Lyophilization R&D and Product Understanding

PDA Israeli chapter
Lyophilization
, Day 11/2017

Yossi Shapira
Lyophilization Expert

Freeze Drying Definition

FDA-7/ 2016 Ellen Huang: (lyophilization definition)

- ”A product after it is frozen and placed under a vacuum, allowing the **ice??** to change directly from solid to vapor without passing through a liquid phase.
- unique, and interdependent processes; freezing, primary drying (sublimation), and secondary drying (desorption).”

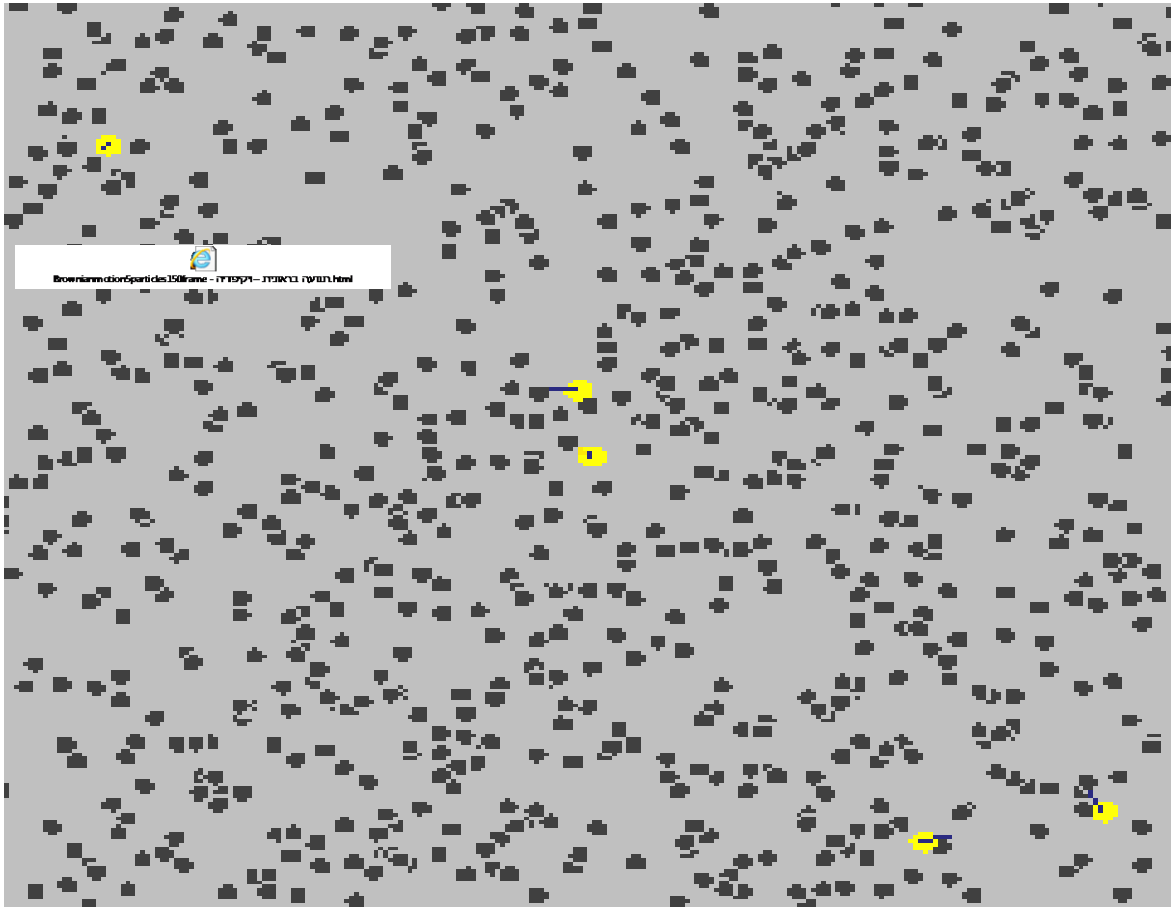
Ice = frozen solvent.

- **“Not enough focus on developing the freezing phase, the most important phase of the cycle.”**

- We acknowledge that for the proposed drug-product vial lyophilization process, you have conducted design of space experiments, and provided cake properties, reconstitution time and moisture content data to justify your proposed primary-drying time and temperature, ramping rate and secondary drying proposed ranges. However, **we are unable to locate any data such as DSC, freeze drying microscopy that must have done to determine lyophilization conditions. Please provide.**
- **We are unable to find any study that determines the apparent end point of primary drying.** We find it important because increase of shelf temperature before all the ice removed may cause collapse/eutectic melt ultimately leading to high residual water content which may affect stability. Please confirm that you have considered this point during development or explain why it is not necessary.
- **Your studies do not include appropriate sampling plans……** that can adequately capture the variation or uniformity of units in different locations on each shelf with respect to the powder properties.

Lyophilization Understanding

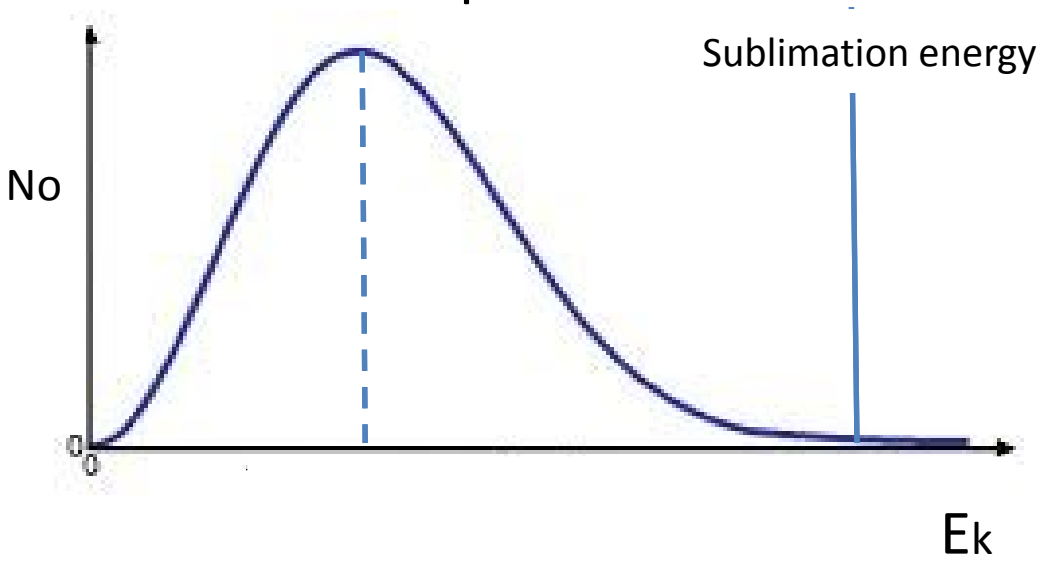
Brownian movement



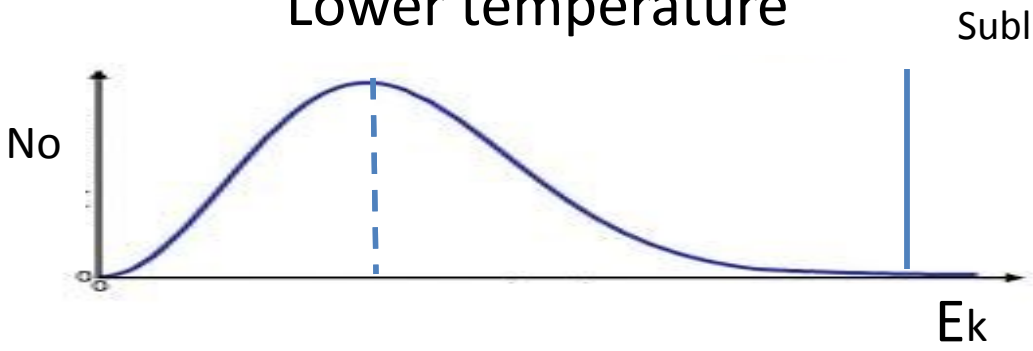
Lyophilization Understanding

Bolzman Maxwell model
Kinetic Energy distribution
VS molecules precentage

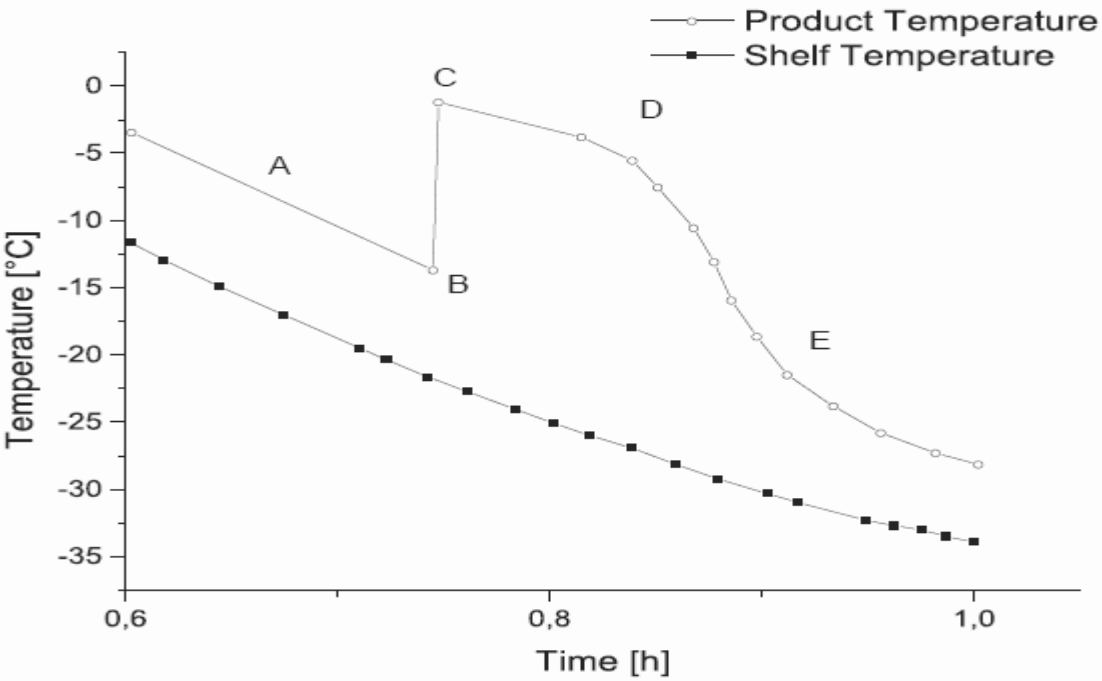
Frozen temperature



Lower temperature

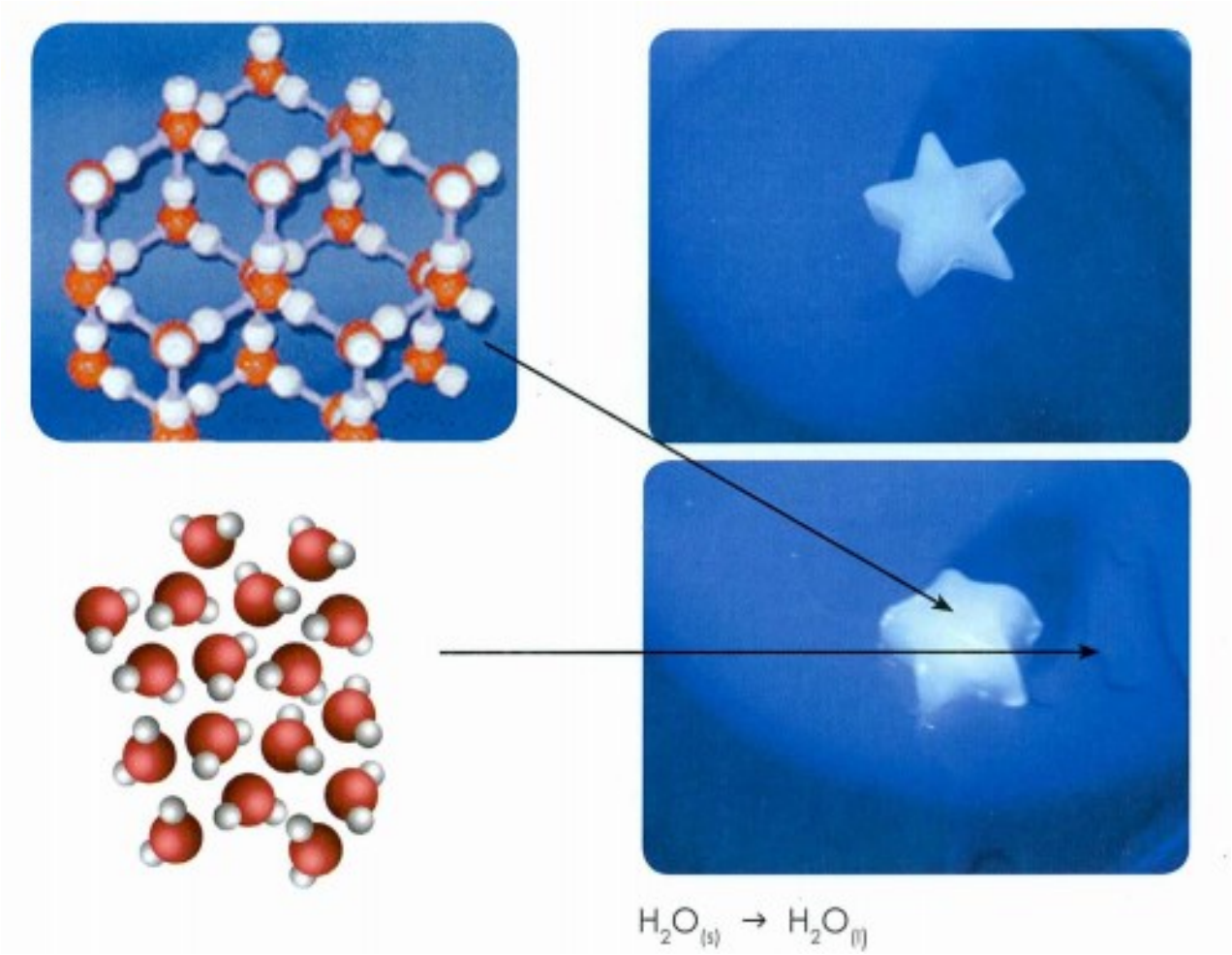


Freezing Phenomena

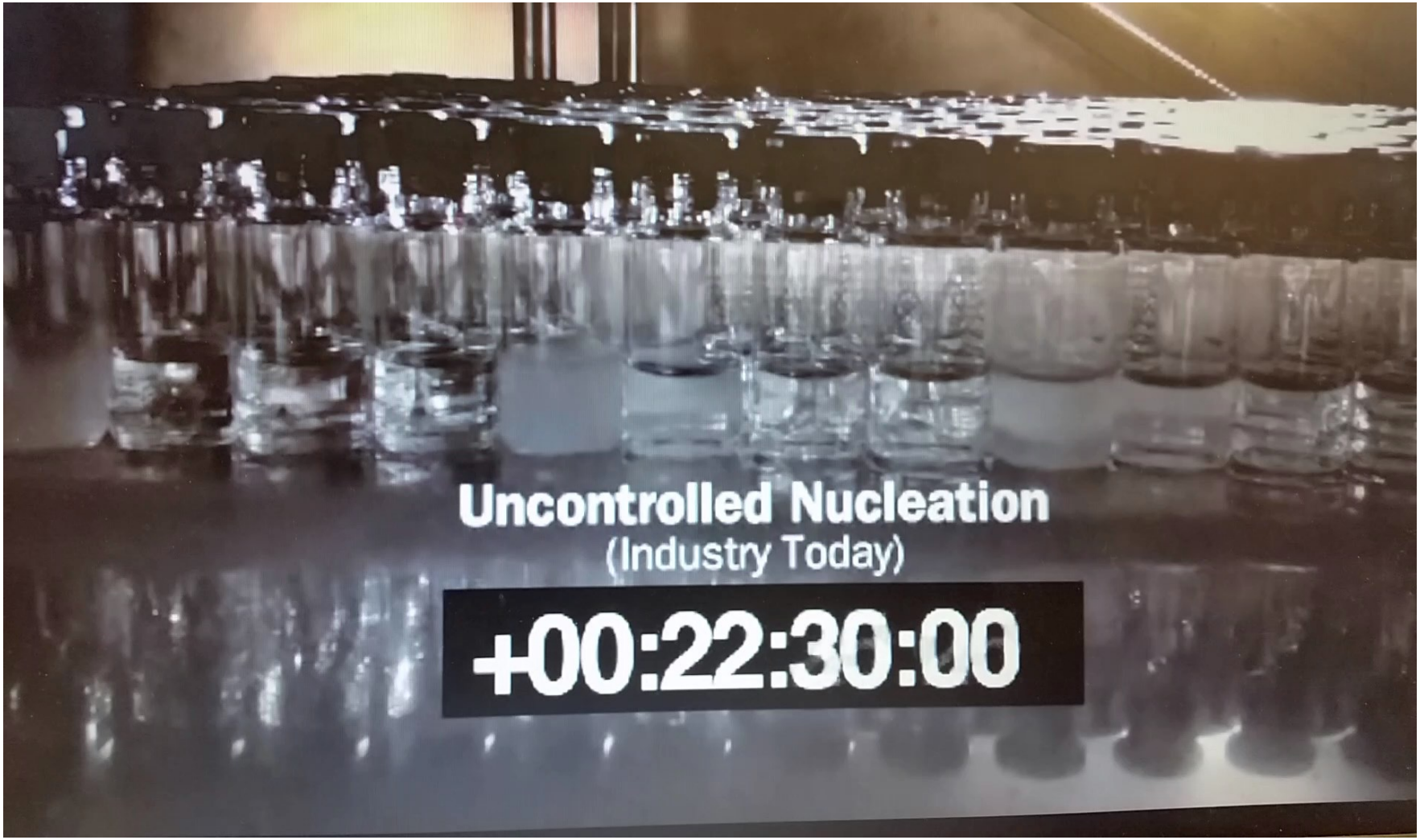


2.2: Freezing behavior: Product and shelf temperatures during shelf freezing with A: supercooling and cluster forming, B: ice crystallization, C-D: Freezing time, ice crystal growth, E: completion of freezing. Adapted from [24].

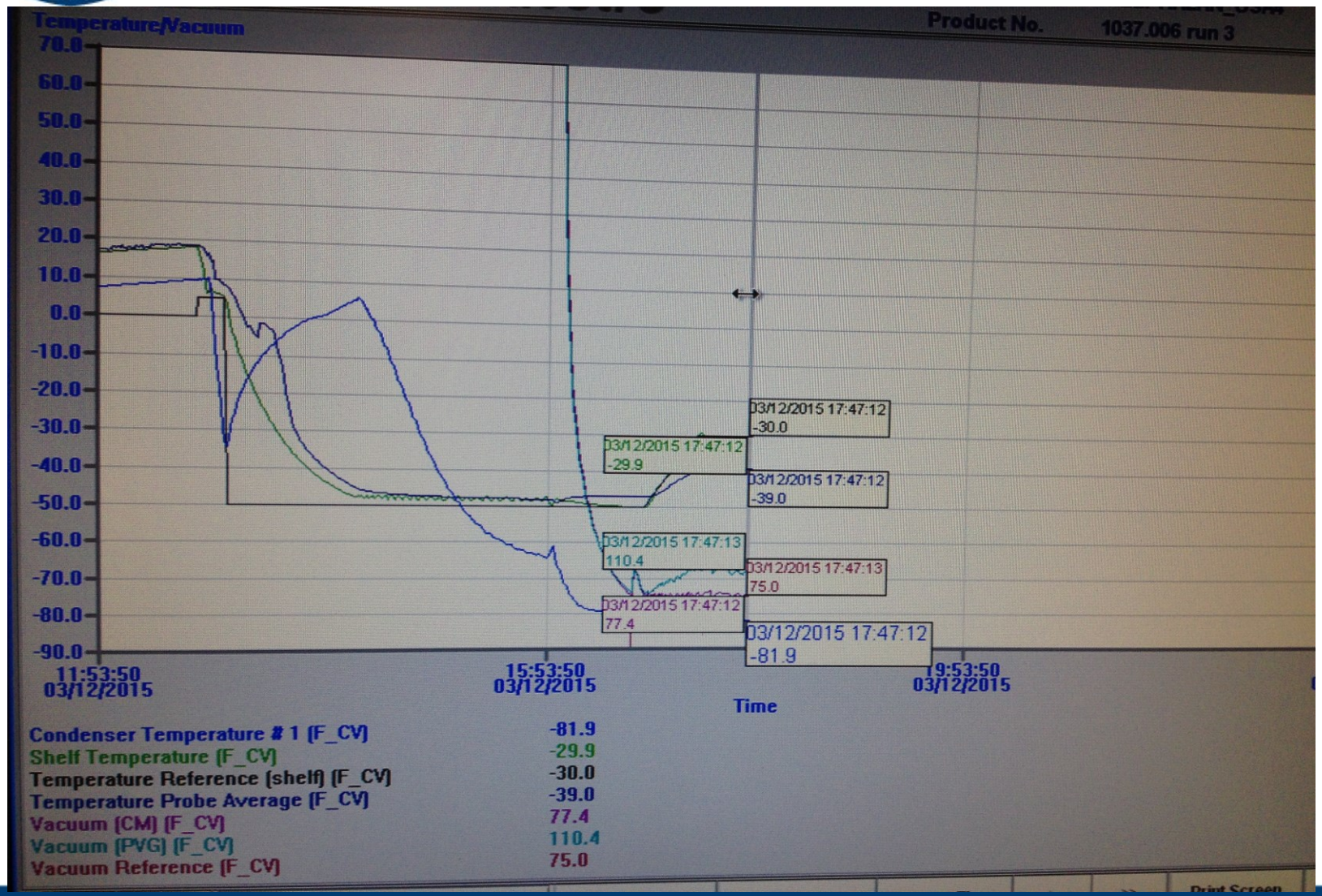
Freezing Phenomena



Freezing - Water



FreezingThermal Analysis



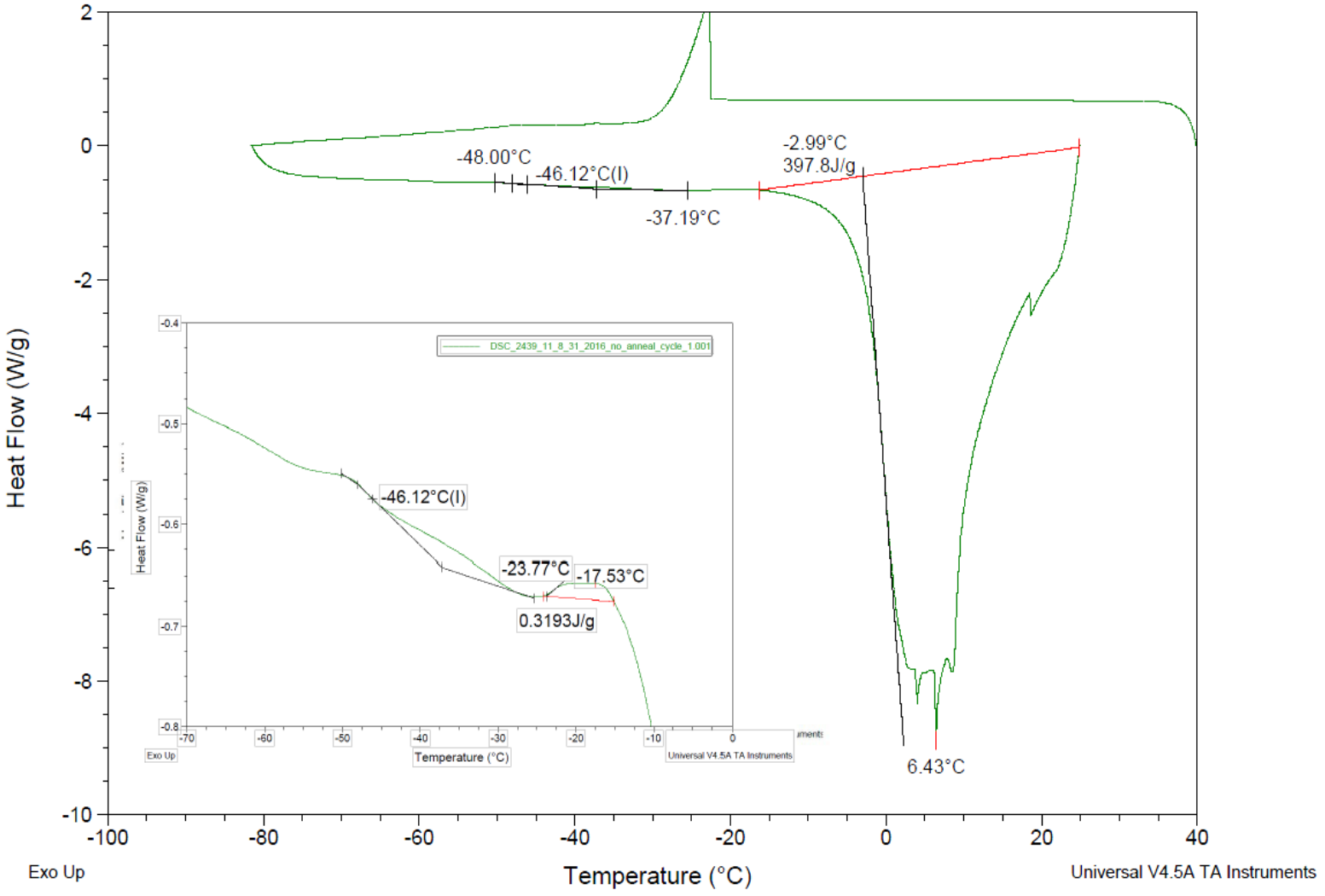
Freezing Thermal Analysis

FDA :Thermal Analysis

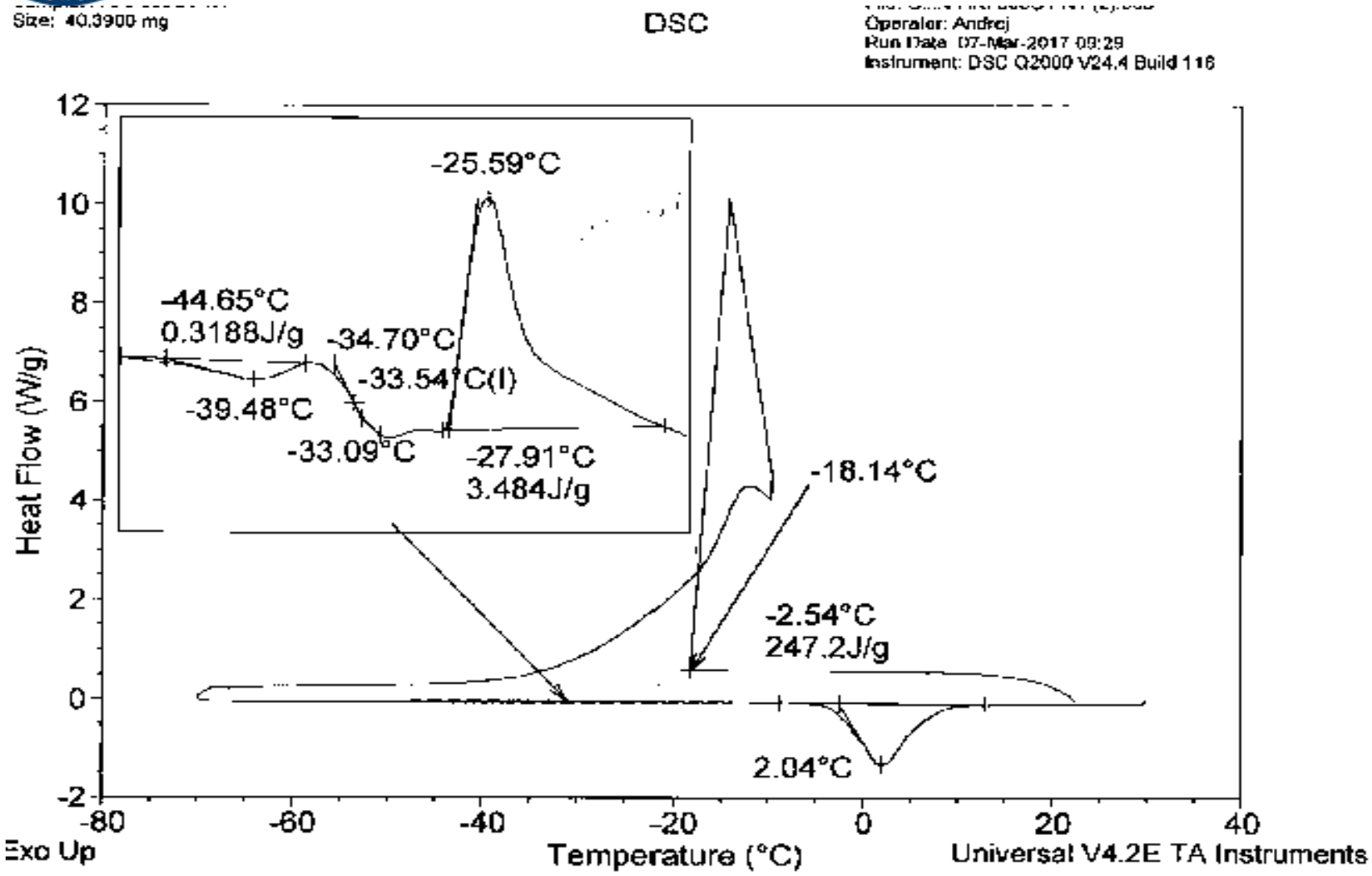
Physical or chemical changes generally accompanied while solution temperature is changed. Energy absorption /release of in the form of heat occurring.

Thermal Analysis are the methods for monitoring and characterizing these alternations. The obtained data will be used for FD process development and quality control and problem solving.

Thermal Analysis -DSC

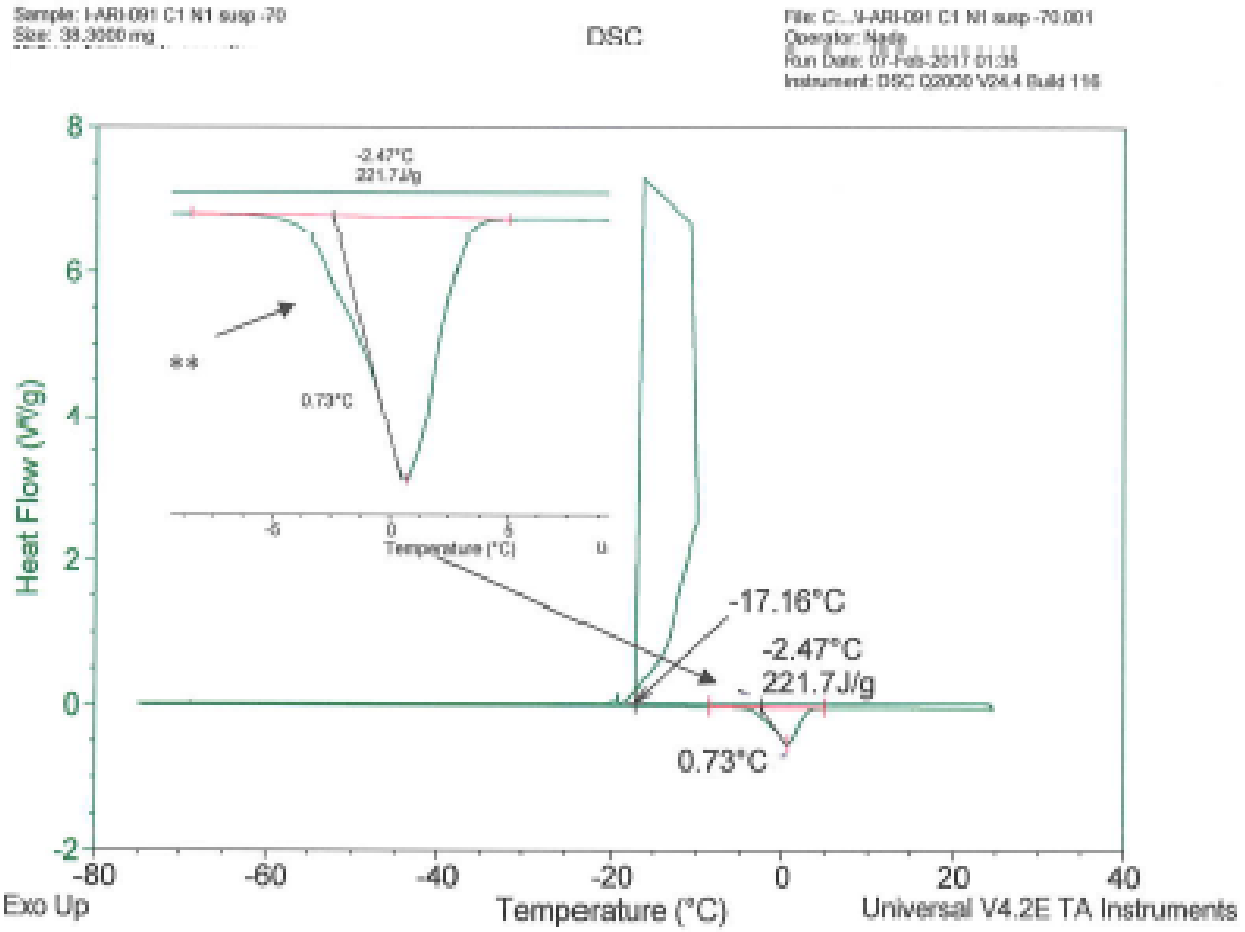


Thermal Analysis DSC

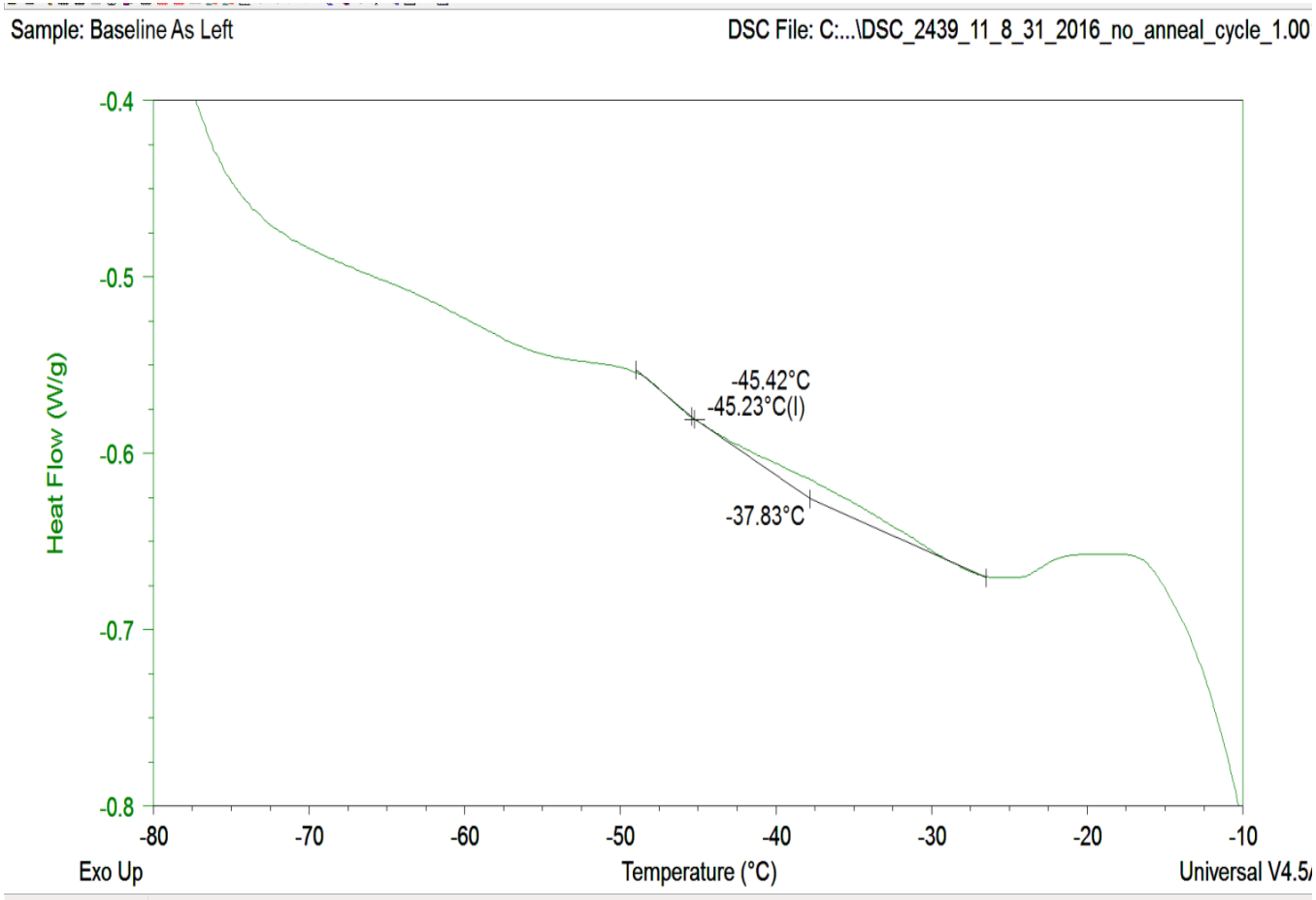


DSC – Thermal Analysis

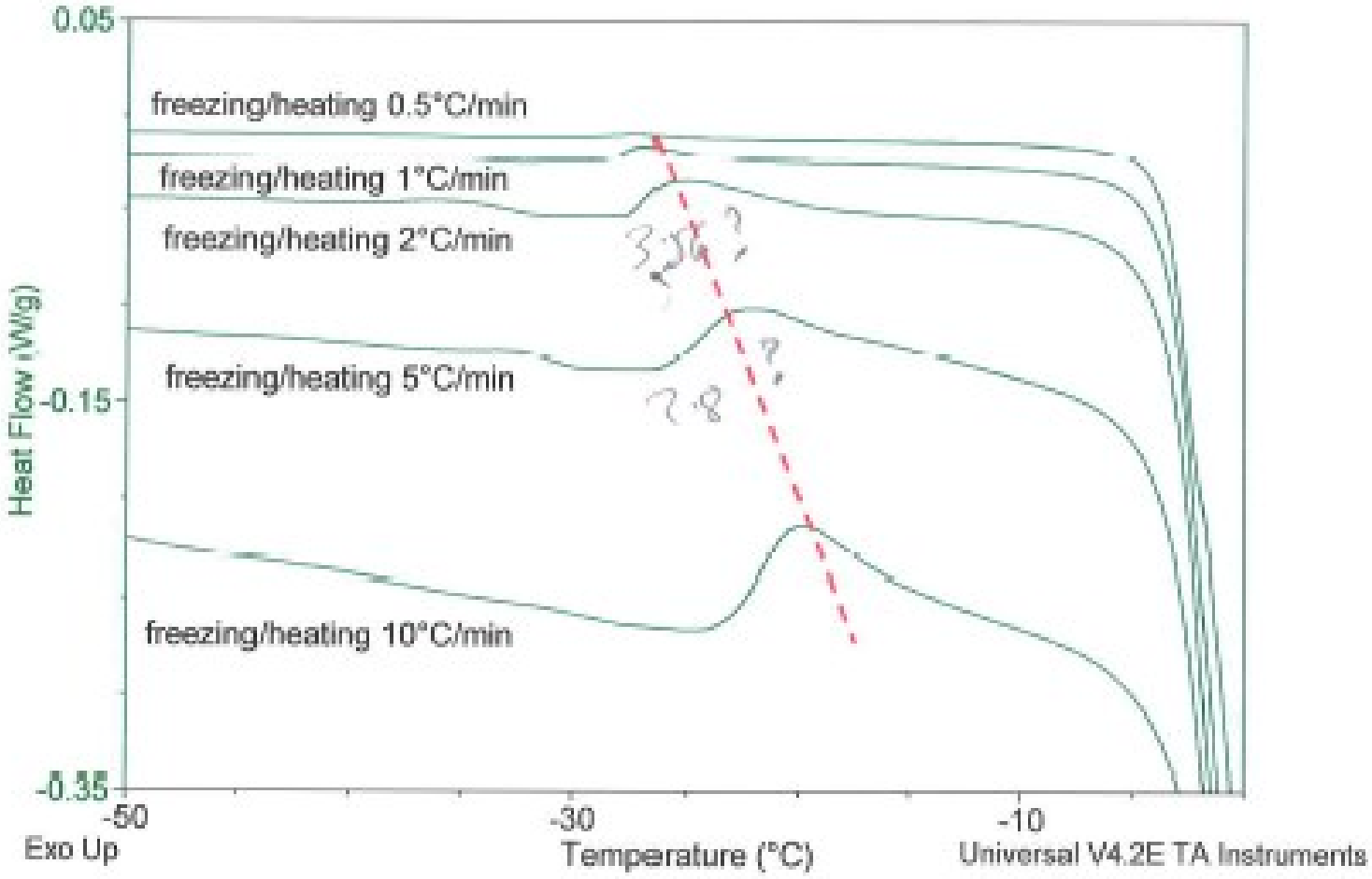
Figure 16: Freezing rate 0.50°C/min, heating rate 0.50°C/min, temperature range -75°C up to 25°C, zoomed ice melting endotherm is added in the left corner



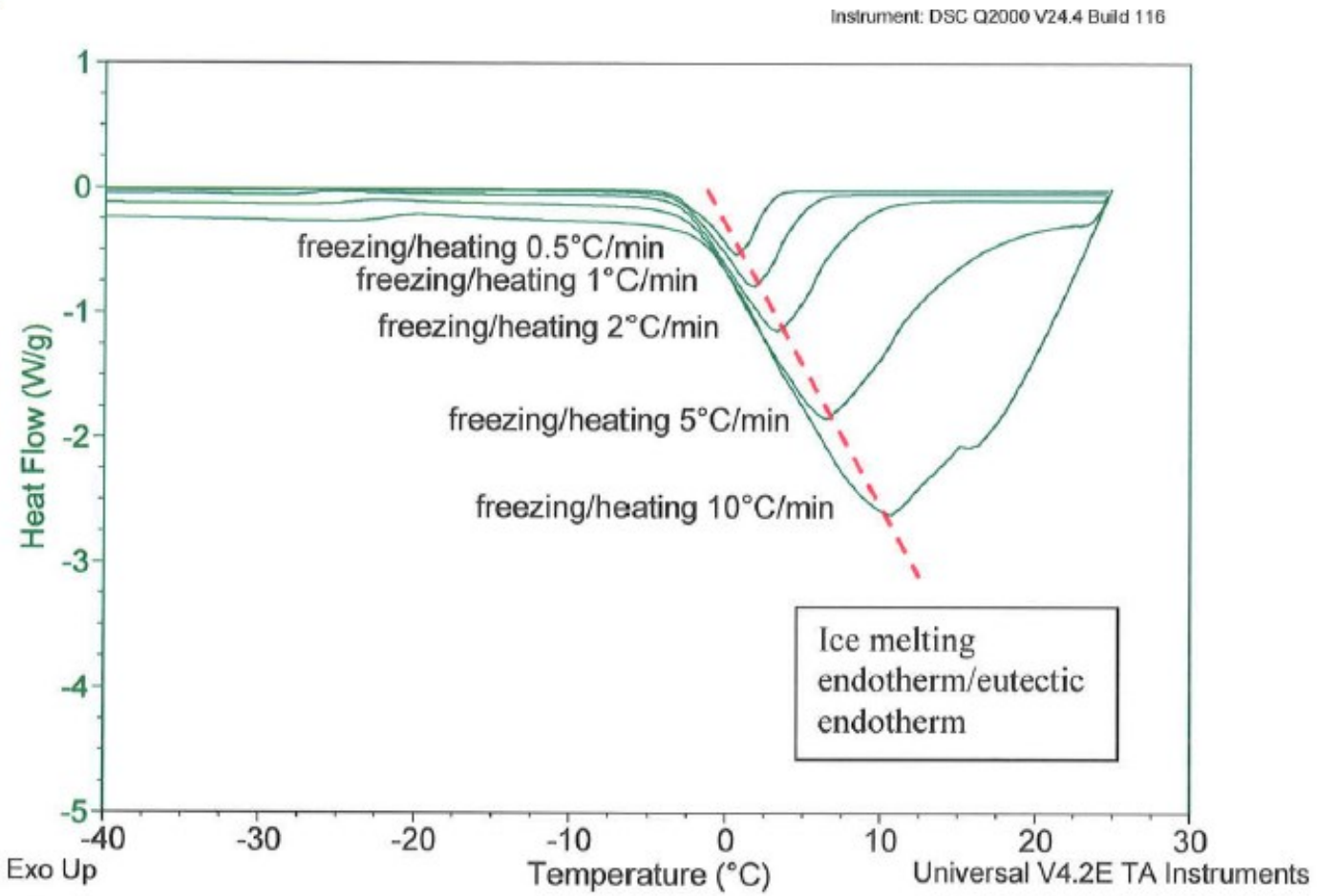
DSC- Thermal Analysis



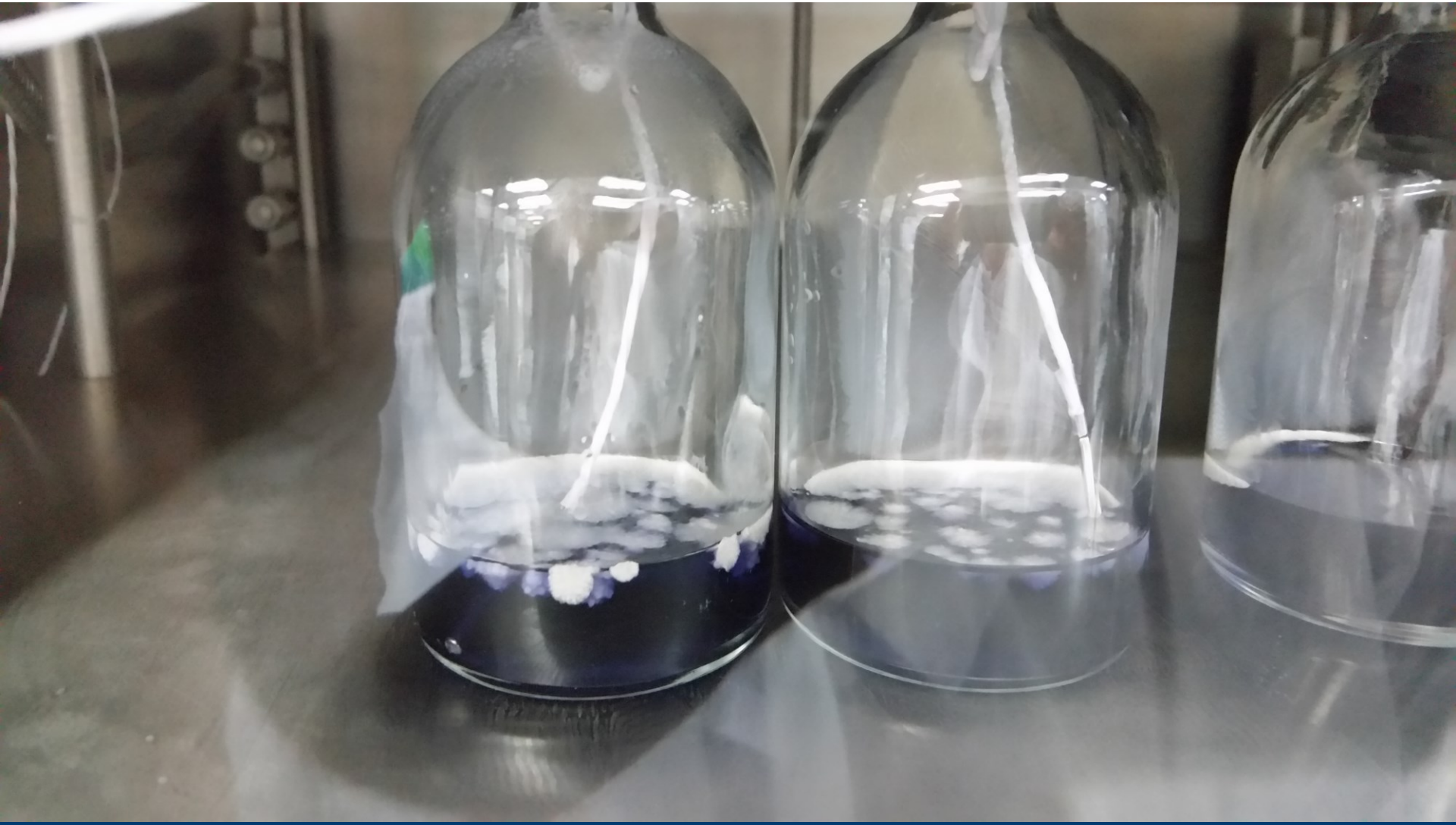
DSC RUNNING USING DIFFERENT RATES



DSC RUNNING USING DIFFERENT RATES

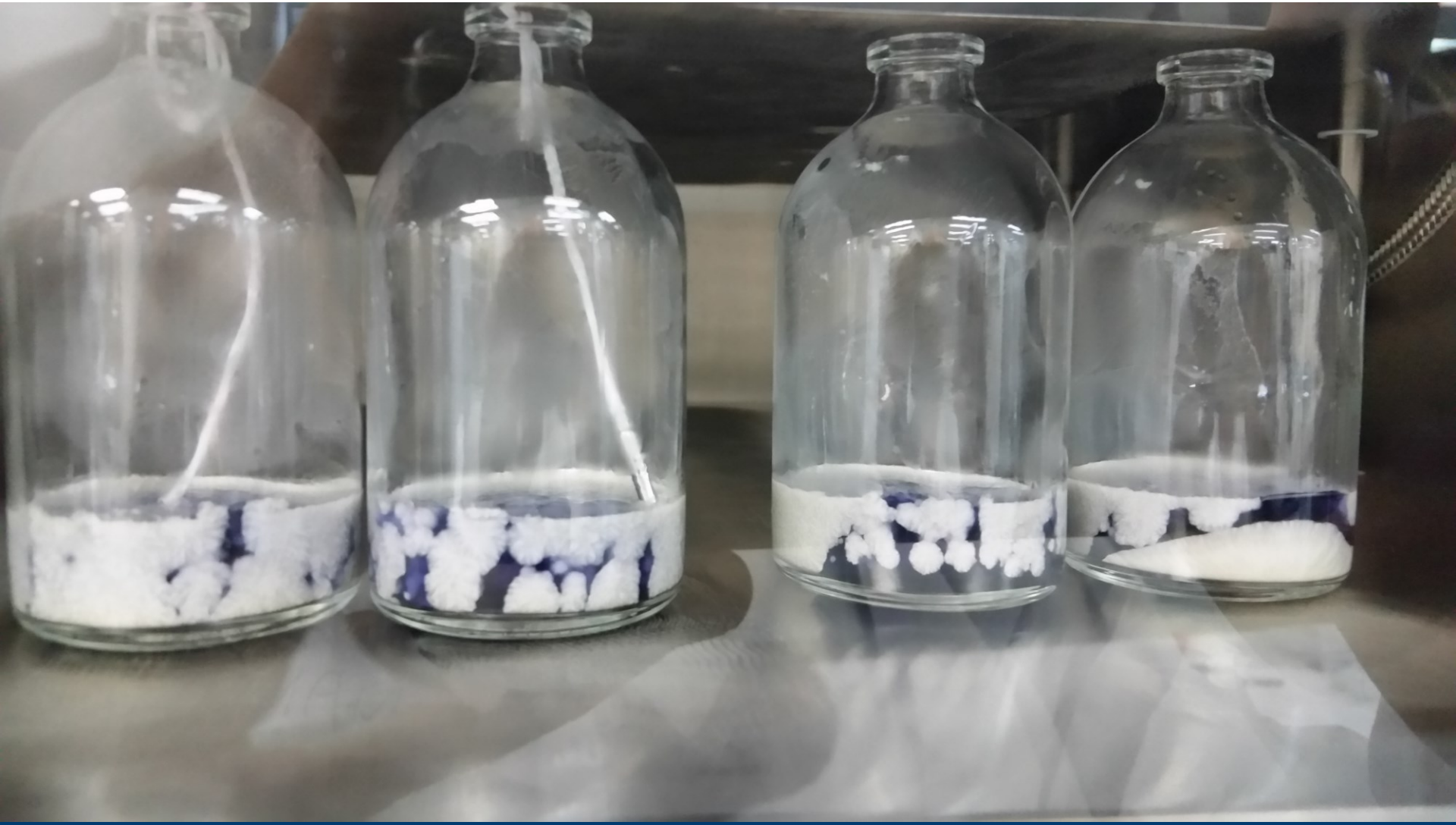


Freezing 1

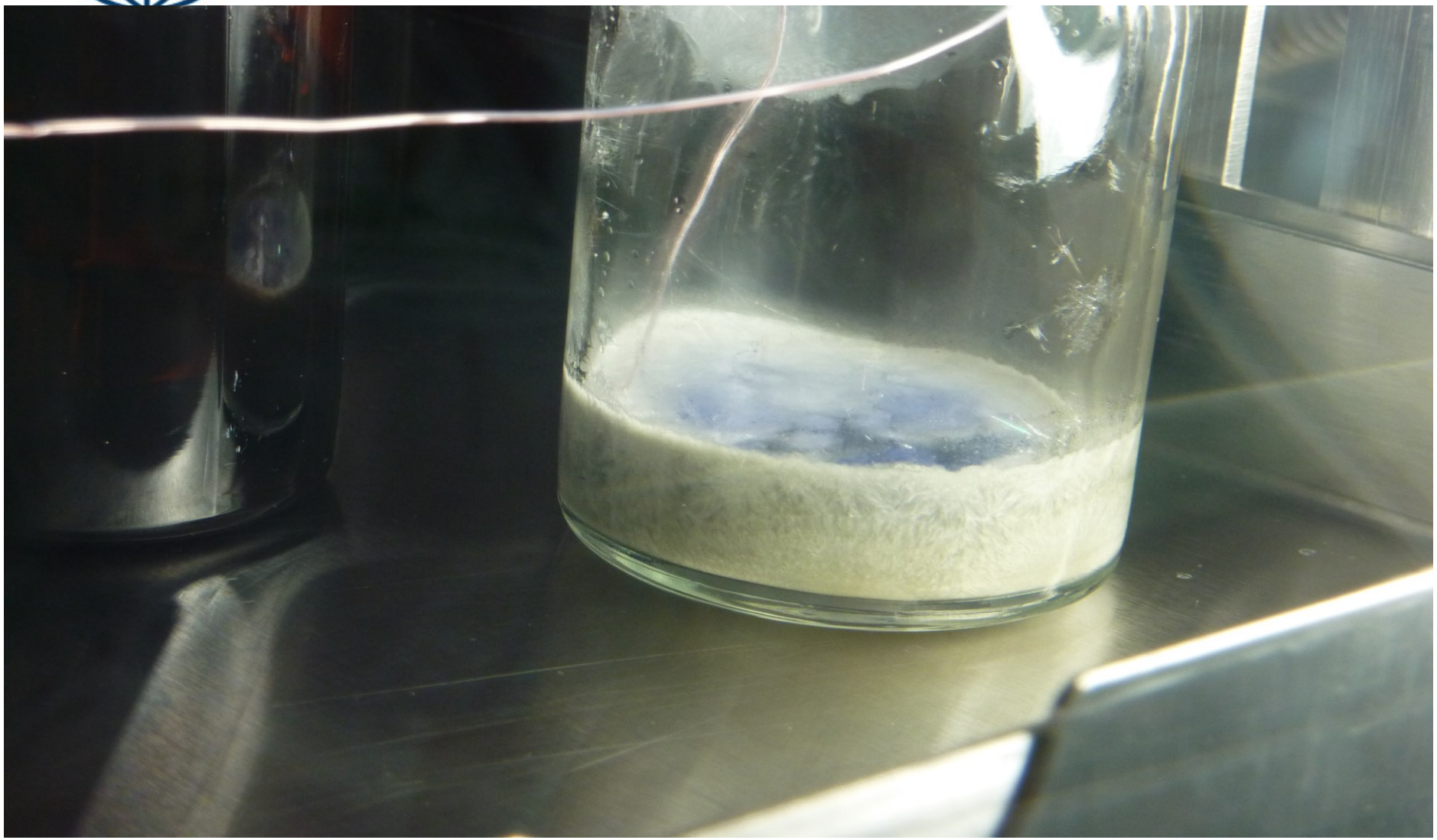


Freezing 2

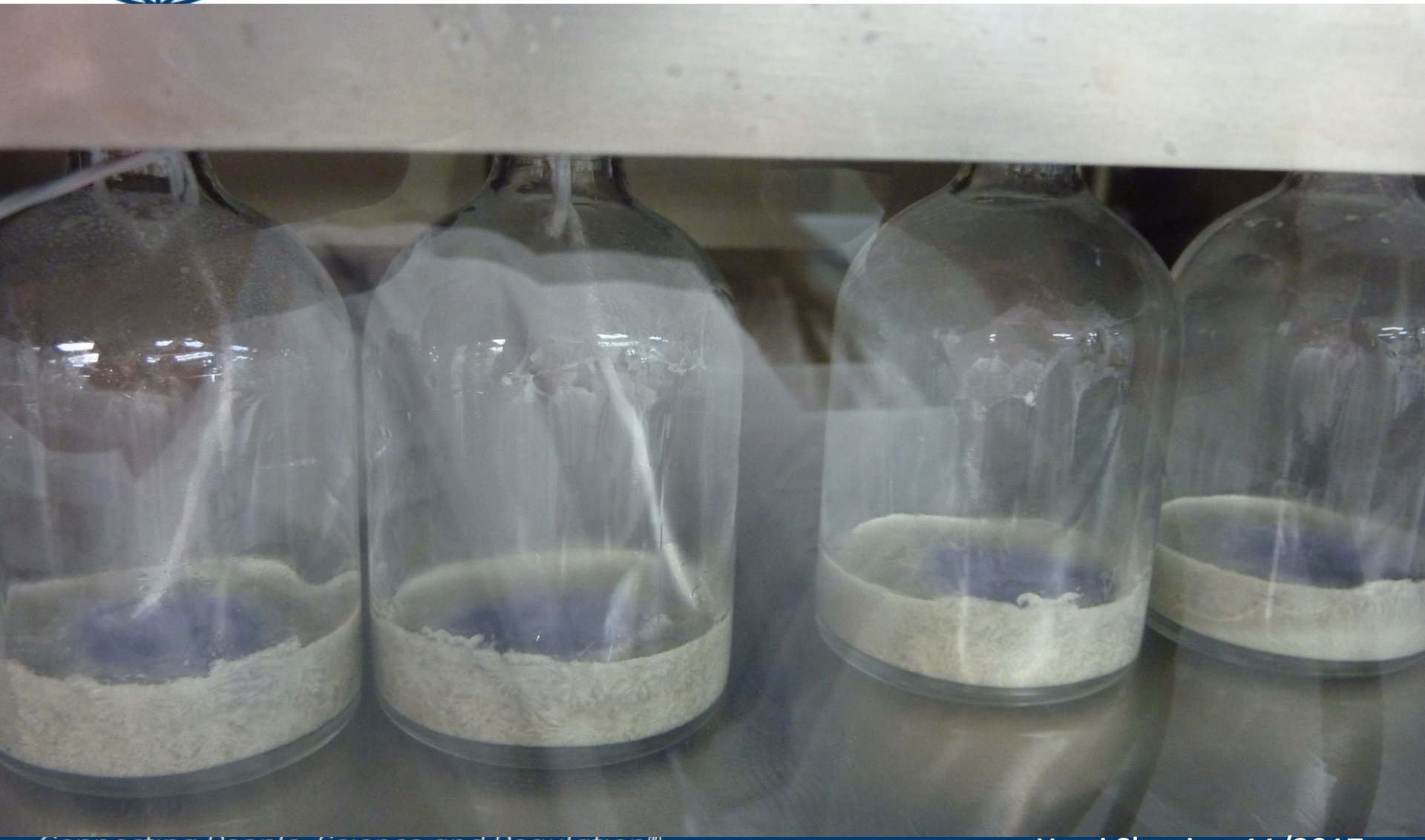
Freezing 3



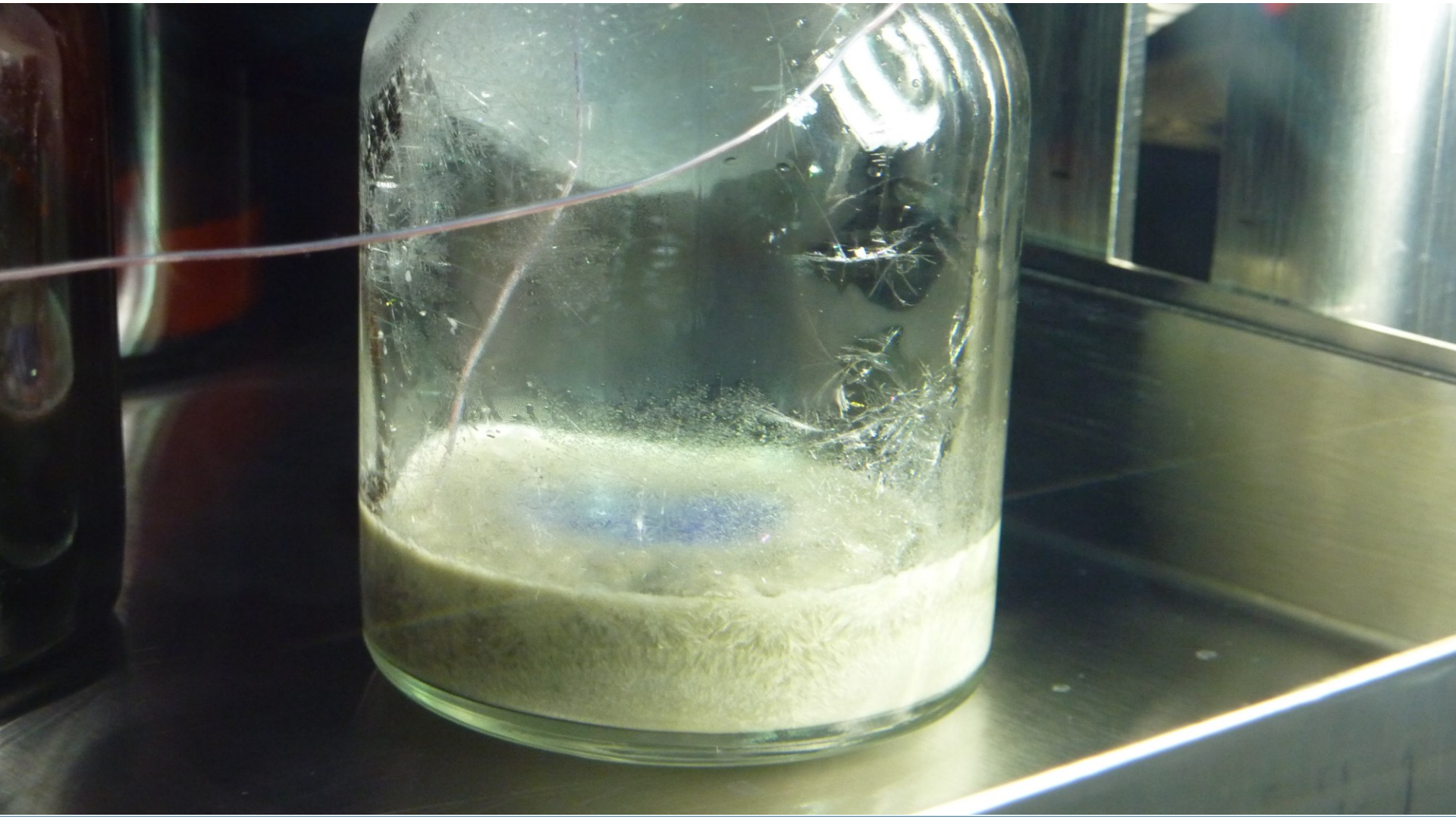
Freezing



Freezing 5



Freezing 6



Dried Cake After Freezing

Wrong Freezing Cakes

- Provide **shelf** temperature, **product** temperature, and **chamber pressure** from the lyophilization cycles executed during the registration batches in graphical and tabular form to better enable us to assess the **robustness** of your lyophilization process.
- Include the **location of product thermocouples** and details regarding how vials were loaded into the chamber and what spaces were left empty. Discuss how the data demonstrates that critical endpoints (freezing, primary and secondary drying) are met to prevent undesirable events such as cake collapse, melt back, etc.
- Explain at what point the primary drying is complete and how much extra drying time is provided before the secondary phase is initiated.
- Include any additional information that may be relevant such as **pressure rise measurements** during drying.

Freezing

Lyophilized product

Annealed lyophilized product

End of freezing

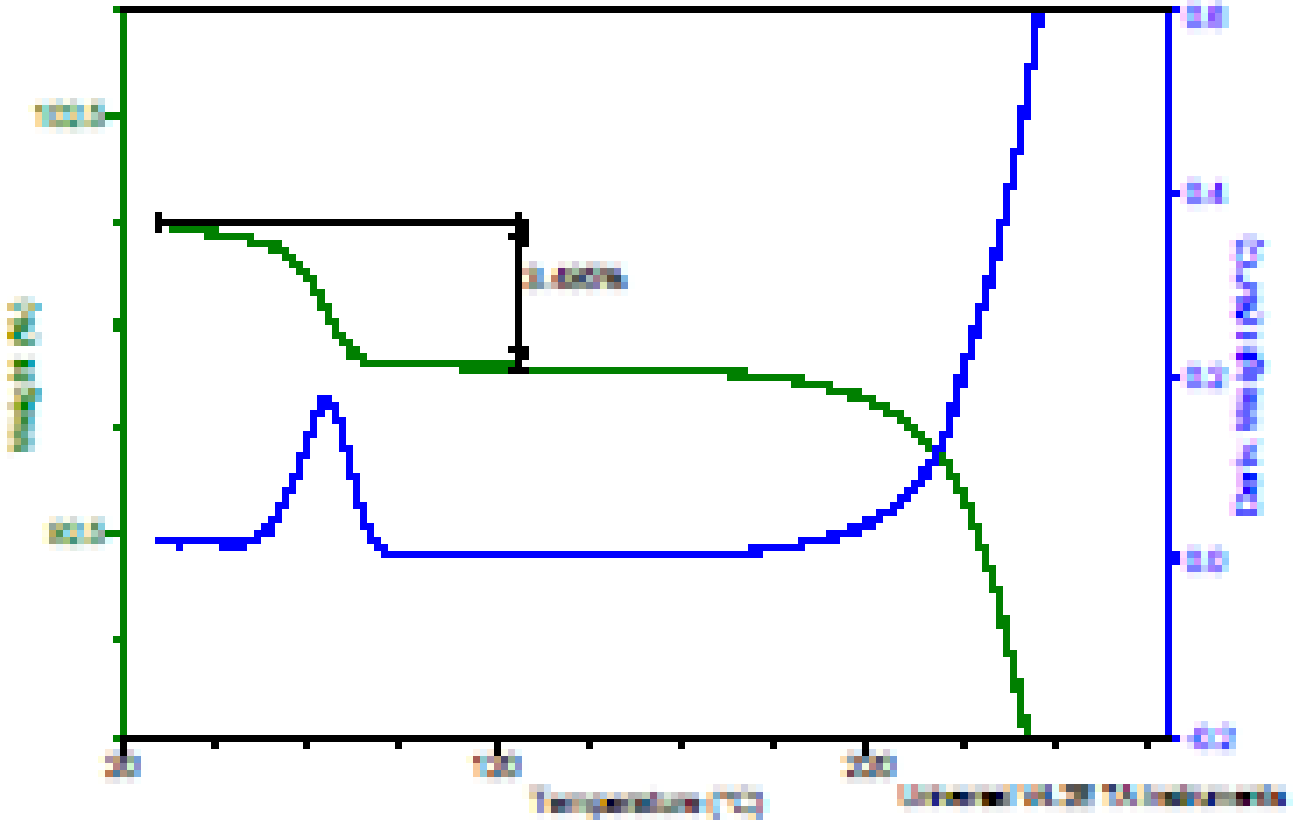
End of Freeze Drying

Faulty drying.....

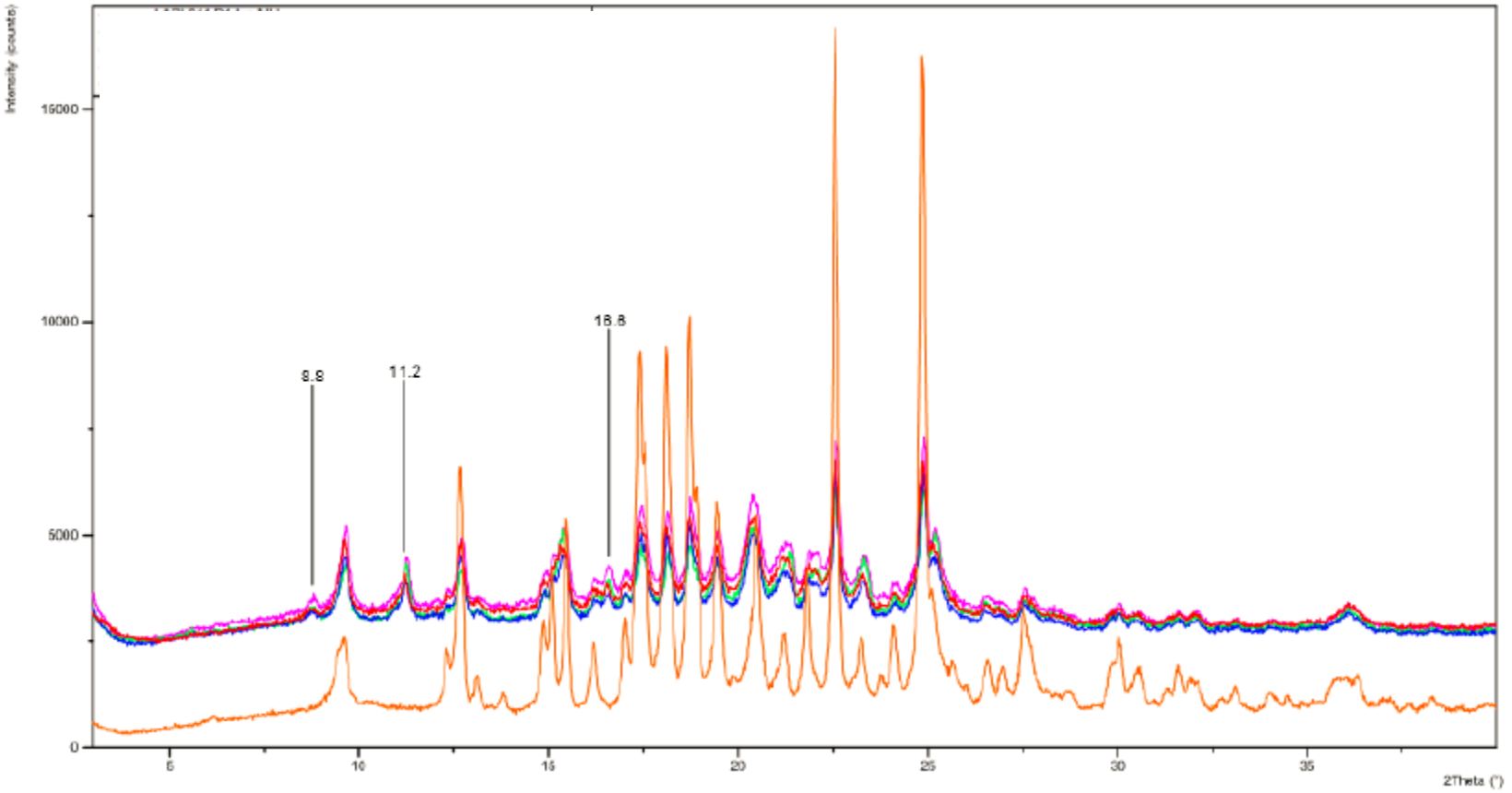
Successful end of drying

Successful and satisfaction

TGA- Analysis –Polymorphism



Similarity proof- XRD



THANK YOU

PDA Israeli chapter
Lyophilization
, Day 11/2017

Yossi Shapira
Lyophilization Expert