Application Note
No. 337/2018

The use of organic solvents in laboratory freeze-dryer

1. Situation overview

Freeze-dryers were initially intended to be used with water as a solvent. With new applications arising, products that are not soluble in water are increasingly present in chemistry applications. Consequently, freeze-drying is being used more and more in combination with organic solvents instead of water.
Organic solvents and inorganic acids and bases are often used in research and development prior to lyophilisation of the sample. The behavior of these new types of samples during freeze-drying must therefore be considered prior to the process.

2. Hardware

Freeze dryers contain plastics (acrylic drying chamber), elastomers (seals and gaskets) and stainless steel (condenser) which can become adversely affected by inorganic and organic solvents. Before starting a cycle, it is important to check the state of the system – mainly the seals, stainless steel parts and the acrylic chamber- and to replace what is worn off.

3. Process

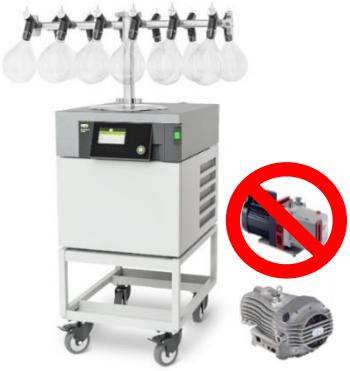
Many aqueous samples can be handled easily during freeze-drying and water will be collected completely on the condenser for most of the experiments. The situation with organic solvents can however be quite different.
Many organic solvents have a low freezing point; some of them well below that of the condenser surface temperature.
In order to understand whether a solvent can be freeze-dried, four main aspects need to be verified using the vapour-pressure curve of the solvent (Table 1)

- "How can the solvent be frozen?" – i.e which method can reach a low enough temperature so that the sample is fully frozen.
- "At which concentration can the solvent be frozen?" – i.e does the solvent need to be diluted in order to be frozen
- "Can the condenser collect the solvent?" - i.e the temperature of the condenser is 15-20°C lower than the freezing temperature of the solvent
- "Will the sample remain in a frozen phase during the process?" - i.e can we maintain a pressure that is low enough so that the sample remains frozen?

1. Organic solvents can be tricky to freeze. They will often require to be diluted with water before freezing or to use liquid nitrogen to reach a low enough temperature.
2. Many organic solvents have such a low freezing point that even a -85°C or -105°C condenser is unable to collect them. The difference of capability between a -55°C and a colder condenser is therefore not that big in terms of vapor collection, as shown in Table 1.
3. If the solvent is not trapped in the condenser, it will leave the chamber as vapor though the pump.
4. Choosing the right pump is crucial when solvent vapors are leaving the system. A scroll pump (Edwards scroll pumps nXds 6ic for the L-200) is recommended for all freeze-drying applications involving organic solvents.
5. Due to the low freezing temperature and triple point of the organic solvents, it might also appear to be difficult to evacuate the system fast enough and to keep a low enough pressure in the system to avoid the solvent to melt, even at ultimate vacuum.
6. For diluted solutions, it is rather common to see solvents melting and evaporating while water remains frozen (yellow fileds in the solvent tables below) If that is a problem or not depends on sample requirements
7. If the solvent amount is too high, the system will not be able to maintain the required pressure and everything will melt and evaporate (red fields in the solvent table). The process must be stopped.

Table 1: Triple points of commonly used solvents (ice pressure curve for water is often not applicable)

Solvent	T_{triple} [°C]	P_{triple} [mbar]
Water	0	6.1
Acetonitrile	-43.9	1.67
Acetone	-94.7	$2.33\ 10^{-2}$
Methanol	-97.7	$1.86\ 10^{-3}$
Ethanol	-123.15	$4.3\ 10^{-6}$



4. How to handle organic solvents in laboratory freeze-dryers?

- If possible, eliminate as much of the solvent as possible prior to freeze-drying using a rotary evaporator for example.
- Some small amount of etching on acrylic parts will appear; it may not create problems or may require periodic replacement. Be prepared to replace components as required.
- Good maintenance is imperative and freeze-dryer should carefully be cleansed after each cycle.
- Do not allow condensate to sit in the condenser. Conduct the defrosting step of the instrument as fast as possible with the drain valve open. Wash out the condenser with water and ensure that it is clean and dry
- Use a dry pump when handling solvents other than water. Make sure that the exhaust port of the pump sits in a fume hood to avoid any human exposure to the solvent.

The following lists give a review of solvents often used in combination with water and show whether or not they can be removed by freeze-drying on the **Lyovapor™ L-200**.

	The sample can be freeze-dried, sublimation occurs.
	The pressure in the drying chamber cannot be set to a low enough value to maintain the solvent in solid form. The solvent will melt while water will remain in ice form. The solvent will evaporate and an increase in pressure can be observed until it is evaporated completely. The ice will then sublimate. Even though the solvent is not sublimating, evaporating it is good enough for many applications.
	NOT WORKING – NOT POSSIBLE

Solvent	100 %	50 %	30 %	10 %	≤ 5 %
Acetic acid					
Acetone					
Acetonitrile				*	*
				*	*
Dimethylsulfoxide DMSO					
Ethanol					
Isopropanol Isopropylalcohol					
Methanol					
Trifluoro aceticacid TFA					

* depending on pressure settings

The following lists give a review of solvents often used in combination with water and show whether or not they can be removed by freeze-drying on the **Lyovapor™ L-300**.

	The sample can be freeze-dried, sublimation occurs.
	The pressure in the drying chamber cannot be set to a low enough value to maintain the solvent in solid form. The solvent will melt while water will remain in ice form. The solvent will evaporate and an increase in pressure can be observed until it is evaporated completely. The ice will then sublimate. Even though the solvent is not sublimating, evaporating it is good enough for many applications.
	NOT WORKING – NOT POSSIBLE

Solvent	100 %	50 %	30 %	10 %	≤ 5 %
Acetic acid					
Acetone					
Acetonitrile					
DMSO					
Ethanol					
Isopropanol Isopropylalcohol					
Methanol					
Tert-Butanol					
Trifluoro aceticacid TFA					