Advances in Liquid Nitrogen (LN₂) Based Lyophilization Technologies

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Agenda

• Introduction
• Liquid nitrogen (LN2) in lyophilization
• Advances in cryogenic heat exchanger and condenser design
• Case Studies – experience with cryogenic systems
• Mechanical verses cryogenic systems
• Selecting the Refrigeration System to Meet Your Needs
• Summary
Advantages of Freeze-Dryers Refrigerated by Cryogenic LN₂/GN₂

- **Greater operating flexibility**
  - reach lower temperatures (required for e.g. alcohol-based formulations)
  - faster cooling and/or freezing (required for e.g. vaccines)
  - maintain desired constant cooling rate
  - refrigeration on demand

- **Improved reliability**
  - minimal maintenance

- **Eliminate use of environmentally harmful refrigerants**

- **Better control over product freezing & structuring**

- **Cost competitive w/ mechanical compressor-based systems**

- **Smaller system footprint**

- **Emergency (freeze down) operation**

- **Quiet operation**
Challenges in Using LN2 as Refrigerant

- **Extreme cold temperatures of LN2**
  - Boiling point at -195 degree C
  - Can freeze most heat transfer fluid in a short period of time

- **Difficult to control the release of refrigerant**
  - The latent heat from boiling represent $\frac{1}{2}$ of refrigeration available
  - Rate of boiling can be effected by pressure and surface temperatures

- **Challenge to control the temperature precisely**
  - The temperature driving force is very large
    - Typically over 150 degree C
Where Can Cryogenic Cooling be Applied?

- Cryogenically chilled heat transfer fluid using cryogenic HX
- Direct Expansion of liquid nitrogen
- Direct contact spray freezing with sterile liquid nitrogen
- Cryogenically chilled heat transfer fluid using cryogenic HX
- Direct Expansion of liquid nitrogen using cryogenic cold shelf
Typical Lyophilization Cycle Requires Freezing & Low Temperature Refrigeration

Shelf Temperature

Product Temperature

Ice Temperature

Max refrig. demand
Long cycle at lowest temperatures (on condenser)

Time [hr]

Source: www.niroinc.com/html/pharma/thermodynamic_lyophilization_control_PAT.htm
Traditional Approach to Control the LN2 Refrigeration Rate

- **Use warmer LN2 at higher pressure**
  - Loss of refrigeration values with high pressure LN2
  - LN2 at 100 psig has 20% less refrigeration than LN2 at 30 psig

- **Use heaters to minimize overshoot in cooling**
  - Any overshoot in cooling is a loss of refrigeration
  - Heater has to be large than necessary
  - High potential to freeze the HTF

- **Use defrosting cycles**
  - Any defrosting cycle is a waste of refrigerant
  - Limit the use of HTF chilled by LN2 for the chamber only

- **Do not measure or record condenser surface temperatures**
Advances in the Heat Exchanger Design with NCOOL™ Heat Exchanger

NCOOL™ Heat Exchanger in Operation

Design with Computer CFD Simulation

Fully Integrated with Process PLC

Non-Freezing: Gas buffer avoids direct contact of LN2 on HTF surfaces

US Patent 5,937,656
Advantages of the Praxair NCOOL™ Cryogenic Heat Exchanger

- Advanced LN₂ Heat Exchangers (NCOOL™ Systems)
  - Utilize both LN₂ and GN₂ refrigeration
  - >95% refrigeration efficiency ⇒ 20-50% less LN₂ vs. alternatives
  - Low LN₂ pressure (colder) required ⇒ 20% saving in LN2
  - >20:1 turn down capability
- Lowest temperature limited only by Heat Transfer Fluid physical properties
- 1/10th HTF minimum velocity
- Minimal frictional heat
- CFD design optimization
- Low cost of ownership

Flexible, Economic, Efficient and Freeze Resistant
NCOOL™ Heat Exchanger in Typical Freeze Drying Configurations

With direct expansion LN2 condenser
Nonfreezing characteristic of NCOOL™ versus the Heliflow

![Graph showing the comparison between NCOOL™ and Heliflow in terms of the coldest achievable temperature.]

- Heliflow: Increasingly difficult to avoid freezing
- NCOOL: Methanol freezes at -143.8 °F
Mechanical Heating is significant at the High Velocities

Base on 38,000 BTU/hr unit with Methanol as HTF
Cryogenic Refrigeration Utilization Efficiency and Cool Down of NCOOL™ Heat Exchangers

150 kW NCOOL™ Heat Exchanger Performance
Calculate the Thermal Efficiency of Cryogenic Heat Exchangers

- **Utilization Efficiency**
  \[ Utilization\ Efficiency = \frac{Actual\ Refrigeration\ Transfer}{Maximum\ Theroritical\ Refrigeration} \]

- **\( U_{eff} \)**
  \[ U_{eff} = \frac{\Delta H_{vap, LN2} + Cp \left( T_{GN2, out} - T_{LN2, in} \right)}{\Delta H_{vap, LN2} + Cp \left( T_{HTF, in} - T_{LN2, in} \right)} \]
Praxair High Capacity Direct Expansion Cryogenic Condenser, HCCC™ for Ice Harvesting

Computer CFD Simulation

HCCC™ Cryogenic Condenser

US Patent 6,505,472 B1
Case Study: Commercial Installations with 100 kW NCOOL™ and HCCC™ Cryo Condenser

Dual NCOOLs for chamber and wall cooling

PLC control from SP Industries
Advanced Technology - Single Cryogenic Heat Exchanger Freeze-Drying Process*

*Non-freezing Heat Exchangers Needed*
Case Study: Fast Temperature Responds with Cryo Chilled HTF for Both Chamber and Condenser

Cryo chilled HTF to chamber and condenser can have very fast responds and good temperature control

*Data during FAT
Case Study: Improved Process Control and Flexibility with Single LN₂ Heat Exchanger

- Precise Temperature Control
  - Shelves
  - Condenser

- Seamless controls integration with freeze-dryer PLC

- Indefinite Cryogenic Heat Exchanger operation without freezing

- Increased reliability
  - Minimal moving parts
Case Study: Improved Uniformity of Ice Deposit on Condenser Surfaces with HTF Fluid Cooling

20 m² freeze dryer with 35 kW NCOOL™

Very uniform Ice Formation at the condenser chilled with HTF from the NCOOL™
LN$_2$ Refrigeration vs. Mechanical Refrigeration Offers:

- Faster cool down rate
- Constant, sustained cool down rate
- Ability to reach lower temperatures
  - Temperatures to -125°C (limited by HTF)

Case Study: 1,000 ft$^2$ Freeze-Dryer with 13 minute cool down time and 5°F/min cool down rate
Cool Down Rate Comparison: LN$_2$ vs Mechanical Refrigeration
Case Study: More Uniform Heat Transfer than Direct Expansion of Freon

- LN2 Cooled HTF in condenser & shelves
- Uniform ice on entire coil from inlet to outlet
- Increased ice capacity
Case Study: Open up Valuable Floor Space with Cryogenic Cooling

150 kW Cryogenic Refrigeration Skid (with heater and pumps) for 1,000 ft² Freeze-Dryer

Mechanical compressor skid for the same 1,000 ft² freeze-dryer
Typical Costs for Freeze-Dryer Refrigeration System: Cryogenic verses Mechanical*

Est. Capital Expenditures:

Est. Costs of Ownership:

* Comparison of a 42 m² mechanical and LN2 freeze-dryer operating in North America
Compare Different Type of Cryogenic Heat Exchangers

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<th>Gas buffered - Nonfreezing</th>
<th>Partial freezing</th>
<th>Thermal mass buffered</th>
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<tbody>
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<td>Thermal Efficiency</td>
<td>&gt;95%</td>
<td>~65%</td>
<td>&lt;60%</td>
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<td>Refrigeration System Cost</td>
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<td>Process Reliability</td>
<td>Enhanced*</td>
<td>Standard</td>
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<td>Approach to HTF Freezing point</td>
<td>+2 C</td>
<td>+10 C</td>
<td>+8 C</td>
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<td>Minimum HTF velocity</td>
<td>1 fps</td>
<td>10 fps</td>
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<td>Mechanical Heat Load</td>
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<td>5-10X</td>
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<td>Operating Flexibility</td>
<td>Best</td>
<td>Worse</td>
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<tr>
<td>Foot print</td>
<td>Good</td>
<td>Best</td>
<td>Worst</td>
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*NCOOL™ is non-freezing type of design*
Refrigeration to Meet Your Needs

Factors Affecting Customer Decision

- **Utility Costs**
  - Cost of power
  - Cost of liquid nitrogen
  - Equipment cost – availability of capital
  - Maintenance cost – planned throughput

- **Facility Resources**
  - Personnel, parts, system redundancy
  - Space availability for refrigeration skid
  - Space availability for bulk tank

- **System Requirements (Formulation Dependent)**
  - Ultra-low temperature requirements (<-50C)
  - Aggressive (rapid change) freezing profile
Advances in Cryogenic Technologies allow additional benefits

Base Benefits

• Achieves lower temperatures (supports non-aqueous solvents)
• Maintains constant cooling rate (better ice structuring)
• Provides faster cooling and/or freezing (vaccines)
• Requires minimal maintenance
• Smaller footprint
• Environmentally friendly (no CFCs)
• Quiet operation
• Nitrogen gas may be available for other uses

Additional Benefits from Advanced Technologies

• Improves reliability - nonfreezing operation
• Improves cGMP operation – precise temperature control
• Maximizes LN2 utilization rate >95% efficiency
• Increases condenser capacity - uniform ice formation
• Can shorten batch time – faster cooling and stable sublimation

Cryogenic systems provide an alternative
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