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Technical Note

Manifold Freeze Dryers – An Overview of Their Use, Limitations and Some Helpful Hints

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Overview of Manifold Freeze Dryers

A manifold freeze dryer is often used as the entry equipment into freeze drying. Researchers who are looking for an active pharmaceutical ingredient or processing HPLC fractions often use a manifold freeze dryer during their initial steps in the lab. The decision to purchase this type of freeze dryer is typically based on criteria that incudes, but is not limited to:

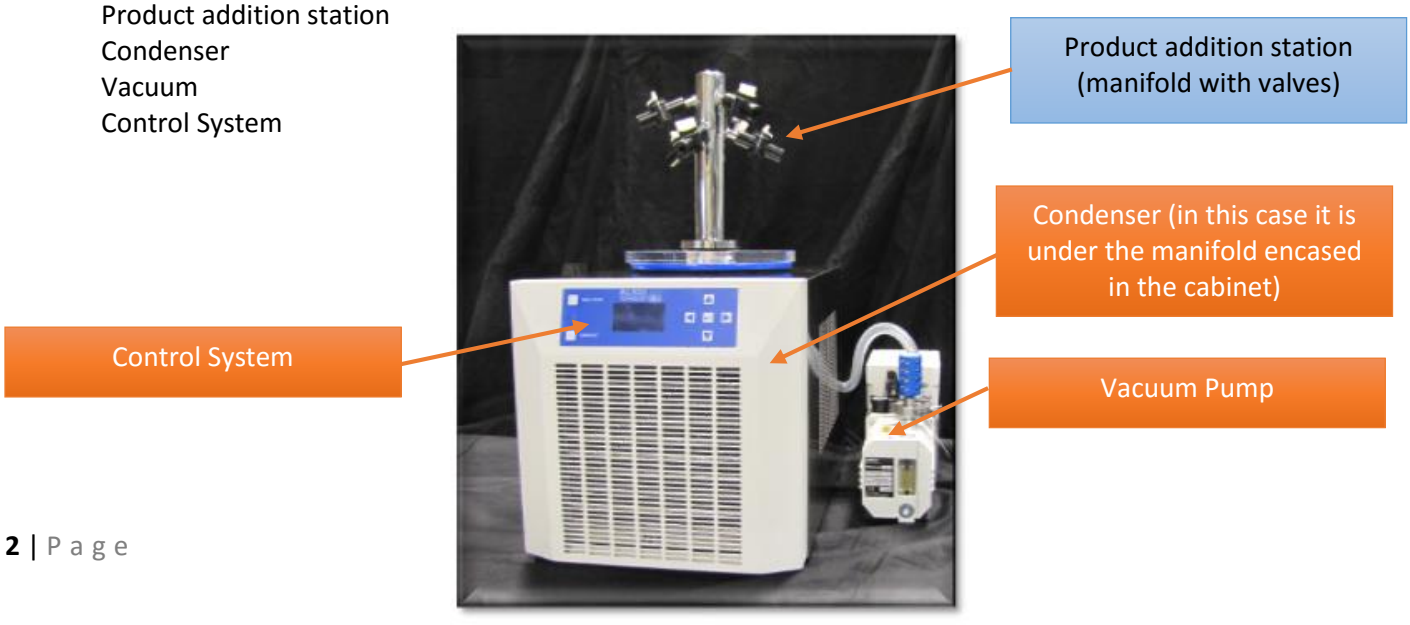
- Number of users in the lab is usually high and the amount of product they are making is small
- Large numbers of small individual samples
- Smaller equipment budget
- Cell banking type of facility
- Freeze dried product not for commercial use at this stage
- Very early stage research
- Minimally critical product processing required

Although large numbers of manifold systems are purchased and are quite adequate for the task at hand, it is important to understand that using a manifold type freeze dryer has significant limitations with regard to the freeze drying process. Ultimately the operator has no control over the freeze drying process, as they would in the more expensive and complex tray or shelf type freeze dryer. However, there are steps that can be taken to create a greater success on a manifold freeze dryer when that equipment is used. This article will explain basic manifold systems, their limitations and strengths and how to mitigate some of the problems that may occur during the freeze drying process.

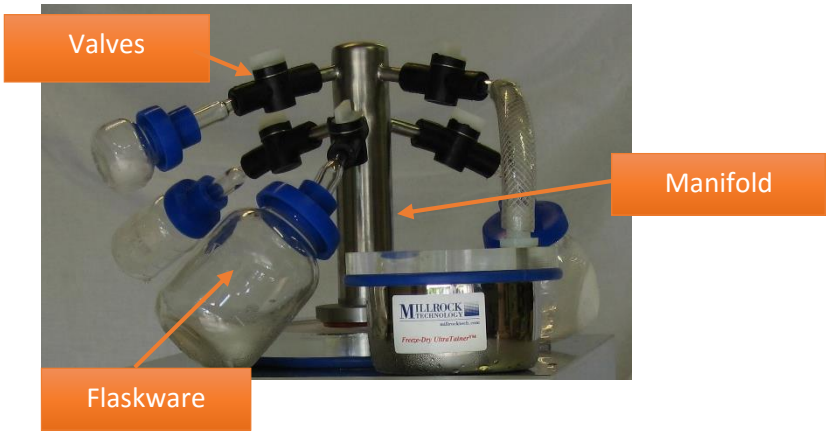
Understanding the Parts of a Manifold Freeze Dryer

Like all freeze dryers a manifold freeze dryer has 4 basic components. These are:

Product addition station
Condenser
Vacuum
Control System



The product addition station is the piece of the equipment that introduces the product to the freeze dryer. In the case of a manifold system the product containers are usually flasks. The product is placed in the flask and most typically statically frozen in a low temperature bath or a freezer. We will discuss the freezing options in more depth later in this tech note.



The condenser in almost all modern freeze dryers is a refrigerated surface that serves to drive the sublimation process by creating a lower pressure area in the dryer. The condenser also serves to trap moisture/solvents and thus preventing them from going to the vacuum pump. Most freeze dryers are offered in a "single stage" (single compressor), "two stage" (two compressors) or "two stage blended" (two compressors with a special blend of gas). Maximum low temperature ranges of -48C (for a single stage unit) to -85C (two stage system) are not uncommon. Some blended systems can achieve even lower temperatures, such as -105C. It is imperative to understand that the vapor pressure over ice is not a linear curve. As temperature gets lower and lower the law of diminishing returns applies.

Vapor over Ice Pressure Table

Temp °C	Press mT
0°	4579
- 4°	3280
- 8°	2326
- 12°	1632
- 16°	1132
- 20°	930
- 24°	526
- 28°	351
- 32°	231
- 36°	150
- 40°	96 .6
- 44°	60 .9
- 48°	37 .8
- 52°	23 .0
- 56°	13 .8
- 60°	8 .0
- 64°	4 .6
- 68°	2 .6
- 72°	1 .4
- 76°	0 .77
- 80°	0 .40
- 84°	0 .20
- 88°	0 .10

Courtesy of Millrock Technology, Inc

The vapor pressure over ice at -48C is equivalent to 37.8 mT. At -85C it is 0.15 mT which translates to a difference of approximately 37.65 mT. You can see however that below -85C a lower temperature only creates a very small incremental decrease in pressure – in the tenths and hundredths of milliTorr. Indeed, most vapor pressure over ice tables that are published stop at approximately -80C because at lower temperatures the pressure differential become insignificant.

The vacuum pump for most manifold freeze dryers is a two stage rotary vane oil sealed vacuum pump. The vacuum pumps sole purpose during most of the freeze drying process is to remove non-condensable vapors (nitrogen, oxygen, carbon dioxide et al) from the freeze dryer. By removing the non-condensable gasses in the system the vacuum pump essentially helps to create the environment for sublimation (ice to vapor without going through the liquid phase) to occur. Because all freeze dryers are have leaks (virtual leaks -- outgassing from stainless steel (yes it may outgas), gaskets, acrylics et al and real -- little pinhole leaks of various configurations and locations within the system, such at the vacuum tube hook up between the condenser and the vacuum pump) the vacuum pump is operated continuously throughout the freeze drying cycle. Theoretically IF the freeze dryer were totally and completely leak free, once the vacuum pump performed the initial pull down it could essentially be turned off and not used any further until the end of the run. In real life this is not possible.

The control system of a freeze dryer is becoming increasingly important in the differentiation of one freeze dryer to another. The amount of automation and user friendliness may vary greatly from one machine to another. Regardless of the brand, it is recommended that automatic on and automatic off are part of the controller's capabilities. In laboratories where manifold dryers are most commonly used, freeze drying is a means to an end and simply another process in a long list of processes that people must use to accomplish their goals. Not everyone is a freeze dryer expert. Having the automatic on and off functions helps to ensure that the proper start-up and shut-down sequences are used to provide system protection and longevity.

Freezing Product for Addition to a Manifold Freeze Dryer

Arguably, freezing the product is actually the most critical part of the freeze drying process. With a manifold freeze dryer freezing occurs away from the machine and the freezing process is not well controlled. In most cases, the researcher has not been able to even detect the freezing point and or melting point (often described as a "thermal fingerprint") of their product. In cases such as this the ideal freezing process typically serves to maximize the frozen surface area as much as possible.

A rule of thumb is that your product containers should never be filled more that 50% by volume. In addition, faster freeze drying will occur whenever you can minimize product volume in the container.

Maximizing surface area can be as simple as taking 20 ml's of product and dividing it among two 100 ml flasks vs putting it in one 100 ml flask.

The most common freezing approach is to stub or statically freeze product. This is the simple process of loading product into the freeze drying flask ware and placing it on the shelf of the lab freezer for freezing. If small test tubes or irregular product containers are being utilized they may be put inside a large flask or product container as a group or individually. Some product containers are designed for direct introduction to the freeze dryer. Below is a photo of a Wheaton Vacuole

This glassware is made for direct introduction to a freeze dryer valve and it can later be flame sealed while still on the system and under vacuum. Containers such as this and test tubes, cryo vials etc are typically stub or statically frozen upright in a low temperature freezer.

Another process, less commonly used, is to "shell freeze" your product. The product container is tilted and rotated on its axis in a low temperature bath. This will cause the product to freeze out in a coating on the interior of the flask, thus maximizing the surface are of the product. If this process is used it is typically a manual job, although some companies may offer a "shell bath". Regardless of technique utilized it is often considered a cumbersome manual approach and is not used with regularity.

Primary Drying in a Manifold System

Once product is frozen it is ready to introduce to the freeze dryer. The freeze dryer should have been defrosted and cleaned out after its prior run but it is always best to check that the condenser is dry and empty prior to starting up the equipment. The freeze dryer should be started-up according to the manufacturer's instructions. In the best case this is a one-touch process and the system will notify you when it is ready to accept product containers.

The frozen product in its container is introduced to the system via a vacuum valve. Once the container is connected the valve is relatively slowly opened. Since there is atmospheric in the container you will see the pressure in the system rise significantly during the introduction of a product container. Care should be taken to introduce one container at a time and allow the freeze dryer to recover to a good temperature and pressure range prior to adding the next product container.

The energy for sublimation to occur in a manifold freeze dryer is provided by the environment around the product container. This simple approach to providing energy can be much more complex and

troublesome than expected. For example, if your freeze dryer is in front of a window in your lab, having the shades open vs the shades drawn can have an effect on the rate of freeze drying. If you have been freeze drying a product in your lab all fall you may find that your process takes longer in the winter if the facilities people turn down the heat at night and your process is an overnight process.

In some instance your product may melt when exposed to a perfectly functioning manifold freeze dryer. This is typically an indication that the critical temperature (melting temperature) of the product is relatively low. Product melting indicates that heat input is simply too high for the product vs the sublimation rate (which is a cooling process as it takes energy away from the product). Whenever melting occurs care should be taken to make sure that the freeze dryer meets its refrigeration and pressure specifications and that there are no blockages between the product container and the condenser (for example, if product somehow has splashed into the port of the flask it will block the freeze drying process until the product in the port is freeze dried itself. Once you have verified that the system meets specification and there are no blockages, mitigating product melting on a manifold freeze dryer may be as simple as putting a layer of plastic wrap around your product container and may become as complicated as having to put your product in a controlled temperature bath that goes to very low temperatures. If keeping your product frozen during the drying process becomes complicated, it is often best to either try to reformulate your product to make freeze drying easier or find a more complicated freeze dryer with shelf temperature control. Regardless of the approach used, the goal is to decrease heat transfer into the product in some way.

Typically, on a manifold freeze dryer, a long freeze drying process is of little to no concern. If you want to decrease the process time, and your critical product temperature is relatively high, you may want to add heat to the process. Pointing a heat lamp at the product is an example of a heat input possibility.

Secondary Drying in a Manifold System

In secondary drying the residual moisture in the product is quite literally sucked out of the product matrix by the vacuum pump. This is referred to as a desorption step in freeze drying. When the product temperature is above its critical temperature it is considered to be in secondary drying. The amount of time that a product is left in secondary drying will usually effect the residual moisture in the product. Longer secondary drying times will typically result in a lower residual moisture content for product. The amount of residual moisture has an effect on the storage time of the product. Products that are to be used quickly can usually tolerate a higher residual water content.

How Do You Know When Freeze Drying is Done?

During freeze drying on a manifold system, since the surrounding environment or ambient air, is providing energy into the flask, your product containers will most likely have condensate on the exterior of the flask. This is a good indication that heat transfer is actually occurring. As freeze drying progresses and as less and less energy is needed for sublimation the amount of condensate on the flask will decrease and eventually disappear altogether. This is one of the indications that you are near or at the end of the freeze drying process.

Another indicator is the condenser temperature. During the freeze drying process, as the condenser collects water vapor, the temperature of the condenser will most likely increase. The amount of product on the system and the condenser design will also have some effect on how much the refrigeration system increases in temperature. However, if there is no increase at all in the condenser temperature during freeze drying it indicates that the drying process is very slow or that there is a very light load on the system. So, another potential indicator that the product is at the endo of the freeze drying process is when the temperature of the condenser goes back down to its maximum low.

Lastly, while freeze drying is occurring you will see an increase in the pressure in the system. Manifold freeze dryers come equipped with pirani vacuum sensors which read high in the presence of water vapor. At the end of the freeze drying run the pressure will approach the same pressure as the system dry and empty.

What About Solvents Other Than Water?

It is not uncommon for small amounts of solvents other than water to be present in product that will be introduced to the freeze dryer. These solvents typically have very low freezing points and melting points (ie ethanol freezes at -117C). These low freezing point solvents will not be trapped on the condenser. It is not uncommon to see them liquefy on the condenser for a period of time and then they will travel to the vacuum pump. Since the vacuum pump is oil sealed every effort needs to be taken to protect it from oil contamination.

A vacuum pump is normally run with its gas ballast closed. This provides the optimal conditions for freeze drying. When using low temperature solvents that you know will not freeze out on your condenser you may want to utilized a different strategy. These high vapor pressure solvents will

typically come off of the product (sometimes called flashing) in the very start of the freeze drying run. The gas ballast of the vacuum pump can be run in the open position during this period. As the high vapor pressure solvent hits the hot vacuum pump oil it will boil out of the oil through the exhaust port. If this exhaust is of concern the pump should be run in a fume hood or it should be vented to an exhaust of some sort (please see vacuum pump manufacturer's recommendations on how to do this). When the pressure in the system starts to come back down this indicates that the majority of the solvent is out of the system and the gas ballast can be closed.

All freeze dryers are made to work with water. If solvents of any kind are being used it will be beneficial to study material compatibility. A discussion with the freeze dryer manufacturer about the components used in the system is beneficial. They may also have some tips on how you can maximize the life of your freeze dryer even if you have some highly corrosive or damaging solvents present in your product.

Monitoring Vacuum Pump Oil is Critical

The vacuum pump tends to be the most neglected part of a manifold freeze dryer, particularly in a multiple user lab. Care should be taken to monitor vacuum pump oil on a regular basis to ensure pump longevity. Most vacuum pump oils are almost clear –similar to the color of vegetable oil. Oil that has a milky white appearance has been contaminated with water. Running the gas ballast in the open

position as mentioned above, may be helpful and allow you to utilize that charge of oil for a longer period of time. Oil that is turning dark indicates that it is contaminated. The oil should be drained and the pump should be refilled with a fresh charge of oil as per the vacuum pump manufacturer's instruction.

A User Log is of Paramount Importance

When used property a manifold system can provide years of solid performance. Using a User Logbook will help you determine the cause of any issues. The log should minimally include the user name, date and time they put their sample on the machine, all of the solvents present (ie water, ethanol, TFA) and when they took their product off.