JAN/FEB 2017

Pharmaceutical Processing

Lyophilization: The Basics

An overview of the lyophilization process as well as the advantages and disadvantages. *By: Meg LaTorre-Snyder*

Lyophilization, defined as a freeze-drying process that removes water from a product after it is frozen and placed under a vacuum, is often messy, but filled with possibilities for potential applications.

Some of the typical pharmaceutical products that would undergo lyophilization include bulk pharmaceutical/biopharmaceutical ingredient (chemical or biologics found in nature), protein, collagen, peptide, oligonucleotide, chemical API, enzymes, and mAbs.

"If the bulk drug ingredients are not stable in liquid or frozen form, lyophilization is necessary. This can be due to chemical reactions, degradation, aggregation, biological growth, heat sensitivity, etc. Lyophilization enables longer shelf life, often as long as two-five years and makes it much easier to transport the product. In addition, products can be stored at room temperature," said Cherish Robinson, Product Specialist, Gore & Associates, Gore PharmBIO Products, detailing why lyophilization—despite some of its challenges—is unmistakably important.

Advantages & Disadvantages of Lyophilization

Some of the advantages of lyophilization, according to the FDA, include:

- Processing a liquid with ease (and thereby simplifying aseptic handling)
- Enhancing the stability of a dry powder as well as the product stability in a dry state
- Removing water without having to heat the product excessively
- Dissolution of reconstituted product (rapidly and easily)

The FDA also lists some of the disadvantages of lyophilization:

- Handling and processing time increases
- Sterile diluent needed upon reconstitution
- Equipment becomes costly and complex

"One of the biggest problems in lyophilization is the mess it can create," said Robinson.

In addition to the process being messy, Robinson details a few other challenges of lyophilization:

- Expensive
- Timely
- Requires large capital investment
- More of an art than a science

The filling of vials that are to be lyophilized can also be challenging, specifically having an open system from filling all the way through the end of the process (and the resulting potential for contaminants to enter the vials).

At present, 80 percent of the market lyophilizes in vials.

"Consider using a closed tray in lyophilization chambers. Using a closed tray can prevent product flyout during the filling, transportation, and lyophilization process, which reduces dryer cleaning time and validation of cleaning procedure," said Robinson.

Lyophilization: The Process

Typically, lyophilization occurs in three stages:

- Freezing
- Primary drying
- Secondary drying

"Freezing takes place in stage one of the lyophilization process. It can take place in the freeze dryer. Some customers freeze in a freezer instead. Freezing temperatures are around -40°C," Robinson explained.

There is no thawing in the second stage, she adds. "The product goes from frozen state to dry powder through the process of sublimation."

"Think of lyophilization as basically freeze-drying—it is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze-drying works by freezing the liquid material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase. This leaves us with a dry powder."

Depending on the type of product and quantity, it can take 12-72 hours to go through all of these stages.

As to the lyophilization process, Robinson broke it down into the following steps:

- Fill tray with liquid solution
- Carry trays over to dryer and load
- Lyophilization (including those three stages)
- Remove tray from dryer and remove powder from try into another bag or sealed container

"Lyophilization is ideally introduced in the R&D phase, but more commonly in Phase 1 of drug development and follows along with the drug development cycle," said Robinson. "End users perform lyophilization in pilot scale in house freeze dryers. At some point, likely around Phase 3, the end user transfers the lyophilization to CMOs unless they have large scale freezer dryers in house."

Regulatory Oversight & Financial Investment

Generally speaking, cleaning protocols involve a lot of oversight. Cleaning validation, for example, is something that the FDA reviews.

Robinson recommends looking for products that help protect the inside of the lyophilization dryers "by containment inside closed and even single-use disposable trays, which can ease the cleaning headaches." Open stainless steel trays—which are effective and often used—necessitate longer and more rigorous cleaning protocols.

In addition, it's important to note that the lyophilization process, itself, is the most expensive operating unit in the production process, according to Robinson.

"Freeze dryers, themselves, are a $2-3 million investment—that equipment is the same regardless if a disposable or reusable SS tray is used. You can have dryers with or without CIP/SIP features," said Robinson.

Lyophilization Trends

There are emerging trends in the pharmaceutical lyophilization space, which Robinson reports are:

- Growth in freeze drying equipment used for pharma/biopharma/biotechnology segment, 13.5% CAGR 2013-20181
- Growth in CMOs used for pharma/biopharma/biotechnology segment, 10.5%
- More complex drug formulations that are not stable in liquid form
- Growth in Oligonucleotides and Peptides, which degrade in liquid form
- Topics being discussed for bulk lyophilization are continuous processing and buffer free solutions

"For bulk drug product, lyophilization improvements are continuing in tray handling, dryer loading, dryer cleaning, and dryer removal," said Robinson, noting that much of the discussion in lyophilization (at present) relates to vials. "Dryer cleaning is a big concern, because of next-batch contamination. This can be a problem and good cleaning protocols are examined to ensure you are not contaminating batch-to-batch."

The Market Today

According to BCC Research, 16 percent of the top 100 pharmaceutical drugs are lyophilized and 35 percent of biologic drugs are lyophilized.

With more than 30 percent of the FDA-approved parenterals lyophilized and soon more than half injectable drugs to require lyophilization—Markets and Markets reports in their 2020 global forecast—there is ample room for standardization and expansion of this freeze-drying process in pharmaceuticals.