MILLROCK TECHNOLOGY

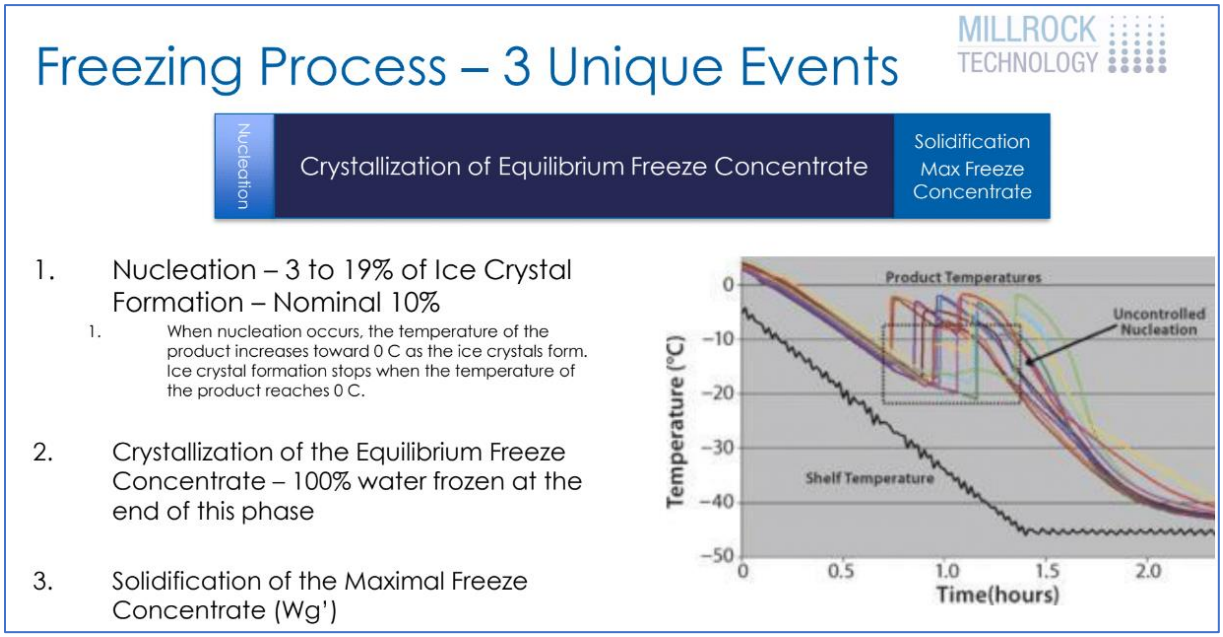
Freezing 101 As It Applies to Freeze-Drying

T.N. Thompson, Millrock Technology

Freezing is the foundation for the freeze-drying process, therefore, understanding the dynamics of freezing is critical.

The freezing process occurs in three unique events. The first event, called “nucleation” is where an ice crystal forms and the available water starts to form ice crystals around it. When freezing product in vials about 10% of the water will form ice crystals during this initial nucleation event. Once nucleation has ended, the liquid product is an *equilibrium freeze concentrate*. By removing more heat through a cold shelf, *the equilibrium freeze concentrate* continues to grow ice crystals. Once all the available water has frozen, it becomes a *maximal freeze concentrate.* The *maximal freeze concentrate* must be reduced in temperature below the Tg’ (Tg prime) or “glass transition” temperature of the product, permitting the primary drying phase. **Fig 1**

Fig 1



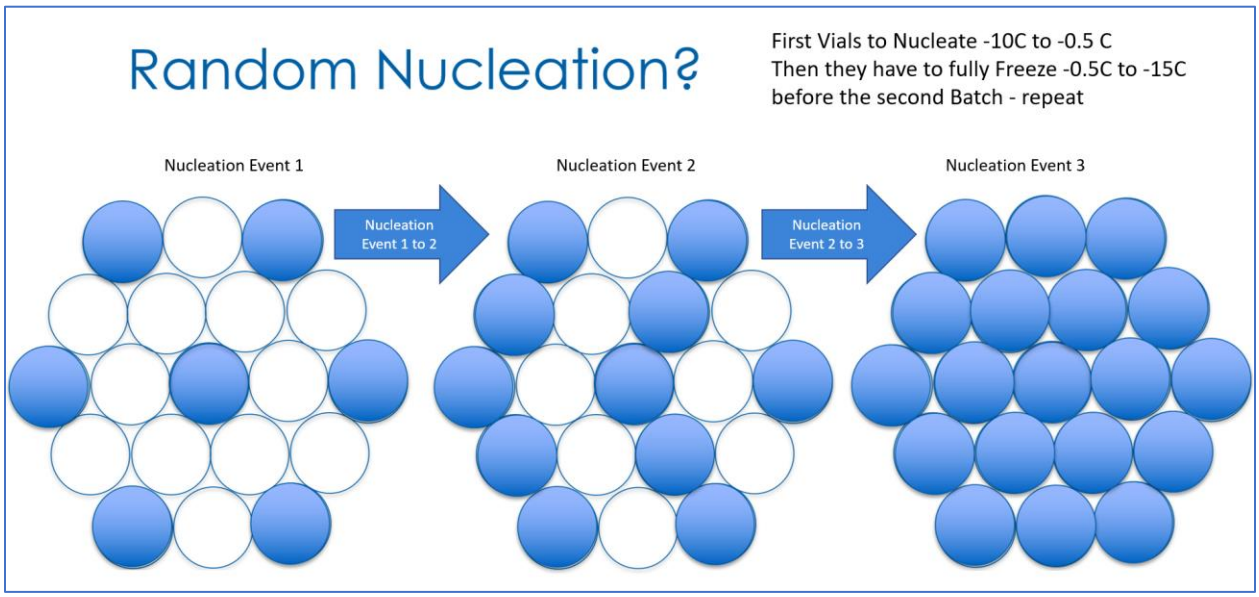
A typical freezing cycle will reduce the shelf temperature at a ramp rate. The cooling shelf reduces the temperature of the vials. The liquid in the vials will super-cool to temperatures between -5C and -20C or lower before any of the vials nucleate.

Ice formation in water is an exothermic event. When the product in a vial nucleates, the vial temperature increases until the temperature reaches about 0 C. The temperature in the vial will remain close to the same as heat is removed by the shelf. Ice formation proceeds from the bottom of the vial to the top. Once all the available water has formed ice, the temperature of the product can start to reduce and then it becomes solidified as a *maximal freeze concentrate*. **Fig 1**

In freeze-drying, vials are closely packed together which creates inter-vial heat transfer dynamics. When one vial nucleates and increases in temperature it inhibits all of the vials in contact with it from nucleating by increasing their temperature. All of the available water in the first nucleated vial must form ice before it can reduce in temperature. Then as it reduces in temperature the neighboring vials will have more energy available to nucleate.

Is nucleation truly random? Perhaps which vial nucleates first is random, however, once initial vials nucleate, the ones around them are inhibited from nucleating. The process of vials becoming heat sources and inhibiting adjacent vials from nucleating can repeat itself four or five times during most freezing cycles. **Fig 2**

Fig 2



Some important points to note are:

- Only a fraction of the water forms ice during nucleation. It is a common misunderstanding that nucleation freezes all the available water. In fact, only about 10% of the water freezes during nucleation. Therefore nearly 90% of freezing takes place after nucleation.

- Fast freezing, by dropping the shelf temperature quickly, creates small ice crystals and results in longer primary drying processes. Small ice crystals are formed due to lower temperatures during the super-cooling phase and more energy being removed during the ice growth process giving the crystal lattice less time to form. The smaller ice crystals inhibit vapor from escaping the product, resulting in lower sublimation rates and higher product temperatures during primary drying.

In production environments, where there are very few nucleation sites, super cooling can result in super-cooled temperatures down to -18 degrees or more. When that happens, ice crystals are formed quickly, they are small and vapor inhibiting.

A slow freezing process creates larger ice crystals and results in shorter primary drying times. That translates into higher sublimation rates and lower product temperatures. If, however, fast freezing is required to avoid precipitation or changes in PH, then an annealing process can be used once the product is fully frozen. For example, annealing the product by taking it up to -15 or even -10 degrees, held for 3 hours and allowing ice crystals to expand and grow from that point, thereby creating a more porous structure for the primary drying process.

In the graph (fig 3.) there are some unique and interesting events: The shelf set points are in gray and the actual shelf temperature is in yellow. The shelf surface temperature is in blue and the green line is the temperature of the product. The temperature of the product will reduce until there is a nucleation event, at which point the product temperature average flattens out while all the nucleation and crystallization is taking place. After all the vials have crystallized, then, the maximal freeze concentrate reduces in temperature.

The red line shows the heat flow measurement of the process. The heat flow begins to drop until there's a nucleation event. This graph shows three nucleation events which are precipitous changes in the heat flux. The depth of the heat flow 'V' pattern is -2000 W/SqM. The greater the heat flow the smaller the ice crystals formed. In this case, the product is poorly frozen which will result in longer primary drying times. Simply slowing the shelf ramp rate from 1 C/min to 0.5C/min will improve the ice formation in the vials.

This batch shows three unique nucleation events, typically, batches have four, and sometimes five nucleation events. Looking at the last event, it has the highest heat flow and probably the lowest product temperature. The last vial to nucleate will take the longest time to dry. Hence the saying, "the primary drying process is only as fast as the worst frozen vial."

During a standard freezing cycle where the shelf temperature is ramped down the vials across the batch will form different ice structures and since the heat flow is changing during the ice formation the ice structure intra-vial will also be non-uniform.

To overcome the problem of vials having different crystal structures, methods for *forced* nucleation or "controlled nucleation" can be used. Millrock Technology offers the Freeze Booster® nucleation station which injects ice fog and ice crystals into the chamber and into the vial to promote nucleation **Fig 4**

Fig 3

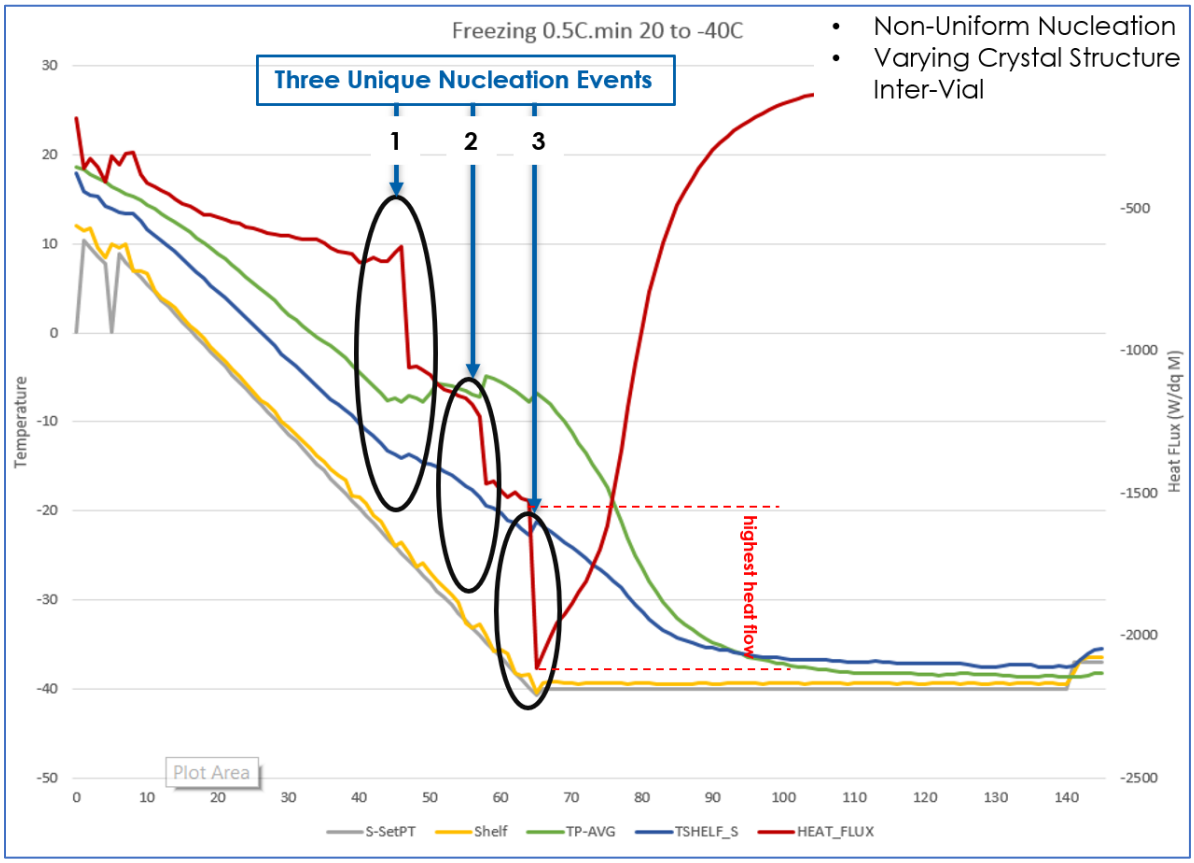

Freezing 0.5C.min 20 to -40C
Three Unique Nucleation Events
1
2
3
• Non-Uniform Nucleation
• Varying Crystal Structure Inter-Vial
highest heat flow
Temperature
Heat FLux (W/dq M)
Plot Area
S-SetPT
Shelf
TP-AVG
TSHELF_S
HEAT_FLUX

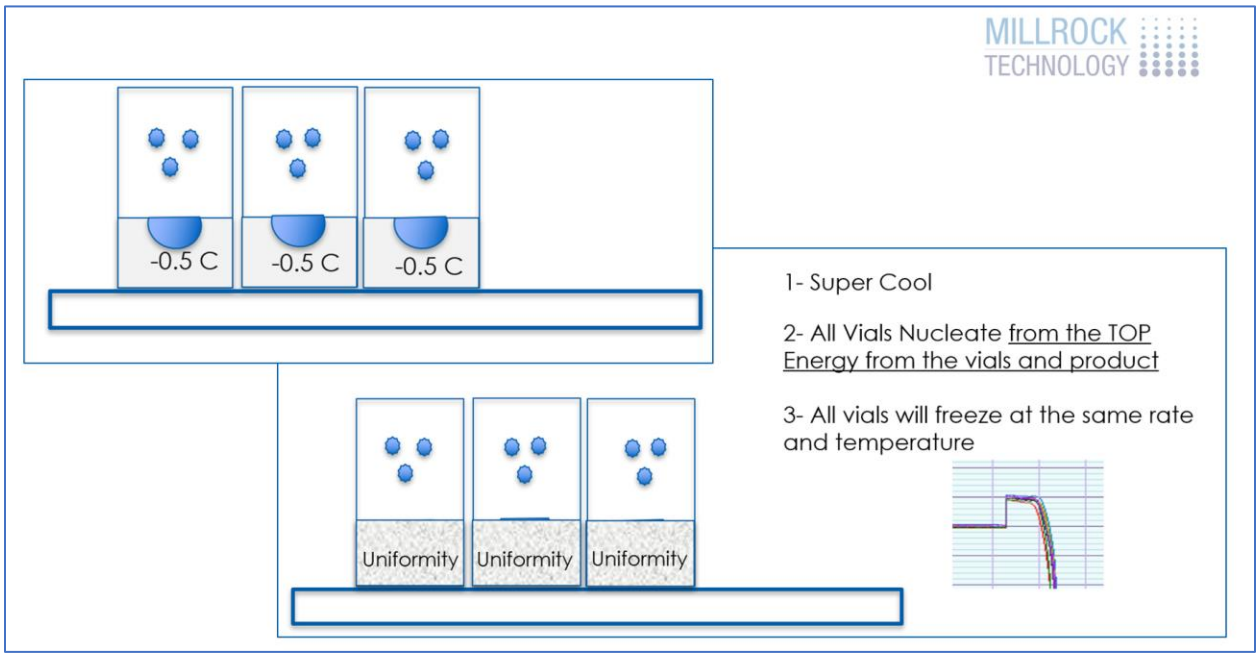
Fig 4


FreezeBooster® Modules
Ice Fog Injection Systems
MILLROCK TECHNOLOGY
Nucleation Station
Controlled Nucleation
FreezeBooster®
Patents: 8839528/8875413

Millrock Technology's FreezeBooster® nucleation station solves the issue by super-cooling the product temperature at -5 degrees, allowing the product to stabilize, and then introduces ice crystals into the product. The ice crystals introduced by the FreezeBooster® nucleation station produces nucleation sites and the ice formation begins. In contrast to random nucleation that happens from the bottom, going up, this controlled method of nucleation progresses from the top-down. **Fig 5**

Employing controlled nucleation forces the vials to nucleate at same time and temperature which results in a very uniform structure throughout the batch. This establishes a very good basis for primary drying. In some cases, this will reduce primary drying times. However, in cases where there is a small fill or a very high solid content, controlled nucleation will not shorten the primary drying time. The most important thing about control nucleation, however, is that it results in consistency across the batch, which improves the quality of the product.

Fig 5



If you would like to learn more about Millrock Technology's FreezeBooster® nucleation station, please give us a call and we will be happy to offer insight and consultation relevant to your specific product and freeze-drying processing requirements.

Millrock Technology is always looking to provide new innovations to the pharmaceutical freeze-drying industry. As an innovator, Millrock Technology listens to the needs of the market, while providing value in our product line. We offer cutting-edge technologies and optimized methods of pharmaceutical freeze drying. Millrock Technology, Inc. manufactures robust and dependable freeze dryers, customized for the pharmaceutical /biotech marketplace. We focus on one technology and one market to best satisfy our customers' needs.

MILLROCK TECHNOLOGY

39 Kieffer Lane
Kingston, NY 12401

Phone: **1-845-339-5700**
Fax: **845-339-7557**
Email:
sales@millrocktech.com
service@millrocktech.com