APPLICATION NOTE

FREEZE DRYING

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Freeze drying (lyophilization) is a dehydration technique where a product is dried under vacuum at low temperature. The water that is contained in the sample is thereby frozen to a solid (ice) and then removed by turning the ice into vapour. Conducting this process under vacuum allows the water to be evaporated without having to pass through the liquid phase. The major advantage of freeze drying is that thermo-labile components, like proteins, flavours or colours, are preserved and the original size and shape of the sample is maintained. This is only possible by keeping the material in a frozen state at low temperatures during the entire drying process. The absence of water in the final dried product minimizes the effects of oxidation and other degradation processes, thus allowing it to be stored over long periods without the risk of infections by micro-organisms or compositional changes (genetically or enzymatically). Freeze drying has therefore become a widely used method in the pharmaceutical and food industry to process heat sensitive materials that require long-term storage at temperatures above freezing.

A typical freeze drying set-up (Figure 1) consists of four basic components: product chamber, refrigeration system, condenser and vacuum pump, whereas the vacuum pump is pumping the chamber through the condenser to protect it from moisture.

The pressure during the freeze drying process is measured by a pressure gauge; usually a pirani or capacitance manometer. Accuracy and repeatability of the pressure measurements are essential for the control of the freeze drying process.

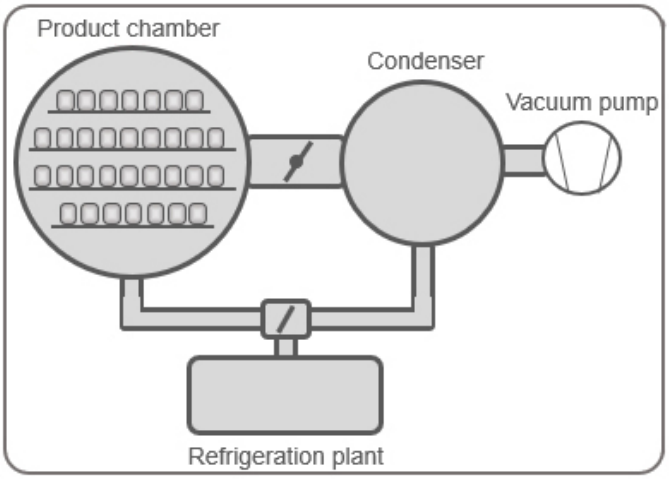

Figure 1: Schematic of a freeze-drying set-up.

The steps required to lyophilize (freeze-dry) a product in a batch type process are as follows:

1. Pre-treatment / formulation.
2. Freezing at atmospheric pressure (thermal treatment).
3. Primary drying under vacuum (sublimation).
4. Secondary drying under vacuum (desorption).
5. Backfilling & stoppering.

After pre-treament and loading onto the shelf trays of the freeze dryer, the product is pre-frozen at atmospheric pressure to a temperature below the eutectic point of the material. Figure 2 shows the phase diagram of water, illustrating the eutectic point at which water is present in its three stages (solid, liquid, vapour).

Typical pre-freezing temperatures are in the range of -40 to -60 °C. During primary drying, the frozen liquid (ice) is removed by the process of sublimation (directly turned into vapour). Primary drying is typically conducted at a pressure of 1 to 0,01 mbar depending on the characteristics of the respective product. The pressure difference related to the corresponding temperature difference between the product's ice surface and the condenser's ice surface is the driving force of the sublimation process.

Under vacuum the air molecules are removed from the chamber, thus driving the vapour molecules out of the product material more easily. During primary drying, the shelf temperature is ramped up from -40 to +20 °C on a timeline ranging from a few hours up to several days. For an effective freeze drying process the temperature of the product must be higher than the temperature of the condenser. The temperature difference creates a pressure differential, which forces the water vapour molecules out of the material and towards the condenser.

The secondary drying process has begun, when the product reaches a temperature above its eutectic point. During this step the remaining water (so called "bound") is desorbed. The removal is controlled and optimized by decreasing the pressure down to about 10^{-3} mbar, while increasing the shelf temperature to its allowed maximum, just before denaturation of the product occurs. In order to optimize drying cycle times, the end of the primary and secondary drying step is usually determined by conducting a pressure rise test (PRT). The freeze drying cycle ends with bringing the chamber back to atmospheric pressure by flushing it with air or nitrogen. The final product then typically contains between 1-3% of residual moisture. An example of a typical freeze drying cycle is depicted in Figure 3.

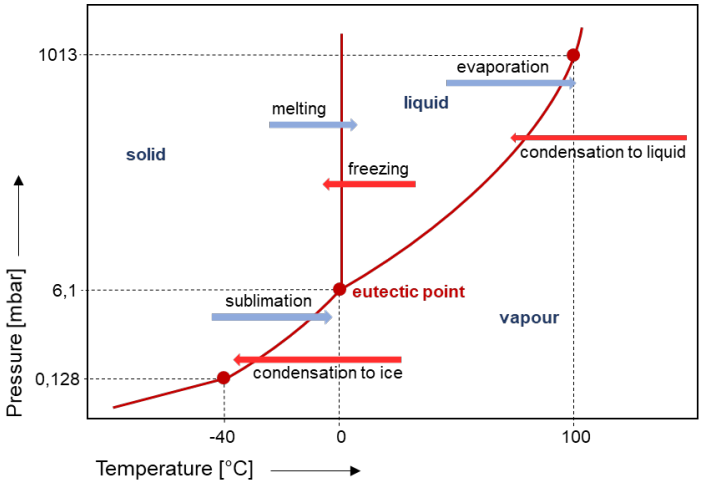

Figure 2: Phase diagram of water, illustrating the conditions for the solid, liquid and vapour phase together with the eutectic point, at which water is present in all three stages.

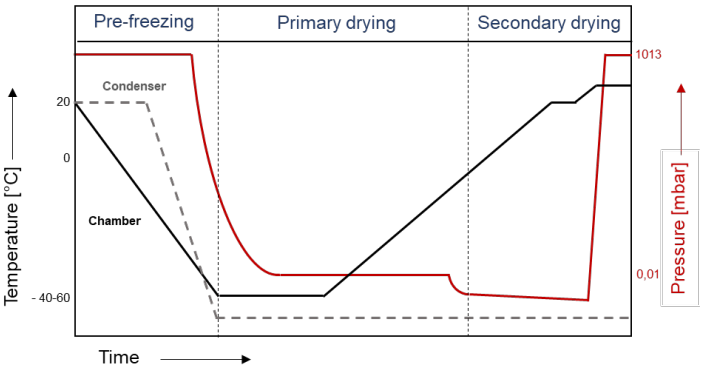

Figure 3: Typical freeze drying profile comprising of pre-freezing, primary and secondary drying.

Together with the refrigeration system, the vacuum system forms the heart of a freeze dryer; its main purpose being to evacuate the system down to the processing working pressure. Furthermore, the vacuum system removes all non-condensable gases during the drying process. The main criteria for selecting a suitable vacuum pump or system are the total volume of the system, that needs to be evacuated, together with the desired pump-down time, the ultimate pressure, that needs to be achieved, reliability of the pump and space availability for the pump installation. Oil-sealed rotary vane pumps are widely used. They have a very robust design, which is particularly advantageous in freeze-drying applications. Generally, they can be single- or two-stage pumps, depending on the ultimate pressure that is needed, and with pumping sizes ranging from 1 up to 800 m^3/h, thus allowing to size the pump according to the chamber volume.

In case the freeze-drying process requires a working pressure below the limits of the primary pump, a booster pump can be added. In addition to the achievable ultimate pressure being about a decade lower than with the primary pump alone, a pump/booster combination offers a higher pumping speed at low pressures, allowing even faster pump-down times.

Conventional oil-sealed pumps always bear the risk of oil back-streaming to the chamber and thus potentially contaminating the freeze-dried product. To avoid this, dry pumping technology can be used alternatively. Pump types typically used here are scroll pumps for smaller volumes and screw or claw pumps for larger systems, as depicted in Figure 4. Apart from generating an oil-free environment, dry pump technology - like the Edwards nXDS/XDS scroll pump series, GXS or EDS screw pumps as well as GV claw pumps - offer a range of benefits, e.g. superior noise and vibration levels, a compact footprint and less energy consumption. For lower pressure requirements these pumps can also be combined to a pump/booster combination. For the final design and dimensioning of the vacuum system, Edwards can support with our in-house application team, carrying out calculations on how to achieve the desired pump-down time and the working pressure, by considering the individual characteristics of the pumping speed curves of each type of vacuum pump as well as performance losses due to leakage or pipework.

Figure 4: Edwards dry pumps used in freeze drying applications. Left: GV110 claw pump, middle: GXS screw pump and pump/booster combination, right: nXDS scroll pump.

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