

Thermoanalytical Perspectives on API Polymorphism A Case Study

Frédéric Ran

F. Hoffmann-La Roche Ltd

Pharma Technical Development Synthetic Molecules

Solid State Sciences ► Particle & Formulation Characterization ► Thermoanalytical Laboratory

4070 Basel, Switzerland

'Credits shall be given to Authors for any use of this materials !'

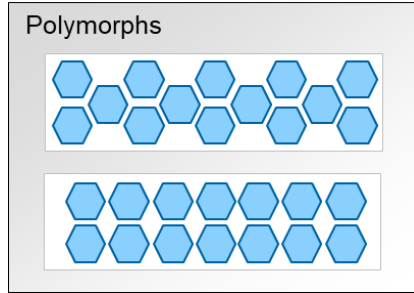
Polymorphism

“Polymorphism is the phenomenon in which the **same chemical substance** exhibits **different internal crystal** arrangements.”


Polymorphism



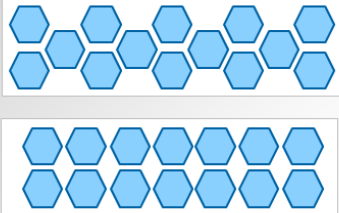
***Active
Pharmaceutical
Ingredient
as
Free Form***



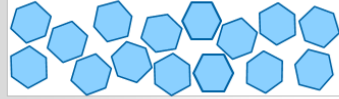
Polymorphism Universe of Solid Forms


**Active
Pharmaceutical
Ingredient
as
Free Form**

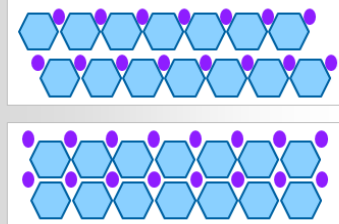
Polymorphs



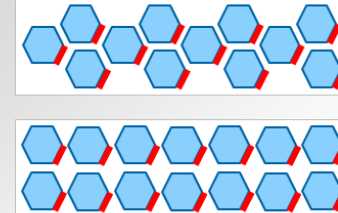
Amorphous



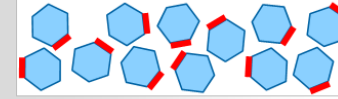
Solvates, Hydrates & Cocrystals



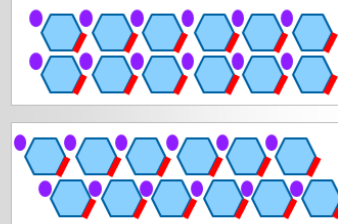
Polymorphs




Amorphous

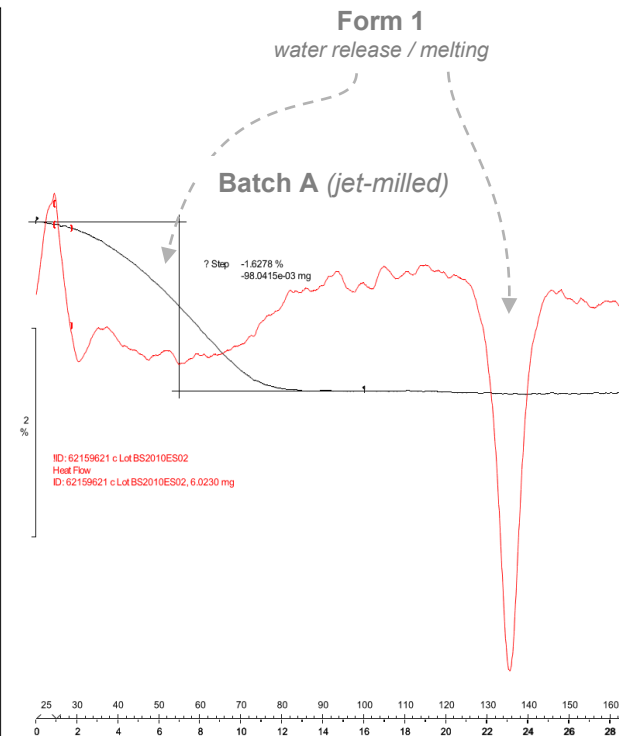
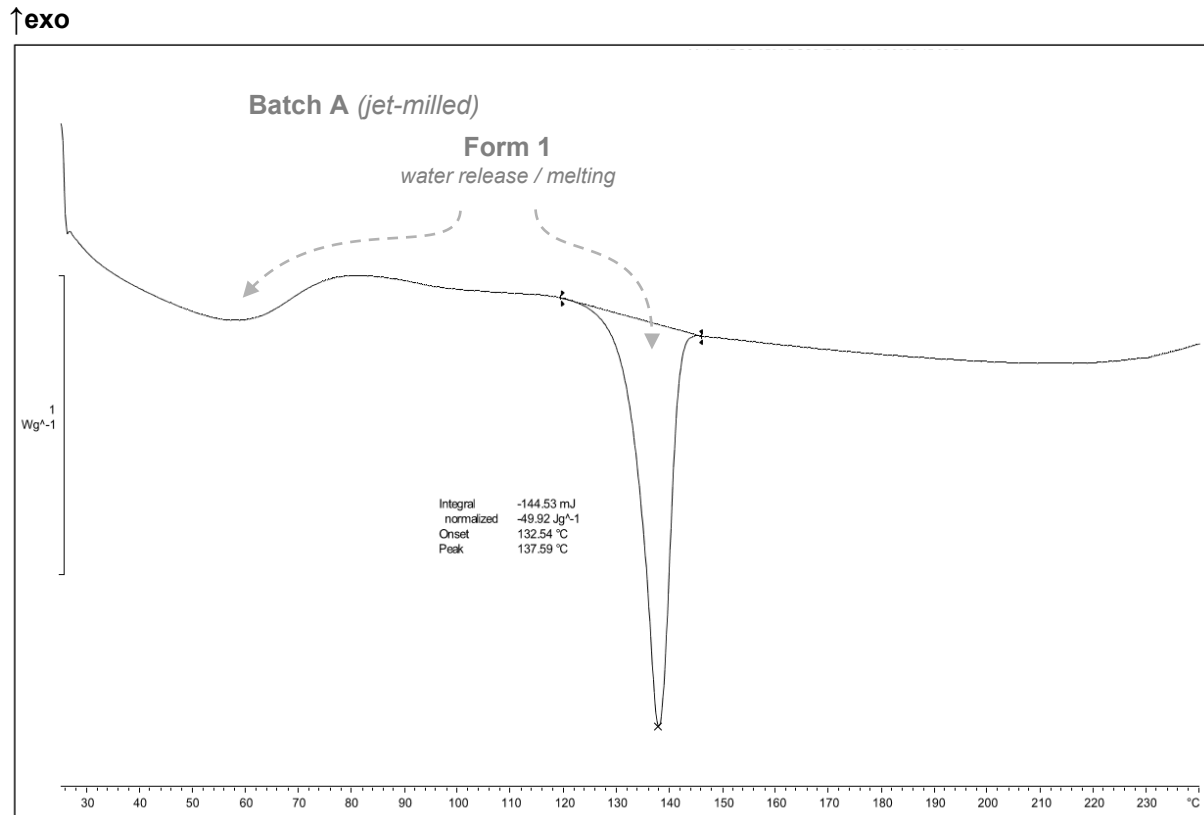


Solvates, Hydrates & Cocrystals




**Active
Pharmaceutical
Ingredient
as
Salt**

DSC and TGA of Form 1 (hydrate)

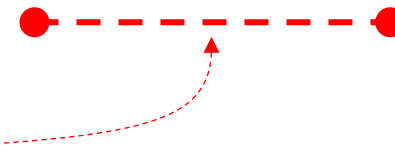
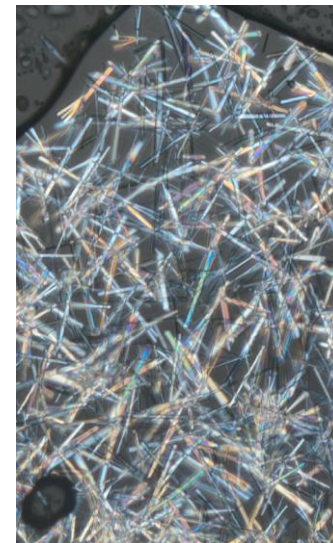
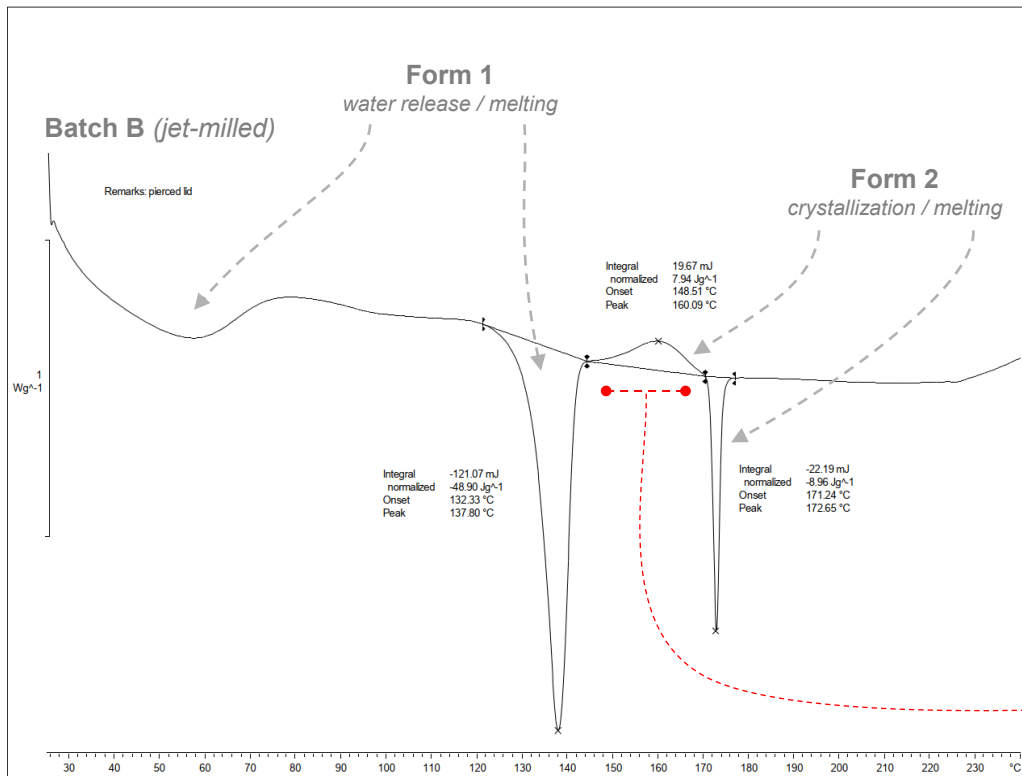


DSC of Form 1 (hydrate)

A new polymorph appears (Form 2)



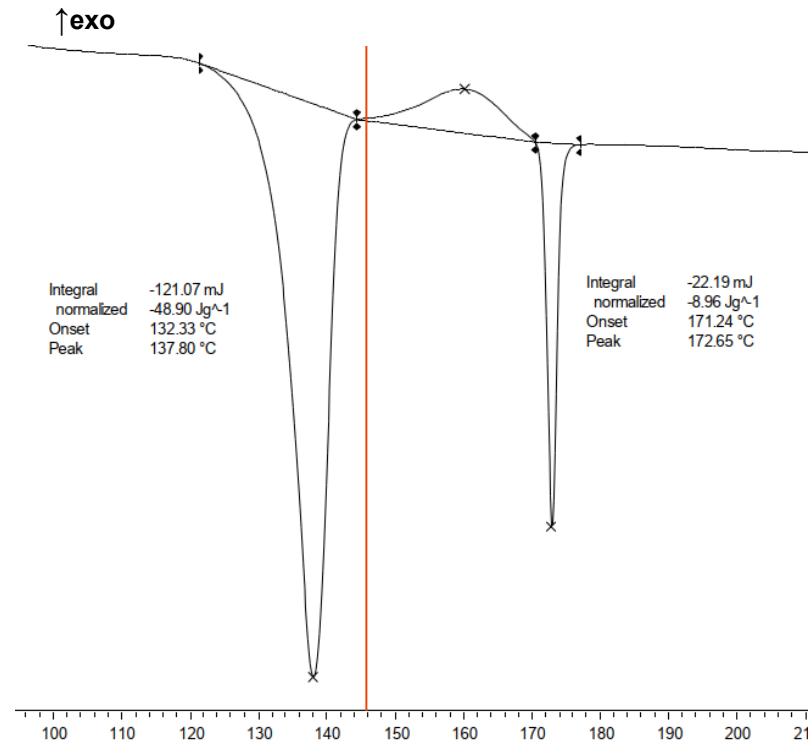
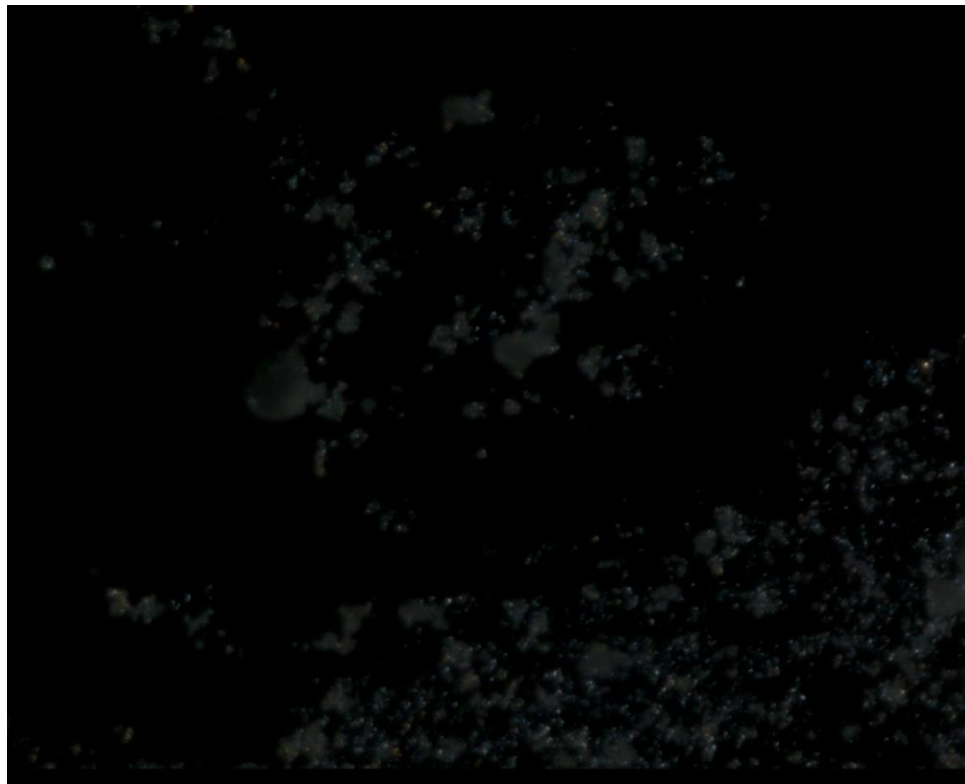
↑ exo



DSC and Hot Stage Microscopy of Form 1 (hydrate)



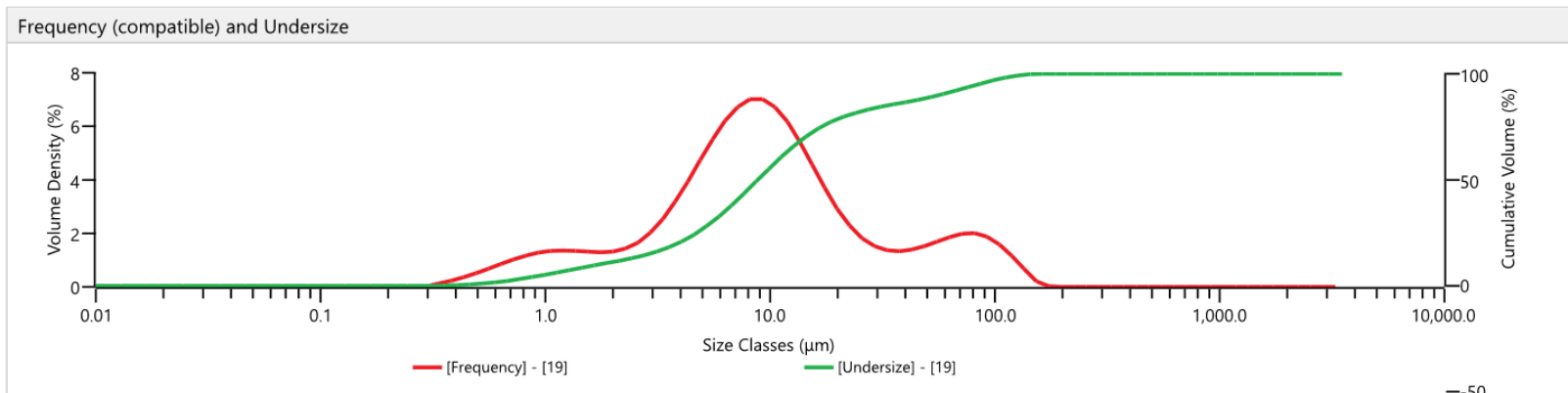
A new polymorph appears (Form 2)



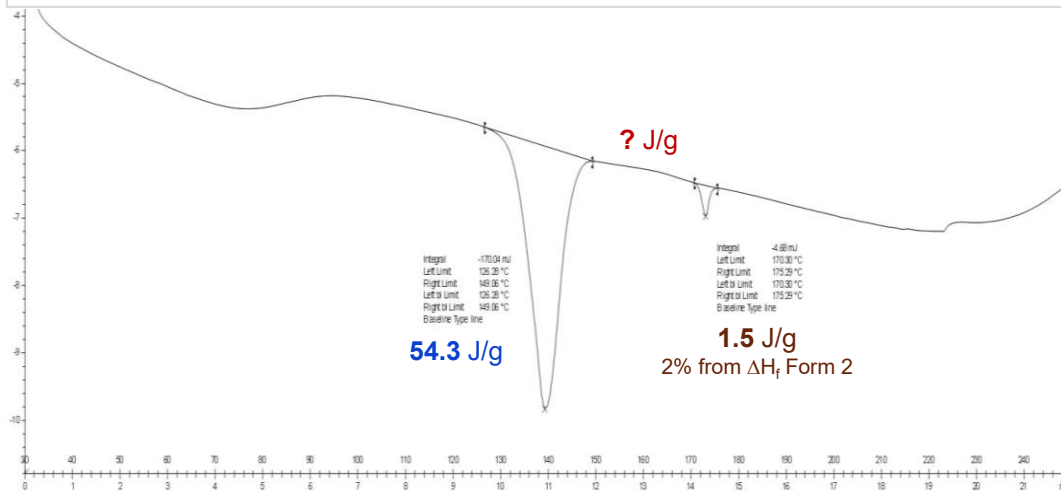
Impact of Milling on Crystallization of Form 2



Batch C, Particle Size Distribution (PSD) and DSC of Form 1 (before jet-milling)



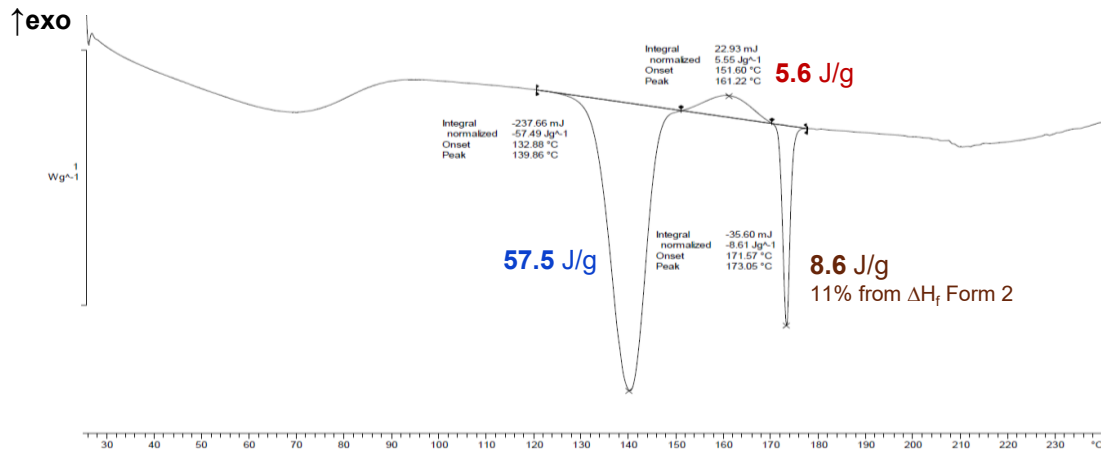
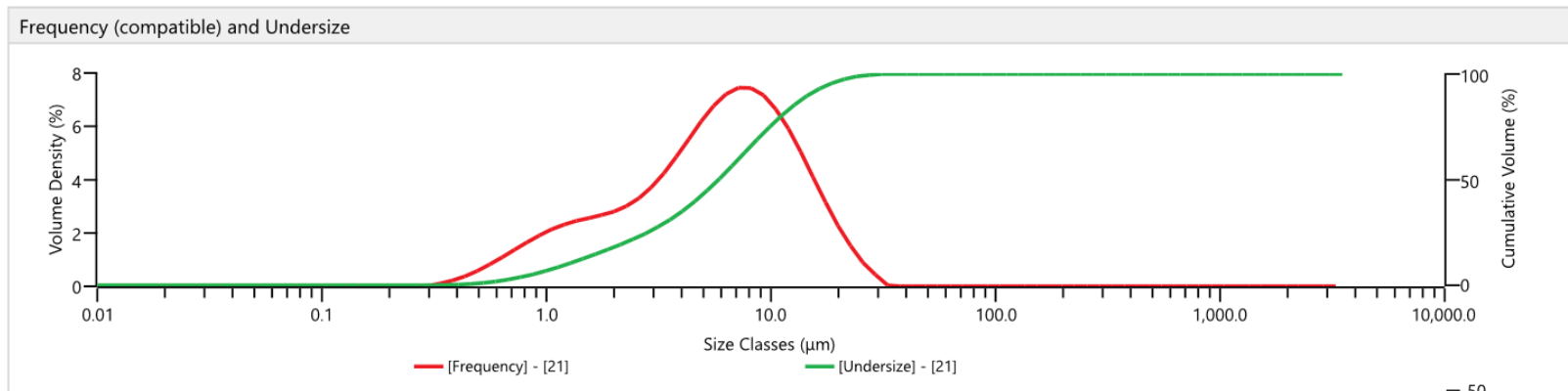
↑ exo



Impact of Milling on Crystallization of Form 2



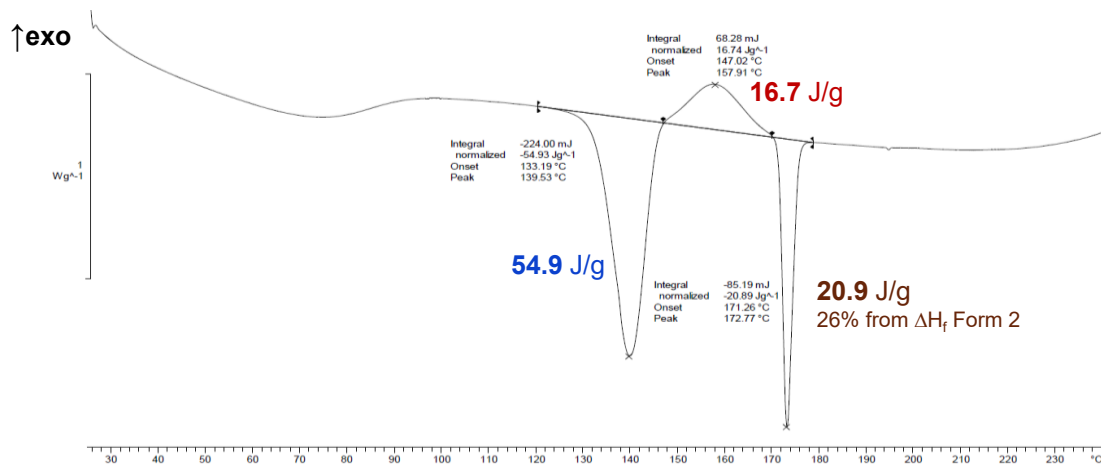
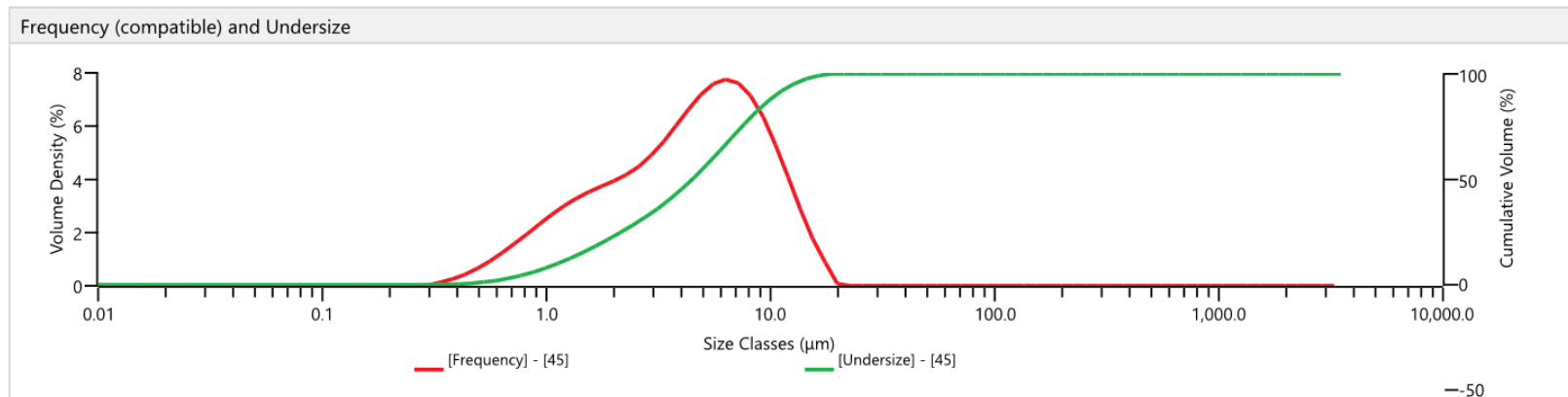
Batch C, Particle Size Distribution (PSD) and DSC of Form 1 (jet-milled, sample 1)



Impact of Milling on Crystallization of Form 2



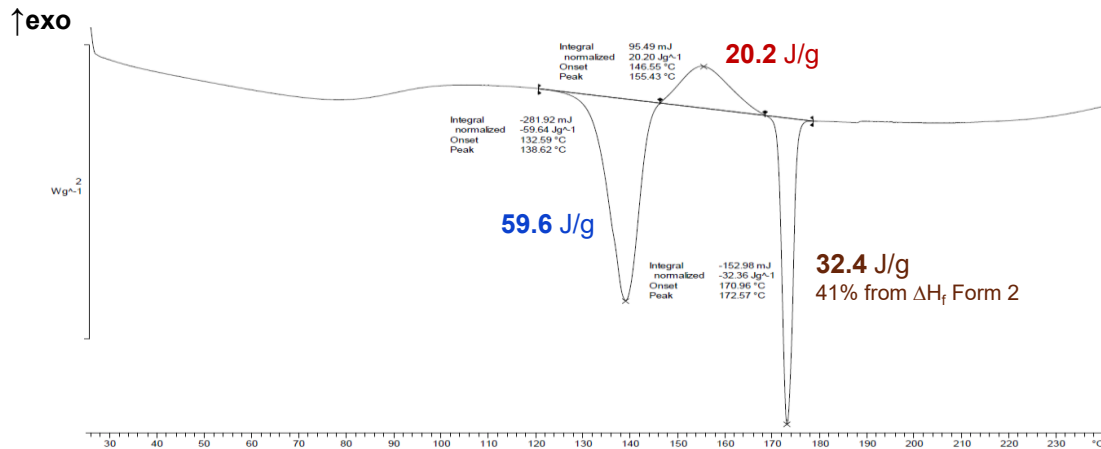
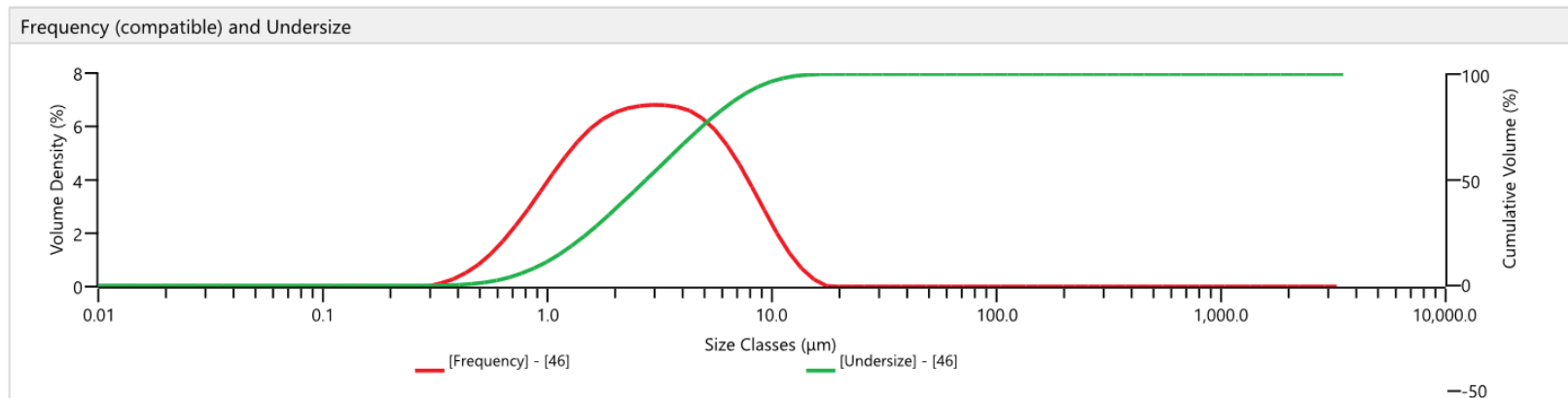
Batch C, Particle Size Distribution (PSD) and DSC of Form 1 (jet-milled, sample 2)



Impact of Milling on Crystallization of Form 2



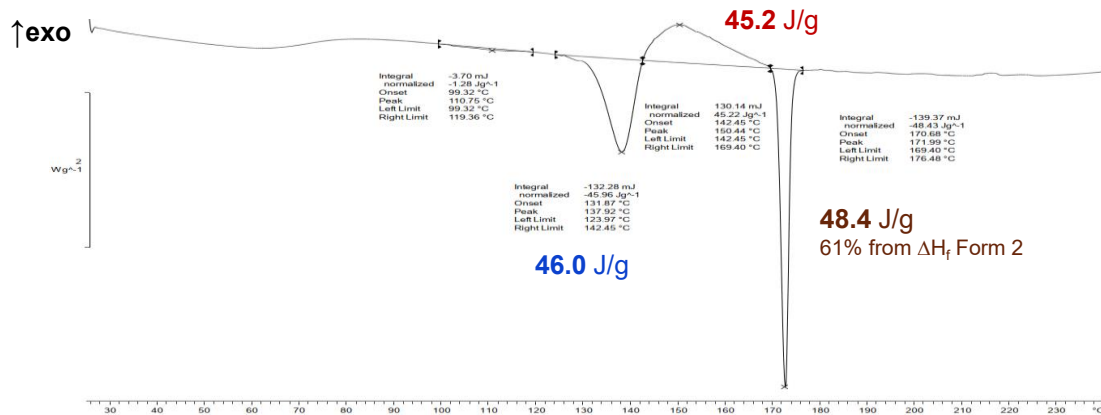
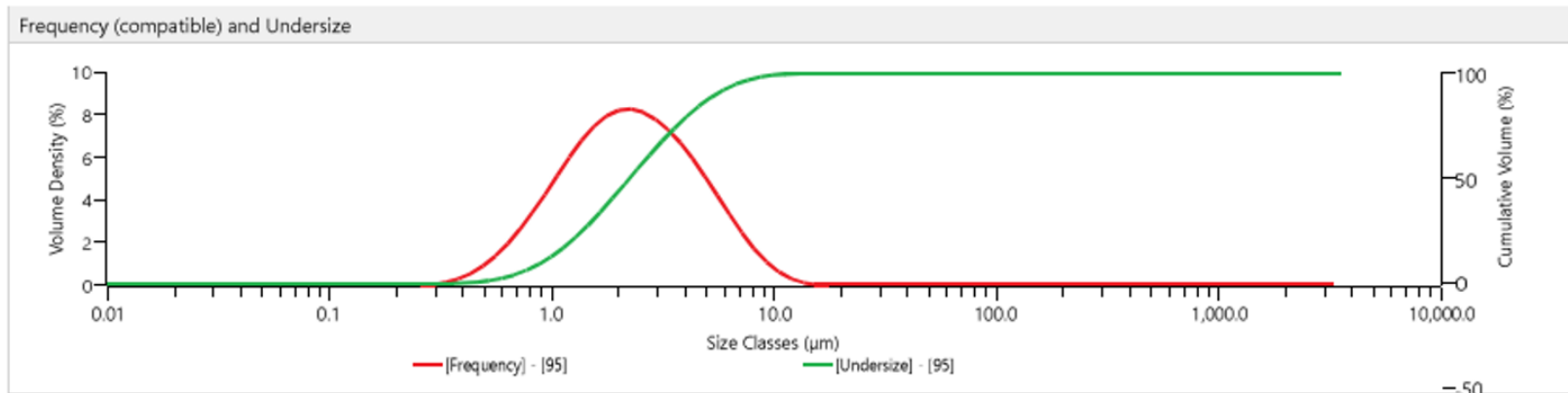
Batch C, Particle Size Distribution (PSD) and DSC of Form 1 (jet-milled, sample 3)



Impact of Milling on Crystallization of Form 2



Batch C, Particle Size Distribution (PSD) and DSC of Form 1 (jet-milled, sample 4)



Acknowledgements

- **DSC & TGA**

Benoit Ackermann

Louise Fonné

Nikolaus Martin

- **Hot Stage Microscopy**

Anna Tomas

Dennis Dimo Enkelmann

Flavio Lack

- **Particle Size Distribution**

Anne-Sophie Javelot

Nathalie Bernigal

Take Home Message

- In the study of polymorphism, DSC is an indispensable tool for characterization as well as for the identification of new polymorphs.
- The interplay between particle size distribution and crystallization during DSC has enabled us to understand the nucleation and growth kinetics of this new polymorph.



Doing now what patients need next