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Technical Note

The Use of Solvents in Laboratory Freeze Dryers – A Discussion of Issues and Some Helpful Tips

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Solvent Use in Freeze Dryers

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Freeze dryers were originally designed and developed for use with water as the primary and only solvent. As protein chemistry and other products that are not miscible in water have developed over the years freeze dryers are being used with solvents other than water. Most commonly organic solvents are being utilized in the discovery and development steps prior to the product being introduced to a freeze dryer. It is not unusual to sometimes see inorganic acids and bases utilized as well. This creates some difficulty for the standard freeze dryer and these issues should be recognized prior to exposing the dryer to these chemicals.

In “chemistry 101” we are taught that “likes dissolve likes”. This sums up the general rule that an organic solvent will dissolve organic compounds and that inorganic compounds will dissolve inorganic compounds. Freeze dryers contain plastics (acrylic doors) and elastomers (gaskets and seals) that will have limited resistance to organic solvents and likewise the stainless steel components may react adversely to inorganic solvents.

Do not be lulled into a false sense of confidence that the solvents that you have in your product are so minimal that they will not have an effect on the dryer. These solvents typically have a high vapor pressure and come out of the product very early in the primary drying phase of the freeze drying cycle. It is important to investigate the material compatibility of all solvents present in your product, regardless of the amount. Material compatibility charts can be found on line. My favorites include http://www.coleparmer.com/Chemical-Resistance for 304 and 316 Stainless Steel and http://www.eplastics.com/Plastic/plastics_library/Chemical-Resistance-of-Plexiglass-Acrylic for information on acrylic compatibility.

Organic Solvents in Laboratory Freeze Dryers

Many laboratory freeze dryers are designed and built with acrylic doors on both the condenser and the tray chamber. This is done primarily for easy visual access to the product sitting on the shelves or in the manifolds as well as being able to watch condenser loading. In the presence of organic solvents in the vapor stream or in the condensate, acrylic will begin to be destroyed. Often this destruction will start with what is referred to as “etching”. The interior of the door will start to take on the appearance of etched glass in some locations. Eventually, as more runs with solvents occur the etching will eventually turn into a hair line fracture. This fracture will make pulling a vacuum virtually impossible and in the worse-case- scenario may result in implosion of the acrylic component.

There are steps you can take to minimize this problem or delay the need for part replacement. The number one priority is to minimize contact between the organic solvent and the acrylic. In most cases a low temperature condenser (-85C or lower) may prove to be helpful. Check the freezing point of the solvent to see at what temperature it will freeze out of the vapor stream. If the temperature is above -85C then the vast majority of the solvent will be caught on the cold temperature surface of the condenser. When using this approach to trapping solvents make sure that the condenser temperature read-out is actually at the surface of the condenser and not somewhere else in the refrigeration system. If the temperature sensor for the condenser is not directly on the condenser surface, then you should de-rate the maximum low temperature of your condenser as a safety measure.

Many organic solvents have low freezing points, well below that of the condenser surface temperature. In such cases the solvent vapor may liquefy in the condenser. Although not totally trapped out of the vapor stream this does help prevent a rush of organic solvent to the vacuum pump. Unfortunately, the liquefied organic solvent is in constant contact with the condenser surfaces. This may lead to accelerated etching of the condenser end plate. In addition, given a higher vapor pressure condition, the liquefied solvent may return to the vapor phase and migrate to the vacuum pump in a process referred to as reflux.

The steps that you take to minimize or eliminate the effects of organic solvents in your freeze dryer are dependent on the amount and frequency of exposure. This is often determined by a trial and error approach to see how much the dryer is affected by the solvent. Regardless of the amount of solvent present, good freeze dryer maintenance in imperative. Steps that can be taken to mitigate the effect of organic solvents are:

For All Freeze Dryers

1. A small amount of etching in a laboratory freeze dryer may not create a problem. Whenever possible eliminate as much of the solvent as possible before introducing the product to the freeze dryer. If you are “stuck” with a small amount of organic solvent on an on-going basis, carefully monitor the condition of the acrylic components. Be prepared with replacement components as required. A small amount of etching may never create a problem or may simply require periodic replacement. Good housekeeping is imperative in this situation and the freeze dryer should be washed down after each cycle.
2. One of the tell-tale signs that a solvent has been used in a cycle is a condenser door that has what appears to have a waterline mark. Do not allow condensate to sit in the condenser during the defrost cycle. Liquefied solvents will etch the acrylic much faster than solvents in the vapor state. Conduct your defrost cycle as quickly as possible with the drain open or possible the acrylic door off. Wash out the condenser with water as fast as possible to ensure that the condenser is clean and dry. Wash any other acrylic parts that may have been in the vapor stream to ensure that they are as free of solvent as possible.
3. If the acrylic components of your lab freeze dryer are compromised quickly by the solvents in the product they should be replaced with stainless steel components. Stainless steel doors will add a cost to your laboratory freeze dryer and should be purchased with at least one sight glass so that you can continue to have visual access to the chamber. The use of stainless steel in place of acrylic is by far the most robust and conservative approach to maintain a freeze dryer that is being used with organic solvents.
4. Solvents will often “flash off” in the first part of the freeze drying cycle, after the vacuum pump is activated. This will manifest as a higher pressure in the freeze dryer. It is best to run the vacuum pump with the gas ballast open during this period. Any solvent reaching the pump will be boiled out of the pump and exhausted through its exhaust port. If exposure to the solvent is a concern steps must be taken to eliminate the solvent from the exhaust in a safe manner. The entire vacuum pump could be placed in a safety cabinet, although this may result in a decrease in system performance if the vacuum tubing connecting the pump to the dryer becomes exceeding longer in length. Another alternative is to put a non-restrictive line on the outlet of your vacuum pump and run the line into a hood or scrubber. When doing this you need to make sure that any vapor that may condense in the exhaust line does not simply run back into the pump. This can be done by making sure the pump exhaust line is lower than the pump exhaust port or by putting a small trap on the line to catch any solvent that may condense and run back down the exhaust line towards the pump. Regardless of the exhaust design utilized, the pressure in the system will start to recover once the solvents are eliminated from the

product. When this happens the gas ballast should be closed. Closing the gas ballast provides slightly better vacuum performance and decreases on the rate of degradation of the oil by running at a slightly cooler temperature. Regular vacuum pump oil changes will be required, and may be required as frequently as after each run.

5. A liquid nitrogen trap can be installed between the condenser and the vacuum pump. It should be equipped with vacuum tight ball valves so it can be put on-line and taken off-line as needed. Once again, during the first part of the run the high vapor pressure solvents will flash off of the product. During this time the nitrogen trap should be cold and on line. Once it appears that most of the high vapor solvent is out of the product the trap should be taken off line. This will help ensure minimum use of nitrogen and that the solvent will not get warm enough to revaporize and go to the pump.
6. If all else fails and or it is anticipated that organic solvent use will be consistent then the use of a dry vacuum pump should be considered. These are pumps that are able to be used effectively on freeze dryers and do not require an oil charge to work. Since it is oil contamination that wreaks havoc on the standard pump used in freeze drying the elimination of the oil in a dry pump eliminates that problem. Dry pumps however have a significantly larger up front cost.

A Few Notes Specific to Manifold Type Freeze Dryers

If you are using organic solvents in a manifold with acrylic components, you can expect much of the same issues as noted above. Minimize the use of acrylic components in the manifold in favor of stainless steel. If your entire manifold is acrylic—including the ports additional steps should be taken to protect your product. The joint between the acrylic ports and the body of the manifold is the “weakest” area of the manifold and solvents will have a greater effect on this joint first. Make sure that product containers are well supported—heavy product containers have been known to pull the port right out of the manifold body. Also note that if you have a vacuum leak while freeze drying that appears to go away when the system is dry and empty, then you may have small leaks at the port-to-manifold-body connections that are leaky when solvent is present and then reseal when solvent is no longer present.

Inorganic Solvents in Laboratory Freeze Dryers

On rare occasions inorganic solvents are introduced to laboratory freeze dryers. In instances such as this it is important to explore material compatibility with stainless steel. In most freeze dryers 316L stainless steel is used for construction, however older units may have 304L stainless steel or even another alternative steel material. Verification with the original manufacturer of the equipment of the materials in contact with the vapor stream is highly recommended.

If the organic solvent being used, such as HCl, attacks stainless steel it is best to make sure that you perform good routine maintenance after each freeze dry cycle. Inorganic solvents are most likely to attack weld joints first as they are typically the most stressed part of the stainless steel components. The weld joint most likely to suffer is the drain port in the condenser. During the defrost cycle the inorganic solvent sits in contact with this joint for extended periods of time. Once the defrost cycle is concluded and the condenser is drained

residual solvent may continue to attack that joint. Make sure that you thoroughly rinse out the freeze dryer to ensure that there is no remaining solvent. This will help protect the stainless steel components from deterioration. In most system, if the stainless has been compromised by a solvent, it will manifest as a vacuum leak that is difficult to find. To further complicate this issue, a small leak in a location that gets cold. may appear when the system is cold due to thermal contraction but may not appear when at room temperature.

There are chemical traps that may be put in-line between the condenser and the vacuum pump. The most notable is soda sorb for the absorption of acid. Most freeze dryer manufactures will include acid traps, molecular sieves in their offerings. When using acid traps be aware that soda sorb is hygroscopic. When first put on the freeze dryer the dryer may not pull to maximum low as it pulls water out of the trap itself. Running the system dry and empty until the max low pressure rating for the system is achieved is recommended. If it is easily done you may want to freeze dry the trap itself prior to putting it on line. Also note that as the soda sorb absorbs acids it will begin to break down and sometimes create a fine dust that may migrate to the vacuum pump. It is a good idea to check your trap before and after each freeze drying cycle.

Good standard operating procedure requires that you understand all of the solvents present in your product and to be sure to make sure you have verified material compatibility with the freeze dryer components. The

use of small amounts of solvents may be mitigated by good maintenance procedures and provide a freeze dryer that needs replacement parts on a regular basis but in a time frame that is acceptable to the user. Higher amounts of solvents may require the replacement of parts with an alternative material to ensure system integrity and longevity.