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Monitoring and Control of Polymorphism in Cocrystallization

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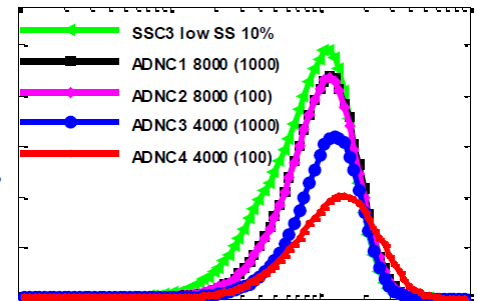
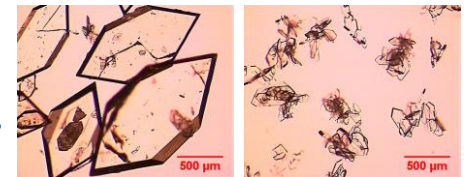
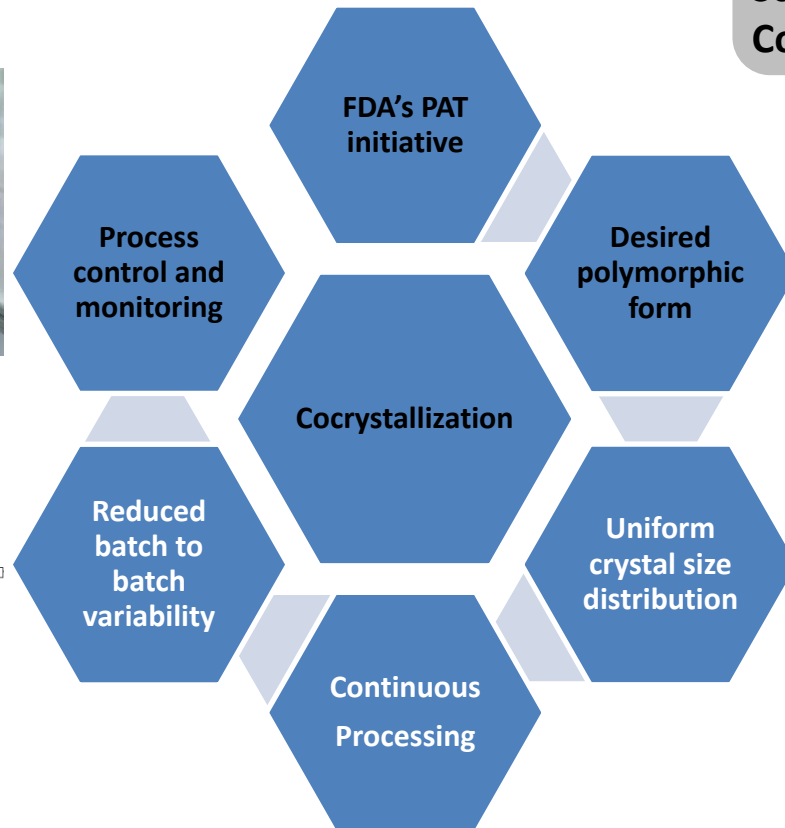
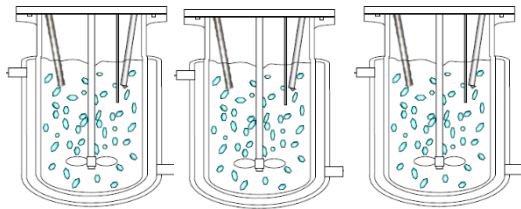
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Why cocrystallization and this study?

NIR, Raman,
FBRM

Mostly carried out at small scale
using evaporation, grinding etc.
Scale-up?
Control?





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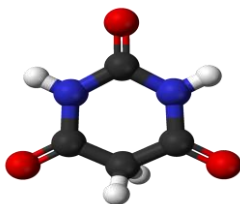
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Model System

Barbituric Acid

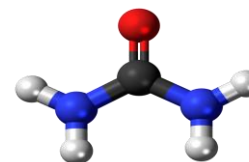


Cooling crystallization



Methanol

Urea



Cocrystals

The system has three enantiotropically related polymorphic forms:

Form 1

Form 2

Form 3 (stable form)



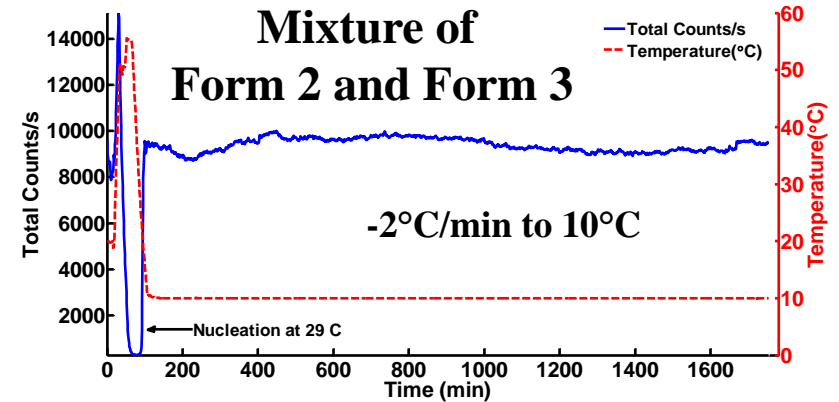
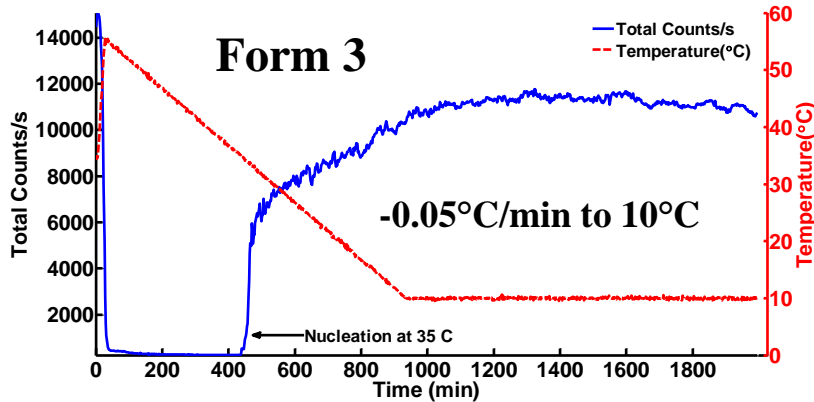
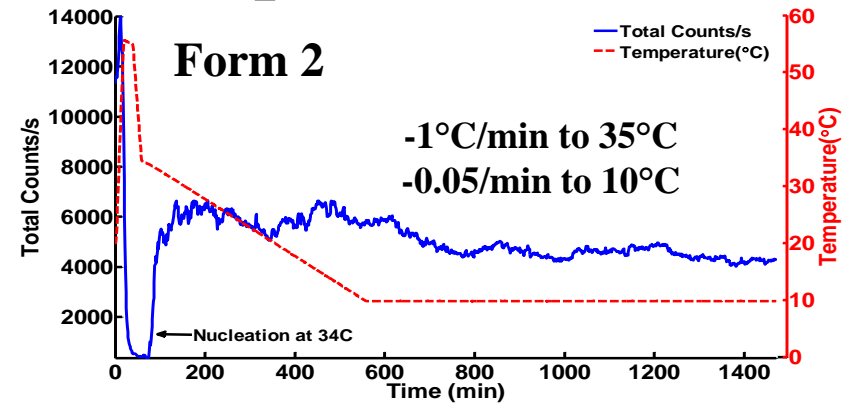
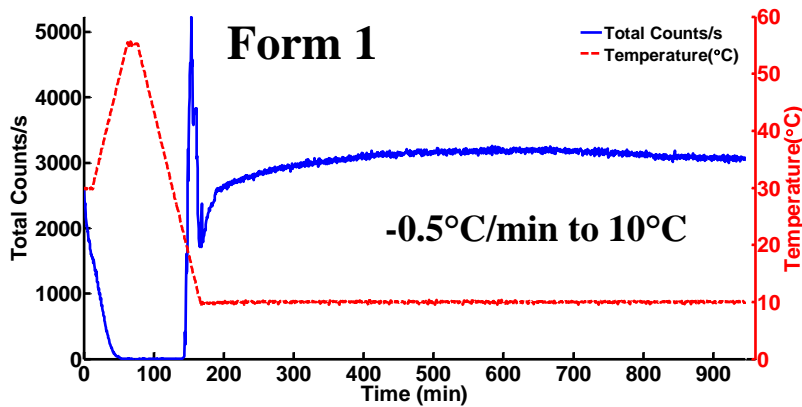
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Polymorphism Control Experiments



- Different cooling profiles were used to produce different polymorphs.
- Experiments were repeated twice for reproducibility.



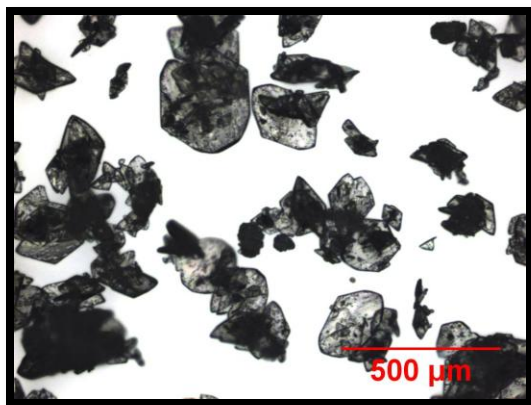
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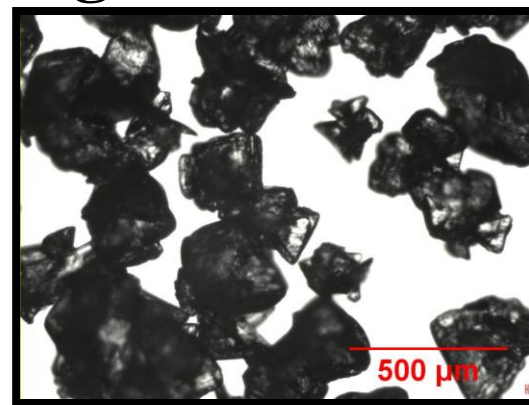
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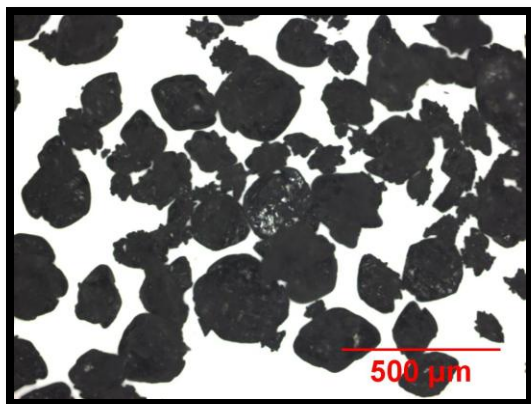
Microscopic Images



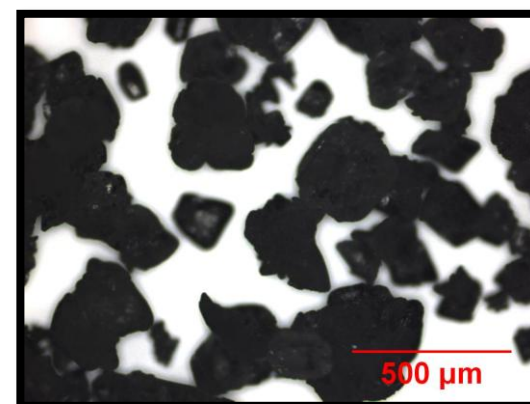
Form 1



Form 2



Form 3



Mixture

Micrographs also show the differences between different forms.



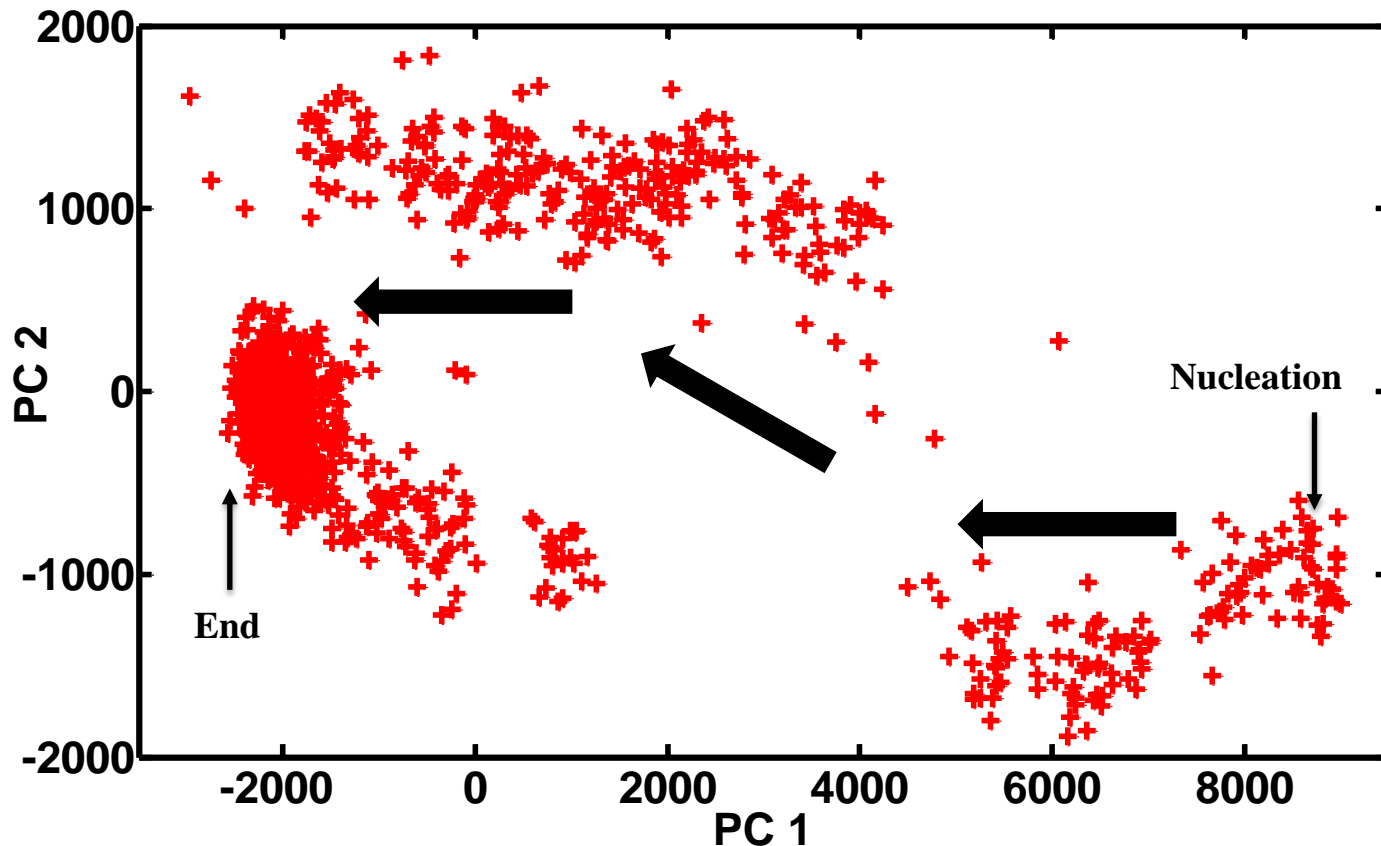
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In situ Raman Principal Component Analysis



Form 2



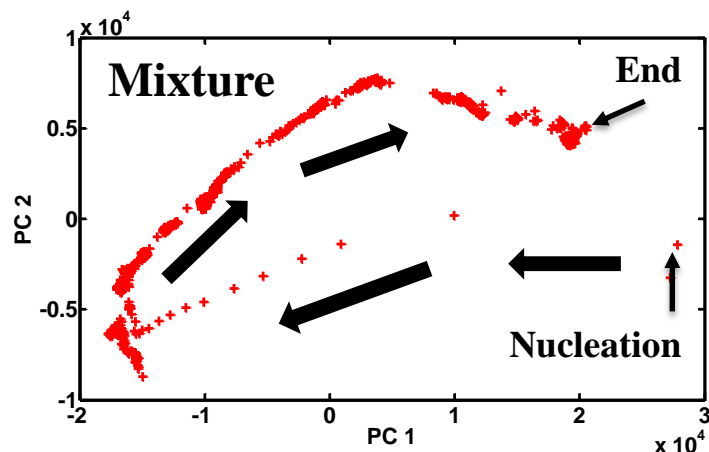
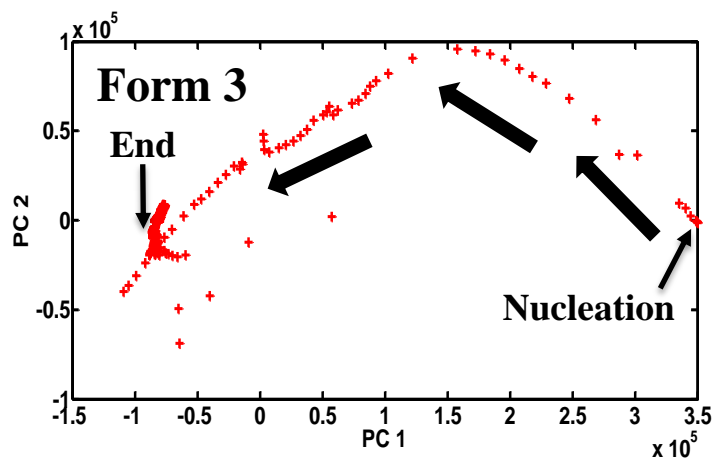
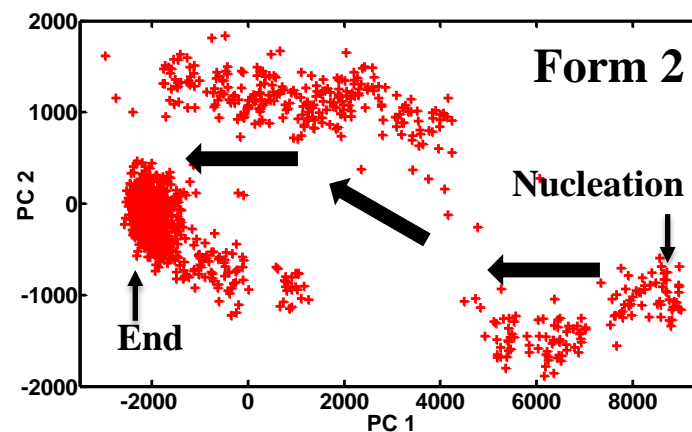
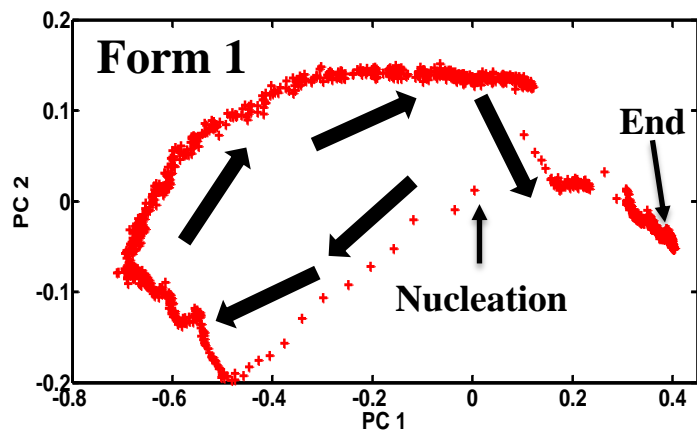
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In situ Raman Principal Component Analysis



PCA plots help in tracking changes during the process



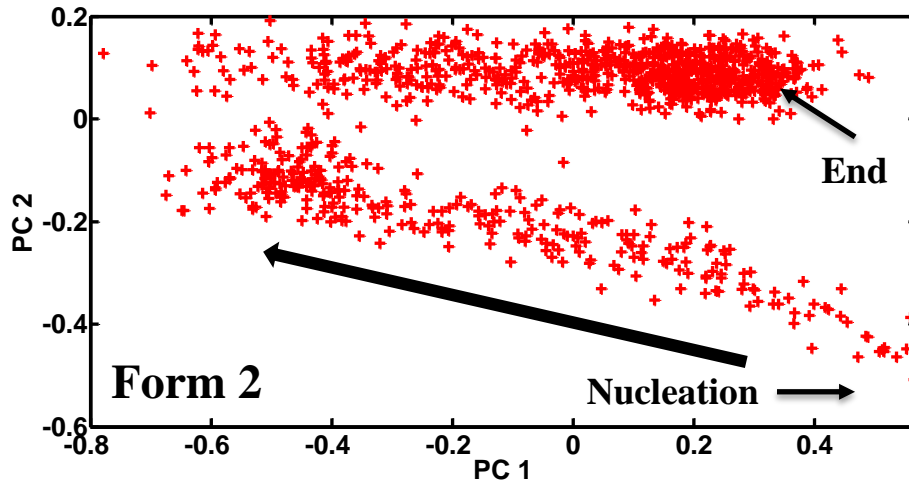
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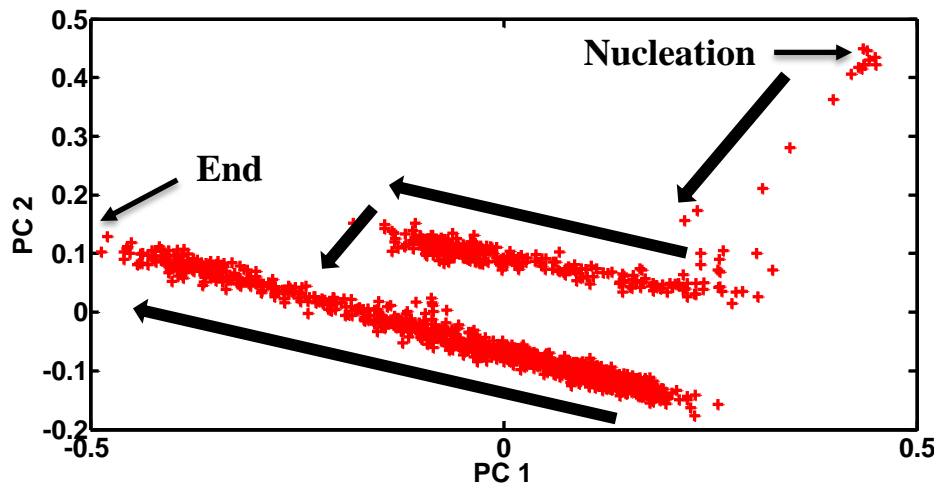
In situ NIR Principal Component Analysis



In situ NIR can also differentiate different polymorphic forms in the slurry.

Different NIR probes were tested.

“Bundle” NIR transmittance probe performed the best.



Mixture of Form 2 and Form 3

Trend indicates that polymorphic transformation is still going on.





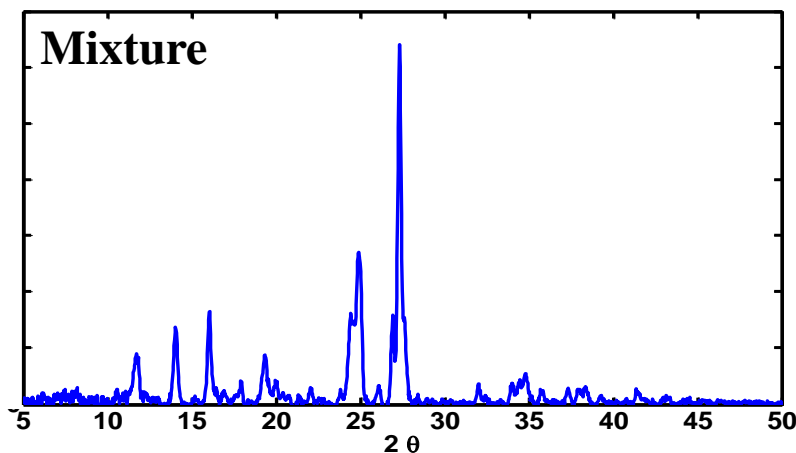
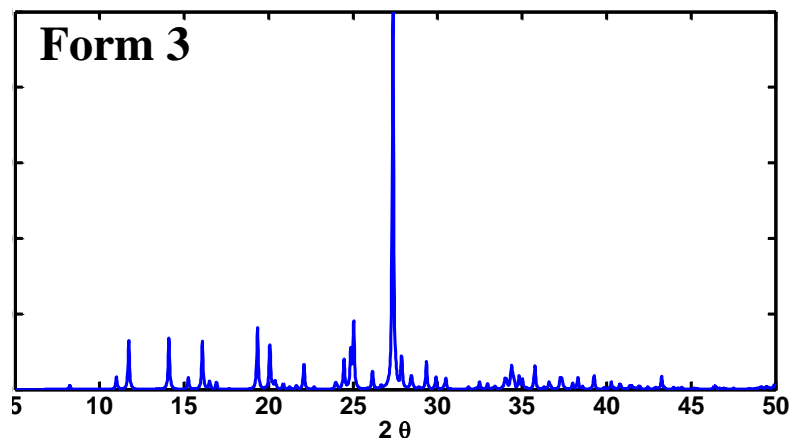
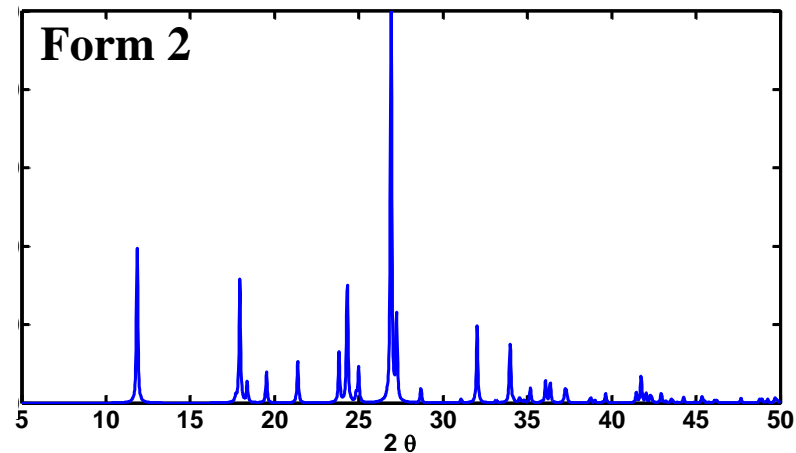
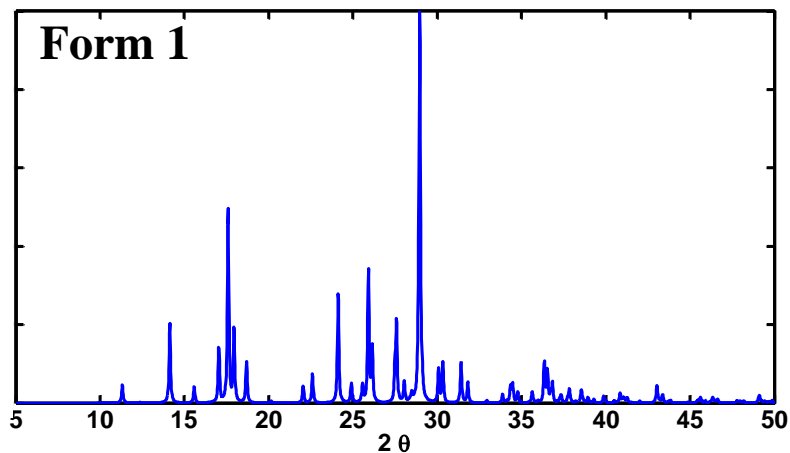
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PXRD Results



Characterization by PXRD showed that different forms were obtained.



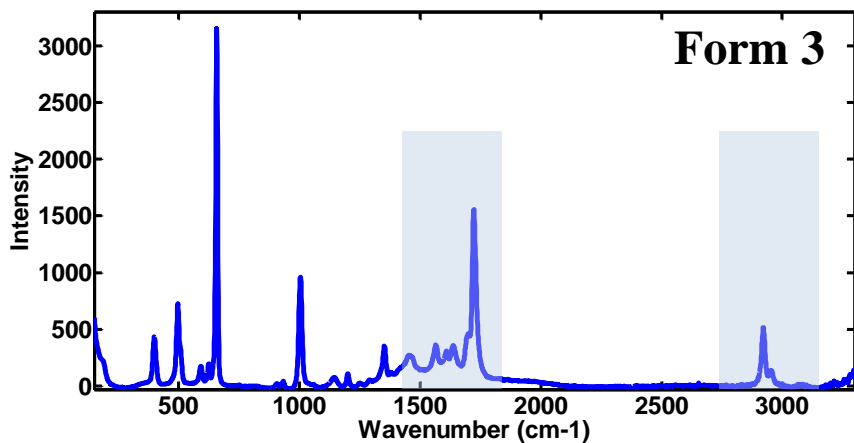
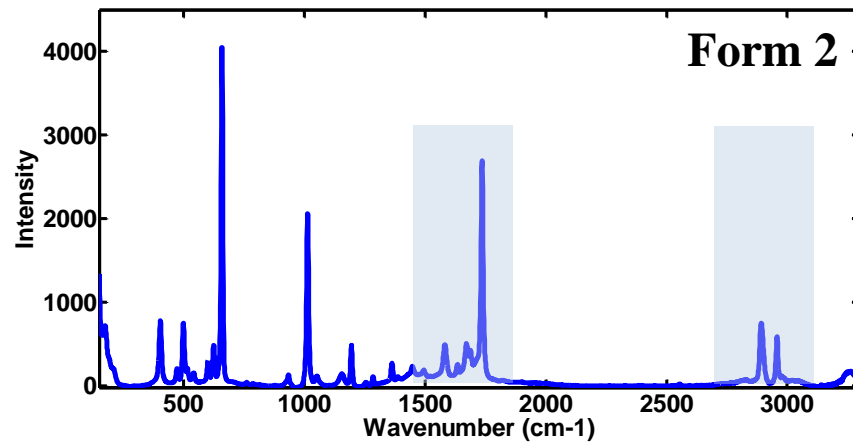
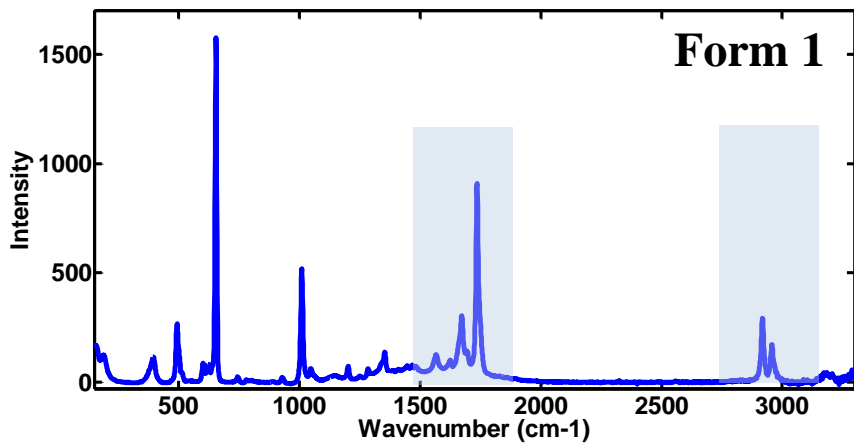
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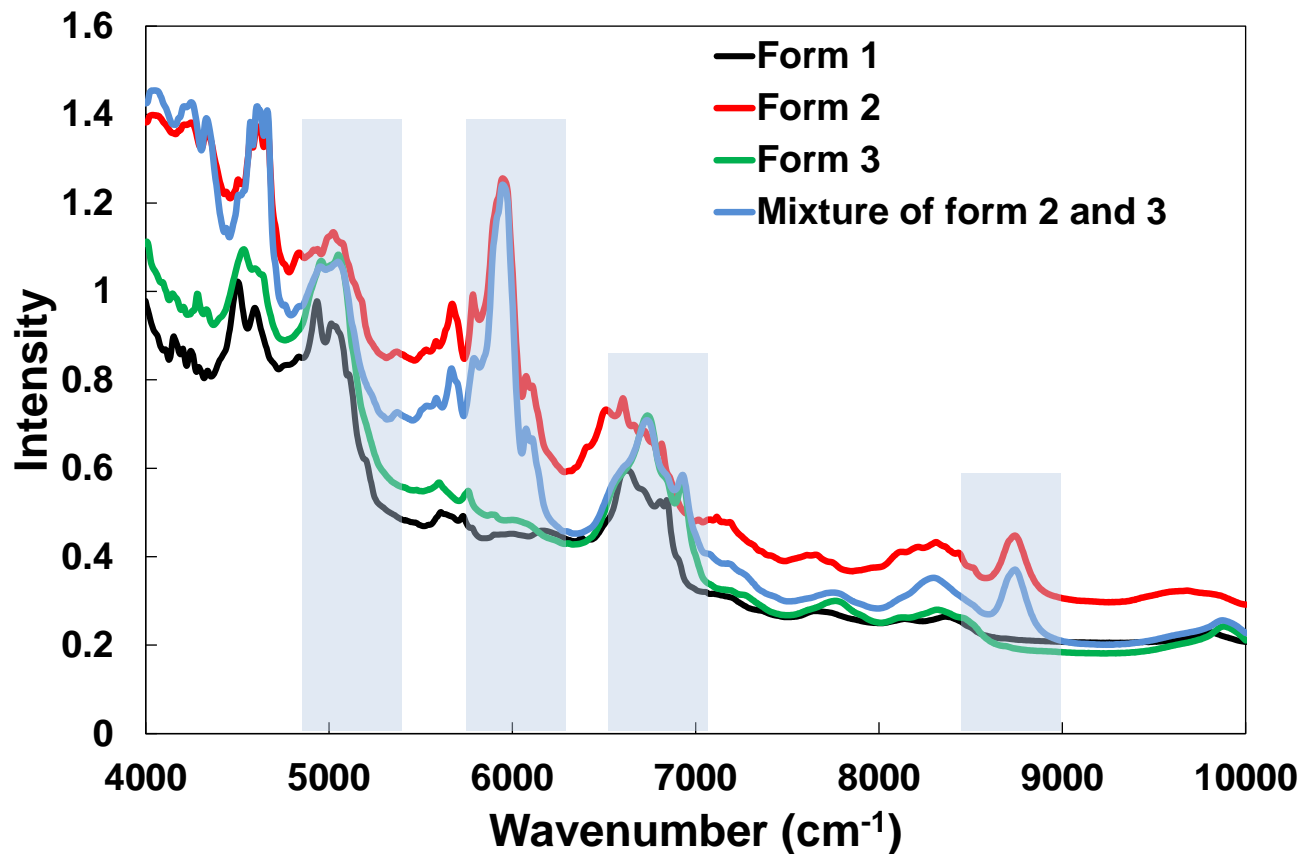
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Raman Microscopy Results



- 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.**



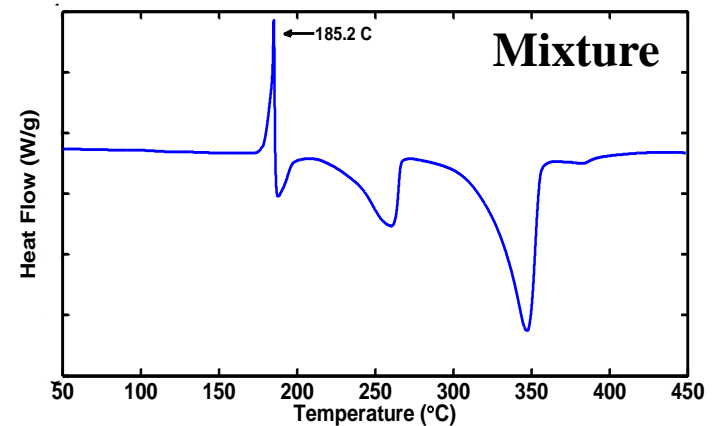
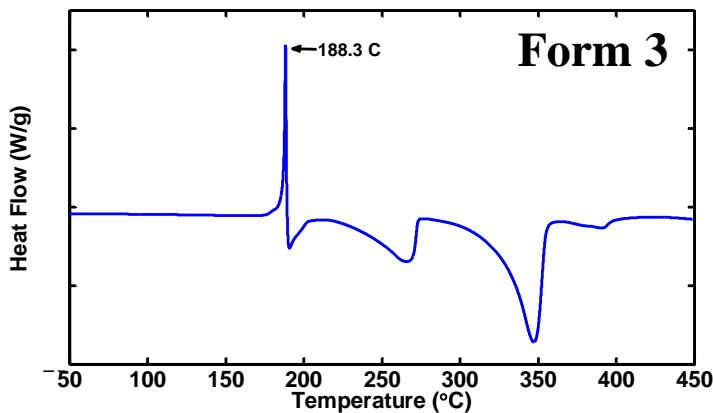
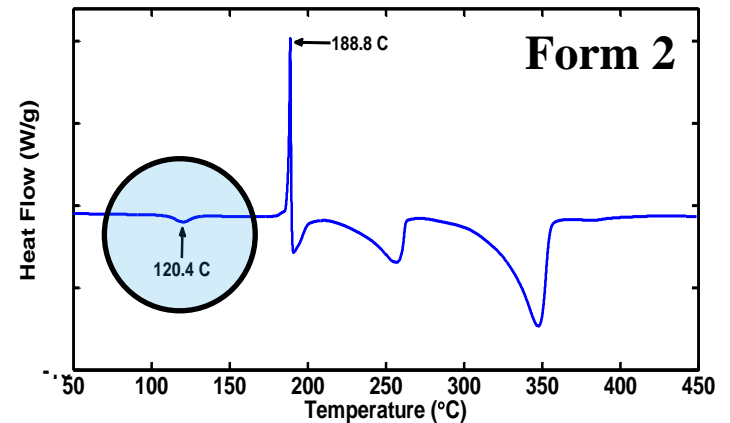
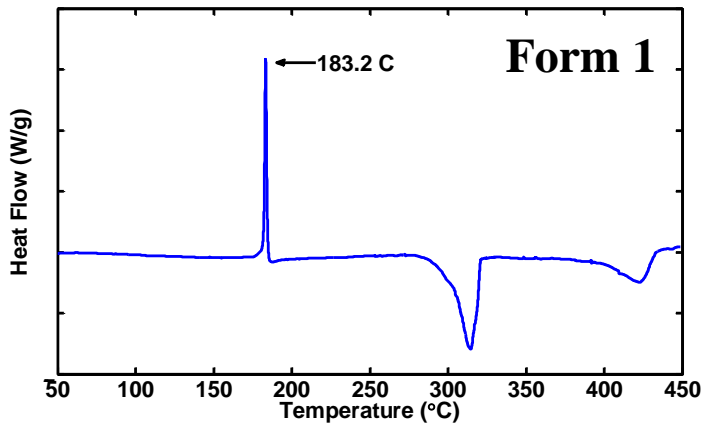
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DSC Analysis



DSC plots show different decomposition temperatures for different forms.
Form 2 thermal analysis show an event at 120°C which was further investigated¹²



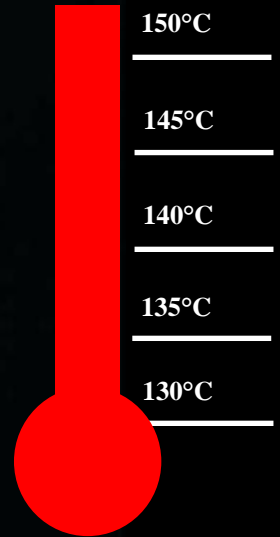
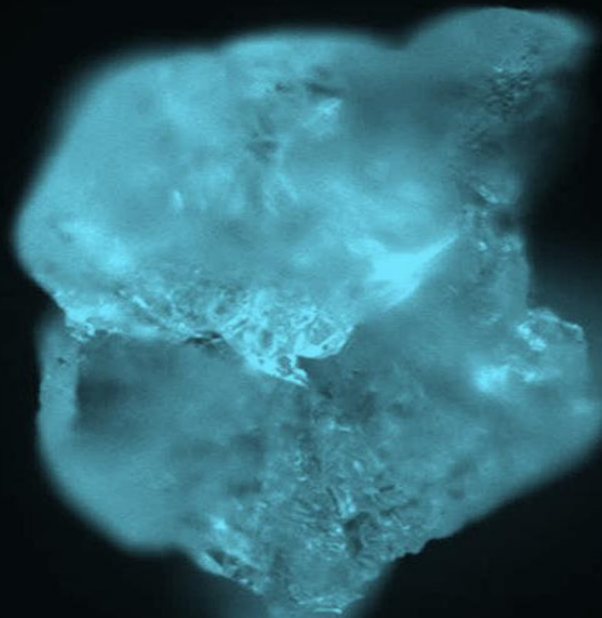
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Hot Stage Analysis of Form 2





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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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AstraZeneca



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