Rheology-Raman spectroscopy: Tracking EVA/acetaminophen mixture crystallization

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Keywords

Rheology, Raman spectroscopy, hot melt extrusion, polymer crystallization, hyphenated techniques, biomedical engineering

Figure 1. The HAAKE MARS Rheometer and DXR3 Flex Raman Spectrometer comprise the Rheo-Raman system.

Introduction

In this application note, the combination of rheometry and Raman spectroscopy is presented as an analytical method to monitor the crystallization behavior of ethylene vinyl acetate (EVA) with and without acetaminophen.

Over the last few years, demand from the pharmaceutical industry has been growing for EVA to be used as a drug-eluting excipient in biomedical engineering as well as in hot melt extrusion (HME) applications. As shown in other works, EVA is an especially suitable excipient for low-temperature HME, thus enabling it to process active pharmaceutical ingredients (APIs) with low thermal stability.[1]

HME has been used extensively in the polymer industry to produce a wide range of plastic products in a variety of forms. However, HME applied to the production of pharmaceutical formulations is a relatively new method being developed as an attractive alternative to traditional batch processing methods for tablets, granules, pellets, and even transdermal films. The biggest advantage of HME is that as a continuous process, it allows for direct in-line monitoring and control of the manufacturing process.

HME is an easier way than traditional methods to produce a variety of different dosage formulations, generating product that can have enhanced dissolution, improved product delivery, and controlled release. During HME, a dry blend of the respective API and a thermoplastic excipient is melt-mixed using extruders. In the ideal case this leads to the formation of thermodynamically stable solid solutions or dispersions, which may provide for extended product lifetimes. One parameter that has a vast influence on final product stability, as well as bioavailability of the API, is the crystallinity of the thermoplastic excipient along with the API.[2] As the crystallization of a given thermoplastic can be induced thermally and/or via applying shear stresses in the extruder, investigation of the behavior prior to conducting large-scale HME experiments is beneficial. Also, it's necessary to understand whether the solid solution of API and thermoplastic will remain thermodynamically stable after the manufacturing step or whether recrystallization of the API will occur. To investigate thermodynamic stability behavior on a lab scale, the Thermo Scientific™ HAAKE™ MARS™ Rheo-Raman system can be used. This system is the hyphenation of two Thermo Scientific instruments: a HAAKE MARS Rheometer and a DXR3 Flex Raman Spectrometer via the HAAKE MARS Rheo-Raman Module. The system used for the work in this application note is shown in Figure 1.

Results and discussion

To demonstrate the capabilities of the Rheo-Raman system, we provide simultaneous Raman and rheological measurements on an EVA copolymer (28% VA) in pure form as well as mixed with acetaminophen (40 wt.%) during a variety of temperature sweep experiments in small amplitude oscillatory shear (SAOS). All rheological tests were conducted with a 35 mm parallel plate geometry at a gap of 750 µm in CD oscillation at a strain amplitude of 1% and an angular frequency of 6.28 rad/s. Raman spectroscopy measurements were performed using the DXR3 Flex Raman Spectrometer and the Thermo Scientific OMNIC™ Series Software. The DXR3 Flex Raman Spectrometer was equipped with a CCD camera cooled to -50°C, a triplet spectrograph providing Raman spectra over the range of 3500 to 50 cm^{-1} Raman shift (Stokes) at 5 cm^{-1} resolution, and a 532 nm laser. A laser power of 10 mW was used on the sample to monitor the crystallization kinetic of EVA. Alignment of the laser, Raman scatter, and aperture selection within the spectrometer were all software controlled. The crystallization kinetic was monitored continuously starting from 120°C with the melt polymer (see details in text below), by collecting spectra every 30 seconds (6 s exposure time for 5 accumulations).

The hyphenated system setup shown in Figure 1 represents a novel integration of instrumentation: a Raman spectrometer and a rotational rheometer are coupled through an optically transparent base modified from the Thermo Scientific RheoScope Module. A schematic of the setup is shown in Figure 2.

To monitor the influence of temperature on the crystallization behavior of the pure EVA, different temperature ramps were run on the rheometer as shown in Figure 3. For each of the three runs, fresh sample was filled in the rheometer at 120°C. Waiting time for melting of the sample was 10 minutes, then the gap was achieved and the sample was trimmed. After another 5 minutes of equilibration time, the temperature was ramped down from 120°C to 60, 65, and 70°C, respectively, at a rate of 2 K/minute. After reaching the final temperature, the sample was tested isothermally for another 20 to 30 minutes.

As can be seen from Figure 3, the three data sets are congruent up to the isothermal stage. At 70°C, the EVA does not show a phase transition at all, whereas at 60°C and 65°C the EVA shows crystallization. The phase transition follows a faster kinetic at 60°C compared to 65°C, and higher G' values are reached at 60°C with a smaller G'' resulting in a smaller damping function tan d (G''/G'). The behavior shown in Figure 3 is supported by the simultaneously recorded Raman spectra as described below.

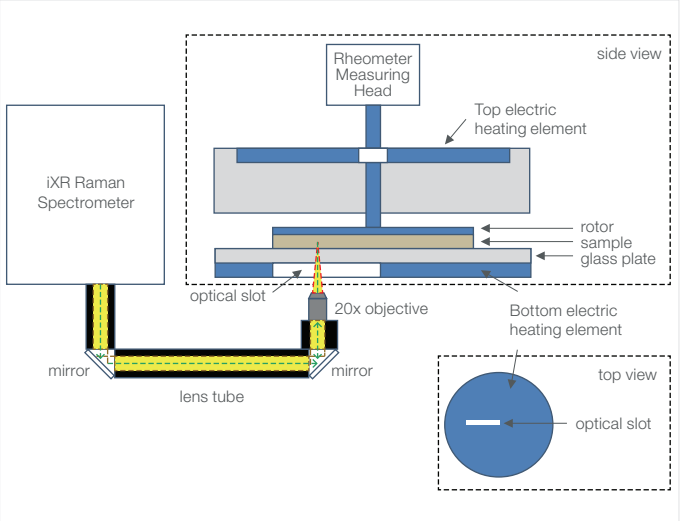

Figure 2. Schematic view of the optical path from the Raman spectrometer into the rheometer.

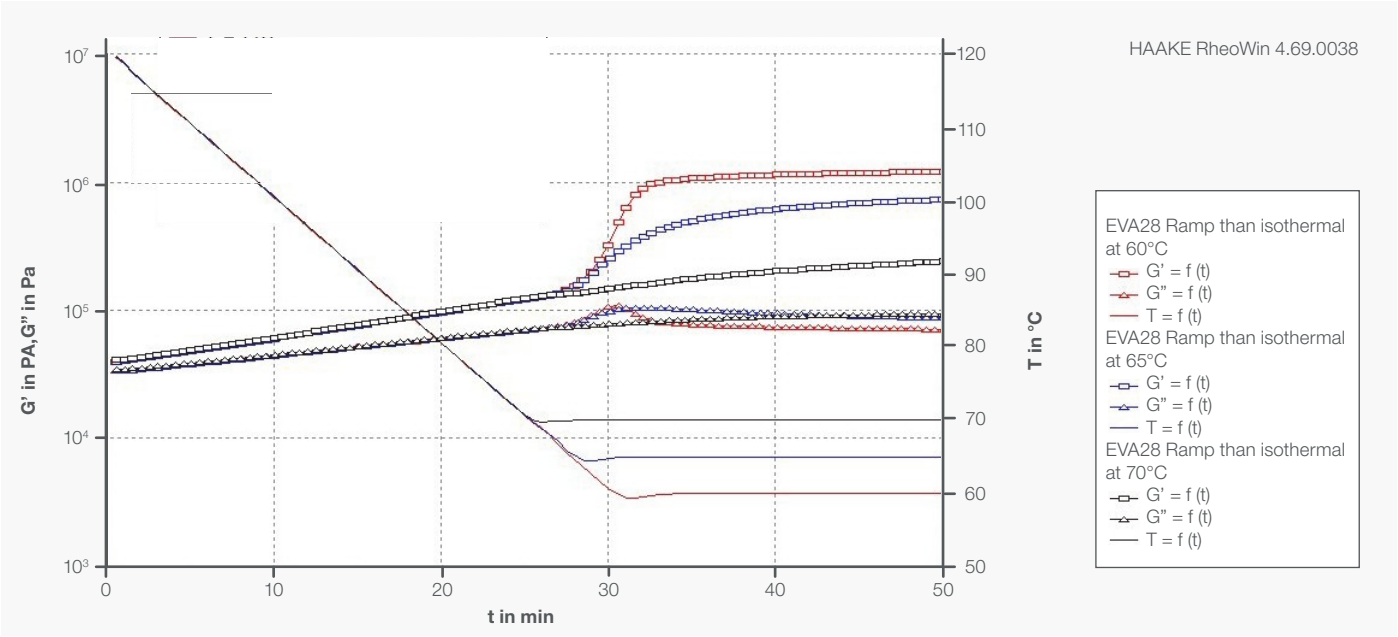

Figure 3. G' and G'' as a function of time and temperature for the pure EVA.

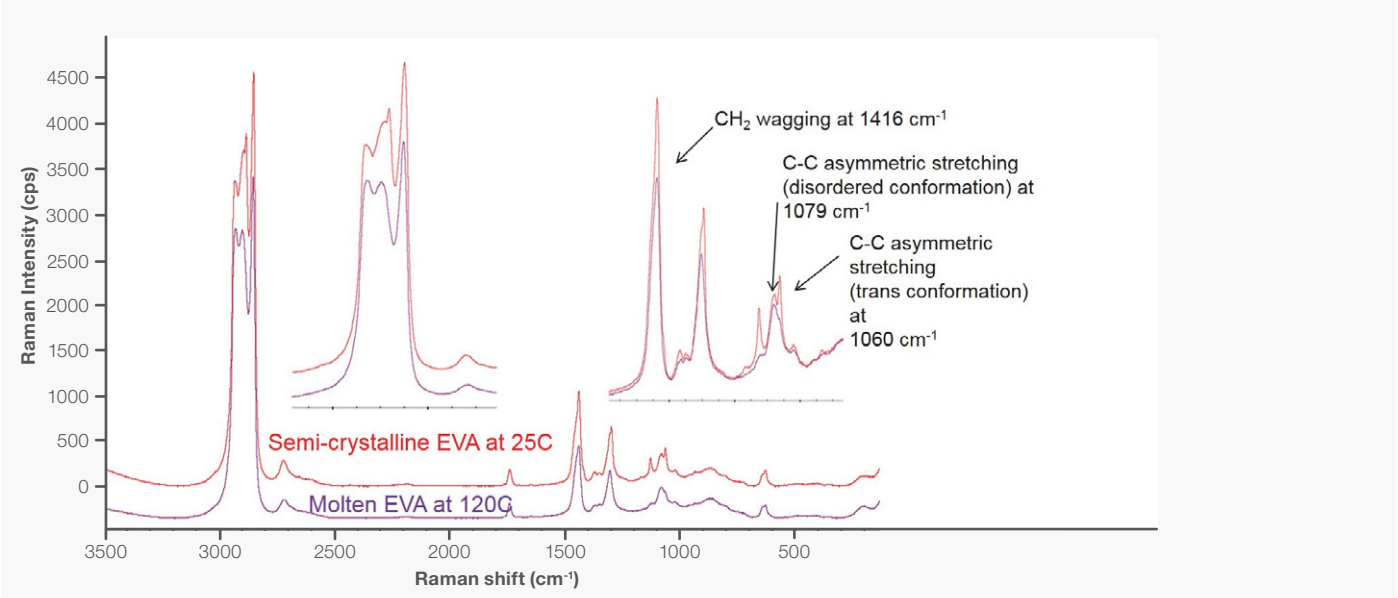

Figure 4. Raman spectra of the pure EVA in molten (blue spectrum) and in the solid (red spectrum); the insets show a magnification of the most interesting region.

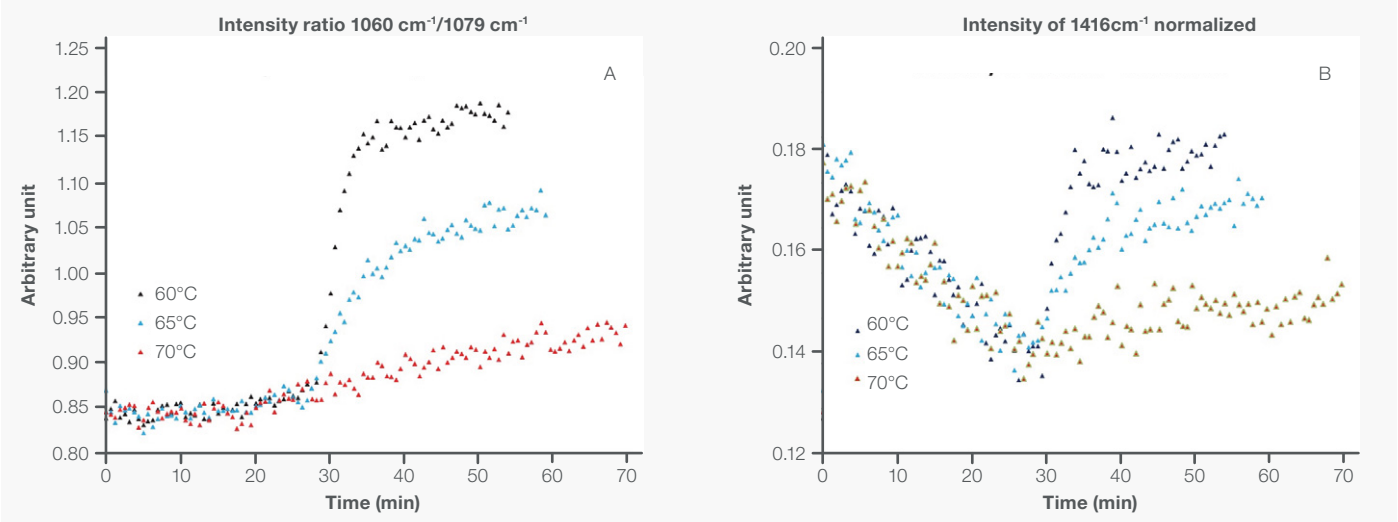

Figure 5. (A) The intensity ratio 1060 cm^{-1}/1079 cm^{-1} and (B) the intensity of the normalized peak at 1416 cm^{-1} for EVA at 60, 65, and 70°C.

Figure 4 shows the Raman spectra of the pure EVA in the molten phase at 120°C just before starting the ramp down to reach the isothermal crystallization temperature of choice in comparison with the solid-phase spectrum collected at room temperature.

As expected, considering the above interpretations, the Raman spectrum of the molten polymer does not exhibit peaks at 1416 cm^{-1} and 1060 cm^{-1} while it shows a prominent peak at 1079 cm^{-1} relative to the disorder and amorphous content (Figure 4). For more details on Raman spectroscopy for polyethylene, please refer to Thermo Fisher Scientific application note V286.[3]

As can be seen in Figure 5A, the ratio of the intensities 1060/1079 cm^{-1} (higher values of the ratio are indicative of a phase transformation and higher order) of the two data sets collected at 60°C and 65°C increase at the time of the phase transition and mimic the rheological data. The steeper slope observed for the isothermal crystallization conducted at 60°C indicates that the kinetic of chain alignment is faster than at 65°C, again in agreement with the rheological data. Whereas at 70°C no phase transition is observed, the EVA stays molten at this point. The crystallinity peak Figure 5B shows very much the same behavior as the ratio; however, the crystalline weight fraction at 60°C is only marginally larger than at 65°C.

Wavenumber/cm^{-1}	Mode	Correlating weight fraction
1416	-CH2 Wagging	Crystalline phase
1079	C–C Asymmetric stretching (conformational disorder)	Amorphous phase
1060	C–C Asymmetric stretching (consecutive trans-conformation)	Ordered phase

Table 1. Relevant polyethylen Raman bands for EVA28.

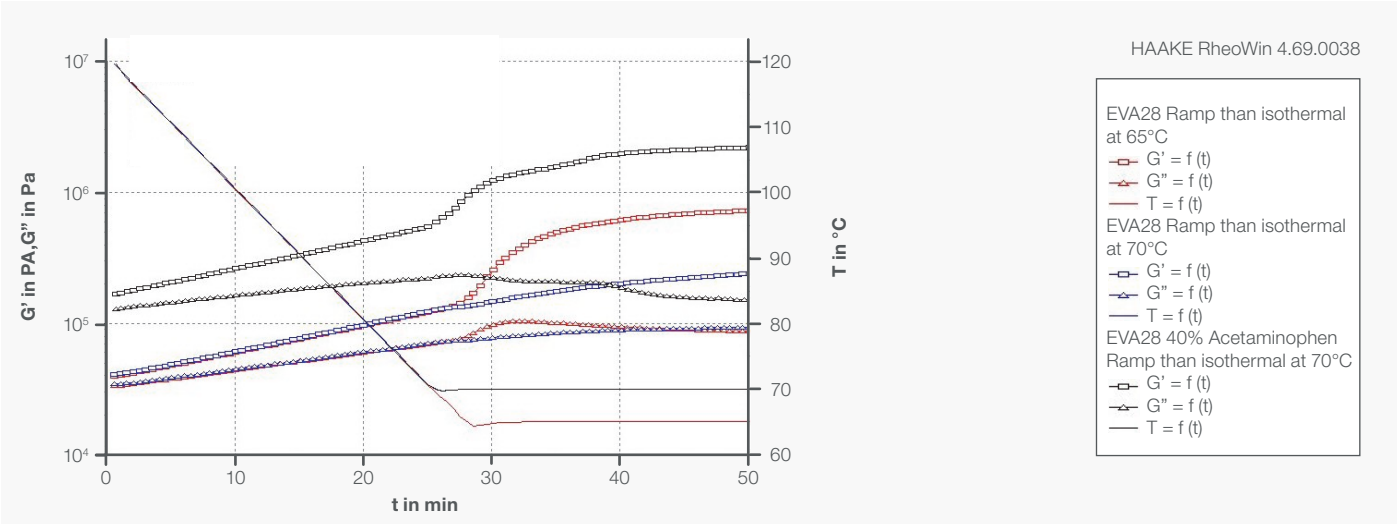

Figure 6. G' and G'' as a function of time and temperature for the pure EVA in comparison to the EVA/acetaminophen mixture.

Adding 40 wt.% of acetaminophen to the EVA changes the viscoelasticity and phase transition drastically (Figure 6). The EVA/acetaminophen blend not only exhibits higher viscoelastic moduli at higher temperatures but also shows a phase transition at 70°C in contrast to the neat EVA. Also, the EVA/acetaminophen blend shows an earlier transition than even the neat EVA did at 65°C. Showing an even smaller value in the damping function tan emphasizes the fact that the added API leads to an overall much more brittle behavior arising from pronounced crystallization.

From the simultaneously collected Raman spectra in Figure 7, you can come to the same conclusion that was derived from the rheological data: the addition of acetaminophen influences the crystallization behavior of EVA and causes a phase transition at 70°C. Monitoring the intensity of the crystalline peak (Figure 7B) provides further information. Clearly, in the case of added API, the phase transition starts 15 minutes earlier than the neat EVA at 65°C. The degree of crystallinity at the end of the isothermal process is higher in the EVA/acetaminophen melt blend as well.

Another valuable piece of information the Raman spectrum reveals is related to the morphology of the API, i.e., changes of the polymorph form of the acetaminophen in the compound caused by the exposure to elevated temperatures during the HME process. Figure 8 shows the comparison of the spectra of the pure acetaminophen and the acetaminophen melt-blended with EVA at the end of the crystallization process. The Raman spectrum of the pure acetaminophen (blue spectrum in Figure 8) can be assigned to the monoclinic form, which is the most common of the commercial products and the most thermodynamically stable. After the process, the acetaminophen (red spectrum) does not change form, but slight differences in relative intensities and peak positions in some regions of the spectra are observed. These may be caused by physical interactions of the acetaminophen with the EVA excipient. While the present set of data does not provide a decisive conclusion, the benefit of the hyphenated Raman and rheology system to investigate complex morphology and phase behavior is apparent.

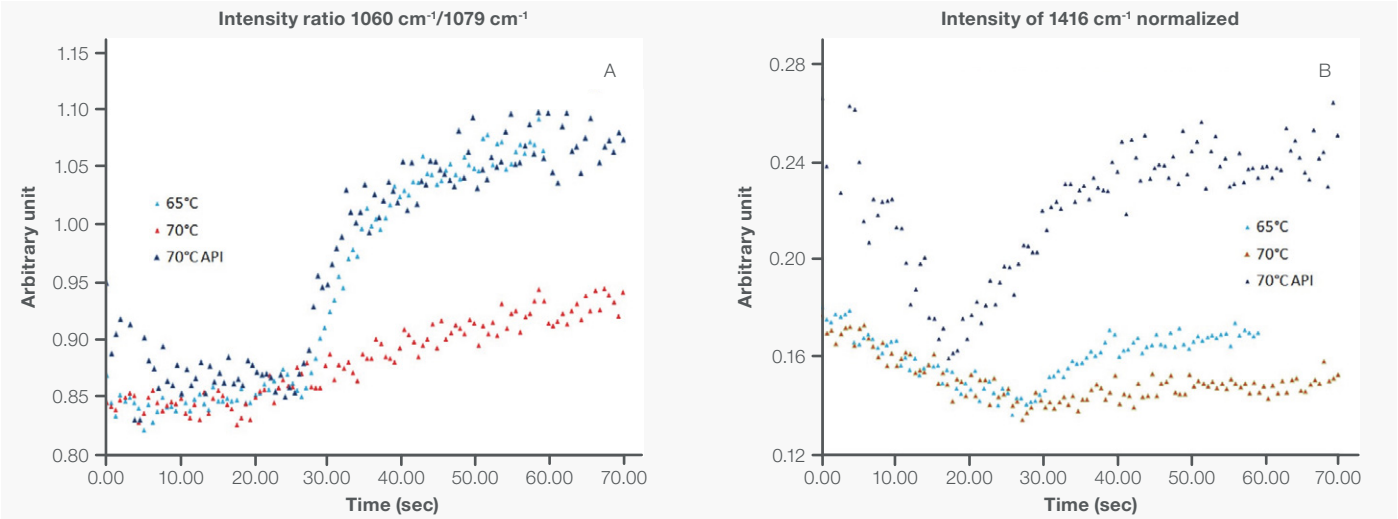

Figure 7. (A) Intensity ratio 1060 cm^{-1}/1079cm^{-1} and (B) the intensity of the normalized peak at 1416 cm^{-1} for EVA at 65 and 70°C as well as the EVA/acetaminophen mix at 70°C.

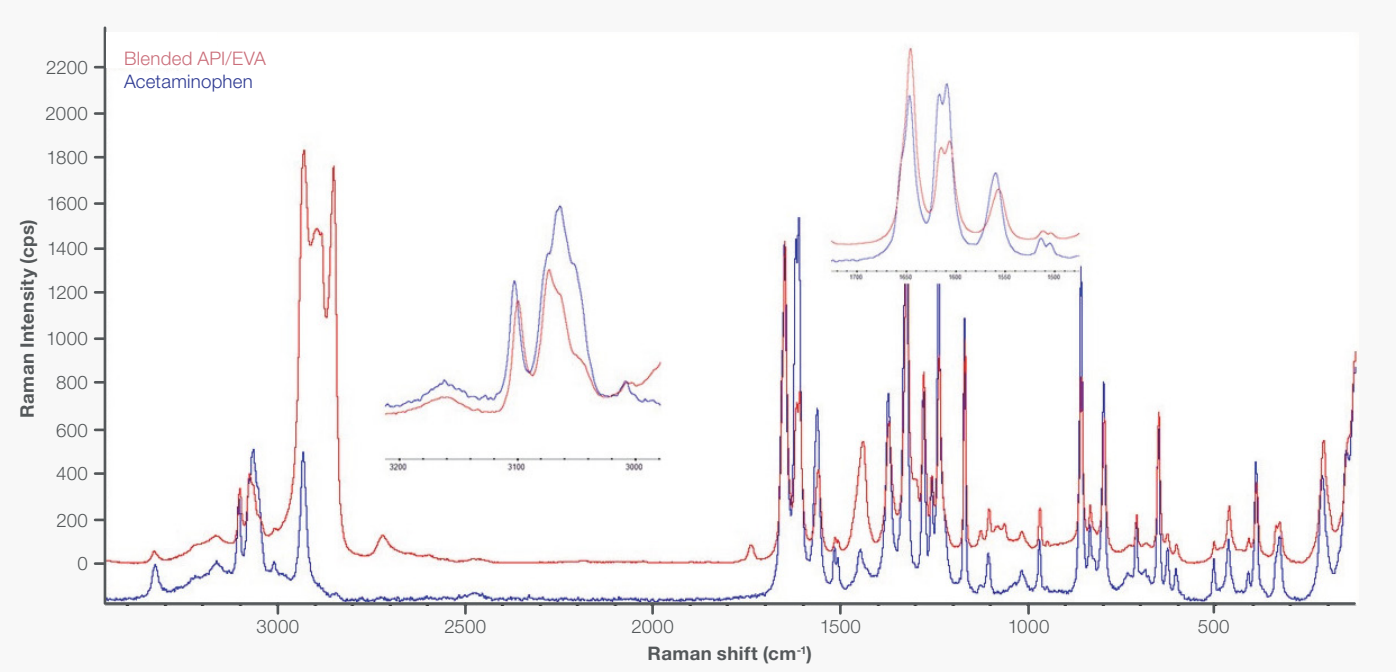

Figure 8. Raman spectra of the pure acetaminophen (blue) and the EVA/acetaminophen mix after the rheological temperature ramp (red).

Summary

It has been demonstrated that the HAAKE MARS hyphenated Rheo-Raman system can yield a wide range of relevant product parameters simultaneously. The neat EVA did not show a phase transition at 70°C, whereas the EVA/acetaminophen mixture not only showed a phase transition but started the transition even earlier than the neat EVA at 65°C. Acetaminophen acts as a nucleating agent during the isothermal crystallization of EVA, leading to a higher crystalline weight fraction in the EVA/acetaminophen mixture. The rheological results allow us to understand the viscoelastic behavior of the materials in a formulation process like HME, while also obtaining data about the morphology of the polymer and/ or API involved. The changes observed in the Raman spectrum for the acetaminophen before and after the temperature cycle are not fully understood yet. Further work will be necessary to allocate those changes to either a change in polymorph or to interactions with the EVA excipient.

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