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Process Monitoring: Crystallization

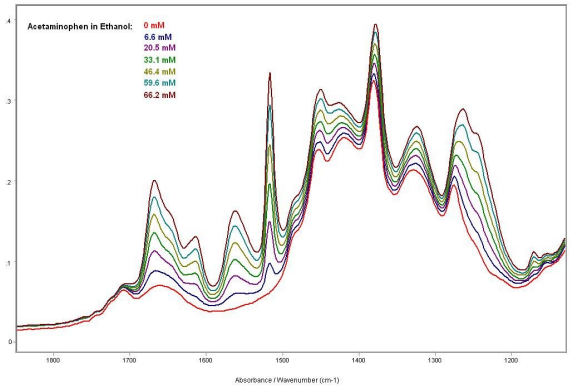
Monitoring the crystallization of paracetamol in a controlled-temperature bath (left) using a ReactionView® system (right)

Monitoring the Crystallization of Acetaminophen

The understanding and control of crystallization processes play an important role in pharmaceutical development and manufacturing. A mid-IR ATR probe analyzes the liquid phase in a crystallization reactor and can often detect concentration changes before the formation of crystals become apparent by other techniques. In this example, the crystallization of acetaminophen (paracetamol) from ethanol solution was studied using a ReactionView® system and an HEL automated reactor system. Follow-up studies were carried out using a glass reactor and a controlled-temperature bath (see illustration above).

Experimental

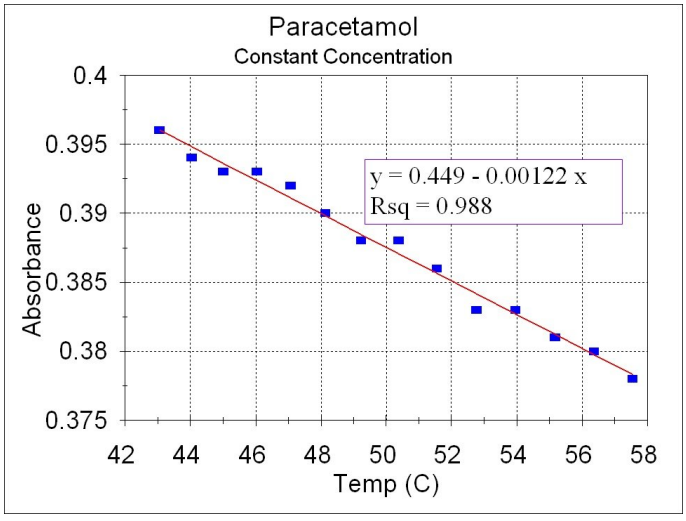
The HEL reactor, with the ReactionView ATR probe fitted into a port, was filled with ethanol and sufficient paracetamol to be in excess at room temperature. The whole system was heated (with stirring) to 60° C to fully dissolve the paracetamol and then cooled in a controlled manner to 35° C. After temperature stabilization, the supersaturated solution was seeded to initiate crystallization. The cooling step allowed us to develop a correction for the effect of temperature on the concentration measurement (see below).

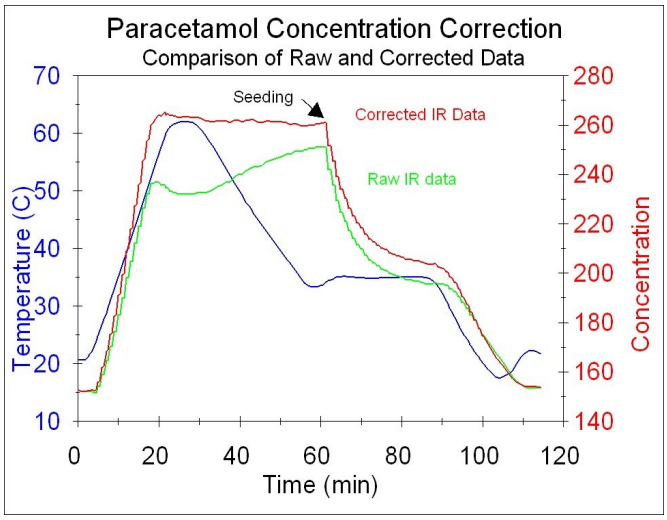


The system was calibrated by making 6 standard solutions, ensuring that the solutions were fully dissolved, and then measuring the samples using the ATR probe. Visual inspection of the resulting spectra allowed an isolated, well-formed peak at 1518 cm^{-1} to be identified for use in the calibration. Both a fitted Gaussian and a two-point, baseline-corrected trendline were used to determine the peak height, which was plotted against concentration. The advantages of this method are that a small number of standards is required and that, within reason, calibrations based on Beers Law can be extrapolated, something that is not true for statistically based chemometric methods.

Results

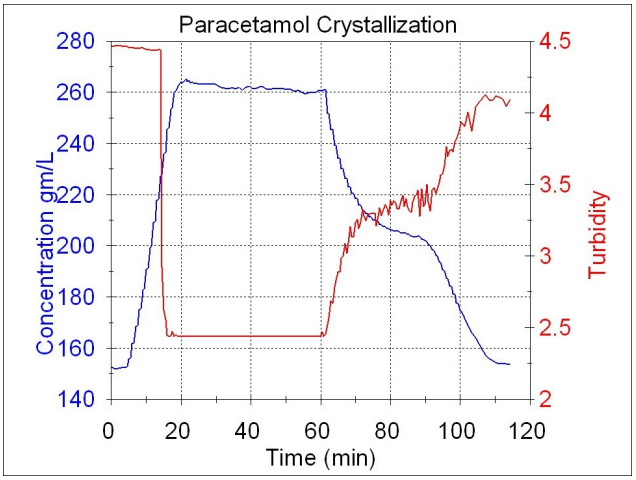
In a crystallization experiment, temperature is a key variable. Infrared spectral peak intensities are temperature-dependent, so a correction must be developed to allow accurate concentration measurements over the full temperature range of the experiment. The graph shown on the right demonstrates that in this case a good empirical straight-line relationship exists between temperature and the peak intensity (measured by ATR).This makes it possible to correct data collected during a crystallization experiment where the temperature changes.





The linear equation developed was used to calculate the percentage change in peak intensity from room temperature to the measurement temperature and from that corrected values for the solution concentration were calculated. It can be seen very clearly that the uncorrected values for solution concentration (Green line) can be corrected to a much more reasonable time-concentration plot (Red line).

It is also instructive to compare the IR and turbidity measurements. It is clear that the turbidity measurement does not detect the onset of dissolution nor does it find the true endpoint of dissolution.



Discussion

The real-time FTIR capability of the ReactionView system provides a useful tool for monitoring crystallization processes and actually proves more sensitive to the onset of dissolution than traditional methods such as turbidity measurement.

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