

**Thibault Brulé, Céline Eypert**  
HORIBA FRANCE SAS, Palaiseau, France.

**Abstract:** Polymorphisms characterization of active molecules is one piece of important information for the pharmaceutical industry, not only on raw powders, but also in the final form. Raman microscopy remains the most appropriate solution for this application. In this paper, we present an example of polymorphisms characterization by Raman microscopy using the super low frequency module.

**Keywords:** Raman microscopy, polymorphisms, pharmaceuticals, carbamazepine, super low frequency

### Introduction

Since the physical state can affect the pharmaceutical behavior of drug substances, it is important to know what controls crystallization, solid state reactions, phase stability, and solubility. There are numerous methods that have been used to measure the solid state composition of pharmaceuticals; these include X-ray diffraction, optical microscopy, thermal analysis, dissolution testing, particle size analysis, NMR, and infrared (IR) spectroscopy. Raman spectroscopy is a newcomer in this industry as a very powerful characterization technique.

Indeed, Raman spectroscopy can provide qualitative and quantitative information of the polymorphy, with 1  $\mu\text{m}$  spatial resolution when necessary. The new generation in Raman technology provides many advantages over the other techniques. As a non-destructive analysis, samples can even be examined in transparent glass or plastic containers. Microscopic samples as small as 1  $\mu\text{m}$  can be easily characterized, and finally, little or no sample preparation is required. Moreover, polymorphic and pseudo-polymorphic phases in microscopic samples can be mapped. This last point is important as the pelletizing can create pressure-induced polymorphic transformation.

In this paper, we investigate different polymorphic phases of carbamazepine, firstly on pure powder, and secondly after tableting.

### Instruments and methods:

Our HORIBA **LabRAM Soleil™** is a Raman microscope offering high throughput with no compromise on resolution. This is a consequence of the unique optical design of this microscope based on dielectric mirrors, with very low signal loss, coupled with high quality gratings, our main expertise. These outstanding characteristics are required to obtain the best quality spectra needed for polymorphy analyses.

By definition, the differences between two polymorphic phases is in the crystal modes, which can be characterized on the low Raman frequencies region. That increases the difficulty for the discrimination of the phases. Thanks to the standard super low frequency standard module available on **LabRAM Soleil™**, it becomes easy to reach 30  $\text{cm}^{-1}$



Figure 1: HORIBA **LabRAM Soleil™** Raman microscope

frequency, and so to characterize polymorphisms without additional options. This spectral range is achievable by changing automatically the angle of the injection/rejection edge filter. Consequently, the Raman throughput is largely better than through “classical” ultra low frequency filters.

## Results

In a first approach, we compared different single spectra obtained on raw carbamazepine powder. Two different spectra are observed. As shown on Figure 2, these spectra are similar, except in the low frequency range, i.e. below 50  $\text{cm}^{-1}$ . In this specific range, we observe on Form I a specific band of this crystal phase at 40  $\text{cm}^{-1}$ . This is exactly the type of bands that helps to discriminate between polymorphisms. Raman is an excellent tool to discriminate between two polymorphic forms on raw product.

Nevertheless, Raman microscopy can also be used to discriminate polymorphic forms on pellets or tablets. In a second approach, we analyzed a homemade tablet of different forms of carbamazepine mixed with excipients. A Raman map was first acquired to identify carbamazepine particles in the tablet, and second, the polymorphic phases of these particles. Based on the spectral range 30-50  $\text{cm}^{-1}$ , it became easy to distinguish between the different forms I and III. Results on the polymorph distribution are shown on Figure 3.

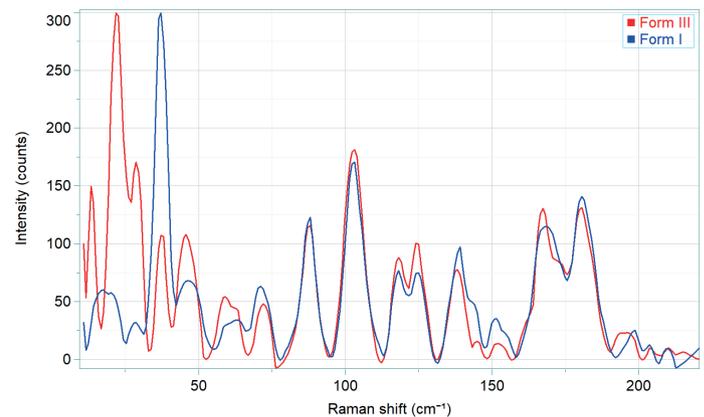


Figure 2: Low frequency Raman spectra of Carbamazepine grains of powder

## Conclusion

Raman microscopy is an excellent tool for polymorphic phases characterization of API. The super low frequency module available on HORIBA **LabRAM Soleil™** as a standard, is a perfect tool to attain crystal phases bands with no compromise on the acquisition time, a must have for genuine product characterization.

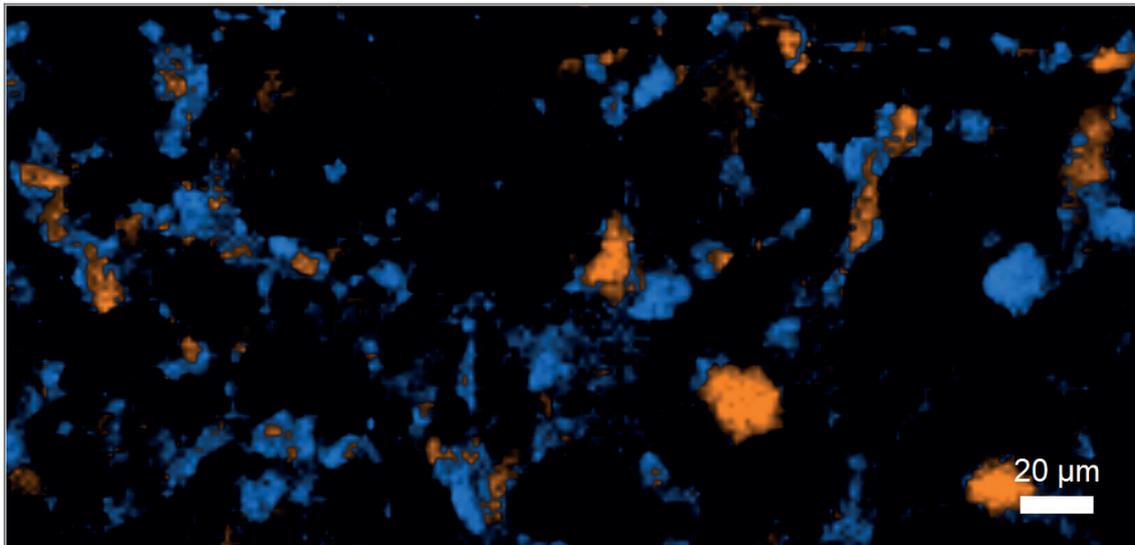


Figure 3: Carbamazepine distribution in tablet (blue: Form I, orange: Form III, black: excipients)

[info.sci@horiba.com](mailto:info.sci@horiba.com)

**USA:** +1 732 494 8660  
**UK:** +44 (0)1604 542 500  
**China:** +86 (0)21 6289 6060  
**Taiwan:** +886 3 5600606

**France:** +33 (0)1 69 74 72 00  
**Italy:** +39 06 51 59 22 1  
**India:** +91 (80) 4127 3637  
**Brazil:** +55 (0)11 2923 5400

[www.horiba.com/scientific](http://www.horiba.com/scientific)

**Germany:** +49 (0) 6251 8475 0  
**Japan:** +81(75)313-8121  
**Singapore:** +65 (6) 745-8300  
**Other:** +33 (0)1 69 74 72 00