Rapid monitoring of antisolvent addition crystallization and dehydration

Benefits at a glance

- Monitoring a crystallization process *in situ* and contactless analysis of crystals
- Raman's specificity enables distinction of solid state forms, including hydrates from anhydrates
- Analyzer stability provides ability to qualitatively distinguish forms and quantify in mixtures

Introduction

Crystallization of a pharmaceutical ingredients is very important because different polymorphs and hydrate forms of a drug compound can have different solubility and hence different bioavailability. The crystallization must be carried out in a controlled manner to yield the right form, so a method of monitoring the crystals *in situ* is needed.

Raman spectroscopy is extremely effective for rapidly distinguishing different forms of a drug compound. The difference is often traceable by the appearance or disappearance of characteristic Raman bands or a shift in their wavenumber positions. Raman spectroscopy can be used with an *in situ* immersion probe or a non-contact probe, depending on the requirements of the application. Raman spectroscopy requires no preparation of the sample and is non-destructive. This note demonstrates an application of Raman spectroscopy to monitoring a crystallization procedure and to monitoring the dehydration of the crystals during storage.

Experimental

The crystallizations were carried out with cortisone acetate (CA, Figure 1). Water was added in a controlled fashion to a ternary solution of acetone (87.00%), water (10.50%), and CA (2.50%). The crystallization was performed with three different rates of water addition: 0.25, 0.50, and 1.00 mL/min. Raman spectra (sum of 5 accumulations of 5 seconds each) were acquired at 1-minute intervals. The crystals were isolated and stored in scintillation vials and the phase change was monitored daily with Raman spectroscopy.

Raman spectra were acquired using a Raman analyzer. Data were analyzed using principal components analysis (PCA).

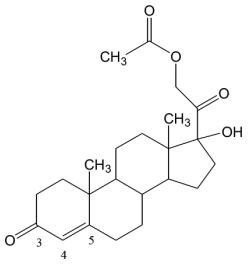

Figure 1: Cortisone acetate (CA).

Results

The Raman shift region of greatest interest is 1610–1680 cm^{-1}, which contains two peaks: one between 1600 and 1625 cm^{-1} and another between 1660 and 1680 cm^{-1}. The former is assigned to the double bond at C4 the latter is assigned to the carbonyl at C3. The peaks are shifted to lower wavenumber due to bond conjugation, which delocalizes the Π electrons and reduces the electron density in each double bond.

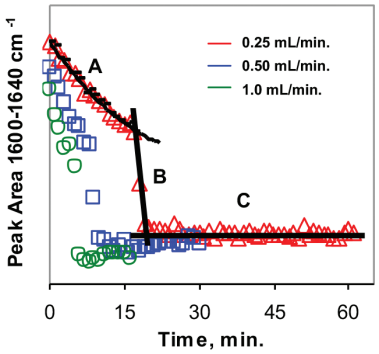

Figure 2: Baseline peak area change between 1600 and 1640 cm^{-1} (solute band) as the crystallization proceeds. (Reprinted with permission from Ref. 1. Copyright © 2003 American Chemical Society.)

Crystallization experiments were carried out as described above. As water was added to the CA/acetone solutions, the solubility of CA decreased until the CA nucleated and crystallized out of solution, which sharply decreased the concentration of CA in the solution. This crystallization

ⓘ All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

is represented in Figure 2 as the sharp drops in the area of the relevant bands. Also contributing to the loss in intensity is the scattering of light away from the collection optic by the crystals. Spectra of the CA crystals at various stages in the experiment are found in Figure 3.

The data were analyzed without any calibration model. This is possible because the Raman analyzer has no moving parts and is extremely stable, with negligible signal drift.

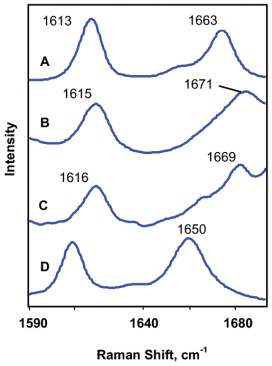

Figure 3: Spectra of cortisone acetate: (A) crystalline, (B) in solution, (C) in slurry, (D) after drying. (Reprinted with permission from Ref. 1. Copyright © 2003 American Chemical Society.)

Solid-state analysis

After crystallization, the crystals were collected and analyzed by light microscopy, Raman spectroscopy, and differential scanning calorimetry (DSC). The size of the crystals produced varied inversely with the rate of addition of antisolvent (Figure 4). The crystals were monitored periodically with Raman spectroscopy as they were stored. Over a period of about a week, a shoulder gradually developed on the 1606 cm^{-1} peak until it became a doublet at 1605 and 1613 cm^{-1} (Figure 5). The 1650 cm^{-1} peak shifted to 1651 cm^{-1} and a shoulder developed at 1669 cm^{-1}.

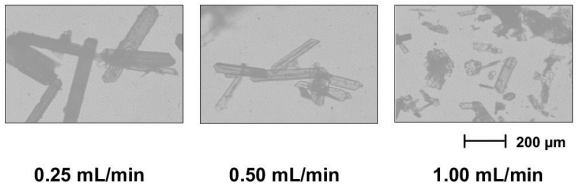

Figure 4: Cortisone acetate crystals from the three experiments. The magnification of the three images is the same. (Reprinted with permission from Ref. 1. Copyright © 2003 American Chemical Society.)

DSC revealed an endotherm at 100 °C in crystals that had not undergone the transformation and none for those that had, strongly indicating that the crystals were hydrates that slowly lost water from the lattice.

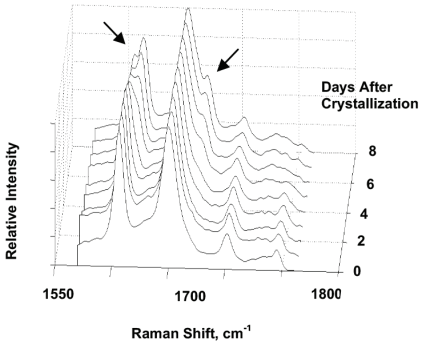

Figure 5: Raman spectra of CA after crystallization. Peaks that change with dehydration are indicated with arrows. (Reprinted with permission from Ref. 1. Copyright © 2003 American Chemical Society.)

PCA

Raman data from the crystallization experiments were analyzed by PCA. The first two factors contained information that was obvious in the raw spectra, but the third factor when plotted versus time for the crystallization increases to a maximum and then decreases steadily. It was determined that the maximum occurred when the solution was saturated, so this technique allowed the determination of the onset of supersaturation. This factor, therefore, appears to correspond to solvent–solute interactions during the addition of antisolvent, providing further information beyond what could be obtained from the raw spectra.

Conclusions

Raman spectroscopy is a useful tool for monitoring crystallization processes and identifying solid state forms. Raman can improve process knowledge, and act as an input for real-time process monitoring and control of pharmaceutically relevant traditional small molecule compounds as well as large molecule biologics.

References

1. Falcon, J.A. and Berglund, K.A. Monitoring of Antisolvent Crystallization with Raman Spectroscopy *Crystal Growth & Design*, Vol. 3, Issue 6, **2003**, 947.