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Optimizing Pharmaceutical Processes: A Guide to Lyophilization Cycle Development

Introduction

Lyophilization, commonly known as freeze-drying, is a critical unit operation in the pharmaceutical industry used to preserve and stabilize both small and large molecule drug products and biologics, including monoclonal antibodies, vaccines and peptides. Lyophilization is a process that involves freezing a liquid drug product and then removing the frozen solvent via sublimation, providing a stable solid matrix of drug product and other excipients. This method is particularly suitable for heat-sensitive molecules, as it dramatically mitigates hydrolysis degradation found in liquid product, is more product-sensitive and practical than other drying methods, and avoids the difficulties of multi-component powder filling.

Biopharmaceutical companies have increasingly favoured lyophilization for the formulation of their pharmaceutical products. Primarily, the driving factors leading to the increased use of lyophilization is the ability to stabilize the drug product and excipients in a solid matrix, increasing the shelf life of the product. This, along with the removal of solvents, has a positive impact on storage and distribution requirements.

For instance, many lyophilized drug products experience an increase in thermal stability and no longer require frozen storage. This provides a more cost effective, lower risk, and efficient way to optimise storage and distribution. This is particularly beneficial for drug products that are shipped to countries with tropical climates or lower infrastructure, where temperature may affect the stability of a product, and cold chain storage may not be available.

As companies continue to pioneer new molecules and treatments, it is clear that the stability of these molecules has increasingly become a detrimental factor upon every iteration, and that lyophilization is the pathway to a solution. At PCI, we believe lyophilization cycle development is not only a science, but an art; each drug product that comes into the laboratory presents unique challenges, and the design of a cycle requires an understanding of individual chemistry, characteristics, and interaction to yield a high quality product in every cycle. While there are a myriad of tools and techniques to perform, the below is an overall guide to the lyophilization process, and some of the steps needed for success.

The Lyophilization Cycle

Lyophilization involves a series of steps to achieve optimal product stability and quality. While there are individual intricacies within these steps, they can be broadly categorized into three phases: freezing, primary drying, and secondary drying.

1. Thermal Treatment (Freezing) Phase

The first step in lyophilization is the initial freezing and subsequent thermodynamic arrangement of the product, known as thermal treatment. Thermal treatment is a simple yet crucial step to ensure full nucleation of the solvent and generate uniform frozen matrix to prepare the product for sublimation. Controlled freezing rates, along with annealing and process knowledge of super cooling effects, are often employed to achieve uniform ice crystal distribution. Newer technologies are also providing the ability to nucleate on demand, further increasing product uniformity across lyophilizer shelves, and is a highlight in future lyophilization technology.

At the beginning of the lyophilization process, products must be formulated in such a way that they are suitable to undergo thermal treatment. This often involves the inclusion of cryoprotectants such as saccharides and polyols to protect the product during freezing. Cryoprotectants help maintain the structural integrity of the product by protecting drug substance molecules against drying stresses and, in the case of biologics, help maintain conformation and prevent agglomeration. Bulking agents may also be added to the formulation to ensure a stable and elegant cake post lyophilization.

2. Primary Drying Phase - Sublimation

Following thermal treatment, the most crucial aspect of the lyophilization process begins - primary drying. Primary drying is the namesake thermodynamic process in freeze-drying and, in turn, the most critical to understand. Initially, a vacuum is applied at a very low temperature (the final freeze temperature) and set to control; for most processes this is typically between 30-300 mTorr. Once the vacuum is controlled, the shelf temperature is gradually increased to provide heat to the frozen product. Once the vapor pressure of the frozen solvent surpasses the pressure of the lyophilizer, sublimation begins. The temperature and pressure set points during primary drying, along with the times required, are critical to achieving efficient sublimation without compromising product quality. PAT tools such as Pirani gauge monitoring and product temperature monitoring, thermal characterization analytics (mDSC, FDM) and technical prowess of analysis (e.g. understanding of product resistivity, evaporative cooling, and thermal treatment impact) are just some of processes that the PCI Development teams use to strike the delicate balance between drying time and subsequent product quality. The process is strictly monitored while solvent undergoes sublimation, and upon completion, will have the appearance of a successfully lyophilized product.

3. Secondary Drying Phase - Desorption

Once primary drying is successfully complete, the process has typically removed between 90-95% of the solvent and produced a physically stable lyophilized matrix. There is one problem, however; there is often remaining solvent that is bound between crystals that cannot be fully removed from the energy input of sublimation alone. The final phase - secondary drying, involves further removal of the residual moisture in the lyophilized product by increasing the temperature and removing bound solvent via desorption. The temperature and rate of drying are primarily limited by the stability of the Active Pharmaceutical Ingredient (API) or Bulk Drug Substance (BDS), so care must be taken to prevent degradation of the product. Monitoring residual moisture content is crucial during this phase, and critical to map and understand.

While there are a plethora of other characteristics and intermediary phases which need to be analysed and gauged throughout the process, successful design of the three phases above should yield an acceptably lyophilized product that can withstand the stresses, pathways, and time to get towards the most critical person in the process – the patient.

Critical Success Factors in Lyophilization

A successful lyophilization cycle can maintain the Critical Quality Attributes (CQAs) of the product throughout the product lifecycle with minimum time and energy consumption. Below are some critical success factors:

1. Product Formulation

The composition of the product, including excipients and the choice of cryoprotectants and bulking agents, significantly influences lyophilization cycle development and the overall efficiency of the cycle. The product formulary must be designed with the lyophilization process in mind, and any changes to the formulary must be heavily scrutinized against each phase of the lyophilization process to ensure quality is maintained.

2. Drying Chamber Design

The design of the lyophilization chamber affects the efficiency of the process. Factors such as chamber design (internal vs. external condensing), shelf temperature uniformity, chamber pressure control, and condenser capacity are critical in achieving consistent and reliable lyophilization cycles. Ideally, chambers are rigorously modelled so that vial-to-vial variability is minimized.

3. Vacuum Level and Pressure Control

Proper vacuum levels and pressure control during the primary drying phase are essential for efficient sublimation. Monitoring and adjustment of these parameters ensure the removal of water vapor without compromising the structural integrity of the product.

4. Temperature Control

Precise temperature control throughout the lyophilization cycle is vital. Both freezing and drying temperatures must be carefully monitored and controlled to prevent product collapse, degradation, or formation of analogous products.

5. Monitoring and Control Systems

Advanced monitoring and control systems are integral to lyophilization cycle development. Real-time monitoring of critical parameters, such as shelf temperature and pressure, and PATs such as Pirani gauges, mass spectrophotometers, and state-of-the-art monitoring software, ensure process consistency and product quality.

Lyophilization Cycle Development Process

Lyophilization cycle development is a meticulous and multifaceted task that requires careful consideration of various parameters to ensure product quality, efficacy, and stability is designed into the product during development. The development of an optimal lyophilization cycle involves several steps:

1. Formulation Design

The product's formulation must be carefully designed to ensure that it is suitable for lyophilization as the composition of the product, including buffers, excipients, and the choice of cryoprotectants, will significantly influence cycle development. The drug product formulation therefore must be optimized to ensure product stability and maintain the desired characteristics throughout the freezing and drying process.

2. Thermal Characterization

Cycle development begins with understanding of what Critical Process Parameters (CPPs) we typically see in the lyophilization process, and leverage that understanding by ensuring a formulation is physically suited to undergo lyophilization at the designed CPPs. Thermal characterization utilizes techniques such as Modulated Differential Scanning Calorimetry (mDSC) and Freeze Drug Microscopy (FDM) to establish the critical temperatures of the product, i.e. the temperatures in which the product undergoes a thermodynamic change in state via glass transition, recrystallization, and eutectic melt. Even a qualitative change of state observed via FDM (collapse onset) is crucial to the characterization of the product. Once established, the focus is placed back on the lyophilization cycle parameters, and temperature and vacuum levels are recommended to ensure product quality and prevent failure.

3. Cycle Design and Optimization

The cycle's parameters, including freezing rate, shelf temperature, and vacuum pressure, are determined based on the product's characteristics and stability requirements. Guided by Quality by Design (QbD) principles, cycle design is fine-tuned through a series of experiments to achieve an overall successful design space and range in which the lyophilizer parameters can operate with success. Lyophilization cycle parameters are optimized for multiple factors such as a low residual moisture, cake appearance, reconstitution, low degradation, and total run time. Optimizing the cycle for total run time can lead to cost efficiencies over the lifecycle of a product.

4. Cycle Validation

The optimum lyophilization cycle is then validated to ensure reproducibility, consistency, and robustness. This step is essential for scalability and to meet regulatory standards.

The Future of Lyophilization and Choosing a CDMO Partner

As the number of biologic molecules in the drug development pipeline increases, more and more products will stand to benefit from lyophilization, many of which may not be commercially viable without lyophilization. As noted in the LyoHub 2023 Annual Report, in the past decade submissions for lyophilized drugs approvals have increased by an average 15%. From 2012 to 2022, a total of 336 lyophilized drugs were approved which constitute 59% of the total fillings since 1954. In 2022, the US FDA approved 32 lyophilized drug products of which oncology and infectious diseases represented 82% of approvals equally.[1]

As a leading global CDMO, PCI Pharma Services is an expert and innovator in lyophilization and offers one of the largest lyophilization capacities in the industry. With over 25 years of experience we have the scientific expertise, global facilities, and scalable equipment to help our clients achieve success. We are uniquely positioned to develop lyophilization cycles from the beginning or to optimize existing cycles, providing a commercially desirable yet economical process. Having developed over 675 lyophilization cycles, client partners rely on us to achieve their Quality Target Product Profile and deliver life-changing therapies to patients.

Client Case Study

Client Challenge

A small US-based biotech company approached PCI Pharma Services seeking support for their labile monoclonal antibody drug product. They were still in the preclinical development phase and had determined that the drug product, in its current form, would not be suitable for Phase I clinical trials due to stability issues. They sought an experienced CDMO with scientific expertise to aid further formulation development and a partner with scalable sterile fill-finish and lyophilization solutions to support not only their early phase clinical studies but also future late phase trials and ultimately commercialization.

Process and Solution

PCI worked with the client to develop a strategic three part plan to address not only their short-term objective of advancing their product into the clinic but also to plan for the later stage clinical trial program. The three part development plan consisted of:

1. An initial quick start lyophilization program to provide a limited study to conserve the client's valuable bulk drug substance, expedite time, and reduce costs. Note: This phase appropriate solution would produce a lyophilized product suitable for Phase I trials, although further development would be required if the product advanced in the clinic.

2. A formulation development program to enhance overall liquid stability.

3. A fully optimized lyophilization cycle to support long-term stability suitable for late stage clinical trials and future commercial manufacturing.

Part One

To address the client's short-term needs of initiating Phase I trials with a lyophilized presentation of their drug product, PCI developed a plan to analyze the thermal properties of the products' current liquid formulation, with the aim to design a cycle without the use of additional compounds. Using mDSC and FDM the development team successfully defined and understood the physical characteristics of the formulated product and gained confidence that even in the current state, a cycle could be generated. This helped to guide a limited, data-based study using just two lyophilization runs in the drug product's current formulation, limiting drug quantity and providing a sufficient design space in which to operate. PCI was able to develop a preliminary lyophilization cycle suitable for Phase I GMP clinical trial manufacturing within an accelerated timeframe of just a few weeks.

Part Two

Following the completion of the GMP clinical trial manufacturing campaign to provide supplies for their First in Human (FIH) clinical trial, the second stage of the program was initiated for future clinical trial supply. During this phase it was agreed upon with the client to undertake a development program for the drug formulation prior to further development of the lyophilization cycle to help gain stability and mitigate elongated cycle times. To maximize the formulation development process, PCI Formulation Development scientists reviewed all pre-formulary data available and developed a plan to evaluate a small number of excipients to further enhance the molecule's stability and assess a number of cryoprotectants, with success of a lyophilized product in mind. A parallel development path was used to evaluate short-term stability of both the liquid and lyophilized presentations of the drug product.

With a view to the long-term cGMP manufacturing costs of the molecule, the various liquid formulations were screened prior to performing further development of the lyophilization cycle. Developing a robust liquid formulation prior to final lyophilization development served several purposes; primarily, having the most stable liquid formulation is beneficial if there are any delays during GMP product manufacturing, or as the program progresses and larger

scale batches are needed. The additional liquid stability is required while the product is sterile filtered and filled into vials.

Additionally, as lyophilized drug products are more expensive (often 50 to 70% higher) to manufacture than GMP liquid fill-finish production, developing a more stable liquid formulation of the finished drug product was deemed worth the additional investment in both development costs and time over the lifecycle of the product due to the significant future cost savings that could be achieved. If the product has adequate stability as a liquid presentation, it may be worthwhile to pursue that pathway and during the development phase, the lyophilized dosage stability would then be used as a backup in the case of the liquid formulation not supporting the required stability.

Part Three

In this case, the stability data did not support the case for a liquid presentation and a lyophilization development and optimization program was initiated. The candidate formulation with the best stability data was selected for further lyophilization development.

The selected formulation was re-analyzed using mDSC and FDM to understand the thermal profile of the product and subsequently, a series of iterative lyophilization development runs were conducted and evaluated against the agreed upon CQAs, including cake appearance, reconstitution time, moisture content, and assayed using HPLC. As the lyophilization cycle parameters were nearing completion, a cycle optimization program was initiated. During the optimization phase of the program, a 'sample thief' was used to collect numerous samples during the secondary drying to map moisture content and residual solvents in real-time. This established an efficient secondary drying cycle and fully characterized the design space of acceptable lyophilization process parameters. This provided for the development of a robust and efficient lyophilization cycle, saving significant long-term manufacturing costs.

To ensure a commercially robust lyophilization process, reduce the risk of collapse and safeguard that the finished product consistently met the finished product CQAs at release, PCI's expert Process Development team continued to characterize the formulation by performing "Intentional Collapse Studies" (ICS) during the final stages of lyophilization development. This intentional collapse of the product allowed the team to fully understand the potential points of failure and verified that macro-collapse does occur in the final vial presentation where the FDM and DSC testing data indicated.

Throughout the course of the client's clinical development journey, our experienced Process Development team maintained focus on the future and planned for long-term success, delivering a robust lyophilization cycle with parameters that were transferable to any large-scale clinical/commercial freeze-dryer to support commercialization.

At PCI, together with providing science driven, flexible scalable solutions, delivering best-in-class services efficiently and effectively, we are committed to meeting the dynamic needs of our client's drug product journey. We immerse ourselves in every client project, working in partnership to provide collaborative, creative and tailored approaches to deliver upon our purpose of bringing life-changing therapies and patients.

Author

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Matt Bourassa is the Manager of the Process Development group at PCI's Bedford, NH facility. During his fourteen years in the CDMO space, Matt has developed more than 30 robust and scalable lyophilization cycles across a wide array of parenteral drug products, medical devices, and diagnostics. As an inaugural member of the Process Development team, Matt now manages highly skilled scientists in the same group, leveraging his process knowledge and technical prowess to inform scientists and clients alike, from small scale preclinical tests to late-stage characterization and aseptic fill-finish. Matt received his B.S. in Chemical Engineering from the University of Massachusetts.

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[1] Pharmahub - Resources: LyoHUB 2023 Annual Report: About