APPLICATION BRIEF

Differential Scanning Calorimetry – Raman Spectroscopy

Polymorphism in Acetaminophen Studied by Simultaneous DSC and Raman Spectroscopy

Introduction

Differential scanning calorimetry (DSC) and Raman spectroscopy are complementary techniques that are often applied to the same problems, principally to study phase transitions in solids. Simultaneous Raman and DSC measurements add a qualitative dimension to DSC data which simply measure heat flow. A typical example is the identification of polymorphs. Acetaminophen has several polymorphic forms which can interconvert with thermal treatment. A single Raman spectrum can identify a polymorph, while DSC uses a temperature scan to observe the relationship between forms that are not all stable at ambient temperatures. Simultaneous measurements are necessary to ensure that the Raman data correspond to the different stages identified by DSC.

Coupling thermal and spectroscopic techniques raises the question of how the methods affect each other. In this case, the main issue is the potential of the laser energy to perturb the temperature of the sample. By exploiting the double-furnace design of PerkinElmer®'s DSC to assure accurate temperature control on the bulk of the sample and the fast response of this design to compensate for the heat induced by the Raman laser, the effects of the Raman on the sample can be minimized. Similarly, the ability of the PerkinElmer RamanStation™ to apply laser only while spectra are being collected also helps maintain sample temperature. This allows accurate measurements with minimal induced artifacts.

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Experimental

The system used here combines a PerkinElmer DSC 8500 with a PerkinElmer RamanStation connected by a fiber optic probe. The probe fits into the lid of the DSC with an additional lens to focus the laser onto the sample pan and collect the Raman scatter. Spectra are measured with an open sample pan or through a quartz lid. For the data shown here, the heating rates were 10 or 20 K/min with spectra typically obtained at 1 or 2 degree intervals. The power of the laser used to generate the Raman spectra affects the DSC, but the rapid response of the dual-furnace design of the DSC 8500 minimizes any perturbation of the sample temperature. Changes in the Raman spectra recorded during the temperature cycle can generate a curve for direct comparison with the DSC heat-flow curve, confirming that the two techniques are responding to the same changes. Thermal transitions appear as peaks in the DSC heat-flow curve but they appear as steps when generated from band intensities in the Raman spectra (Figure 1).

Results

Raman spectra of the various forms are seen in Figure 2. Although the spectra of Forms I and III appear very similar, there are significant band shifts, while the spectrum of Form II is clearly different. The spectra of the melt and the amorphous solid are extremely similar to each other with much broader bands than the crystalline forms.

DSC is needed to understand the relationship between the different forms. Commercial products contain Form I which is the thermodynamically most-stable polymorph. However, cooling from the melt normally produces an amorphous glass. Figure 3 shows a thermogram and spectra obtained by heating the amorphous material from 30 to 200 ˚C. The glass crystallizes at about 80 ˚C to Form III. At about 130 ˚C, this is transformed into Form II which melts at about 160 ˚C.

When the amorphous glass is allowed to crystallize at room temperature, it can convert to Form II. Although Form II melts at 160 ˚C as in Figure 3, it may convert to Form I when heated from ambient temperature. Figure 4 shows a Raman thermogram and spectra obtained by heating a sample of Form II from 20 to 200 ˚C, cooling to 20 ˚C and heating to 200 ˚C again. Conversion to Form I occurs at about 120 ˚C with subsequent melting at 170 ˚C. After cooling, the amorphous glass undergoes the expected transitions to Form III and then to Form II. The conversion from Form II to Form I is not always seen.

The amorphous glass crystallizes very slowly unless heated. However, the presence of small particles to act as nuclei can promote crystallization. A sample of acetaminophen containing a small concentration of zinc oxide crystallizes at around 100 ˚C on cooling from the melt at 10 K/min. Spectra from before and after the transition in Figure 5 (Page 3) show that, in this case, crystallization results in Form III.

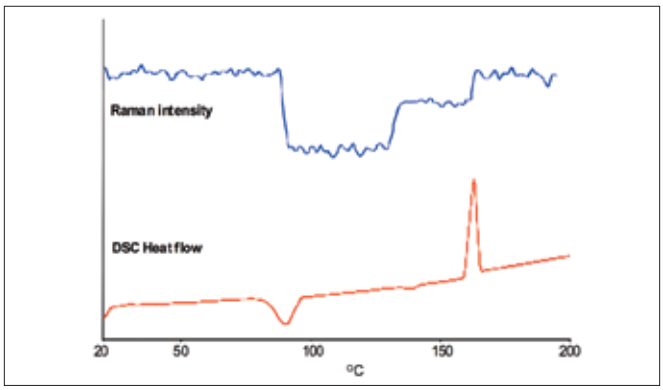

Figure 1. Thermograms from DSC and Raman spectra.

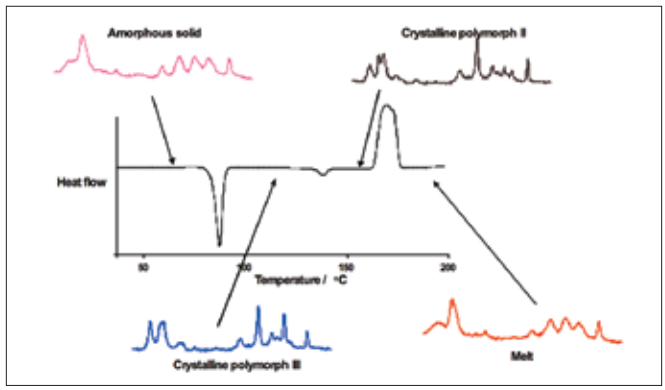

Figure 3. Raman spectra (1700-1100 cm^{-1}) from a DSC run.

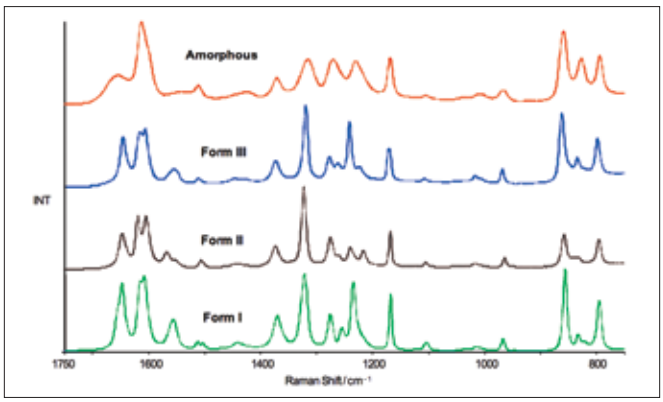

Figure 2. Raman spectra of samples of acetaminophen with different thermal histories.

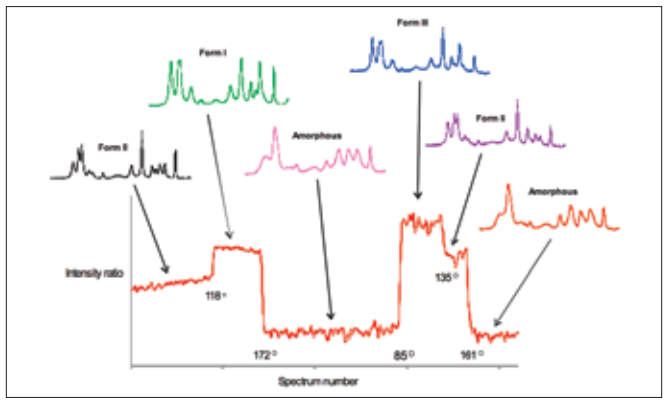

Figure 4. Thermogram and spectra from heating acetaminophen Form II.

Summary

Acetaminophen exhibits a number of transitions between different forms and the behavior is not always reproducible. Simultaneous DSC and Raman measurements can identify unambiguously which forms are involved in any transition.

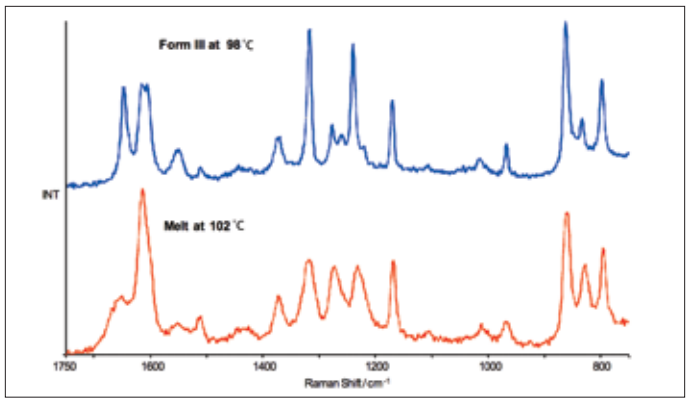

Figure 5. Spectra before and after crystallization on cooling.

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