Considerations for Bulk Freeze Drying
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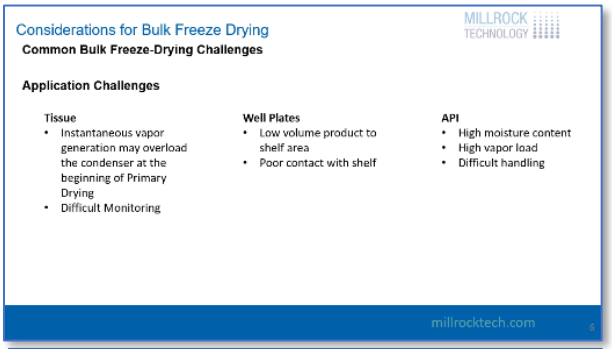
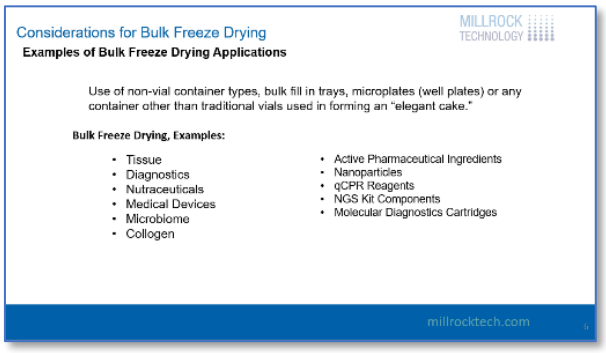
Today's presentation, "Considerations for Bulk Freeze Drying" will include a discussion about a few processing challenges and remedies. We will discuss some common freeze drying challenges, the handling of bulk material, pre and post freeze drying and the freeze drying process itself. We'll also talk about a few of the available technologies that benefit bulk freeze drying. We will also showcase one Millrock Technology freeze dryer that is often a good candidate for a bulk freeze drying process.



When people think of bulk freeze drying, they often think of material that is processed in a bulk tray, usually a liquid fill, and they tend to not think of other applications that are often considered as a bulk freeze drying application such as a micro plates tissue applications, or in general, any container that other than a traditional vial that is typically used in forming an elegant cake. So, there are many applications that are considered bulk freeze drying applications. It's just a matter of people's perception and definition.

A few of the different applications of bulk freeze drying are, for example, tissue diagnostic kits, nutraceuticals, medical devices, microbiome, collagen, active pharmaceutical ingredients or APIs, nanoparticles, qPCR reagents, NGS kits, components, molecular and diagnostics cartridges. Each of these applications tend to come with its own unique challenges. Not all of them can be completely addressed by adjusting or changing the freeze dryer or the container type, or

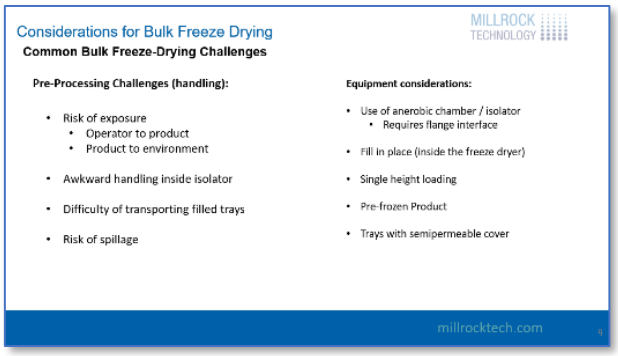


by applying a specific technology. However, many of them could be, at the very least, improved by implementing one or more of technologies or options available on the pharmaceutical / life-sciences grade freeze dryers.

Speaking about some of the application challenges, not necessarily to a specific piece of technology or a specific way that a freeze dryer is equipped, one of the big categories that is considered a bulk freeze drying category is tissue. A main challenge that we see with tissue is the instantaneous vapor generation that may overload a condenser at the beginning of freeze drying. Also, we run into a challenge of the difficulty of monitoring the product during the freeze drying cycle.

Those are issues that we'll talk about later and discuss what technologies are available to help remedy these scenarios and how to get around those challenges. Another application that can be a little bit of a challenge is well plates. These typically hold low volume of products compared to the shelf area. So, they really have a low throughput when we talk about volume compared to other applications like APIs, for example. They also tend to have poor contact with the shelf, which does not allow very efficient heat transfer, which comes with its own challenges that we'll address later in this webinar.

And of course, we can't talk about bulk freeze drying without mentioning APIs. These are typically liquid fills. The challenges are around high moisture content, high vapor load and difficult handling of those products.



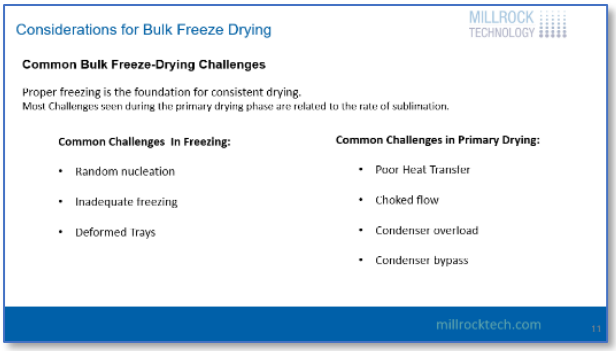
Before we even get into the freeze drying process, we must talk about the handling of the materials. The handling of the bulk materials sometimes comes with its own challenges. For example, pre-processing challenges could include one of the risks of exposure, the operator to the product or the product to the environment around it. Many of the products that are processed as a bulk are typically either sensitive to oxygen, for example, or to just the general environment around it, or they could be toxic and could harm the operators if exposed.

There are things that we could do at about that, for example, most of these are handled inside of isolators or inside of an aerobic chamber, which kind of link to more challenges. For example, the awkward handling inside of an isolator. We all, or many of us know how difficult it is to move trays around within a glove box or inside of an aerobic chamber. Also, once the trays are filled, they become typically heavy especially with APIs and moving them around isn't necessarily easy. And this gets worse as the trays, or the amount of material gets larger. We also increase the risk of spillage. Materials can spill either during filling, transporting, or even loading onto the freeze dryer itself.

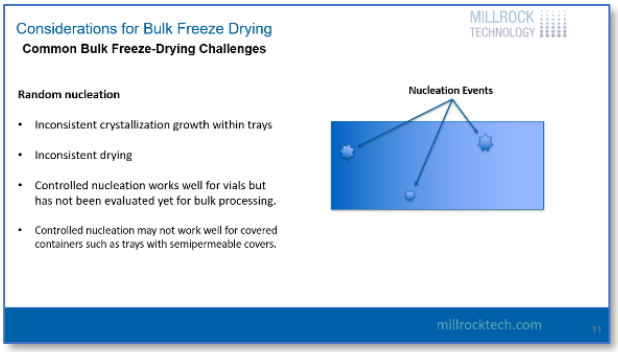
A few things that we could do to remedy these challenges regarding equipment is the use of anaerobic chambers and isolators. Typically, we want to consider a freeze dryer that has an isolator interface or flange. This is usually a smooth surface that allows to connect to the isolator and create a seal from the outside environment. Another thing that we could do to reduce the risk of handling challenges is filling trays in place.

Often with APIs, what a lot of people will do is will load empty trays on the shelves of the freeze dryer, pull them off the shelf partially, fill in the material and then push them back in. This will help minimize the amount of transportation and minimize the movement, especially when there's a liquid slashing around, thereby reducing the risk of spillage. Another thing that people can look at, and this is an option typically on production machines, is single height loading. Some freeze dryers can be equipped with what's called a “single height loading door” with shelves that move to a specific position at that single height, allowing the ergonomics to take over making conditions a little easier on the operator, where they do not have to reach for top shelves, that could be high especially with production systems.

Another approach that is typically seen is pre-frozen product, where people would freeze the product in containers outside of the system, and then bring those in pre-frozen so they don't have to deal with the liquid material. Another remedy is to use trays with semipermeable covers. Those types of trays, even though they tend to reduce the amount of sloshing around, are not really perfect. Just like many remedies, it's not perfect, but it does help. Semipermeable covers do have multiple benefits especially when we're talking about “flyaways” and avoiding the materials coming out of those trays. Those are a few of the challenges that are seen during the handling phase, and this applies really on the loading or even the unloading after the freeze drying cycle is done.



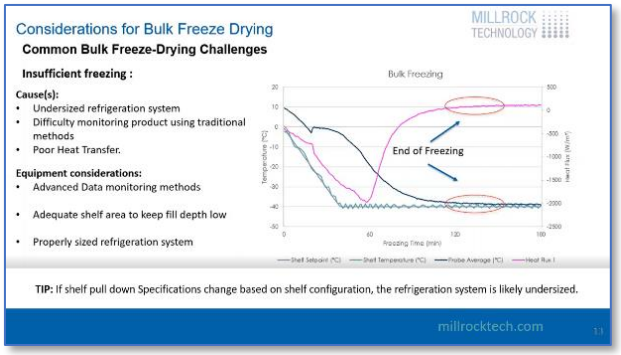
Now that we talked about the pre-processing and post-processing, we can go right into the freeze drying process itself, and what challenges that we can encounter during that process. It is important to talk about the challenges that are seen in all phases of the freeze drying cycle, primary drying and freezing phase included because the freezing phase is typically the foundation for primary drying, and proper freezing is the foundation for consistent drying. When we're talking about the primary drying challenges, most of those are typically attributed to the rate of sublimation in one way or another. Usually, with bulk applications, the issue is the high amount of vapor generation that's happening during the primary drying cycle. Some of the common challenges that we see in freezing are random nucleation, inadequate freezing, and deformed trays. Some of the challenges that we see during primary drying are poor heat transfer, choked flow, condenser overload, and condenser bypass. While not every single one of these issues may be resolved to a hundred percent satisfaction, at least we can often greatly improve in one way or another on them and reduce the risk for each of the challenges.



Starting with the freezing challenges, we can start with random nucleation. With bulk trays, this is typically a problem with liquid fills. It's not typically a problem with, for example, tissue applications or such. Random nucleation is when multiple nucleation sites occur within a tray. What this causes, usually, is an inconsistent crystallization in crystal growth within the tray, which would lead to a different size

crystals, leading in turn to inconsistent drying throughout the trays. Within the tray, therefore, differences in the crystal sizes may lead to problems, or at least if not problems, inconsistencies.

With vial applications, typically people talk about controlled nucleation as a method to try to reduce the effect of random nucleation. However, in bulk freeze drying, this is not very well studied. There aren't many studies that have been done on bulk freeze drying in trays with controlled nucleation. That is not to say that it does not work. There have been people who have used it in a past. It has its own challenges and limitations. For example, controlled nucleation may not work for covered containers or with semipermeable covers very well. This is usually because the container barriers prevent the controlled nucleation method from reaching the product itself. For example, if we're talking about fog controlled nucleation or the "ice fog controlled method", if you have a semipermeable cover, it prevents the ice fog from getting into the product, which would force nucleation.



Another big issue that we tend to see when we're talking to people about freezing bulk material is insufficient freezing. Insufficient freezing is very common when materials are very thick and the fill depth is high. This could cause major problems during primary drying such as collapsed product and condenser and vacuum overloads. The causes of such a problem are typically an undersized refrigeration system and difficulty monitoring the product using traditional methods and heat transfer. People typically don't know whether their product is fully frozen or not, and of course, poor heat transfer. And that could occur for many reasons such as the trays themselves or the product geometry.

Some of the equipment considerations that we have when we're looking at bulk applications to try to at least prevent as much as possible of the insufficient freezing is advanced data monitoring. You could look at, for example, the heat flux data if available on your equipment, or if you are specifying new equipment, this is something that you could request to have on your freeze dryer. This could enable you to use that data to be able to distinguish the end of freezing. For example, if the heat flux goes to zero that there's basically minimal heat transferred between the shelf and product. And that would tell you, this is the end of the freezing phase. When possible, for some of the applications you could use thermal couple data to detect end of freezing. When that is possible, you could monitor the product temperature and when that product temperature reaches the shelf temperature that would typically be considered the end of freezing. Unfortunately, both these methods sometimes could be limited due to the application itself, especially when we're talking about a commercial scale where you are unable to put product probes in your product for monitoring. In that case you may have to just rely on the predetermined cycle that you've developed, to ensure that you have sufficient freezing time. Another thing that we could do while we're specifying a freeze dryer is making sure that we have adequate shelf area to keep the fill depth low.

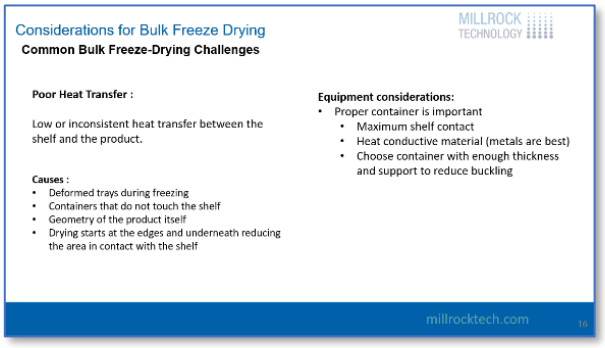
As mentioned earlier, this issue is typically when the fill depth is very high. A standard way of looking at it is keeping the fill depth somewhere between a half inch and an inch. An inch is even often considered on the very high end of where you want to be. So, if you have your tray and you're filling the tray to an

inch and a half or two inches, you're probably going to start seeing issues and inconsistencies in freezing, and you could run the risk of insufficient freezing during your freeze drying cycle. A properly sized refrigeration system is an absolute must when we are talk about freezing. The largest load, the refrigeration system will see is typically during the shelf pull down while you are trying to freeze your product, pulling down from let's say room temperature to your final freezing points.

That is the largest load on the refrigeration system. An undersized refrigeration system will either be unable to keep up with the ramping rate that you have specified, or you will not be able to reach the bottom temperature and maintain that temperature sustainably for freezing to occur consistently. A very good tip to use when you are looking at a freeze dryer, to figure out that your system is going to be capable of freezing is looking at the shelf ramp rates. Typically, that is specified between room temperature and minus 40. Some manufacturers may choose different specs, but the idea is the same.

Be very careful when you're reading the specifications. If you see that the specifications are done, for example, on a five shelf unit, and then there are specification exceptions in the footer indicating that the ramp rate will decrease based on the number of shelves. This is a tell sign that the refrigeration system might be undersized. This is because if you increase the number of shelves, you're going to have an insufficient ramp rate that would lead to problems later. This is a sign that you could watch out for when you're looking at equipment specifications.

Another issue that we see during freezing is deformed trays. Freezing can apply a lot of stress on trays while you are processing the material in them. And if you have thin trays, those thin trays may tend to buckle and become deformed during freezing. And here you could see in this picture, we have two trays on two shelves. One has a thinner bottom, which would, after a while during freezing, buckle up and lose contact with the shelf. You can see the difference between the top tray and the bottom tray here with the gap between the tray and the shelf. This can result in poor shelf contact, which leads to poor heat transfer in primary drying, and further problems down the road. Typically, a larger tray is more prone to deformation than a smaller tray, and a thinner tray is more prone to the formation than a thicker tray. So, it is important to choose your container with enough bottom thickness and support material to reduce buckling and deformation.



Poor heat transfer is an issue that can be seen in both freezing and primary drying. It's typically not as much of an issue during freezing because in most scenarios you are processing at near atmosphere, or what's often referred to as a door seal pressure. At that level you still have a little bit of convection going on. So, heat transfer tends to still occur no matter what you're doing, even

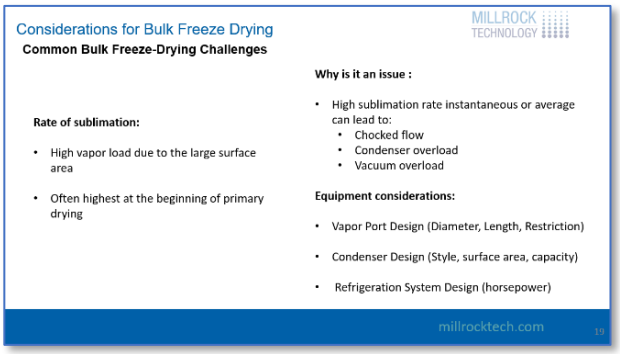
though the freezing phase could extend, but it's not as significant as in primary drying.

In primary drying, poor heat transfer due to any factor could be a problem. Some of the causes for poor heat transfer is deformed trays. Like we mentioned earlier, if you have a tray that is not touching the shelf, you're not going to have sufficient, consistent heat transfer between the product and the shelf. You could have containers that do not touch the shelf to begin with. For example, a lot of well plates applications tend to rely on radiant heat, which is really an inconsistent source of heat transfer and thermal energy that could cause problems run to run because of that inconsistency. Sometimes it's the geometry of the product itself, especially in tissue applications.

Think of a bone, if it's not ground to basically a powder form, it's going to have very limited amount of contact with the shelf. Also, another cause for the poor heat transfer could be related to the drying dynamics themselves. In an API application where you have a liquid fill, drying tends to start around the edges and underneath the product eventually limiting and reducing the surface area available for sublimation throughout the primary drying cycle. This all contributes to reduced sublimation rates, and due to the poor heat transfer or the inconsistent heat transfer throughout the cycle. What can we do about this? We can't do a whole lot. Sometimes it's a matter of fact that this is going to happen.

However, a proper container is an absolute must. So, it's important to specify the proper container from the beginning to avoid these issues. Look for a maximum shelf contact such as trays, typically metal. if you are choosing materials other than metal materials, heat conductivity might be a problem. Those are out there, and some people use them. Also, choose a container with enough thickness and support to reduce buckling, to avoid any problems down the road.

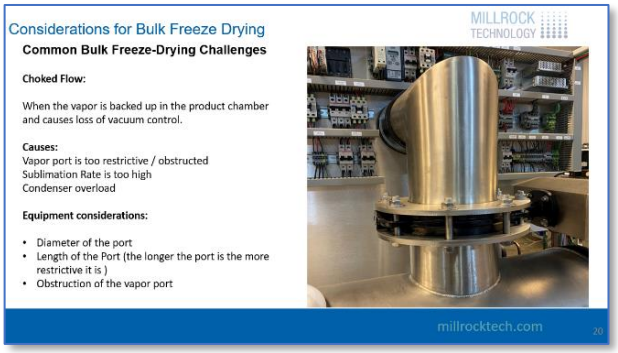
We have talked enough about freezing, let's get into primary drying. And this is typically where everybody wants to hear about issues, and what to eliminate, and what to do about it.



Most of the issues seen during primary drying for bulk applications are related to a high rate of sublimation especially in applications such as API and tissue applications. Bulk processing is a very demanding process in terms of condensing capacity due to large surface area of the product, which leads to a high rate of sublimation that could lead to issues or at least challenges down the road. So, with the rate of sublimation, with that surface area being very high includes many of the applications. API and tissue are especially important here. At the very beginning of primary drying, we could see a much higher rate of sublimation, and that could lead to issues such as choked flow, condenser overload, and condenser bypass.

Some of the things that we could look at, and we will discuss these in a little bit more details in the upcoming slides are going to be the vapor port design to make sure that we don't have any restrictions that would lead to choked flow. The condenser design, the style, the surface area, and the capacity of the condenser to make sure that we can condense all the vapors coming out of the product. And as mentioned earlier, the refrigeration system design, the horsepower of it and making sure that it is adequately sized for the application.

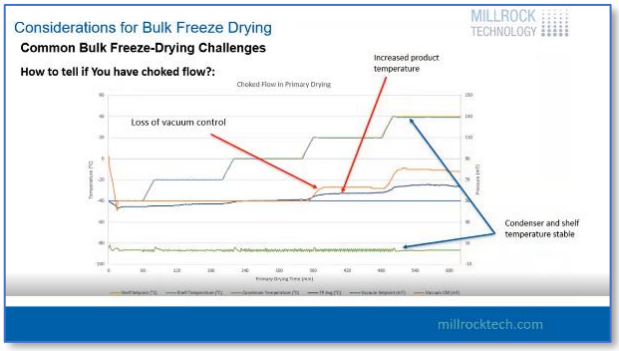
To start, we're going to talk about choked flow. Choked flow is when the vapor is backed up in a product chamber and it causes loss of vacuum control. Typically, the vapors pass from the product chamber into the condensing chamber through what is referred to as the vapor port. The vapor ports allows those vapors to go through, and it should allow them to go through fairly quickly. Vapors typically travel at the speed of sound between the two chambers due to the large differential in pressure. And if that vapor port is too restrictive, vapors tend to get backed up into the product chamber, and vacuum control at that point is lost, and that will introduce problems in the cycle. Some of the causes for such an issue are going to be a vapor port that is too restrictive or obstructed, a sublimation rate that is too high for the vapor port size or a condenser overload condition where the condenser is unable to handle all the vapors coming through the vapor port itself.



It is important, therefore, when you are specifying a freeze dryer to look at the vapor port size, and by size I mean both the diameter and the length. Just the diameter is not really enough because the longer the vapor port, the more restrictive it is going to be even if the vapor port diameter is efficient on a different machine that has a shorter vapor path. And be mindful of any obstructions of the vapor port, for example, instrumentation that can be installed on the vapor port itself. In the picture here, you see an isolation valve that is typically used to isolate the condenser chamber from the product chamber in case of a failure, a power outage or during condense defrost or after the cycle was complete, and just trying to isolate the two chambers from each other.

You could, for example, think of an isolation valve that is undersized for that vapor port and that could cause a restriction. Sometimes instrumentation could be installed that would lead to extending the vapor path or reducing the diameter of the port. Both circumstances could lead to choked flow problems.

What does choked flow look like? This is a cycle that we ran to force the system into choked flow by increasing the sublimation rate using with the shelf temperature over, until we hit the choked flow. Typically, the first sign you would see is loss of vacuum control. You would notice that the pressure inside of the product chamber goes up and typically it settles at what's referred to as a minimum controllable pressure.



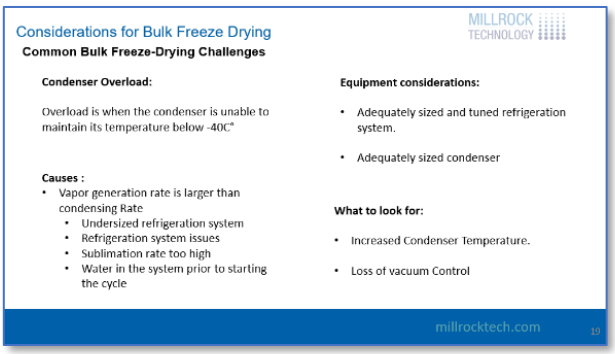
This is limited by how much the condenser can condense or the condensing rate to the condenser to remove the vapors. For example, here we have the vacuum set point and the pressure starts with controlling at that set point until we start increasing the product temperature. And when we increase the product temperature to a point where the sublimation rate is high enough, and the vapor port is unable to pass all that vapor to the condenser, the vapors start to accumulate inside of the product chamber, and the pressure goes up. Typically, the product temperature is also going to go up with the

pressure because pressure and temperature are correlated. And as a result, the product might either melt or collapse depending on where you are in your design space.

The condenser and shelf temperatures tend to be stable if the choked flow is an isolated event not triggered by a shelf control issue where a condenser overload problem to begin with. So, if those do not exist, then the condenser temperature tends to be still stable, and the end of shelf temperature tends to be stable as well.

We talked about the vapor path to the condenser, and now we're going to talk about the condenser itself. One of the most common failure modes for a condenser is a condenser overload. This happens when the condenser is unable to maintain its temperature, typically overload temperature is considered at minus 40 degree C.

Most condensers need to be somewhere between the minus 50 and the minus 85 degree C for the process to be stable, depending on the application of course, and what temperatures are needed to condense the vapors coming at out, whether you have solvents, whether you have only water vapor, the condenser temperature may need to be lower. Typically, in an aqueous solution minus 50 is just fine. A minus 85 will give you a little bit more room, and buffer, and capacity to handle a little bit of a larger vapor load, but it's not an absolute necessity. So, if a condenser hits a minus 40, then that's considered an overload condition because at that point, the vapors are no longer depositing efficiently on the condenser coils. And at that point we could run into either, again, a choked flow situation or worse yet, we could bypass the condenser altogether, and those vapors would go into vacuum pump, which would be considered a condenser bypass we'll talk about in just a few seconds.

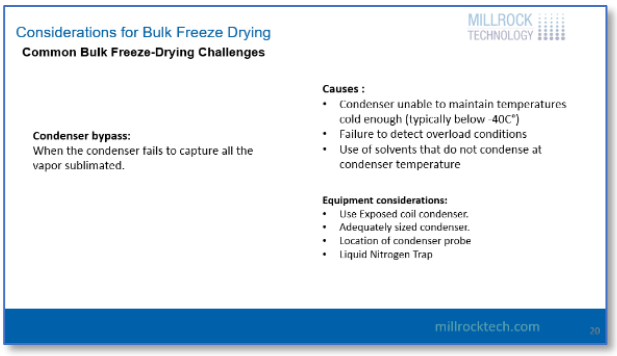


What causes a condenser overload? Typically, a vapor generation rate that is larger than the condensing rate. So, when we're looking at sizing a condenser for a freeze dryer, the condensing rate or the maximum condensing rate through a cycle needs to be considered, and the condensing rate of the condenser needs to be higher than that highest sublimation rate. An undersized refrigeration system could also be a reason when the condenser is unable to maintain its temperature because the refrigeration system doesn't have the capacity. The temperature starts to go up, and you could hit the condenser overload conditions quickly. Refrigeration issues sometimes could cause that. It is important to follow through your maintenance programs and preventative maintenance programs to prevent any refrigeration system problems prior to them happening.

As mentioned previously, the sublimation rate could be too high and that could cause an issue. Another common cause is water in the system prior to starting the cycle. Often people either forget to defrost condensers, or if there's a spillage through at the time of loading the system, that water sits at the bottom of a product chamber or the bottom of a condenser and during primary drying, it starts to evaporate due to the vacuum levels. When it evaporates, it hits the condenser with a very large load and all of a sudden, you'll run into a condenser overload situation. So, what we can do, equipment wise, to help remedy an overload condition is adequately size and tune our refrigeration system and adequately size a condenser so it can handle all the vapors coming out of the products.

What to look for when we're watching out for a condenser overload is going to be an increased condenser temperature and loss of vacuum control. So like choked flow, we saw loss of vacuum control and the pressure increased to the minimum controllable pressure. Here we would see the same thing. You are likely to see loss of vacuum control as well as the obvious one, which is an increase of temperature on the condenser side.

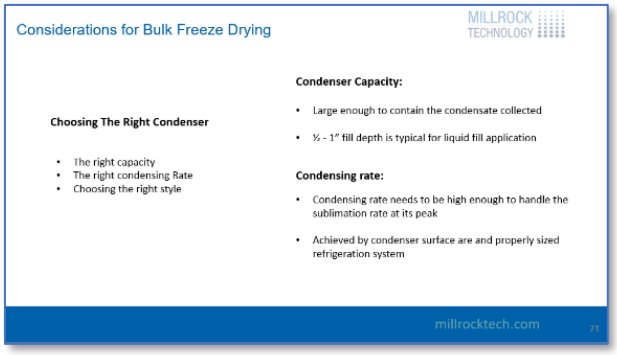
Next, we're going to talk about condenser bypass. This is when the condenser fails to capture all the vapor sublimated. Typically, this is caused by a condenser overload condition that the system did not react properly to.



Most systems will detect that overload condition being the condenser, getting to a minus 40 or above, and react to that condition by slowing down the sublimation. Different manufacturers do it differently. For example, they could rephrase the shelves or recall the shelves so that the sublimation rate slows down. You could also reduce the pressure inside of the product chamber to slow down the sublimation as well if possible. Sometimes it's not possible because you don't want the vapors to bypass the condenser. So, you would shut off the vacuum pump to begin with.

Another common cause is the use of solvents that do not condense at condenser temperatures. If you have solvents that do not condense at minus 50, and your unit is expected to have a minus 50 condenser temperature, then those are going to stay in either the liquid or vapor phase. And then they would bypass the condenser, and would go right to the vacuum pumps, and solvents could be very bad for vacuum pumps. Typically, with solvents, most people tend to use a dry vacuum pump. They are a little bit better, but that is not to say they are tolerant of solvents. They could still be harmed by solvents. So, what we can do about the equipment to reduce the risk of condenser bypass is use an exposed coil condenser. This is a style of condenser. We'll talk about it in just a few minutes. And adequately size the condenser to handle the vapor load, and location of the condenser probe.

On condensers, different manufacturers place the probes differently depending on the style of that condenser. And if the probe is unable to accurately detect overload conditions, then the vapors could bypass that condenser and go into vacuum pumps. Another option, and this is commonly used with solvents, is using liquid nitrogen traps. A liquid nitrogen trap tends to have a much lower temperature than most standard condensers. And that would allow the capture any of the solvents or vapors of materials that do not condense at standard temperatures of the condenser.



We talked a lot about vapor, the vapor path, and the generation of the vapor through the sublimation process. How do we choose a right condenser? What to look for? We should be looking at the right capacity volume wise, the volume of the condenser needs to be sufficient.

The right condensing rate, and the right style condenser. The condenser capacity needs to be basically large enough to contain the condensate collected.

As mentioned at the very beginning of the presentation, a half inch to one inch fill depth is typical for a liquid fill application. So, you would calculate based on the volume of product placed on the shelf, the amount of liquid that's going to be sublimated and then deposited into the condenser, and then you would need a condenser capacity that is equal or larger than that amount.

The condensing rate needs to be high enough to handle the sublimation rate at its peak. This is typically achieved by the condenser surface area and a properly sized refrigeration system. Typically, most condensers have a surface area that is sized to hold the liquid that is collected during the sublimation process. And when it's condensed on that coil or in the condenser, you would look for about an inch to two inches thickness of ice buildup. And if the condenser surface area is sufficient for that, they typically tend to handle that amount of vapor well. It is important to still look at the exact numbers of what the system is rated for. Typically, they're rated in liters per hour, or a certain number of liters per 24 hour or something similar, in that matter.

Next, we will talk about the styles of the condenser. So, you got the condenser capacity right because you know how much product you're placing on the shelves. And you have the surface area and condensing rate because the product that you're processing is going to sublimate at the specific rate, and you got your condenser condensing rates equal or higher to that amount. Now let's look at the different styles of condensers that could be used. The very first is the smooth wall condenser. These were used on old systems. They're not very popular these days. They have their own issues. For example, the surface area reduces as ice builds up. The ice deposits on the wall of the condenser.

So, when the ice is building up, you have a smaller cylinder where the vapors are being deposited, reducing the surface area, which means that you're reducing your condensing rates in capacity as the cycle progresses. Another challenge with this is that they have no actual temperature monitoring. They tend to have the temperature probes on the outside of the shell monitoring the coils that cool those shells. So, you're far from the point where the vapors are being deposited, and you could run into the risk of not detecting an overload condition like we mentioned before. And if you run into that, we know that at that point the vapors are going to bypass that condenser and get into vacuum pumps, which could harm them.

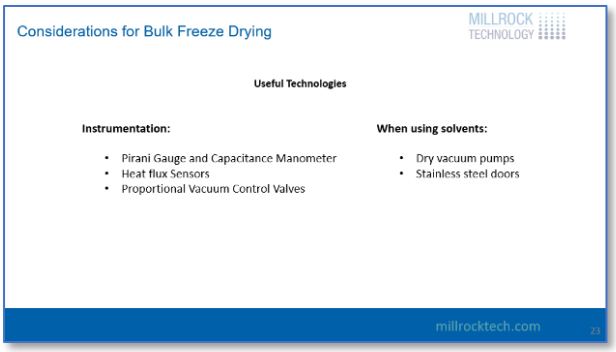
The second type of condensers is known to be an exposed coil condenser. This is considered typically the best type of condenser coil. The surface area tends to increase versus the smooth wall condenser, which decreases. This is because as ice builds up the surface area increases because it's a larger cylinder that you're looking at now, and allowing more surface area to come in. And the ice that accumulates on the coils themselves also acts as an insulator. And since it has basically the same temperature as those coils, it even improves the performance of the condenser as the cycle progresses. It is easy to detect

overload conditions with an exposed coil condenser because the probes can be put really close to the condensing surface.

Typically, you need to watch out whether some manufacturers put the probes on the inlet or the outlets of the condenser. If they are put on the outlet of the condenser, you could detect overload conditions fairly accurately. If they are on the inlet, then you're basically measuring the temperature before the deposition process occurs, which at that point, if there's an overload condition, you'll detect it fairly late if at all, at that point you run to the risk of bypassing the condenser.

With the exposed coil, there are two styles typically. There's an internal coil and an external coil. Here in the third picture the coils of the condenser are actually placed in the same chamber as the products. In this scenario, they are on either side of the shelf stack where the product would sit. An internal condenser does have advantages; however, it does have disadvantages to it as well. It has the highest throughput compared to any of the other types. It has no choked flow because there is no vapor port to go through to begin with. However, the downside is because you have this cold surface sitting next to these shelves that you are trying to heat up to drive sublimation, that cold surface could affect the temperature of the product.

These condensers could be placed in multiple locations. Some systems have them, like you see here in a picture, on the sides of the shelf stack. Some systems will have them underneath the shelf stack, under the bottom shelf, and some will have them in the back. Depending on where they are, they could affect the product temperature differently. Typically, if they are underneath the product, they would affect only the bottom shelf where you would notice the product on the bottom shelf dries differently. It extends the drying cycle for that shelf and the temperature of the product would be typically lower. So, these are the few considerations that we would take when we're looking at a system and choosing a system for a bulk application.



Next, we'll take a look at just a few of the technologies that are also considered when we are looking at specifying freeze dryers for a bulk application, even though these are not specific to a bulk application, they could be very, very useful. On the instrumentation side, we could use a Pirani Gauge and Capacitance Manometer. And the advantage here comes to a bulk application where bulk applications really do not have many technologies available for monitoring product. So, the Pirani Capacitance Manometers are two of the very few technologies available and therefore we should make use of them. Where they become that valuable is really to detect the end of primary drying.

Typically, the Pirani is a gauge that is affected by moisture, or the reading is affected by the moisture level in the surrounding environment while the Capacitance Manometer reads the absolute pressure. Therefore, during sublimation, there's vapor in the product chamber that affects the Pirani, but it doesn't affect the Capacitance Manometer, and therefore they would read differently. Once they converge, you know that the vapors are no longer in the chamber that sublimation has ceased. This is a very common way to be able to tell that sublimation has ended, and the primary drying is done. Heat flux sensors could be used to, like we mentioned earlier, detect end of freezing or even end of primary

drying just by looking at the level of heat flux throughout the cycle. When it goes to, or near zero that there's very minimal heat transfer, and the phase change from liquid to solid in the case of freezing or from solid to gas in the case of sublimation has also ceased. And because in a bulk application, we don't always have the ability to use thermocouples and many of the other instrumentations available for other applications. This could be of a very high value. Proportional vacuum control valves are also important. In bulk applications there's typically an issue of “flyaways” when we're processing in open bulk trays where the standard vacuum controls typically use, it's called a needle valve and an on off control. It lets backfill gas in and then stops it once the pressure is over the set point, and waits for it to drop down.

This creates a little bit of a rush of the backfill gas flying over the trays that would contribute to more flyaways per portion of vacuum control. Valves tend to not have that problem because instead of the on / off control, they have an orifice size that changes based on a signal that comes from the control system. And you have a very even nice slow flow of gas that eliminates the issue or reduces the issue of flyaways. Many of the bulk applications out there do use solvents. And for those applications, it is important to look at the system as a whole to make sure that all the materials of construction are compatible as well as the components that for example, the vacuum pumps are capable of handling the products itself.

For example, dry pumps are known to be better at handling solvents than rotary vein pumps or oil pumps. So, it is highly recommended if you use any product with solvents to use a dry pump as well as the materials of construction, for example, the doors are at least in the lab scale units, tend to be acrylic as a standard, opting for a stainless steel door is an absolute must if you are using solvents. A lot of bulk applications tend to use solvents, so that's probably a good choice.

We talked about a few things, so what I'll do next is pull up an example of a freeze dryer that could be suitable for a bulk application. Now, of course, every application is different and unique on its own. However, there are systems that you could look at and just highlight a few of the points that I would personally watch out for when I'm looking at a brochure of a system that I'm trying to select for a bulk process. So here we have a brochure. Of course, it's a Millrock Technology system. It's our Epic system. Things that I would be looking for are the things that are highlighted here. For example, we could look at the shelf area, making sure that the shelf area is sufficient for the amount of product we're placing on the shelves.

Again, keeping it between a half inch to a one inch is preferred. Look always at the condenser temperature, make sure that you have sufficient condenser temperature for your application. If you're looking at a minus 85 system, this is probably a good choice for a bulk application, especially. Look at the condenser capacity like we said. Make sure for example, here we have a 50 liter capacity on the condenser. This needs to be equal larger than what you are placing on the shelves. Condensing rate, for example, here we're looking at 40 liters in 24 hours. If you have a process that sublimates at a much

higher rate, this is probably not a good idea, but typically for this shelf area, most applications will not sublimate anywhere near this rate.

We're looking at the condenser style so we could tell here it's an exposed coil with an eight inch of vapor port. The compressors here are sizes at five horsepower. So that is something that you need to be looking at. We look at the Pirani Capacitance Manometer and proportional vacuum control options. Those can be important to use when we're looking at a bulk application. Another one here is the trays that are included with the system obviously. The size of the trays here is important because we have the shelf size we're looking here, per shelf.

That gives you an idea of how big the tray is, making sure that it is small enough where it's not running into the issue of buckling. It's not going to be heavy to transport, and ease of handling. So, this is just an example of the things that you would be looking for in a system.

This concludes the presentation for today. I'm hope that you have had a great benefit listening to this, and hopefully it helps you select your next freeze dryer.