Monitoring and Control of Polymorphism in Cocrystallization

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Why cocrystallization and this study?

- Process control and monitoring
- Desired polymorphic form
- Uniform crystal size distribution
- Continuous Processing
- NIR, Raman, FBRM
- FDA’s PAT initiative
- Reduced batch to batch variability

Mostly carried out at small scale using evaporation, grinding etc. Scale-up? Control?
The system has three enantiotropically related polymorphic forms:

- Form 1
- Form 2
- Form 3 (stable form)
Polymorphism Control Experiments

- Form 1: -0.5°C/min to 10°C
- Form 2: -1°C/min to 35°C, -0.05/°C/min to 10°C
- Form 3: -0.05°C/min to 10°C
- Mixture of Form 2 and Form 3: -2°C/min to 10°C

- Different cooling profiles were used to produce different polymorphs.
- Experiments were repeated twice for reproducibility.
Micrographs also show the differences between different forms.
Insitu Raman Principal Component Analysis

Form 2
Insitu Raman Principal Component Analysis

Form 1

Form 2

Form 3

Mixture

Nucleation

End

Nucleation

End

Nucleation

End

PCA plots help in tracking changes during the process
**Insitu** NIR Principal Component Analysis

**Insitu** NIR can also differentiate different polymorphic forms in the slurry.

Different NIR probes were tested.

“Bundle” NIR transfectance probe performed the best.

Trend indicates that polymorphic transformation is still going on.

Mixture of Form 2 and Form 3
Characterization by PXRD showed that different forms were obtained.
Raman Microscopy Results

- Raman microscopy also confirms the results obtained from PXRD.
- Normally a single crystal is analysed at a time.
- In each case several crystals were analysed to confirm the presence of a particular polymorphic form.
Offline NIR Analysis

- Compared to Raman microscopy, NIR scans a bigger area.
- Bulk samples can be analysed.
DSC plots show different decomposition temperatures for different forms. Form 2 thermal analysis show an event at 120°C which was further investigated.
Hot Stage Analysis of Form 2
Conclusions and Future Work

• A scale-up study from evaporative to cooling crystallization at laboratory scale was carried out.
• A strategy for obtaining different polymorphic forms was developed.
• In-situ Raman and NIR are useful tools for real time process monitoring.
• Offline characterization tools give valuable information about the products.

• Solubility curves for each polymorphic form.
• More detailed analysis of spectroscopic data using chemometrics.
• More robust strategies for polymorphism control.
• Comparison between different platforms such as MSMPR, COBC etc.
• Strategies for controlling polymorphism in platforms other than batch crystallizers.
• Control over crystal size distribution, yield etc.
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