

Continuous Real Time Monitoring of Pharmaceutical Crystallization Processes Using Process Analytical Technology Array

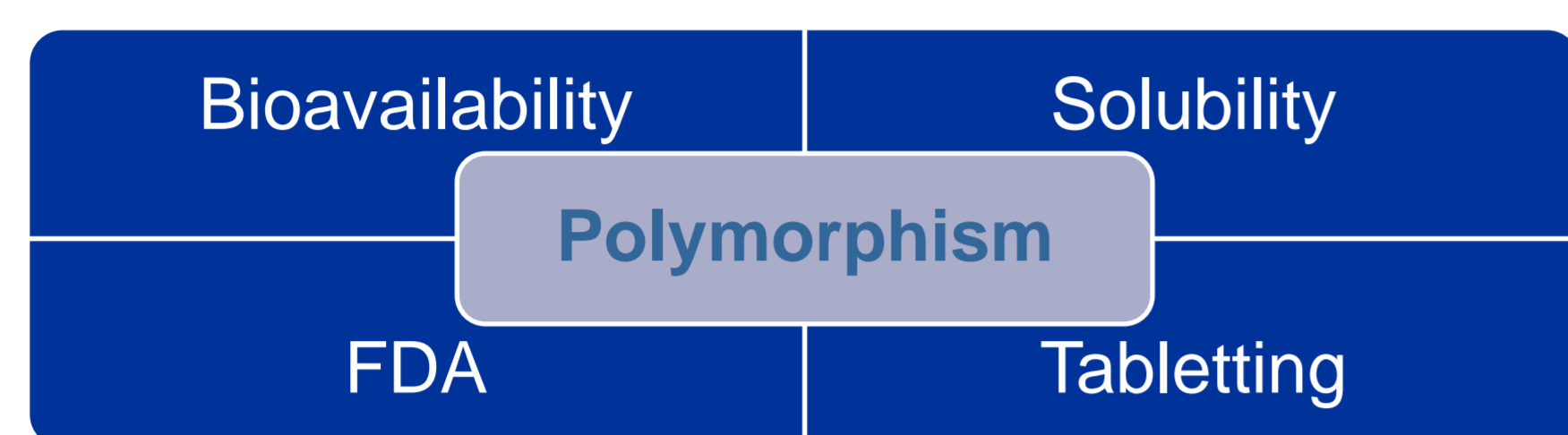
A.N. Saleemi^{1*}, C.D. Rielly¹, Z.K. Nagy¹

¹Department of Chemical Engineering, Loughborough University, Loughborough, LE11 3TU

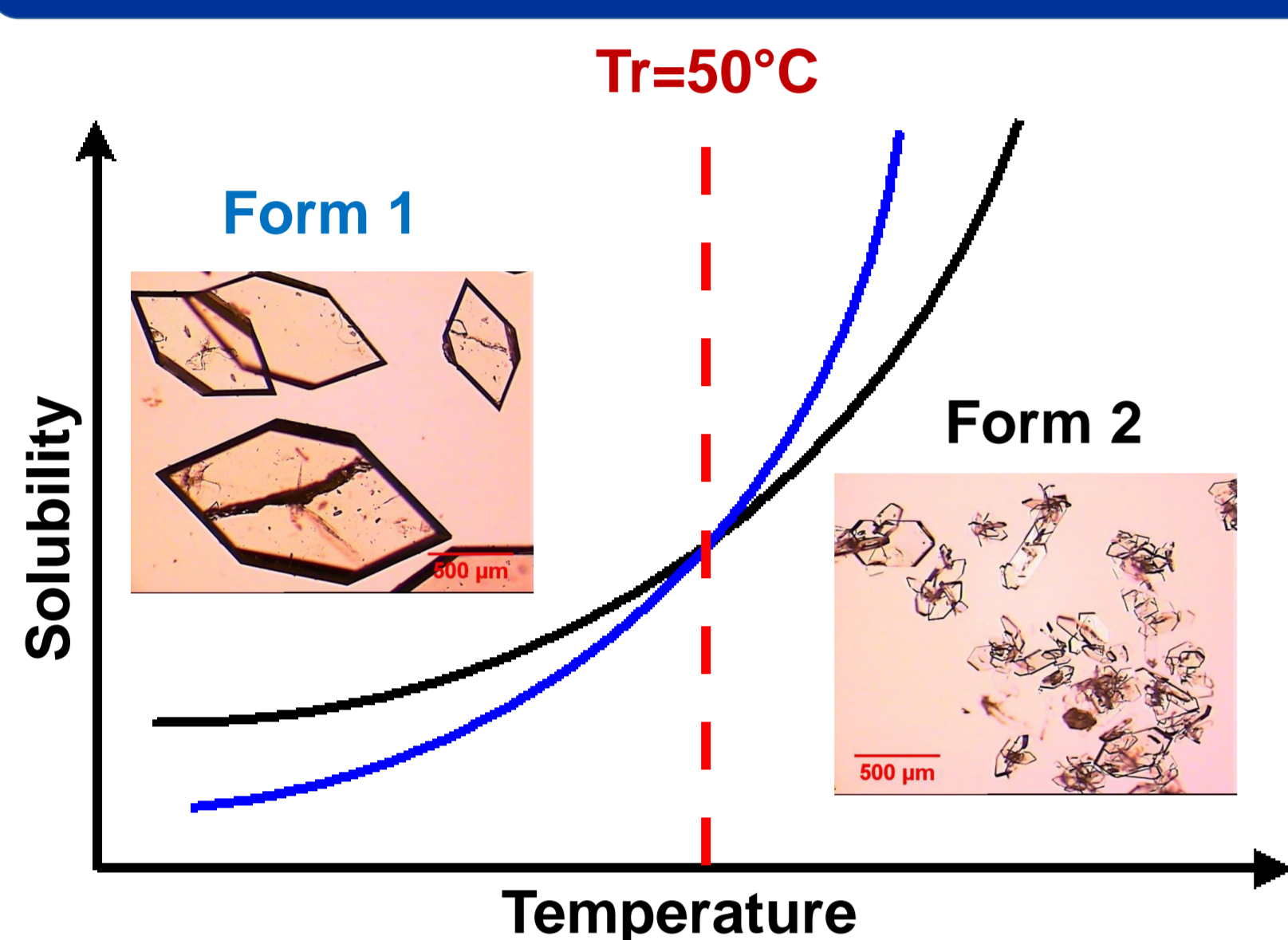
*Email: Z.K.Nagy@lboro.ac.uk

Introduction

- Polymorphism is the ability of a substance to exist in more than one crystalline forms
- Drug properties sometimes are strongly dependent on the polymorphic form and therefore strict monitoring and control is required.
- FDA therefore encourages the use of quality-by-design (QbD) to improve product quality



Methodology

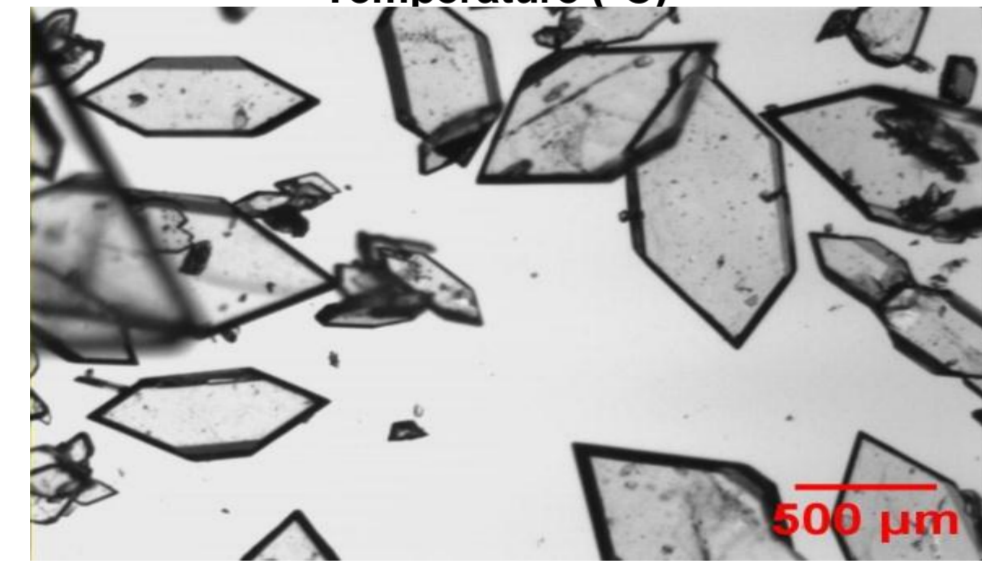
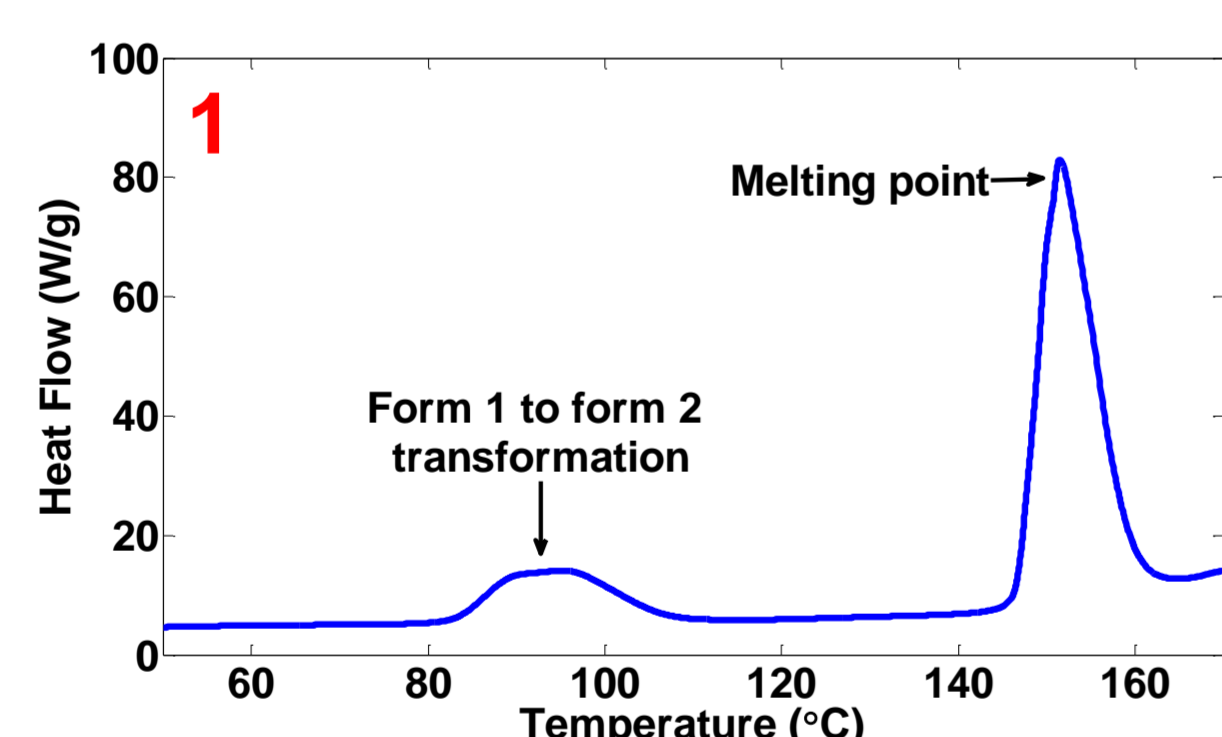
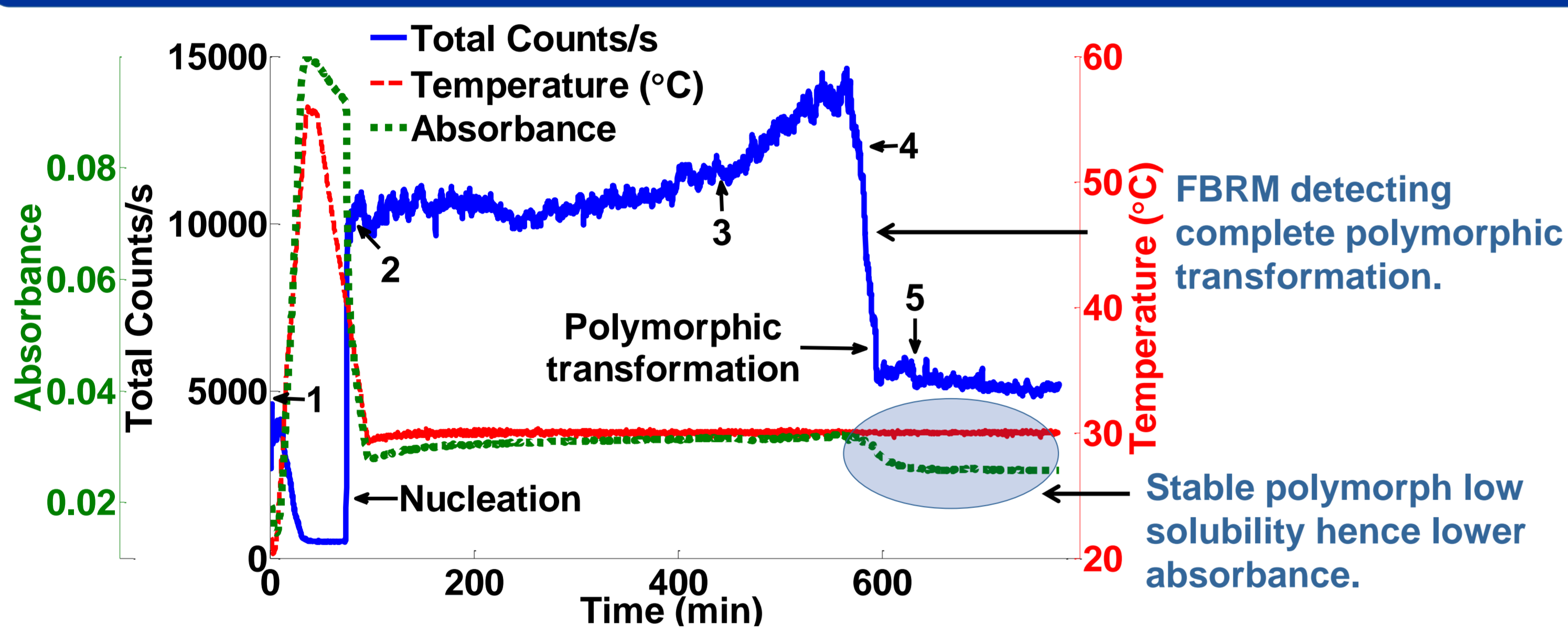


Model system:
Ortho-Aminobenzoic Acid
in 64% water and 36% IPA.

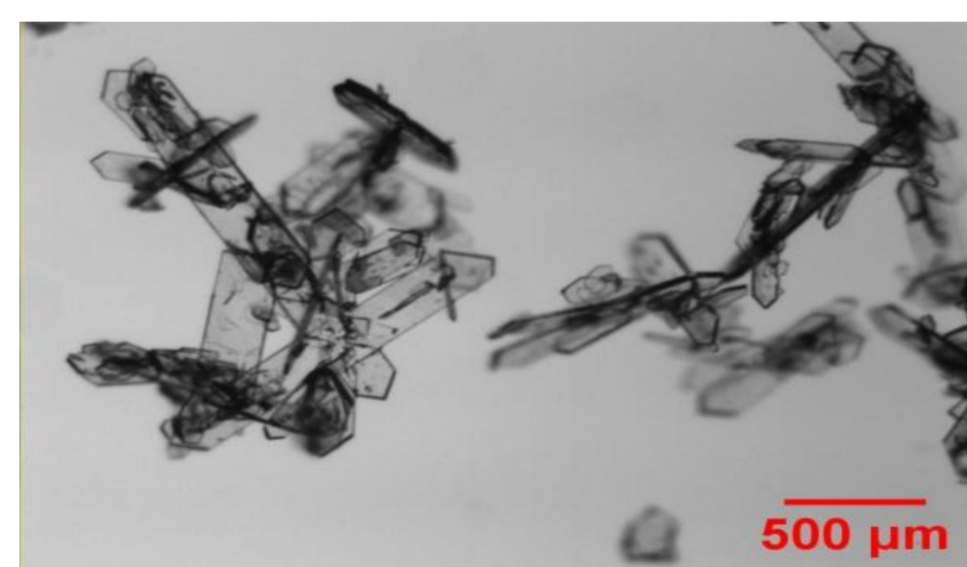
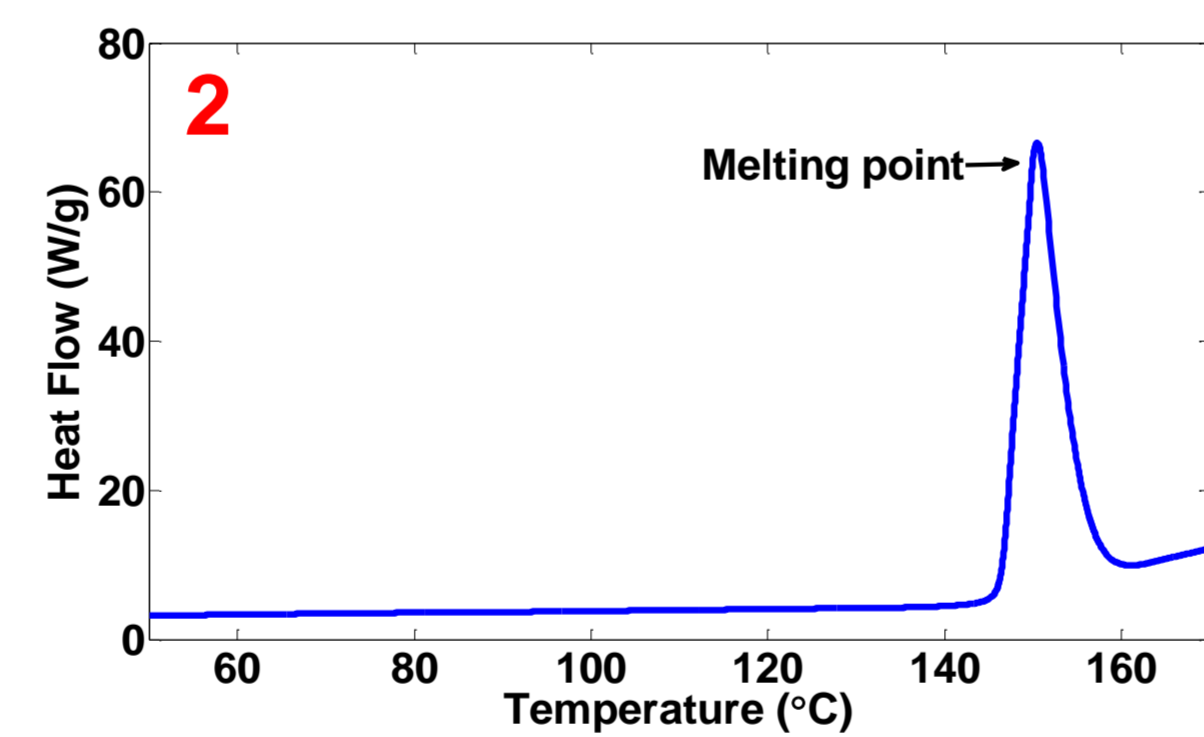
Aims and Objectives

- Monitoring and subsequently controlling formation of desired enantiotropic form.
- Application of PAT tools i.e. FBRM, ATR-UV/Vis, at-line image analysis using particle insight® and microscopy for monitoring and control.

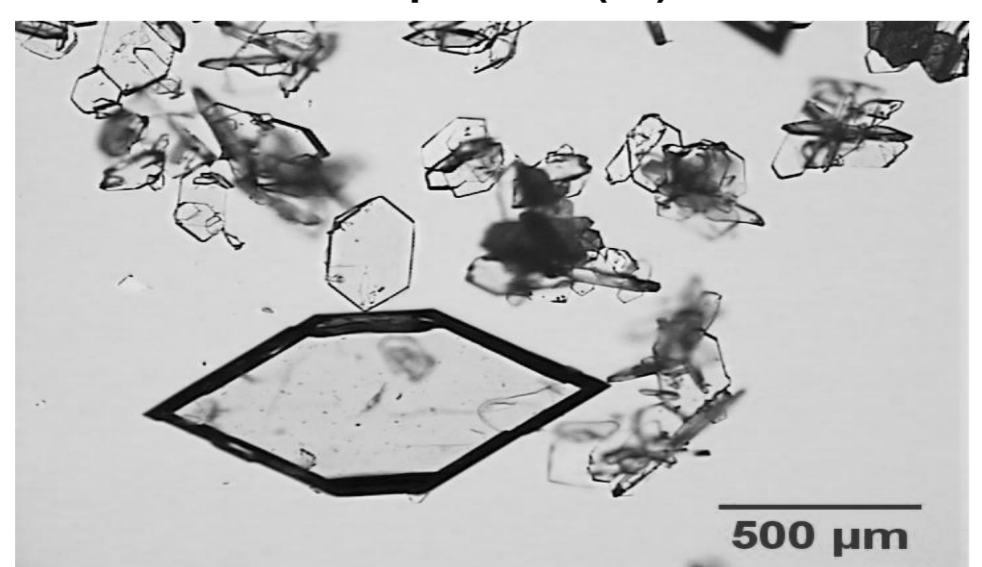
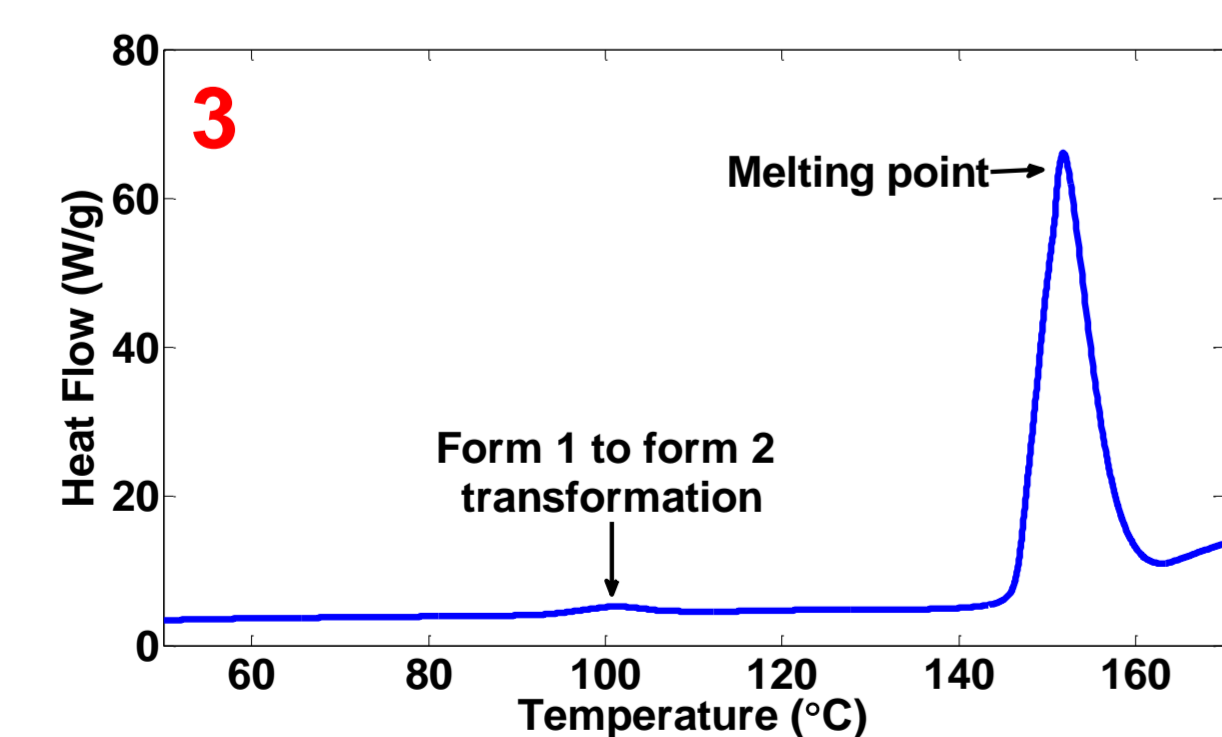
Run1, monitoring with PAT tools



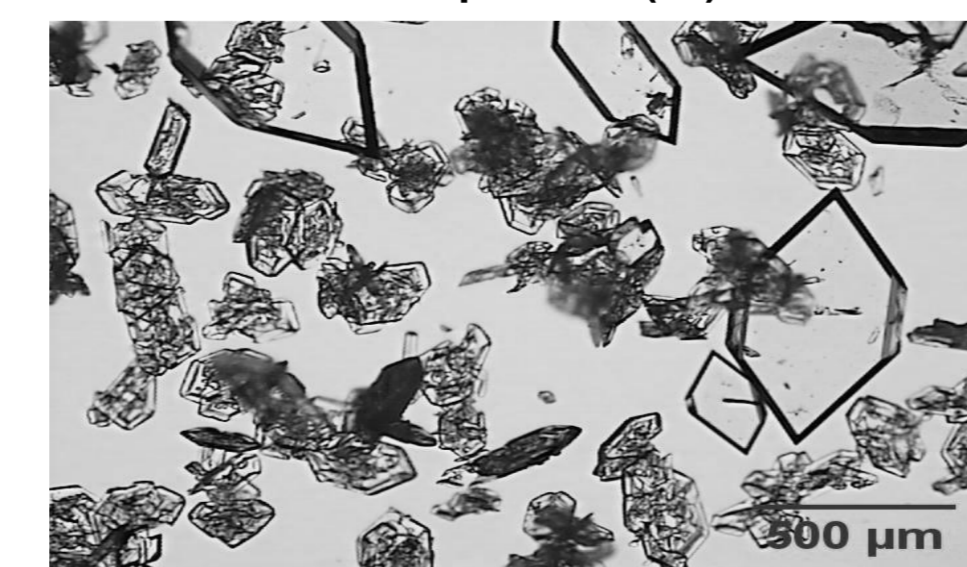
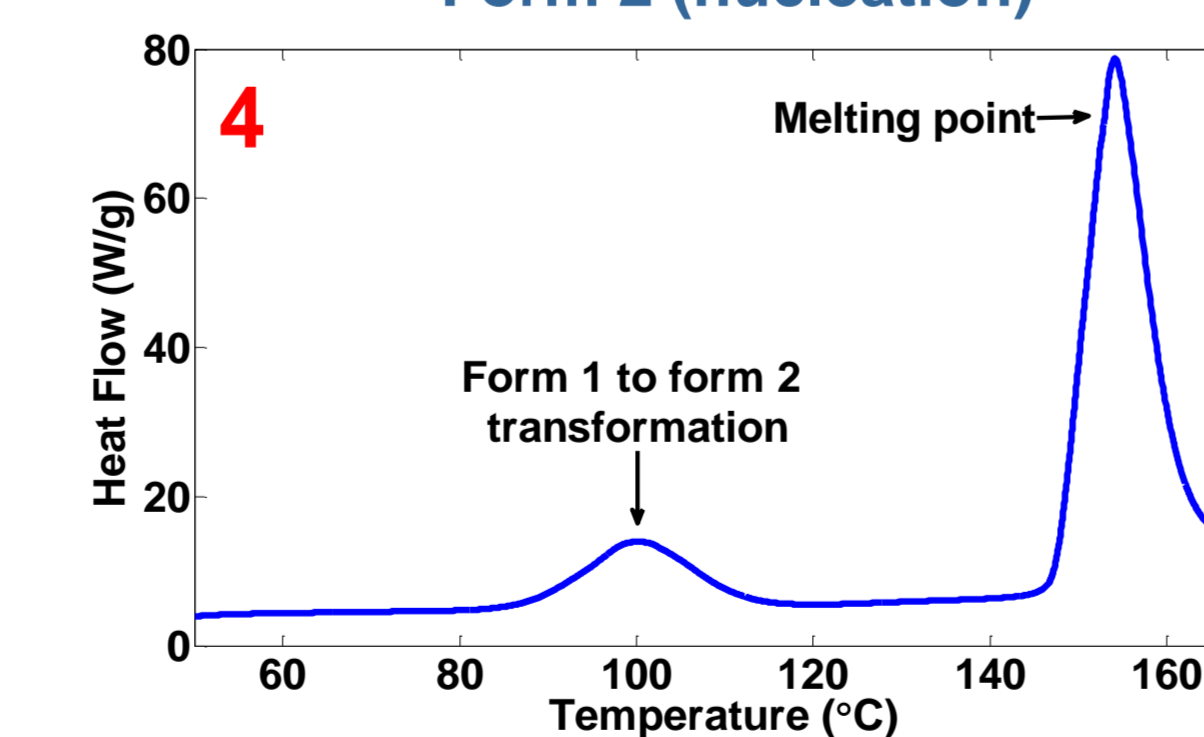
Form 1 (raw)



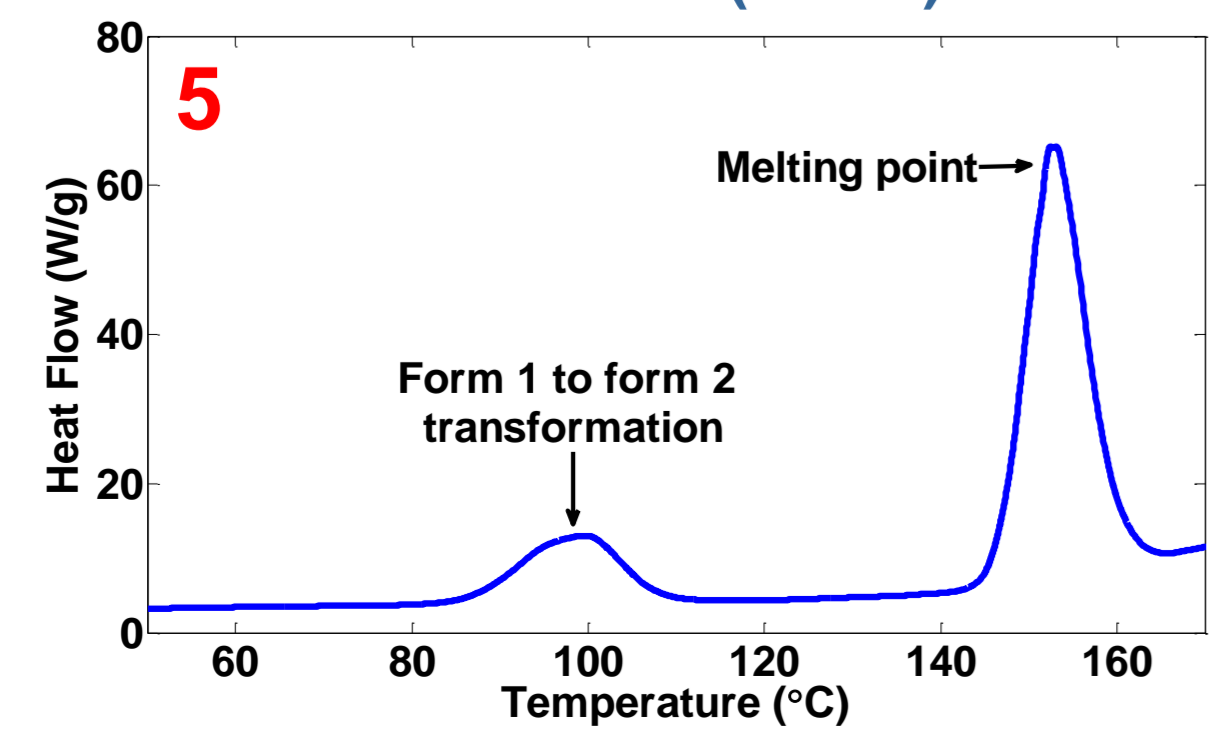
Form 2 (nucleation)



Form 2 + 1 (starts)

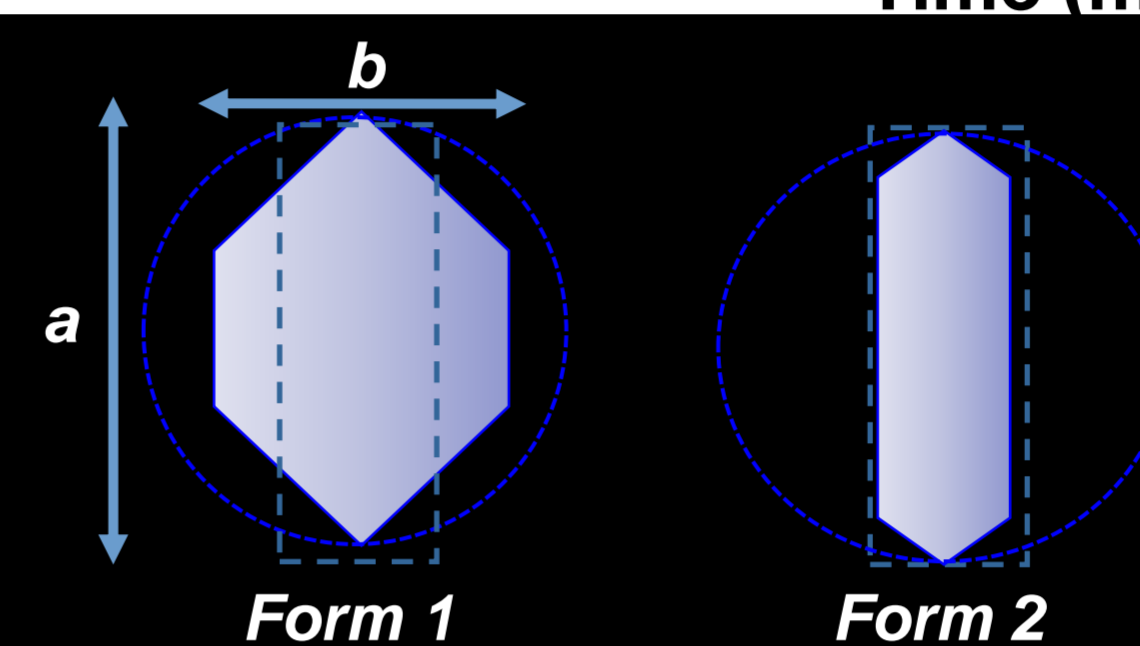
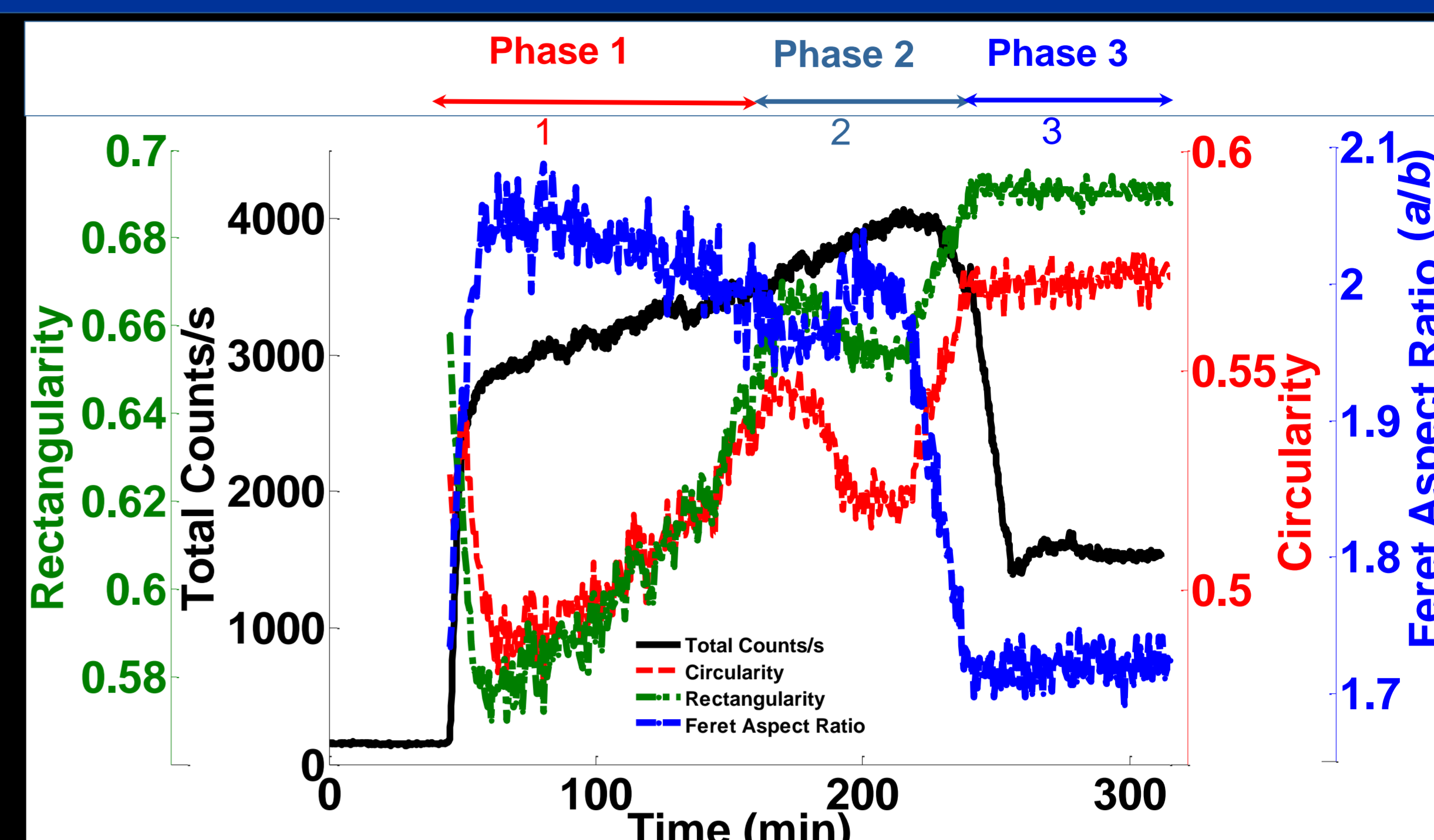


Form 2 + 1

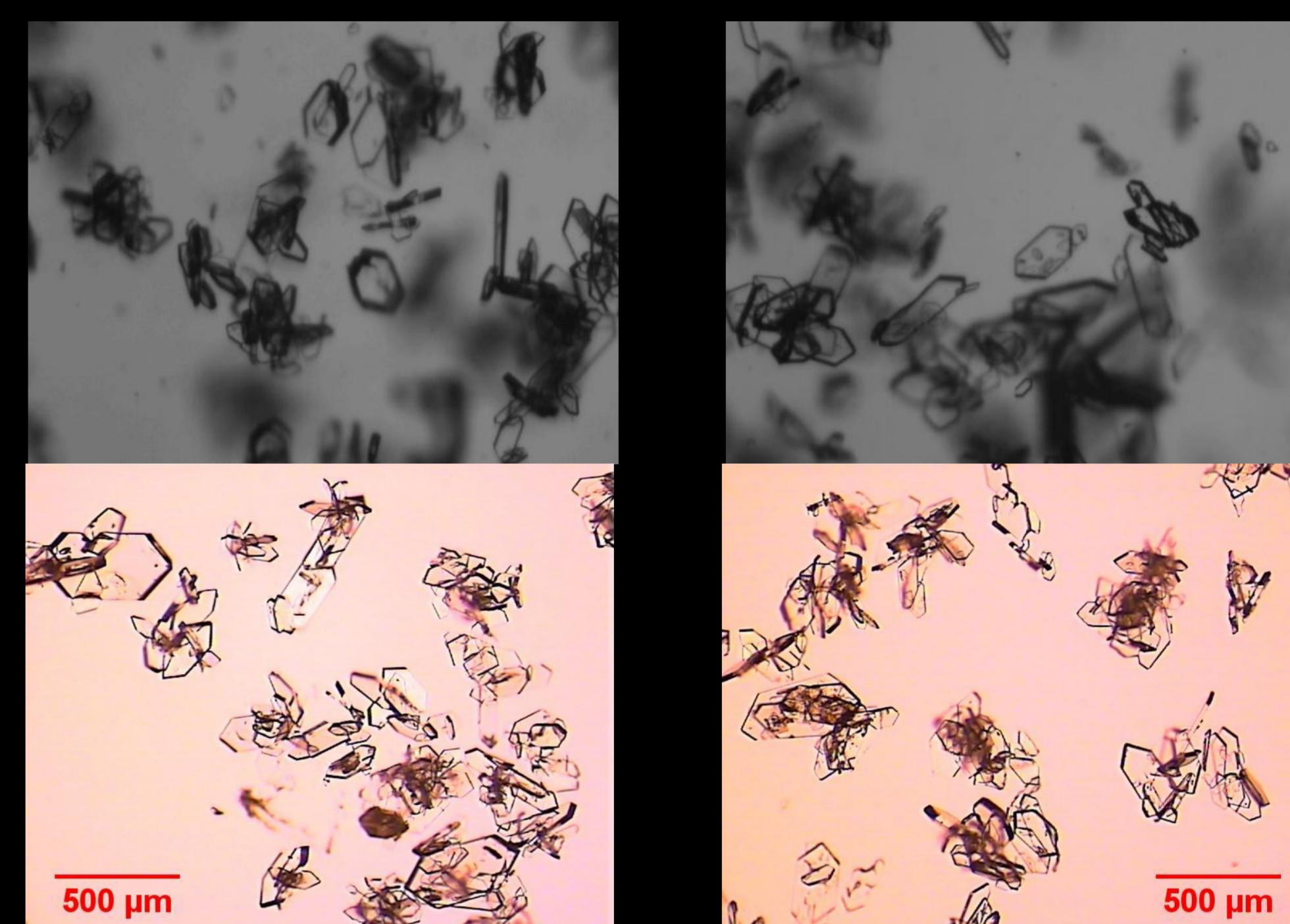


Form 1

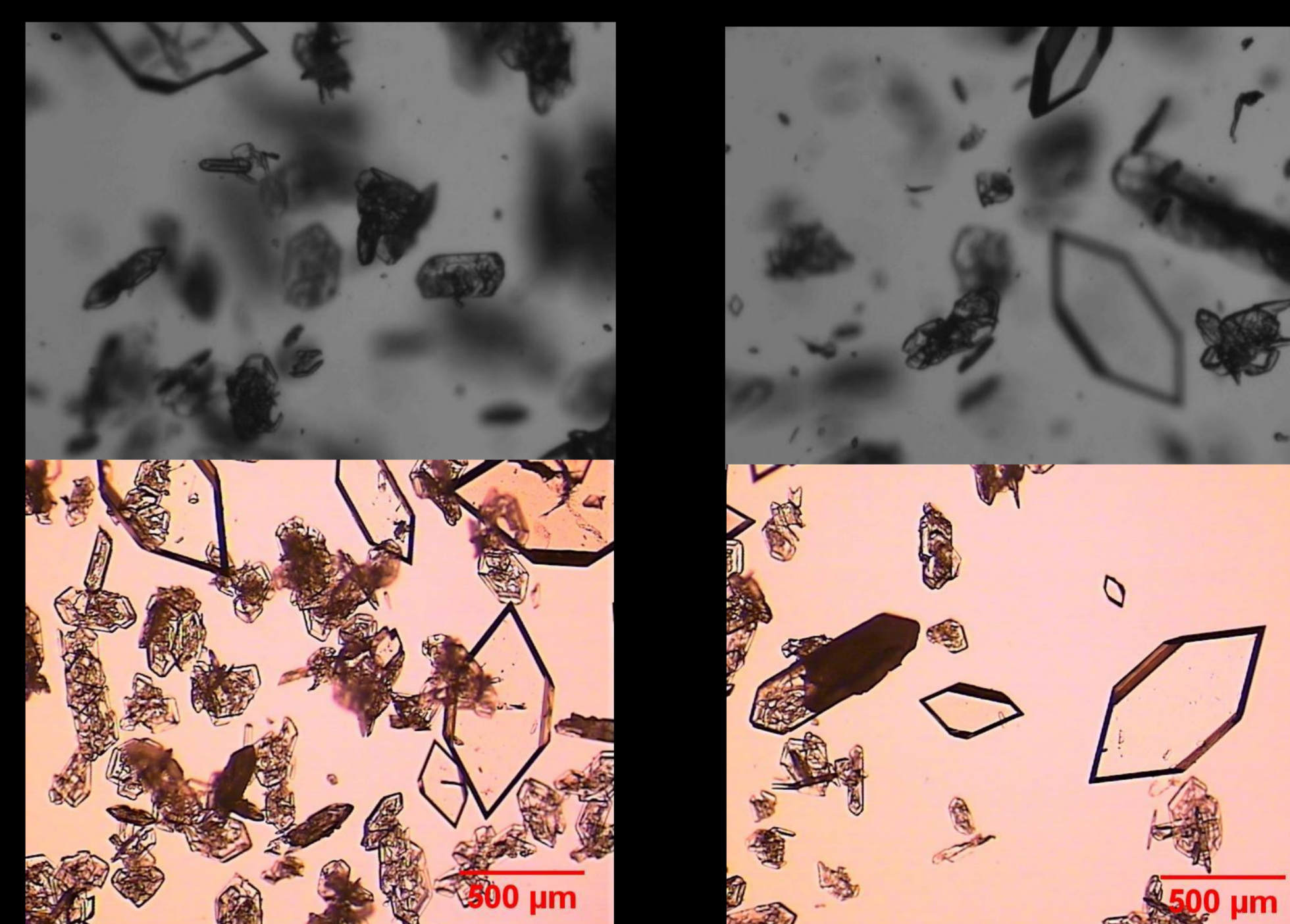
Run2, monitoring with PAT and Image Analysis



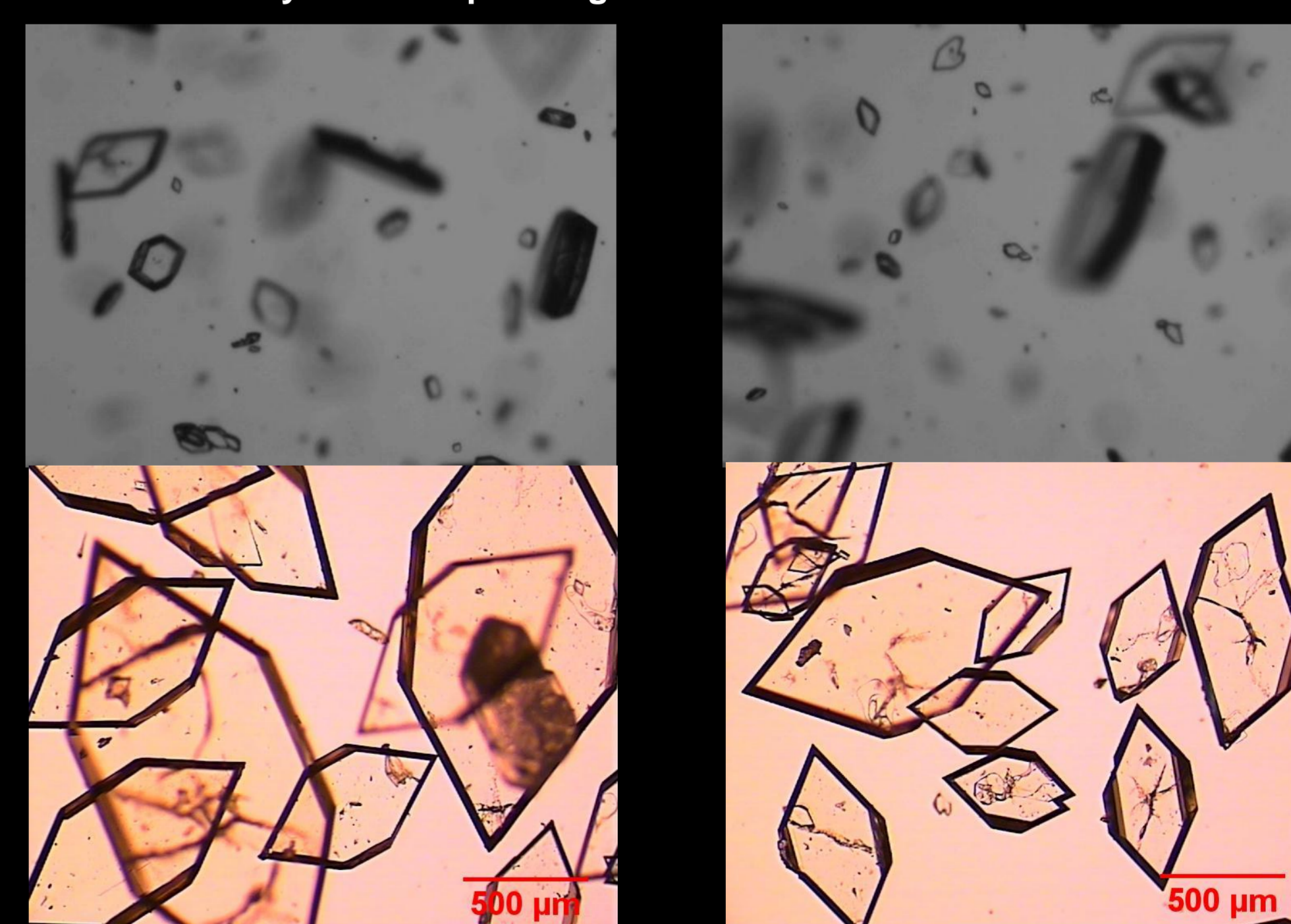
- Decrease in aspect ratio
- Increase in circularity
- Increase in rectangularity and de-agglomeration



Real time images at stage 1 showing agglomerated form 2 crystals and confirmation by microscopic images.



Real time images at stage 2 showing concomitant presence of both forms and confirmation by microscopic images.



Real time images at stage 3 showing only form 1 and confirmation by microscopic images.

De-agglomeration

Increase in amount of stable form 1

Lower aspect ratio for form 1 but higher circularity

Conclusions

- PAT offers a better monitoring and control approach for polymorphic systems.
- Image analysis complement PAT and help in further understanding transformation mechanism.
- Approaches such as supersaturation control can be used to produce the desired polymorphic forms.