concave rubber band correction [3])
- upgrade option for FT-Raman (minimizes fluorescence; up to four excitation lasers)
- validation (GMP; 21CFRp11)
- integrated software tools like Cluster Analysis, Principle component Analysis etc.

Pressure induced polymorphism

The most common form of pharmaceutica is the tablet. Usually, the Active Pharmaceutical Ingredient (API) is mixed with excipient(s) and pressed into a tablet. The pressure involved (10 – 100 kN) can induce a polymorph change as illustrated in figure 2.

The sample was placed between two diamond windows. The focal plane of the laser was at sample height. Pressure was generated by pressing the diamond windows with tightening screws. The permanent spectral changes indicate a polymorph transition. In this case the tablet press would need to be set to a lower pressure to avoid the transition.

Temperature screening for stability testing

The stability of a drug regarding temperature is of major concern as this defines the conditions for storing this drug. Extensive studies are performed to evaluate the most suitable temperature for storage.

The change of polymorph A to B can be induced by raising the temperature (Figure 3).

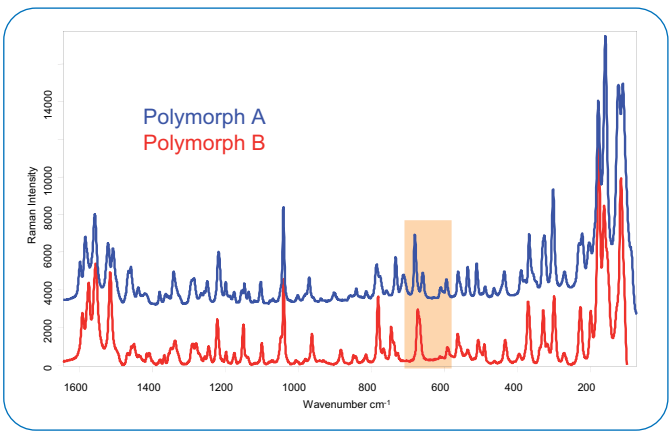

Figure 3: Metastable form of an API in form A and form B.

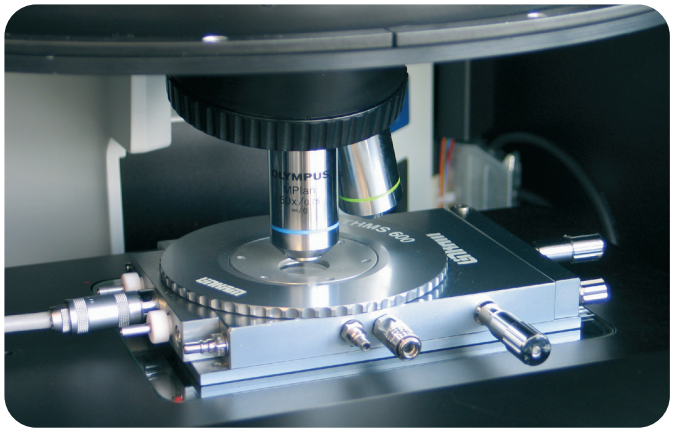

Figure 4: Linkam stage in the sample compartment of the SENTERRA II[4].

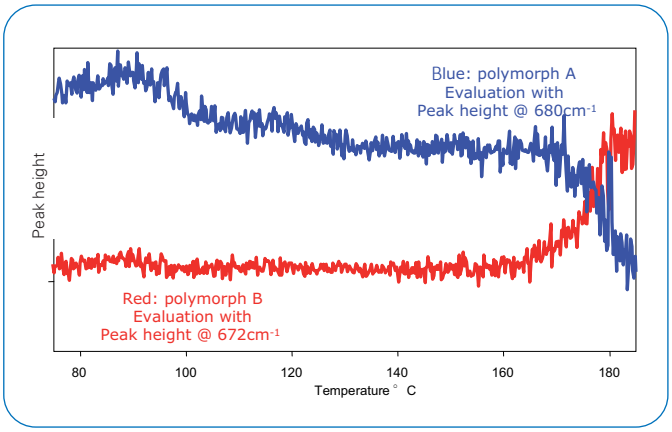

Figure 6: Relative peak intensities as a function of temperature.

The accessory used to investigate this change is the Linkam THMS 600® heating and cooling stage (-196 – 600°C) with software controlled temperature-ramping using Bruker Optics spectroscopy software OPUS (Figure 4).

A more detailed view of the spectral changes induced by the temperature change is given in Figure 5.

Evaluation of the peak heights as a function of the temperature leads to the graph in Figure 6.

As the change from form A to B occurs obviously between 160°C and 180°C the storage at room temperature seems to be appropriate for this drug and no cost-intensive cooling is required.

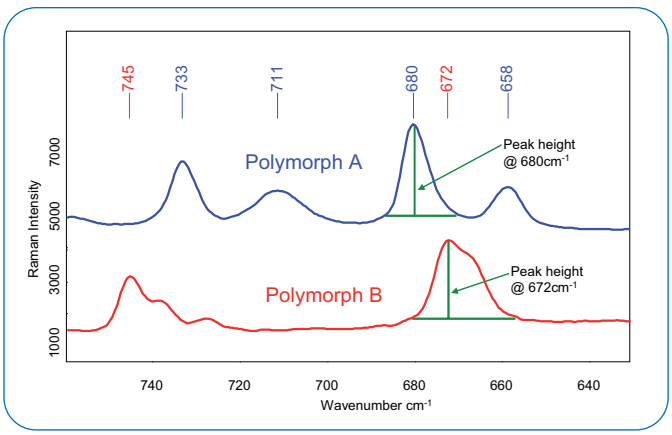

Figure 5: Raman spectra of polymorph A and B; relevant spectral region.

Summary

During the last decade Raman spectroscopy has developed into a routine analytical instrument with potential in bulk analysis, microscopic investigations and high sample throughput screening. Polymorphic investigations can benefit from the inherent non destructive character of Raman, the analytical speed ("a spectrum in seconds") as well as from its high information content. In combination with powerful but easy-to-use spectroscopic software tools many analytical questions regarding the polymorphism of an API can be addressed.

References

[1] SureCal™ technology, provides a wavenumber accuracy better than 0.1 cm^{-1}; see Bruker Optics Product Note R18

[2] FlexFocus provides a novel approach for easy change between high sensitivity and confocal Raman measurements; see Bruker Optics Product Note R26

[3] Concave rubberband correction (pat.) advanced algorithm e.g. for minimizing fluorescence residues in Raman spectra.

[4] See Bruker Optics Product Note M99

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