Freezing, The Foundation for a Robust Freeze-Drying Cycle
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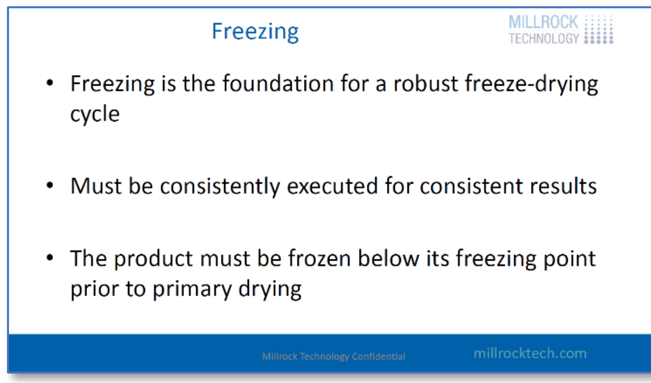
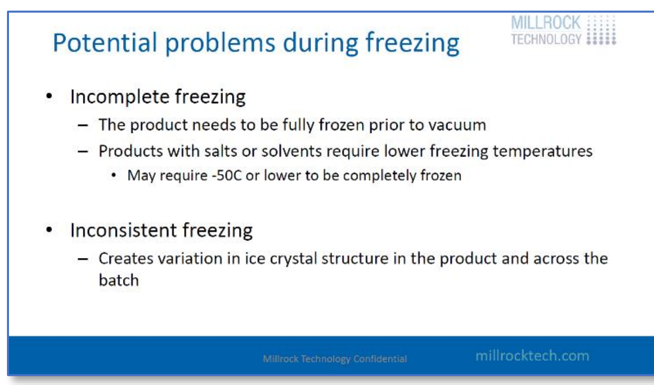
Freezing is the foundation for a robust freeze-drying cycle. It must be performed consistently to get consistent results in the freeze-drying process.

The product must be frozen below its freezing point prior to primary drying. If it's not, it's going to cause problems with the process. So, you have to fully understand not only the freezing point, but how long it takes your product to freeze. The thicker the product, for example, the longer it's going to take.

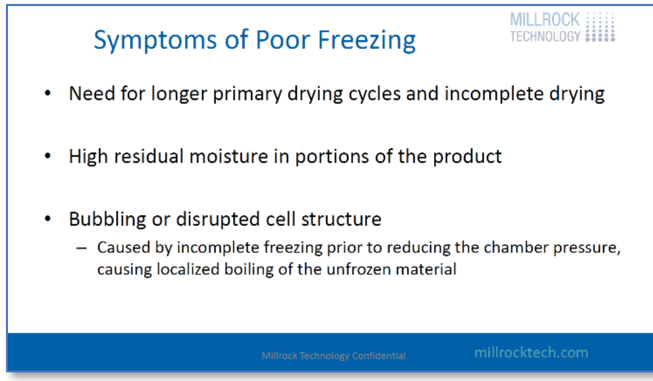


What are the potential problems during freezing? The first is incomplete freezing. Since the product needs to be fully frozen prior to pulling a vacuum on it, it's very important that you understand that your product, number one, is frozen, and it's been frozen long enough that all of the product is frozen. For example, if you have a thick material, that can take a very long time to freeze, and it's important to understand that all of your product is frozen. Inconsistent freezing is another problem. Inconsistent freezing can create variations in ice crystal structure in the product and across the batch, which results in variation to the process.

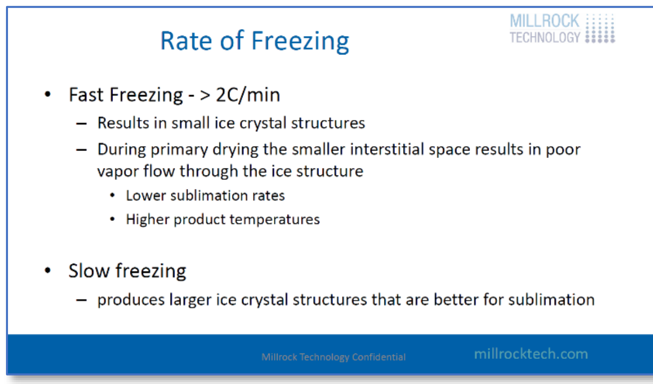


So, when I say inconsistent freezing, what does that mean? That means that sometimes it's frozen at one degree C per minute, sometimes it's frozen at five degrees C per minute, sometimes it's frozen to -15 instead of -30. That's going to lead to process variation, so it's highly recommended that you freeze in the freeze dryer when you can, and it is done at a controlled rate, so you get consistent ice crystal structures across your batch.

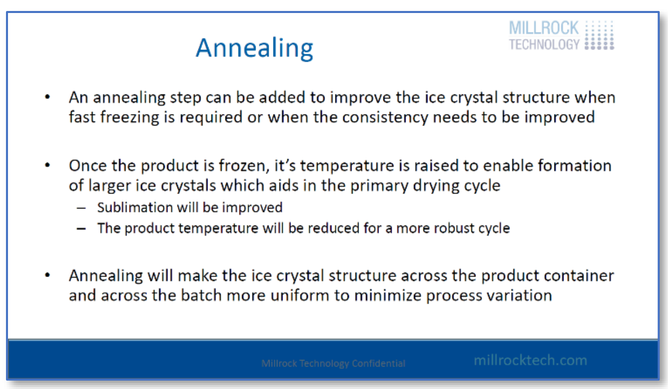
Symptoms of poor freezing. Poor freezing can lead to longer primary drying cycles and incomplete drying. Can result in higher residual moisture content at the end of the freeze-drying run, and if you have a batch product or a bulk product, that can result in just portions of your product having high residual moisture. Can also lead to bubbling or disrupted cell structures, which is caused by the incomplete freezing process, and once you start to reduce the chamber pressure, you can get localized boiling of the unfroze material causing problems. So, how does the rate of freezing affect the process? It actually has a very big impact on it.



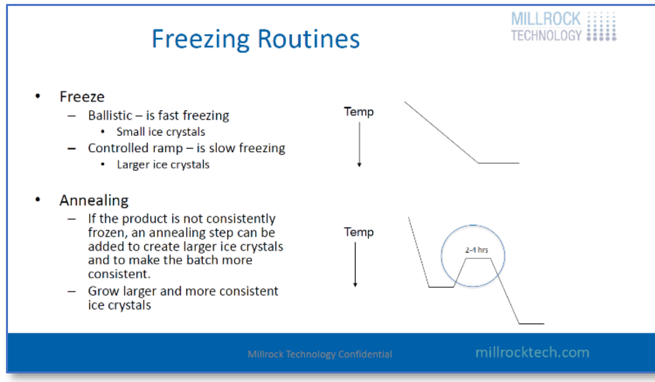
First, we'll discuss fast freezing. Now, fast freezing for this discussion is going to be anything greater than two degrees C per minute. Typically, a ballistic freeze would be something like if you put your product into a freezer and just let it get cold as fast as possible. Number one, that's uncontrolled, and number two, is probably a rate faster than two degrees C per minute. Fast freezing results in small ice crystal structures. What does that mean? Well, it means that during the primary drying cycle when sublimation is going to occur, there's a smaller interstitial space between the molecules between the ice crystals, and that results in poor vapor flow through the ice structure. So, it actually inhibits or hampers the sublimation process. So, it's going to lead to lower sublimation rates, and ultimately higher product temperatures because the vapor can't escape as you're adding heat, then the sublimation rates lower and it leads to an increased product temperature. Slow freezing, on the other hand, we'll consider that anything two degrees C per minute or less, produces larger ice crystal structures that are better for sublimation. So, it's important to understand and control that freezing process.



There's an ability in your freezing process to actually overcome any process variation, and that's called annealing. Annealing is the process where we increase the product temperature after it's been frozen to a higher temperature, let's say, -20 or -15 degrees, hold it there for a period of time, depending on your product, might be one to three hours, for example, and that allows the ice crystals to grow in size and to make it actually more consistent across the batch. So, if you've got variation inside your product, annealing will actually make it more consistent. And then if you have multiple trays or multiple vials, it'll actually make it more consistent across the batch.



So once the product's frozen, the temperature's raised, larger ice crystals are created, and then it's going to enable an improved sublimation rate. And it's also going to protect the product better, because the product temperature's going to be reduced during the primary drying cycle. So, the annealing will make the ice crystal structure across the product container more consistent, and across the batch more consistent.



So, let's take a look at freezing routines. The first is just what we'll call freezing. If it's ballistic, which means it’s at a fast freezing rate, you're going to create small ice crystals. If it's controlled and ramped, then we're going to get larger ice crystals. So, we've got a time down to temperature, and then we get down to temperature and we hold. If our freezing process is inconsistent or needs improvement, we can always add the annealing step where we have a ramp rate down to a temperature hold for a period of time, raise the temperature of the product to let's say -20, -15, hold it for a period of time, and then freeze it again before we go into primary drying. This is going to grow larger ice crystals, and it's going to make them more consistent.