High-throughput Screening Application Note

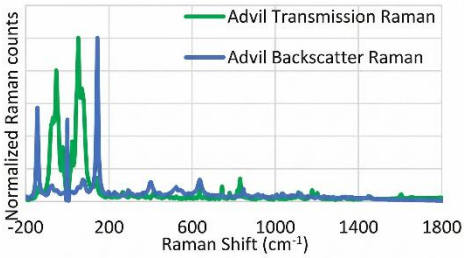
Crystallization Kinetics in Intact Tablets: Transmission-THz-Raman™

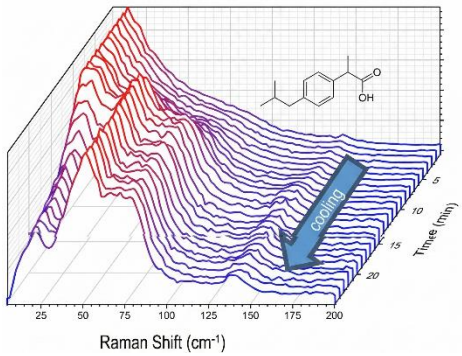
The Challenge

Many active pharmaceutical ingredients (APIs) exhibit polymorphism, where different forms or molecular structures of a compound can dramatically affect the efficacy, stability and bioavailability of the drug. Studying polymorphic forms and transformation in intact compacted and coated tablets is a challenge.

Traditional Methods

Standard approaches to crystallinity detection like XRD and ssNMR are generally not able to detect phase transitions that occur over a period of minutes. Both these methods require sample handling, which together with long acquisition times makes them not amenable to real-time/ online analysis. During polymorphic transformations, subtle changes in fingerprint Raman are usually difficult to detect. Additionally, for intact tablets which are usually coated, standard backscattering collection of Raman spectra only represents the coating material. A prime solution to study fast polymorphic transformations in bulk material/API would be using transmission Raman in the THz/low frequency regime (5-200 cm^{-1}), where crystal lattice modes that correlate to material structure in the bulk can be detected with high SNR.





The Ondax - TRS Solution

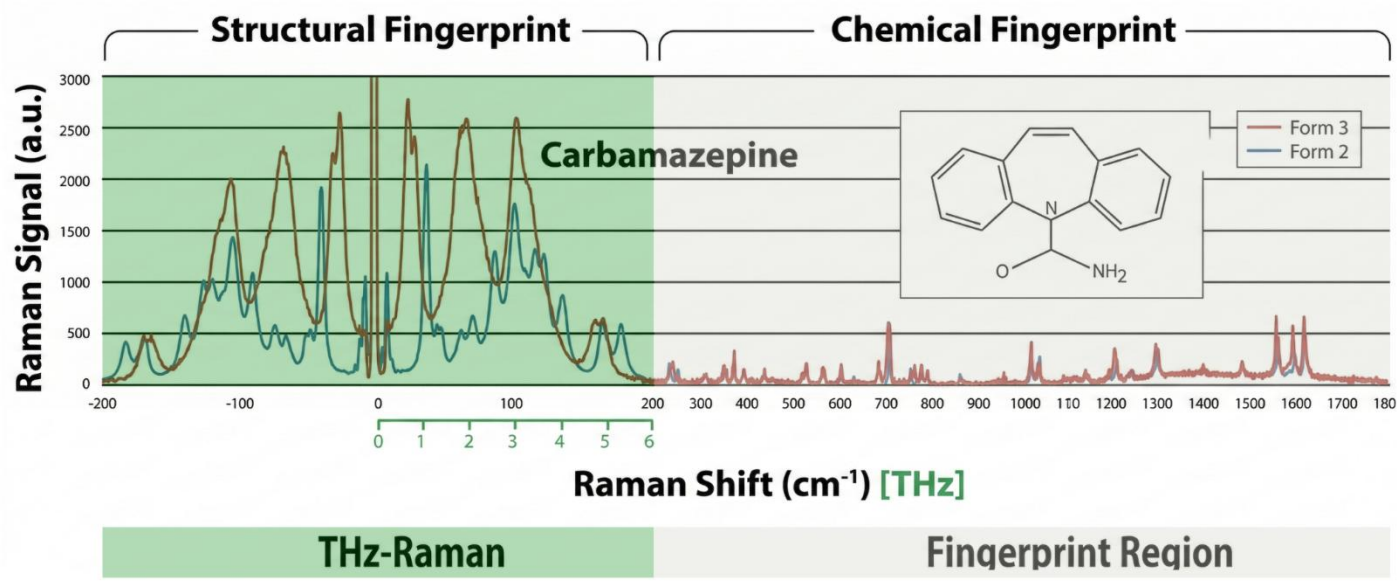
Ondax's Transmission Sampling Accessory adds transmission Raman capability to the TR-Probe THz-Raman™ platform. This can be very beneficial when coatings or other materials affect backscatter measurements, particularly with pharmaceutical tablets. Since transmission Raman is a multiple scattering process, it is the best method to get an average measurement over the entire volume of the sample.

In the example illustrated here, an Advil tablet was heated to 80 C in an oven for 15 min, which is slightly above the melting temperature of the API ibuprofen (76 C). The tablet stayed intact with no visual signs of physical changes. The tablet was then inserted into the Transmission sampling accessory and allowed to cool to room temperature. The non-isothermal crystallization can be monitored using the THz-Raman™ region which clearly highlights that the low frequency peak associated with the boson peak of the amorphous ibuprofen disappears as the lattice modes associated with crystalline ibuprofen appear at ~50 cm and ~75 cm^{-1}. The high frequency modes do not reflect these changes with suitable SNR. Additionally, Raman spectra collected in backscatter mode did not change during the heating or cooling cycle, which indicates that there was no appreciable change in the coating. Finally, each TR spectra is collected in 10 sec, a temporal resolution that allows for fitting to extended Avrami-like functions for non-isothermal kinetics.

Attalon

THz-Raman™ PLUS fingerprint region measurement with the same system

Many compounds undergo structural changes due to formulation/processing methods and environmental conditions. The spectra below shows two polymorphs of carbamazepine (Form 2 and Form 3). The THz-Raman™ range (green background) exhibit strong, distinguishing signals when compared to the traditional fingerprint region (grey background), improving the ease and reliability of polymorph identification.



Ondax's patented THz-Raman™ Spectroscopy Systems extend the range of traditional Raman spectroscopy into the terahertz/low-frequency regime, exploring the same range of energy transitions as terahertz spectroscopy - without limiting the ability to measure the fingerprint region. This enables simultaneous analysis of both molecular structure and chemical composition for advanced materials characterization.

All THz-Raman™ systems are compact, robust plug-and-play platforms that deliver incredible speed, throughput and ease of use, all at an extremely affordable price. With a broad selection of excitation wavelengths from 488nm to 1064nm, optional polarization control and a wide variety of sample interfaces, there is a THz-Raman™ solution for any application.