Increasing Lyophilization Productivity, Flexibility, and Reliability Using Liquid Nitrogen Refrigeration

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Part 1

ABSTRACT

Because lyophilization dries a product from the frozen state under temperature controlled conditions, the refrigeration system's process capabilities and performance are critical to a successful commercial lyophilization operation. Part 1 of this article outlines recent trends in pharmaceutical manufacturing and their impact on the evolution of refrigeration technology in lyophilization. It also explains the advantages and disadvantages of choosing a refrigeration system that uses liquid nitrogen instead of mechanical compressors, and its affect on the overall operation. Part 2 of this article, to be published in the December 2007 issue of *BioPharm International*, will detail design and performance considerations for cryogenic nitrogen refrigeration in a freeze-dryer. The relative cost affect of choosing a cryogenic versus a mechanical refrigeration system will also be discussed as related to the lyophilization process.

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Lyophilization (freeze-drying) is increasingly used to gently stabilize pharmaceutical and biopharmaceutical products, and intermediates.[1–4] Its recent growth is being driven by the escalating global demand for aseptic packaging and preservation of parenteral drugs, as well as by the rise in the production of biologics, including protein-based therapeutics and vaccines.[2–4] According to industry experts, the corresponding increase in lyophilization capacity has been fueling double-digit growth in global cGMP freeze-drying equipment sales, which have reached approximately $250 million per year. The global installed base is estimated to be in excess of 3,000 cGMP production units.

During lyophilization, most of the solvent (e.g., water or alcohol) is removed from a product after it is frozen and placed under vacuum. The process actually consists of three separate, but interdependent steps: 1) freezing, 2) primary drying (ice sublimation), and 3) secondary drying (moisture desorption). During primary drying, more than 90% of the solvent changes directly from solid to vapor phase through sublimation. The residual solvent remains adsorbed on the product as moisture. Some of this remaining solvent is desorbed during secondary drying to attain a moisture level too low to permit biological growth or chemical reactions, while still preserving the activity and integrity of the freeze-dried product.[3,5]

Key advantages driving the growth of lyophilization as a preferred fill-and-finish step include the enhanced stability of freeze-dried powder, the ability to remove solvent with minimal heating and concentration effects, the relative ease of aseptically processing a liquid in a freeze-dryer, and rapid and easy dissolution of the product upon reconstitution. All these advantages facilitate minimizing the time to market of a novel therapeutic agent, establishing an early marketing lead, and collecting increased revenues. Disadvantages of this method include increased handling and processing time, the need for a sterile diluent upon reconstitution, and the cost and complexity of related equipment, including its operation and maintenance.[1,3,5,6]

REFRIGERATION TRENDS IN FREEZE-DRYERS

During lyophilization, the product is first frozen, then dried from this frozen state under precise temperature- and pressure-controlled conditions. The refrigeration system's process capabilities, flexibility, reliability, and performance are all critical to a successful commercial lyophilization operation. Historically, most freeze-dryers have used mechanical refrigeration. Even though approximately 80% of lyophilizer service problems arise in the mechanical refrigeration system,[7] these compressor-based units have accounted for 90–95% of freeze-dryer installations.

However, since the early 1990s, cryogenically refrigerated freeze-dryers have been claiming an increasing market share.[7–11] These reliable, flexible, and well-proven systems use liquid nitrogen (LN_2) or cold gaseous nitrogen (GN_2) to cool the components of the freeze-dryer.

In recent years, both the efficiency and flexibility of cryogenic refrigeration systems

Key Components of a Lyophilizer

A typical lyophilizer, or freeze-dryer, has nine main components plus auxiliary systems to carry out the lyophilization cycle:

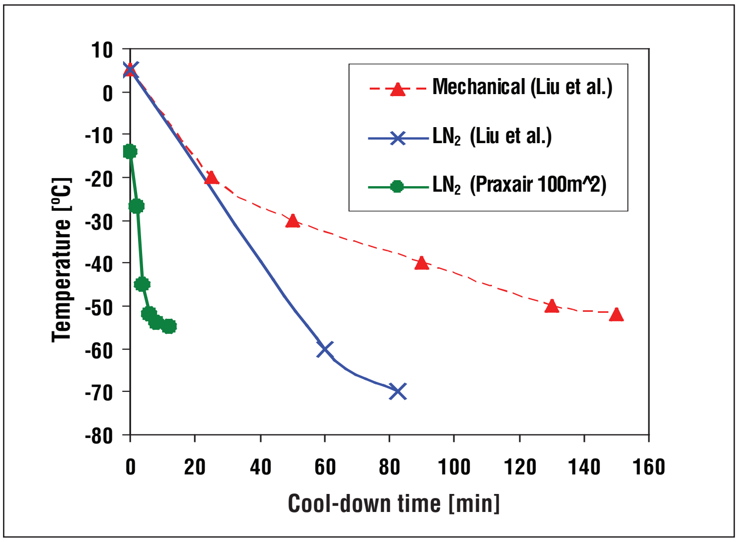
1. A **vacuum chamber** contains the shelves and the formulation to be lyophilized.
2. Hollow **shelves** hold the formulation and control its temperature.
3. **Heat transfer fluid** circulates inside the hollow shelves to precisely communicate cooling or heating through the shelves to the product.
4. **Product** to be lyophilized is specially formulated and typically contains the active ingredient, a solvent system, and several stabilization agents. Lyophilization of this formulation takes place in specialized containers on the shelves. These containers may be vials with stoppers, ampules, syringes, or—in the case of bulk lyophilization—pans.
5. A **condenser** removes the sublimated and desorbed solvent from the vapor phase by condensing or freezing it to maintain adequate vacuum inside the freeze-dryer. The condenser can be internally located in the chamber, or may be a separate external unit communicating with the chamber through an isolation valve. Most production freeze-dryers have external condensers. The capacity of a condenser is given in kilograms or liters of ice that it can hold frozen on its cooled surface.
6. The **mechanical or cryogenic refrigeration system** provides refrigeration to the shelves and condenser (and sometimes the walls) of the freeze-dryer by cooling the heat transfer fluid or directly expanding a refrigerant in the space to be cooled.
7. A **heater** (typically electric) provides heat to the HTF to slowly sublimate the ice and desorb solvent from the frozen cake on the shelves.
8. The **vacuum pump** pulls vacuum in the chamber and condenser.
9. **Control hardware and software systems** direct various parts of the complex freeze-drying equipment and carry out the preprogrammed lyophilization cycle. The controller may also provide documentation, data logging, and security capabilities.

In addition, auxiliary systems provide capabilities including :

- cleaning and sterilizing the lyophilizer, e.g., steam-in-place (SIP) or clean-in-place (CIP)
- stoppering vials
- auto-load and unload
- supplying extra or significant backup power, cooling water, and lubrication for the mechanical refrigeration system (cryogenic systems do not need these)
- supplying liquid nitrogen (LN_2) to a cryogenic system, which includes an insulated LN_2 tank and piping to the refrigeration skid (mechanical systems do not need these).

All these systems must work together seamlessly to ensure desired end-product quality.

Figure 1. Typical shelf cool-down capability of large commercial freeze-dryers with >20 m^2 shelf-space. Note the inferior performance of mechanical versus cryogenic liquid nitrogen refrigeration systems in terms of cool-down rate, cooling rate sustainability, and lowest temperature.



for freeze-drying have further increased, and their cost of ownership has decreased.[8–11] With these improvements, LN_2/GN_2 systems are ready for mainstream processes. In this article and the subsequent cryogenic lyophilization article, we outline key considerations to help users make informed decisions about what type of refrigeration is best for a particular lyophilization situation.

REFRIGERATION REQUIREMENTS IN LYOPHILIZATION

There are two key considerations in providing refrigeration to a process: 1) the refrigeration temperature required, and 2) the maximum cooling power required. First, the refrigeration temperature required by the process determines the type of refrigeration system needed. Commercially available refrigeration technologies have different fundamental thermodynamic limitations in terms of operating temperature, cooling rate capability, efficiency, and cooling power. Second, the peak and turn-down capacities of the chosen type of system are determined by the refrigeration load profile over time.

Lyophilization is a unique process from a refrigeration point of view, not only for requiring ultralow-temperature refrigeration (below –50 °C),[12] but also because the load is extremely variable, often requiring a system turn-down in excess of 10:1.[7] Both these key requirements favor cryogenic refrigeration over mechanical systems.

Chamber shelves (and sometimes walls) need to be cooled down to between –40 °C to –60 °C. The actual target temperature may vary from product to product, but it must always be set below the eutectic temperature of the solution to be lyophilized. The eutectic temperature is the lowest value at which a mixture of materials will melt. Meanwhile, the lowest temperature in the condenser typically needs to be between –60 °C and –80 °C, and sometimes as low as –100 °C, to make sure the solvent condenses out at a rate that will maintain an appropriate vacuum in the chamber. These temperatures depart from the comfortable realm of "industrial refrigeration," defined as refrigeration from –35 °C to –50 °C.[12] Thus, the requirements of lyophilization mainly reside in the "ultra low-temperature refrigeration" space, defined as –50 °C to –100 °C.[12] The efficiency and reliability of mechanical systems deteriorates as refrigeration temperature drops. Cryogenic systems, in contrast, provide practically constant cooling power throughout the temperature ranges of any lyophilization cycle.

Depending on the effectiveness of the condenser, the condenser surface is kept at a temperature approximately 10–20 °C lower than the shelves, i.e., –50 to –80 °C during drying. It is critical to ensure that the temperature of the accumulating ice remains cold enough to condense out the solvent vapors. If not, the vacuum in the chamber can be lost, leading to loss of process control and possible destruction of valuable product. Meltdown of the cake occurs when the temperature of the product rises faster than the removal of the moisture or solvent. In addition, vacuum pump seal fluids may become contaminated by the solvent coming in through the condenser. Vacuum levels are typically controlled by adding refrigeration to the condenser, thus causing further condensation of the solvent vapors. Some experts therefore, view the condenser as a vacuum pump operated by refrigeration. Reliable and flexible cooling of the condenser is also crucial to lyophilization.

Refrigeration Temperature and Cool-down Rate

Operating temperatures below –50 °C negatively affect the performance, efficiency, and reliability of mechanical systems. However, such operating temperatures have no impact on cryogenic systems driven by liquid nitrogen (which has a normal boiling point of –195.8 °C). The cooling rate and efficiency of a mechanical compressor-based system starts to deteriorate below –20 °C.[7,8] Figure 1 shows the typical shelf cool-down of large commercial freeze-dryers equipped with mechanical compressors versus cryogenic heat exchangers. Cryogenic systems are capable of providing a rapid, constant cool-down rate throughout the entire ultralow temperature range. Mechanical refrigeration systems, on the other hand, cannot maintain their initial cool-down rate. This is probably the reason why original equipment manufacturers (OEMs) of freeze-dryers relying on mechanical compression equipment typically specify the cool-down rate in terms of overall time to reach a certain temperature. Citing an average rate can mask a deteriorating cooling rate over time. Only cryogenic systems can maintain cool-down rates of 1 °C per minute or higher over the entire temperature range of a lyophilization cycle.

Figure 1 also shows that LN_2 systems can reach –55 to –70 °C setpoint for the heat transfer fluid (HTF) inlet temperature to the shelves one to two hours faster than comparable mechanical units reaching a –50 °C setpoint. If the lyophilization cycle requires rapid cooling, this means increased productivity in terms of cycle time reduction. The manufacturers of sensitive products, such as vaccines, attain product viability benefits from rapid cooling. In addition, LN_2/GN_2 systems can easily go to even lower temperatures if required. Their lowest operating temperature is limited by the characteristics of the HTF, not those of the refrigeration system.

In summary, LN_2 systems offer a wider processing window of operation leading to added flexibility and productivity benefits. They do not suffer from the fundamental thermodynamic limitations of mechanical refrigeration systems, such as deterioration of efficiency and cool down rate, or limits on operating temperatures.

Highly variable refrigeration at temperatures between –40 °C and –80 °C is best served by cryogenic refrigeration.

Refrigeration Load Profile

Lyophilization has special demands due to the extreme variability of the refrigeration load requirements. There are two main cooling circuits in a freeze-dryer: one for the shelves and another for the condenser. The shelf cooling circuit needs high-peak refrigeration power for the relatively short time (two to three hours) required to cool down the freeze-dryer and its contents, and to freeze the entire batch. This peak load on the shelf circuit is followed by a relatively longer period (one to three days) requiring significantly lower refrigeration power for the condenser circuit, but at a lower temperature. This load serves mainly to condense out the ice, which is slowly sublimating and desorbing from the product during primary and secondary drying. The corresponding refrigeration power required to run the condenser circuit is typically an order of magnitude lower than that required by the shelves for initial cool down and freezing.

This type of highly variable refrigeration at temperatures between –40 °C and –80 °C is best served by cryogenic refrigeration. LN_2/GN_2 systems are much more flexible in this temperature range, and are capable of efficient turn-down. Mechanical refrigeration systems are better suited to meeting steady demands. Compressors are ill-suited for short duration peak loads followed by extended operation at low load and ultralow temperatures. Under such conditions, compressors run inefficiently, using a lot of power while providing minimal cooling. They are designed to meet the short period peak load, yet are operated under suboptimal efficiency conditions for most of the lyophilization cycle time. Cryogenic systems, on the other hand, easily meet the variable refrigeration demands of lyophilization. Unlike mechanical systems, cryogenic systems operate with only small changes in thermal efficiency during the entire process cycle.

Table 1. Overview of the properties of some low-temperature heat transfer fluids (HTFs)[12,13]

Heat transfer fluid	Density [kg/m^3] @ –80 °C	Viscosity at –80 °C [mPa(s)]	Flash point [°C]	Reported freezing point [°C]	Boiling point [°C]	Temperature at which kinematic viscosity >10 cSt [°C]
d-Limonene			43	–96	176	–80
Dynalene HF	870	60	>60	<–112	186	
Dynalene MV	>920	10	53	–118	176–179	
Ethanol	810	6.3 @ –50 °C	12	–117	78	–60
Novec HFE 7000	1700		Not flammable	–122	34	<–110
Novec HFE 7100	1720		Not flammable	–135	61	<–95
Hydroflouroether			Not flammable	–130	60	–30
Methanol	867	6.1	12	–98	65	–90
Polydimethylsiloxane	965 @ 25 °C		>110	–50	<200	
Syltherm XLT	968	33.7	42	–111		

The above data are derived from manufacturers' websites, MSDS publications, and public sources.

The thermophysical properties of the heat transfer fluid circulating in the freeze-dryer have a significant impact on the unit's performance.

REFRIGERATION SYSTEMS USED IN FREEZE-DRYERS

All lyophilization refrigeration systems feature an HTF loop, which is the passive component from a refrigeration point of view. The HTF loop includes the fluid, piping, and pumping system with controls. The main differences between refrigeration systems are in 1) the active component(s) that drive the system, and 2) the necessary auxiliary systems. The active refrigeration system cools the low temperature HTF, which in turn refrigerates the shelves. Typically, a separate active circuit needs to provide the cooling for the condenser by direct expansion of a refrigerant, except in some advanced designs.

Low Temperature HTF

The thermophysical properties of the HTF circulating in the freeze-dryer have a significant impact on the unit's performance. Many of these properties are highly temperature-dependent. For example, the viscosity of the HTF can significantly increase as the temperature declines and approaches first the HTF pour point and then the freezing point. Although high pump-around rates ensure low temperature differences between the shelf inlet and outlet temperatures of the HTF, they may also lead to significant frictional parasitic heat generation. Hence, care must be taken in choosing the proper HTF. Table 1 summarizes key properties of some popular HTFs.

Mechanical Refrigeration Systems

In mechanical systems, compressors driven by significant electric power provide the active cooling. In general, ultralow-temperature mechanical systems that match the refrigeration demand at the necessary operating temperatures are increasingly complex and less flexible. They involve multistage or multirefrigerant cascade compression systems.[12] The complex refrigeration package includes compressors, heat exchangers, expansion devices, evaporators, and extensive controls. Necessary auxiliary systems include a cooling water loop, oil lubrication system, and an extra power infrastructure (including an extra supply and backup system) to support the significant power draw of the compressors. The rotating compression equipment involved can be screw or reciprocating types, with a trend towards costlier screw compressors because of their better reliability.[7,10,12] The cooling duty is provided by appropriately chosen refrigerants, such as R-23, R-404a, R-507, and R-508b (an azeotropic mixture of R-23 and R-116).[12] The refrigerants are first vapor compressed, condensed, adiabatically expanded, and evaporated 1) in a heat exchanger to cool the HTF, and 2) directly in the condenser to freeze out the solvent ice. These refrigerants are typically single or multiple component mixtures of hydrofluorocarbons (HFCs), which are often toxic or flammable.

Cryogenic Refrigeration Systems

Cryogenic cooling systems recover the stored cold from liquid nitrogen in specially engineered cryogenic heat exchangers. The necessary auxiliary systems include a liquid nitrogen storage tank, a set of cryogenic valves, and piping from the tank to the refrigeration skid. All of these components are highly insulated to minimize cryogen losses, e.g., by vacuum jacketing or superinsulation. The cryogenic LN_2/GN_2 cools the HTF in an initial cooling circuit. Typically, a second LN_2/GN_2 cooling circuit cools the condenser by direct expansion in the coils or plates. A more advanced cryogenic refrigeration system is noq available that uses a single nonfreezing cryogenic heat exchanger to simultaneously cool both the shelves and the condenser at different temperature set-points using two HTF loops.

SUMMARY

As demand for parenteral and biologically-derived products expands, companies are increasingly using lyophilization to protect and stabilize their sensitive pharmaceutical and biologic products. Freeze-dryer performance is key to achieving the required activity, stability, quality, and shelf-life for the finished products. As products are becoming more complex, cryogenic nitrogen refrigeration is gaining favor over mechanical refrigeration because of its inherent reliability and responsiveness to meet stringent and flexible cooling profiles while achieving ultra-low shelf and condenser temperatures. This will be further discussed in Part 2 of this article, to be published in the December 2007 issue. ◆

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Increasing Lyophilization Productivity, Flexibility, and Reliability Using Liquid Nitrogen Refrigeration

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Part 2

ABSTRACT

In part 1 of this article, published in the November 2007 issue of *BioPharm International*, the lyophilization process, related equipment, and refrigeration requirements were discussed. This part 2 introduces key design considerations related to cryogenic refrigeration systems and provides guidance on relative cost factors for using cryogenic versus mechanical refrigeration in lyophilization operations. The article also discusses reliability and maintenance requirements; flexibility in terms of operating temperature range, cooling rate capability, and precision of temperature control; cost of ownership; footprint; and environmental impact.

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Flexible, precise, and reliable cooling of the shelves and condenser in a lyophilizer is critical to effectively freeze-dry and protect a broad range of sensitive, high value pharmaceutical products. Conventional cooling methods, as introduced in part 1 of this article, include using either mechanical or cryogenic nitrogen-based refrigeration. Part 2 begins with an overview of the fundamental thermodynamic characteristics of cryogenic nitrogen and the factors influencing the maximum amount of refrigeration available from cryogenic systems. An optimal refrigeration design provides flexible, robust cooling at reduced cost of ownership versus mechanical alternatives.

We will now review the fundamental thermodynamic characteristics of cryogenic nitrogen, and the factors influencing the maximum amount of refrigeration available from the cryogenic fluid.

FUNDAMENTALS OF CRYOGENIC REFRIGERATION

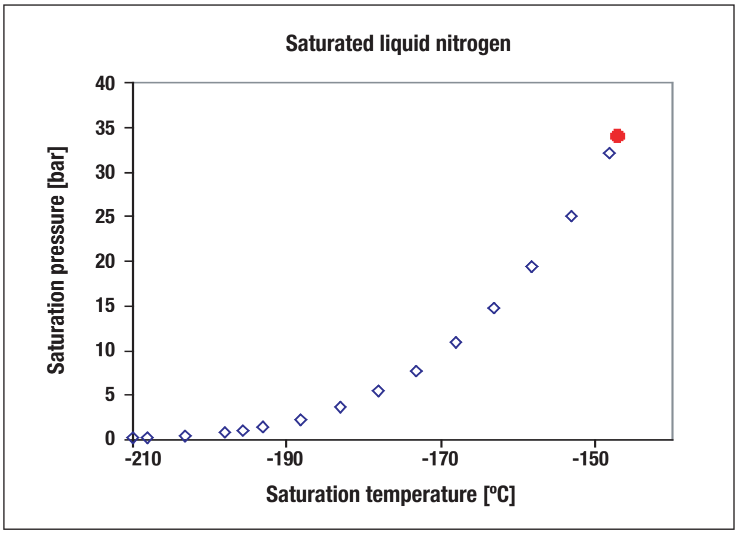
Liquid and Gaseous Nitrogen

Pressure and temperature are two key intensive thermodynamic variables that determine the state of any saturated fluid and thus the refrigeration available from it. The saturation pressure of liquid nitrogen as a function of temperature is shown in Figure 1.

Maximum Refrigeration from Liquid Nitrogen

Saturated liquid nitrogen stores refrigeration in the form of its latent heat of vaporization, i.e., the energy associated with the liquid changing state to gas without a temperature change. Boiling the liquid nitrogen (LN_2) to gaseous nitrogen (GN_2) provides the refrigeration in a cryogenic heat exchanger. Figure 2 illustrates the available latent heat as a function of operating pressure and tem-

Figure 1. Saturation pressure and temperature of liquid nitrogen up to the critical point (marked in red), above which a distinct liquid phase cannot exist[1]



perature. The lower the pressure and temperature, the more refrigeration is available for recovery.

Maximum Refrigeration from Gaseous Nitrogen

Sensible heat is the energy associated with a change in the temperature of a substance. Depending on the cryogenic system design, the sensible heat from warming the gas may also be recovered in the same or another heat exchanger. The two key factors that determine the maximum amount of refrigeration recoverable per unit mass of cryogen are the heat capacity and the temperature rise of the fluid.

Maximum Refrigeration Recoverable from Liquid and Gaseous Nitrogen

We can calculate the total recoverable refrigeration from cryogenic nitrogen by adding the two key components, i.e., the latent and sensible heat. Figure 3 shows an example of total available refrigeration as a function of gas exhaust temperature for near-atmospheric-pressure operation. The latent heat from vaporizing the liquid and the sensible heat from warming the gas each account for approximately 50% of the available refrigeration capacity under typical operating conditions. At higher pressures, the latent heat of vaporization decreases, as shown in Figure 2, thus reducing the total available refrigeration.

COMPARISON OF VARIOUS CRYOGENIC REFRIGERATION SYSTEMS

This section describes cryogenic heat exchange technologies in terms of freezing characteristics, efficiency of refrigeration utilization, and operating parameters as related to system design. Additional critical design considerations are also outlined.

Refrigeration Utilization Efficiency of Cryogenic Systems

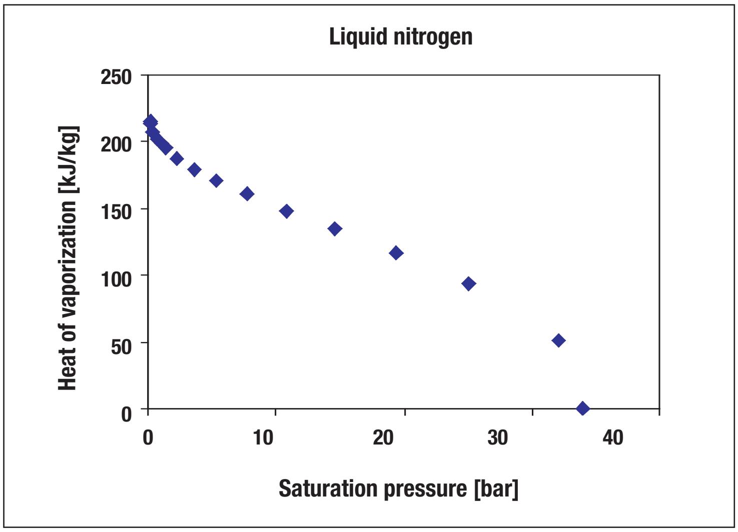
At a given operating temperature and pressure, the fundamental thermophysical properties of cryogenic nitrogen (discussed earlier) make a certain amount of refrigeration available from the fluid. If a 100% efficient cryogenic refrigeration system existed, thermodynamics would still limit the amount of refrigeration available. The design and implementation of the cryogenic cooling system determines what percentage of the available refrigeration is actually recovered by first vaporizing the LN_2, and subsequently warming the GN_2. The majority of current designs recover most of the latent heat of vaporization. However, designs vary in their capability of recovering the sensible heat by warming the gas. The closer the approach temperature of the gas exhaust is to the heat transfer fluid (HTF) outlet temperature, the higher the efficiency of the cryogenic heat exchanger. We have demonstrated a design that recovers 95–98% of the available refrigeration in a single cryogenic heat exchanger. These efficiencies have been achieved in commercial systems with refrigeration capacities up to 150 kW and operating temperatures as low as –80 °C.

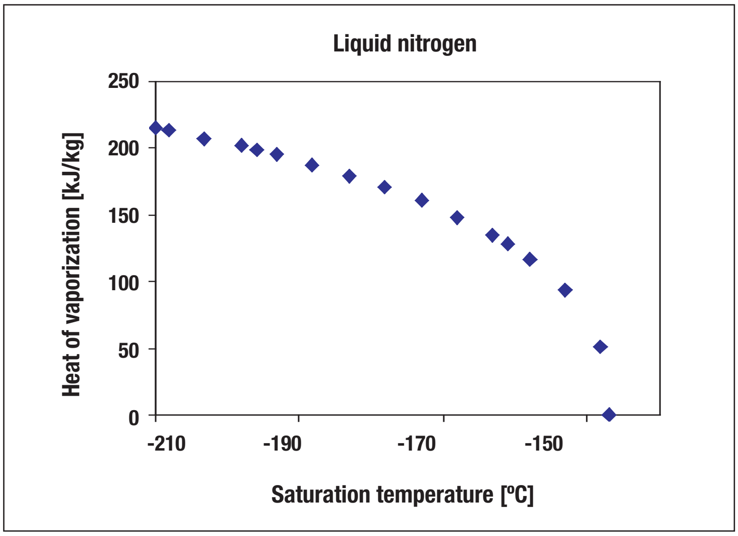
Freezing Characteristics

When cryogens are used to cool anything, freezing the entire heat exchange system is a serious concern. LN_2 boils at –195.8 °C at atmospheric pressure. As discussed earlier, almost all HTFs used in lyophilization freeze at well above this temperature. Freezing of the HTF has limited the widespread application of cryogenic heat exchangers. Some cryogenic heat exchanger designs freeze after only a few hours of operation.[2] For longer cooling cycles, several such units are needed to enable parallel defrosting of the frozen heat exchangers and to compensate for refrigeration capacity losses due to the insulating properties of ice.

Recent years have seen the development of

Figure 2. Latent heat of vaporization of liquid nitrogen as a function of saturation pressure and temperature[1]





nonfreezing cryogenic heat exchanger designs that eliminate the need to switch between frozen and defrosted units. Such nonfreezing designs enable cooling over the long cycles used by lyophilization. They include both a single heat-exchanger design[3] and multi-heat-exchanger systems, which use high-pressure fluid ejectors[4] or plate-and-frame designs.[5] These designs avoid any heat transfer surfaces where HTF is on one side and boiling LN_2 on the other by first boiling the LN_2 against GN_2, and then using only the GN_2 to cool the HTF. Consequently, the HTF exchanges heat with only nitrogen gas, thus avoiding the extremely low temperatures of LN_2. The nonfreezing single heat exchanger incorporates this capability into one special heat exchanger unit using a proprietary design.[3] Nonfreezing multi heat-exchanger systems need multiple heat exchangers, and in some cases an ejector, to accomplish the same result.[4,5]

Impact of Operating Pressure on Cooling Capacity and LN_2 Use Efficiency

The absolute amount of refrigeration recovered from the LN_2 will also depend on the operating pressure of the cryogenic system. As Figure 1 shows, increased pressure leads to warmer operation. This is a strategy often used to delay or avoid freezing the HTF in the cryogenic heat exchanger.[2,4,5] The main downside to this approach becomes obvious in examining Figure 2. While the warmer temperature may alleviate freezing problems, the available latent heat of vaporization drops significantly with increasing pressure and temperature. An example of such a system is the LN_2/GN_2 recirculation system with high-pressure fluid ejector technology as shown in Figure 4. The proposed 11-bar LN_2 may boil almost 30 °C warmer than at atmospheric pressure, however, it also has over 40 kJ/kg less heat of vaporization to give off. That is approximately 20% of all the available refrigeration from the phase change. Praxair has developed a system that operates with as little as 3 bar LN_2 pressure. Operating at a lower pressure helps the system recover more refrigeration, which is available for cooling, reducing the amount of LN_2 consumed in the process.

Impact of HTF Velocity

Many conventional cryogenic heat exchangers require a high HTF velocity to delay freeze up.[2] A highly viscous fluid like an HTF at low temperature flowing at high velocity will generate significant frictional heat, i.e., parasitic heat, which will add to the refrigeration demand of the system. Therefore, choosing a refrigeration system with the lowest minimum HTF fluid velocity requirement is important.

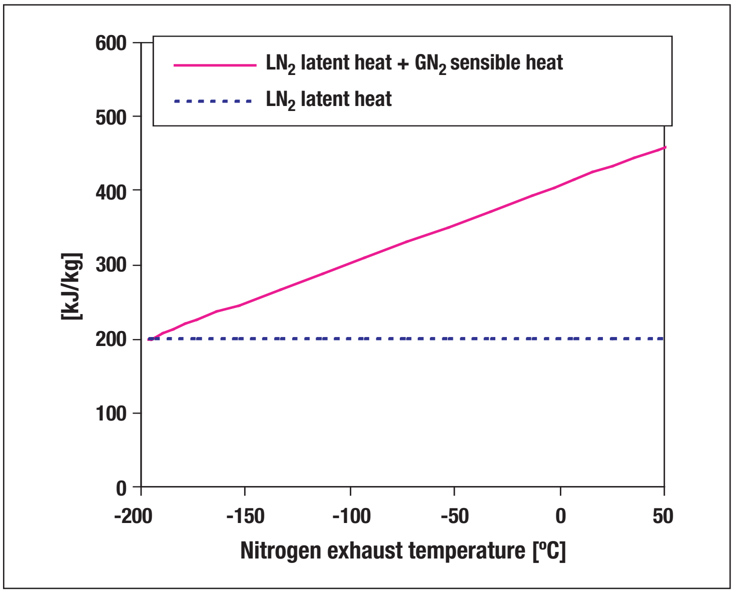
COOLING THE CONDENSER

The condenser is typically cooled by direct expansion of a refrigerant into the coils or plates (DX condenser). In the case of a mechanical refrigeration system, the refrigerant is usually a hydrofluorocarbon type chemical or a mixture of chemicals.

Cryogenic systems often use direct expansion of LN_2 and/or GN_2 to cool the condenser surfaces. A simplified process-flow diagram is shown in Figure 5. In all these cases, the liquid refrigerant vaporizes in the DX condenser, forming a two-phase flow. The significant heat transfer coefficient difference between the liquid and gas phase refrigerant causes uneven cooling rates at different points in the condenser. The result is uneven ice formation and nonuniform use of the condenser surface.

To avoid two-phase flow and the related nonuniform performance of the condenser, a so-called fluid condenser option is also available. In this case, one or more dedicated compressors or cryogenic heat exchangers may cool a separate HTF loop, which in turn cools the fluid condenser. The downside of a fluid condenser is the potential for frictional heat generation. If a cryogenic heat exchanger is applied, a low HTF velocity helps minimize the parasitic heat generation. The efficiency benefits gained from more uniform use of the condenser surface often outweigh the minor increase in frictional heat generation. A simplified process flow diagram of the refrigeration system for a freeze-drying application developed by Praxair is shown in Figure 6. In place of separate dedicated refrigeration systems for the shelves and condenser, we recommend a unique configuration with a single nonfreezing cryogenic heat exchanger. This heat exchanger cools two HTF loops with differing temperature setpoints and refrigeration demands. The warmer HTF loop cools the shelves, the colder one the condenser. Major advantages of the single-heat-exchanger configuration include significantly reduced capital cost for the refrigeration system and lower LN_2 consumption compared to cryogenic refrigeration systems that use both a heat exchange system and a LN_2 DX condenser to meet the cooling requirements of the lyophilization process.

Figure 3. Total available refrigeration from liquid and gas nitrogen at atmospheric pressure as a function of the exhaust temperature of the gas.



COST OF OWNERSHIP ANALYSIS FOR LIQUID NITROGEN AND MECHANICAL REFRIGERATION IN FREEZE-DRYING

Table 1 illustrates the key components of the cost of ownership of the refrigeration part of a freeze-dryer. Both the capital items and operating costs were considered. Overall, if one considers the cost of auxiliary systems and maintenance for mechanical refrigeration, LN_2 units are less expensive. After many years of operation of commercial mechanical units, the same conclusion was drawn by Liu.[6]

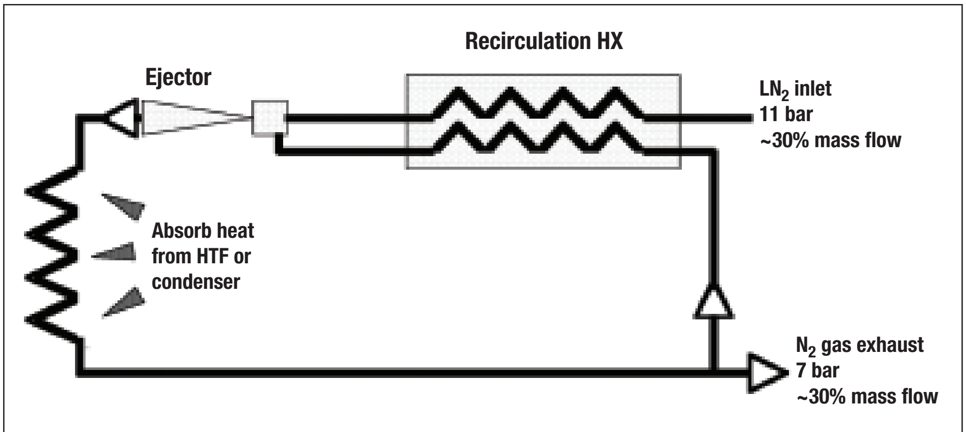
The amount of nitrogen required for refrigeration will depend largely on the thermal efficiency of the cryogenic heat exchange system. High efficiency, nonfreezing systems that operate at low pressure use 15–30% less nitrogen than high-pressure nonfreezing systems and systems that do not use a nonfreezing design. LN_2 costs can account for as much as 50% of the overall costs to operate a cryogenic freeze-drying system. Therefore, LN_2 refrigeration efficiency should be considered while selecting the cryogenic refrigeration system.

OTHER KEY CONSIDERATIONS

Reliability

The inherent reliability of cryogenic refrigeration systems is important to manufacturers of high-value and sensitive products, such as

Figure 4. LN_2/GN_2 recirculation heat exchange system using high-pressure ejector technology[4]



protein therapeutics and vaccines. Lyophilization production managers often worry about the breakdown of the mechanical compressors on their freeze-dryers, which would lead to the loss of entire batches. A cryogenic refrigeration skid contains no moving parts unlike compressor-based mechanical refrigeration skids. Properly used and maintained, LN_2/GN_2-based refrigeration systems can run for decades with minimal maintenance requirements and a low chance of failure. The resulting savings in maintenance and repair of both parts and labor can amount to hundreds of thousands of dollars over the life of a commercial freeze-dryer. In addition, the value of the significant reduction in the risk of mechanical failure and subsequent loss of a batch due to catastrophic compressor or power failure can often be measured in excess of a million dollars, depending on the product.

Table 1. Comparison of estimated cost of ownership for mechanical versus cryogenic refrigeration of a typical commercial freeze-dryer operating in North America.[7]

Relative capital expense	Mechanical compressors	>95% efficiency cryogenic heat exchanger
Refrigeration skid	Comparable	Comparable
Cooling water systems	Moderate	None
Upgrade power	Low	None
Liquid nitrogen vacuum jacketed piping	None	Low
UPS battery	Low	Low
Operating cost factors	**Mechanical**	**Cryogenic**
Cooling water/treatment	Low	None
Power	Moderate	Low
Liquid nitrogen	Not applicable	Moderate
M&R parts	Moderate	Low
M&R labor	High	Low

Flexibility

Calculating the exact cycle specifications for product cool-down rate, freezing, and temperature profiles to be delivered by the refrigeration and heating system depend heavily on the particular characteristics of the product. These profiles may differ radically depending on the product formulation. The more flexible the design of the refrigeration system, the more versatile the unit will be. Additional flexibility and control will better position the owner for processing new formulations with new requirements. Cryogenic refrigeration using LN_2/GN_2 enables manufacturers to operate across a broad range of processing parameters, both at cool-down and at constant cooling to temperatures lower than –80 ºC. Using a cryogenic system, the lowest temperature on the shelves is limited by the thermo-physical properties of the HTF, not the refrigerant. Direct expansion of cryogens in the condenser or a nonfreezing cryogenic heat exchanger with a high performance HTF can provide temperatures below –100 ºC in the condenser.

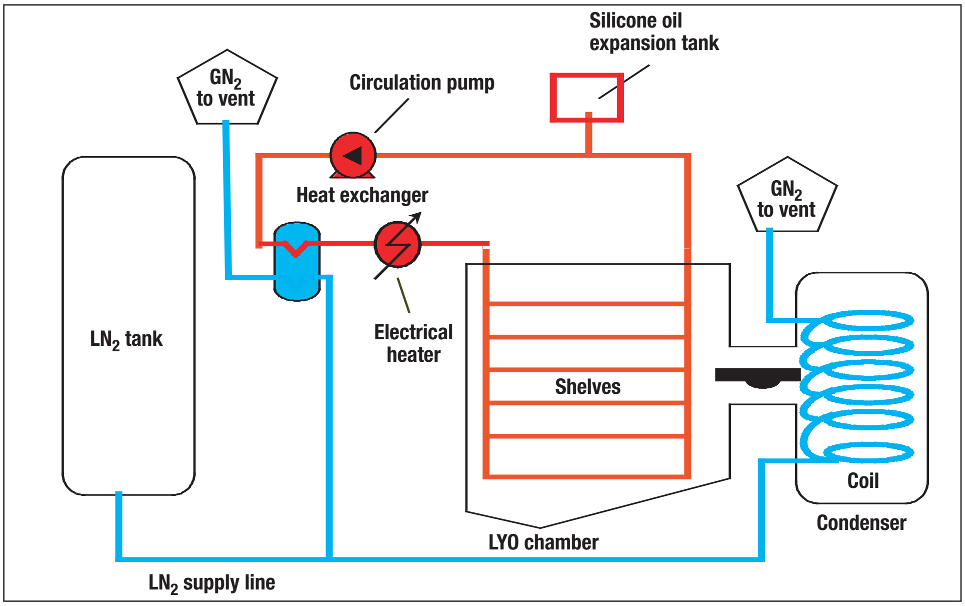
Footprint

A cryogenic refrigeration system requires fewer and less complex components. Typically, a cryogenic refrigeration skid only requires approximately one-half to one-third the space of a comparable mechanical compressor-based skid.

Environmental Impact

Nitrogen is an inert molecule that is nontoxic and nonflammable, with no ozone-depleting or global warming potential. It comes from, and returns to the atmosphere after giving off its refrigeration. Most HFC-based refrigerants

Figure 5. Liquid nitrogen (LN_2) freeze-dryer unit with heat transfer fluid heat exchanger and direct expansion of liquid nitrogen in condenser[8]



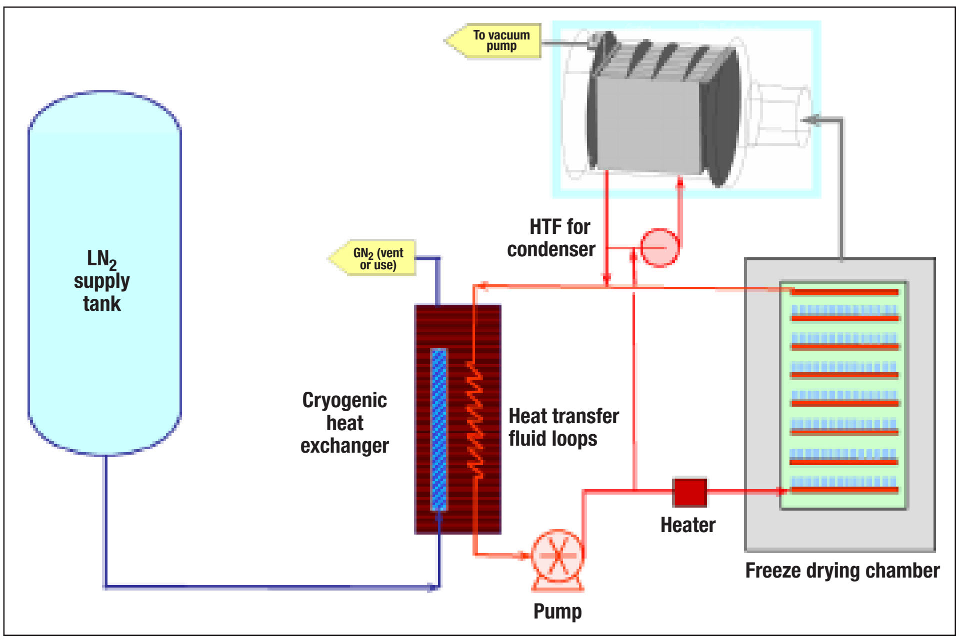


Figure 6. Simplified process flow diagram of a liquid nitrogen freeze-dryer using a fluid condenser and a single cryogenic heat exchanger to cool both the shelves and the condenser heat transfer fluid circuits.

are either toxic, flammable, or both. LN_2/GN_2 refrigeration of the lyophilization operation reduces space requirements and noise, and is environmentally friendly.

CONCLUSION

The growth of LN_2/GN_2 freeze drying is particularly driven by the need for 1) increased reliability for high-value products, 2) enhanced flexibility, 3) increasing number of formulations containing biologics and 4) dosages with high-fill depth and high volume. The users of lyophilization technology and related equipment are just starting to realize many of its benefits. Many decision makers, still unaware of the benefits associated with LN_2/GN_2 systems, are also surprised at the lower cost of ownership of a well-designed LN_2/GN_2 system offering high LN_2 efficiency at a low capital expenditure. These features are also worth considering for manufacturers aiming to increase the efficiency, operating flexibility, and profitability of lyophilization systems while controlling costs. ◆

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