Monitoring $CaCO_3$ polymorph formation in the presence of polymeric additives

Key Issues
- *In situ* crystallization monitoring
- Results from *in situ* Raman spectroscopy in agreement with off-line XRD

Introduction

Many materials can crystallize in different forms called polymorphs that differ in the three-dimensional arrangement of atoms or molecules in the crystal lattice. These polymorphs often have very different physical properties despite their chemical similarity, so their crystallization must be carried out in a controlled manner to yield the right form. One of the requirements for this process is a method of monitoring the crystals *in situ*.

Raman spectroscopy is extremely effective for rapidly distinguishing different polymorphs. The difference is often traceable by the appearance or disappearance of characteristic Raman bands or a shift in their wave-number positions. Raman spectroscopy can be used with an *in situ* immersion probe or a non-contact probe, depending on the requirements of the application. Additionally, Raman spectroscopy requires no preparation of the sample and is non-destructive.

This note demonstrates the application of Raman spectroscopy to monitoring the selective crystallization of polymorphs of Calcium Carbonate ($CaCO_3$) in the presence of polymeric additives (Table 1). The three polymorphs of $CaCO_3$ are calcite (rhombohedral), vaterite (hexagonal), and aragonite (orthorhombic), in descending order of thermal stability.

Table 1: polymeric additives used in this work

Polymeric additive	Abbreviation
Acusol®	
Poly(aspartic acid)	PAspAcid
Poly(acrylic acid)	PAA
Polymaleimide synthesized by KOH initiator	PMI_KOH
Polymaleimide synthesized by PbO and t-butyl benzyl alcohol initiator	PMI_PbO
Polymaleimide synthesized by bis(triphenylphosphine) Cu(I) nitrate and t-butyl benzyl alcohol initiator	PMI_Cu_sys

Experimental

A full experimental description can be found in Reference 1. Briefly, crystallizations were carried out in Sodium Carbonate (Na_2CO_3) solution (500 mL, 1000 ppm with respect to carbonate) with polymeric additive (1.4 ppm) in an automated laboratory reactor at 25 °C. A solution of Calcium Chloride ($CaCl_2$) (54 mL, 6250 ppm) was added to the reaction solution at a rate of 1 mL/5 min. The reactor stirred the mixture at 400 rpm.

Raman spectra were acquired every 10 minutes using a Raman analyzer operating at 785 nm with a 785 nm Invictus laser. The results from Raman spectroscopy were verified by x-ray diffraction (XRD) on grab samples.

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

Calibration

Raman spectra and XRD data were calibrated using peak intensity ratios. In the case of Raman, the peaks corresponding to the carbonate plane bending modes of vaterite (690 cm^{-1}) and calcite (711 cm^{-1}) were used[1]. (Aragonite is formed only at temperatures above 90 °C.) Results are shown in Figure 1.

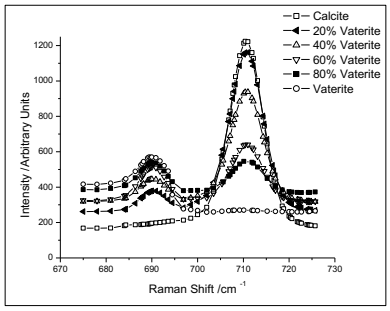

Figure 1: Raman spectra of prepared mixtures of $CaCO_3$ polymorphs. The intensities of the bands at 690 and 711 cm^{-1} vary with the concentration of calcite and vaterite, respectively. *(Reprinted with permission from Reference 1. Copyright © 2003 American Chemical Society.)*

A calibration curve was constructed by ratioing peak intensities from known concentrations of calcite and vaterite. The data were fitted to a second-order polynomial to obtain the calibration equation. [Figure 2]

Results

The results from the experiments are shown in Figure 3. PMI_PbO appeared not to affect the phase equilibrium at all, while two of the other polymeric additives, Acusol® and poly(acrylic acid), led predominantly to vaterite. In the experiment with *Acusol*, calcite

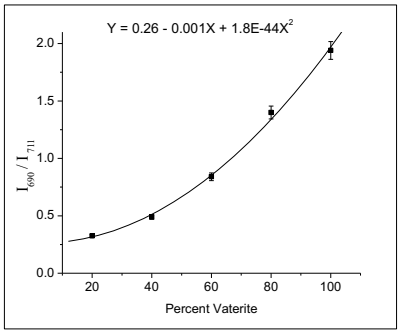

Figure 2: Calibration curve obtained by ratioing the 690 and 711 cm^{-1} Raman bands. *(Reprinted with permission from Reference 1. Copyright © 2003 American Chemical Society.)*

appears never to have formed in the solution, while with poly(acrylic acid) vaterite is preferentially formed over the course of the crystallization. With PMI_Cu_sys, vaterite is never formed. Other polymeric additives gave results between these extremes, only partially affecting the phase equilibrium.

The analyzer's axial transmissive spectrograph design allowed the entire spectrum to be collected simultaneously, rather than scanning successively across fragments of the spectral range. This was important because the reaction mixture is heterogeneous and is being stirred rapidly, so scanning would result in different regions of a spectrum being collected from different materials as they pass through the focal cylinder of the probe.

Conclusion

Results determined by Raman spectroscopy and by XRD agreed to within 2%, demonstrate that Raman spectroscopy to be an effective and convenient alternative to more traditional methods of polymorph determination. This agreement also shows that particle size effects did not affect the quantification.

Raman spectroscopy shows great potential as an on-line control method for polymorph identification during crystallization and has the chemical specificity to enhance process understanding (e.g., identifying new polymorphs or intermediates) during the reaction monitoring, optimization, and scale-up steps of drug substance development.

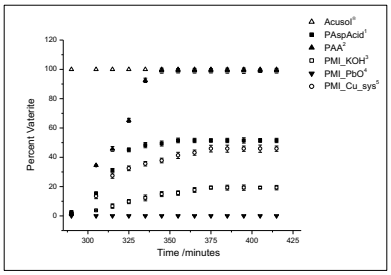

Figure 3: Percent vaterite during the course of the experiments, as determined by Raman spectroscopy. *(Reprinted with permission from Reference 1. Copyright © 2003 American Chemical Society.)*

Reference

1. Agarwal, P. and Berglund, K.A. *"In Situ Monitoring of Calcium Carbonate Polymorphs during Batch Crystallization in the Presence of Polymeric Additives Using Raman Spectroscopy"* Crystal Growth & Design, Vol. 3, Issue 6, 2003, 941.

**Acusol is a registered trademark of Rohm and Haas Company.*