Simultaneous DSC-Raman Analysis of a Pharmaceutical Polymorph

ABSTRACT

This paper discusses the application of simultaneous DSC-Raman to analyze a polymorphic transition in carbamazepine, a common pharmaceutical compound.

INTRODUCTION

Many drugs are formulated as solids. Although convenient and compact, solid drug formulations can be problematic because potentially the active pharmaceutical ingredient can exist in more than one thermodynamically or kinetically stable crystalline or amorphous form, and can interconvert between these forms during processing or storage. The ability of a compound to exist in different solid state crystalline forms (polymorphism) impacts the solubility, and thus the bioavailability, of the pharmaceutical. Interconversion from a more soluble to a less soluble form may occur during manufacture of the pure drug, during formulation processes, and after long-term storage, thereby changing the pharmaceutically-active properties of the final product.

Differential Scanning Calorimetry (DSC) is a powerful tool in the analysis of polymorphic transitions. The transformation of a drug from a metastable to a stable polymorphic form gives rise to quantifiable changes in heat which manifest as discrete transitions in the DSC thermal curve. The analyses of these transitions provides fundamental insights into the thermodynamics and kinetics controlling the reactions. However, DSC does not provide a full chemical identification of the resultant polymorphic form.

Similarly, Raman spectroscopy can identify a polymorph or provide quantitative information about a mixture of polymorphs, but typically does not provide information regarding the temperature or time dependence of the polymorph.

In this paper, we describe a simultaneous DSC-Raman analysis of a pharmaceutical polymorph, carbamazepine. By performing the simultaneous analysis, the complementary DSC and Raman data can be correlated and a more complete characterization of the material is accomplished.

INSTRUMENTATION & METHODS

In this study, carbamazepine (a drug used for the treatment of epilepsy and trigeminal neuralgia) was analyzed with a TA Instruments Q2000 Modulated DSC® which was interfaced to a Kaiser *RAMANRXN1*™ (Kaiser Optical Systems, Inc.) using a MR Probe and custom immersion optic. Figure 1 shows the Raman probe installed on the Q2000 DSC. The spectral range of the Raman was ~150-3425 cm^{-1} with a laser power of ~70 mW (25% full power).

In this experiment, the temperature was ramped from 20°C to 200°C at 10°C/min with a Raman spectrum collected every 5 seconds continuously. Raman data collection consisted of 1 sec exposure with 1 accumulation and a cosmic ray filter (total 2 sec collection).

The Q2000 DSC is particularly suited for DSC-Raman analysis, as the thermal mass of the Tzero® transducer is sufficient to attenuate the inherent heating of the sample from the laser irradiation. The result is a reproducible baseline shift which is easily quantified and corrected in the resultant DSC data.

Figure 1. Raman Probe Interfaced to Q2000 DSC

RESULTS & DISCUSSION

Figure 2 plots the DSC result from the experiment. The polymorphic transition (Form III to Form I) occurs near 175°C, corresponding approximately to the 30 minute point in this figure. The transition is clearly detected in the DSC data. (The simultaneous DSC-Raman experiment requires that the sample pan remain uncovered, which can compromise the DSC peak quality).

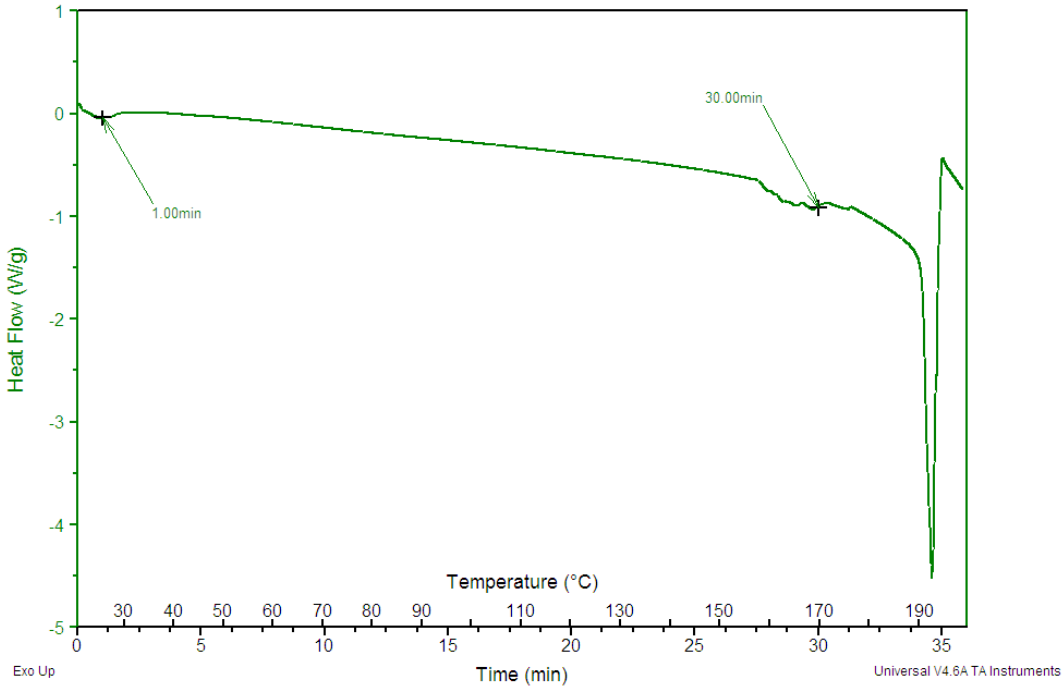

Figure 2. DSC Analysis of Carbamazepine (10°C/min)

Figure 3 contains the Raman spectra collected at 1 minute (~30°C) and 30 minutes (~175°C). The 1 minute spectrum corresponds to Form III, and the 30 minute spectrum to Form I.

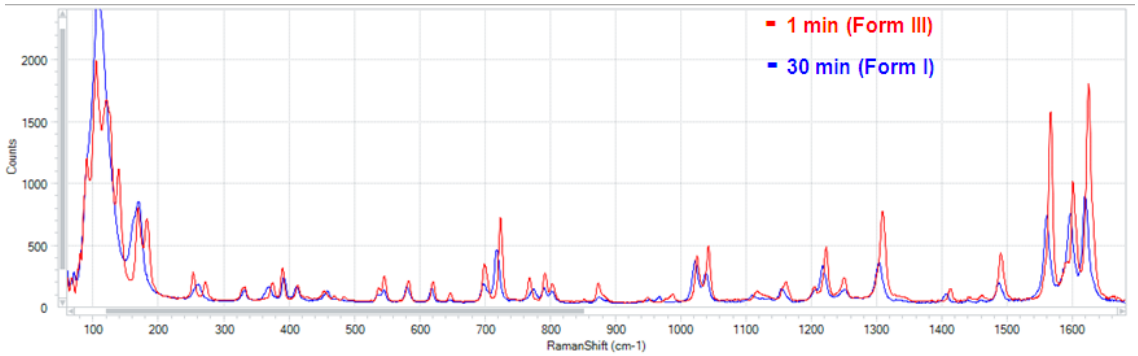

Figure 3. Raman Spectra for Carbamazepine

It is clear that both DSC and Raman are sensitive to the polymorphic transition in this experiment, with the DSC providing temperature dependence and thermodynamic information, and the Raman spectra providing the qualitative chemical fingerprint.

Principal component analysis (PCA) is a data reduction technique where the goal is to represent the variation present in many variables using a small number of factors or Principal Components (PCs). For spectral analysis, PCA decomposes user selected regions into their changing component spectral patterns. Each resulting PC has two vectors: a score vector and a loading vector. Scores plots (PC vs. PC or PC vs. time) show trends or groupings which help describe relationships among sample spectra. Loadings plots help to interpret spectral variance (such as peak location/shape changes for different samples. PCA is very useful for determining where Raman spectra are changing as a function of time, or in this experiment, as a function of time and temperature. In this analysis, Kaiser software was used to create PC plots versus time, which were then correlated to the DSC results. Figure 4 contains the correlation of the first PC factor (PC1) versus time, compared to the corresponding heat flow result.

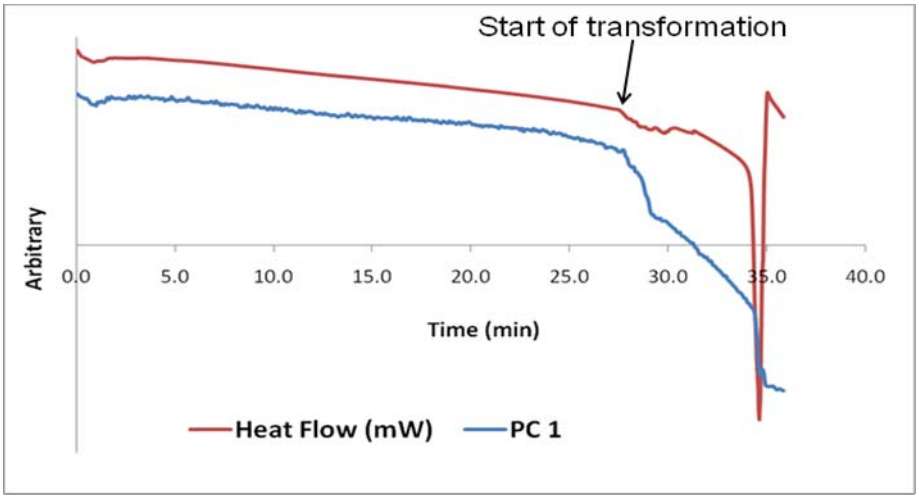

Figure 4. PCA Correlation to Heat Flow

The result in Figure 4 clearly demonstrates the correlation between the polymorphic transition as measured by DSC, and indicated by the principal component analysis of the Raman spectra. The event is clearly detected in both techniques, and structural changes can be interpreted from each independent analysis, as well as the combined simultaneous technique.

CONCLUSIONS

The study described in this paper clearly demonstrates the utility of the simultaneous DSC-Raman technique in the analysis of pharmaceutical polymorphs. The complementary techniques provide information from one experiment which is not accessible individually. Further, the application of principal component analysis of the resulting Raman spectra allow for precise time and/or temperature based correlation of the structural changes occurring in the sample, as measured by both DSC and Raman.

ACKNOWLEDEGEMENT

The contribution of Maryann Cuellar and David Strachan of Kaiser Optical Systems, Inc. to this paper is gratefully acknowledged.