Lyophilization, or freeze-drying, is a drying process often used in the pharmaceutical industry to stabilize parenteral products, particularly biologicals, and to modify or enhance physiochemical properties such as dissolution rate and bioavailability.

Typically, a lyophilization process comprises three stages: freezing (solidification), primary drying (ice sublimation), and secondary drying (moisture desorption).

Because lyophilization dries product from a frozen state, the refrigeration system is a vital component of a lyophilizer. This system cools both the shelves on which product vials are placed and the condenser, which converts water removed from the product back to ice. Traditionally, refrigeration systems in commercial lyophilizers have been driven by compressors. In recent years, liquid nitrogen (LN$_2$) has been increasingly used for pharmaceutical manufacturing because it provides better control over the freezing process and offers a broader range of operating parameters (1, 2).

**PERFORMANCE ADVANTAGES**

Refrigeration systems based on liquid nitrogen provide a lyophilizer with a number of performance advantages over a conventional compressor-based system.

**High Condenser Capacity:** Condenser performance plays an important role in the lyophilization process, especially because lyophilizer capacity can be a limiting factor in process design. An undersized refrigeration system may cause an overload of the heat- or mass-transfer capabilities of the condenser system, which typically leads to a loss of chamber pressure control and, ultimately, product temperatures in excess of the target temperature. LN$_2$-based condensers have cooling capacities higher than compressor-based systems. Lower condenser temperatures can be readily achieved, and more uniform and consistent condenser temperatures can be controlled throughout the entire process, including the peak load in primary drying.

**High Shelf-Cooling Capacity:** Using compressors, the maximum attainable cooling rate is dictated by the temperature range of the specific freeze-drying operation (the lower the operating range, the slower the cooling rate). In a screw-compressor–based lyophilizer, the shelf-cooling rate normally tapers off at –20 ºC (Figure 3). The lower the temperature range, the slower the cooling rate will be. Comparably, a liquid-nitrogen–driven system enables a product to attain a lower shelf temperature at a faster and more constant rate than the compressor-based system would (Figure 3). Table 1 compares the cooling capacity of a screw-compressor–based dryer with a liquid-nitrogen–driven lyophilizer. High capacity in the cooling shelves and condenser will significantly broaden the applicability of a lyophilizer in manufacturing products with specific formulations.

**Reduced Mechanical Stress:** After sterilization in place (SIP), a chamber and condenser cooling system are often operated to assist in maintaining product integrity. Using liquid nitrogen, a lyophilizer can achieve a more constant and uniform cooling rate, reducing the mechanical stress on the product and improving product quality.

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**PRODUCT FOCUS:** PROTEINS, ANTIBODIES

**PROCESS FOCUS:** FILL AND FINISH

**WHO SHOULD READ:** PROCESS DEVELOPMENT AND MANUFACTURING

**KEYWORDS:** LYOPHILIZATION, LIQUID NITROGEN, PARENTERAL PRODUCTS, BIOPHARMACEUTICALS

**LEVEL:** INTERMEDIATE
To reduce the likelihood of tripping a “High Head Pressure” failure, screw compressors typically are not activated until the shelf temperature is the 30 ºC range. With LN\textsubscript{2} systems, this is not a concern, so cooling can take place immediately upon drying of the internal surfaces. Furthermore, LN\textsubscript{2} refrigeration systems substantially reduce the cooling-down time after SIP. For example, it takes 3.5 hours to cool down to 25 ºC on a screw-compressor lyophilizer compared with 1.5 hours to cool down to 15 ºC on a liquid-nitrogen–based lyophilizer.

**WIDENED APPLICABILITY**

Freezing is a critical step in a lyophilization process. The freezing of a formulation solution starts with ice nucleation, followed by ice growth. In the freezing stage, most water separates into ice crystals through a matrix of glassy and/or crystalline solutes. The microstructure of both ice and solute formed during freezing strongly influences the characteristics of primary and secondary drying and ultimately the quality of the final product.

The freezing of products in vials is controlled practically by the shelf temperature. Consequently, the superior cooling capacity of a liquid nitrogen system significantly widens the applicability of a lyophilizer to pharmaceutical products with difficult formulations or in specific dosage forms. More detail is offered below.

**Formulations of Biologics:**

In contrast with traditional chemically synthesized drugs, biopharmaceuticals and biologicals (proteins, antibodies, and vaccines) require more specialized lyophilization cycles. To minimize in-process deterioration and achieve acceptable shelf life after lyophilization, more precise control of freezing temperature and cooling rate is required. LN\textsubscript{2}-based lyophilizers demonstrate superior performance in freeze-drying biopharmaceutical products.

**Formulations with Nonaqueous Solvents:**

In the development of lyophilized parenteral pharmaceuticals, nonaqueous solvents have been increasingly used to modify the physical properties of formulations and/or facilitate the process by increasing sublimation rates. In the lyophilization of such products, a high-capacity cooling system is needed to ensure the solidification of the formulation during the freezing. In addition, condensation of the removed solvent in the condenser during primary and secondary drying demands a refrigeration system of high cooling rate and low condensation temperature.

**High Fill Depth and High Volume Dosages:**

For a dosage form with high fill depth/volume, a larger amount of water is contained in each vial. To convert the product in a vial into a uniform frozen state...
readily provide a constant cooling increase in the batch size. When the required operating temperature is below –20 ºC. This means a rate ranges from 0.5 to 1 ºC/min (based liquid-nitrogen). Maximum condenser temperature to as low as –30 ºC to –80 ºC. This maximized capacity comes in direct response to the large demand for lyophilization by the biopharmaceutical industry.

Lyophilizers offer faster freezing (up to 2 ºC per minute) and control of freezing rate simplifies scale-up of a lyophilization process and product temperature (heavy load) during drying, when the lyophilization cycle is scaled up to the LN based and depends greatly on the refrigeration systemy is needed for the shelf freezing rates and thus product freezing rate is often unnecessarily slow, particularly when the required operating refrigeration expertise. Using a liquid-nitrogen system, a liquid nitrogen system is simple to design and maintain, eliminating the need for expansion valves, compressors, and refrigeration systems, no extensive maintenance is needed for a liquid-nitrogen–based system. So a refrigerator system can turn out to be more expensive per kilowatt cooling output than the electric energy needed for the same cooling effect. However, the cost of LN cooling can be comparable. Unlike with compressor-based systems, a liquid-nitrogen–based system is also potentially shortens cycle time.

REDUCED COMPLEXITY

MAXIMIZING CAPACITY

PRODUCT PROTECTION AND SECURITY

REFERENCES

ECONOMIC CONSIDERATIONS

A manufacting plant has to be specially designed for installation footprint requirements and reduce the batch heterogeneity of freezing-induced changes. The noise level generated by LN –based systems is also much lower than that generated by compressor-based systems. In case of power failure, LN –based cooling systems provide much lower risks for product quality. The risk of an explosion that may occur with a compressor-based system is also nontoxic and cannot be detected by smell in the plant. Therefore, it is a colorless, odorless, and tasteless gas that is nontoxic and cannot be detected by smell in the plant. The noise level generated by LN –based systems is also much lower than that generated by compressor-based systems. In case of power failure, LN –based cooling systems provide much lower risks for product quality. The risk of an explosion that may occur with a compressor-based system is also.
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