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LYOPHILIZATION VS. LIQUID FORMULATION: WHY LYO OFFERS ADVANTAGES FOR DRUG MANUFACTURERS

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As biologics such as vaccines, gene therapy and therapeutic proteins continue to advance to commercial viability, their complexities when compared to small molecules will necessitate new and novel approaches. These drugs are susceptible to conformational changes, protein aggregation, and other issues resulting from temperature changes, freeze-thaw cycles, the introduction of certain excipients and buffers, and various other factors.

Lyophilization offers some alluring advantages in today's complex and challenging market: by removing the moisture from the product, developers can extend its stability for more than two years, which can prove crucial in paradigms like the current COVID-19 pandemic.

However, the advantages inherent to lyophilization exist in concert with its challenges. Maintaining product stability, overcoming scale-up issues, and optimizing freezing for complex formulations are a few of the hurdles that biopharmas and CDMOs alike are working to surmount through research. Liquid formulation is the traditional, incumbent choice for many manufacturers, and its ubiquity has rendered it a comparatively straightforward process. The choice for manufacturers is further compounded by the cost of lyophilizing a product, particularly in early development, when a therapeutic's uncertain future can make added investment a tough sell.

Despite this, many companies are recognizing the value in getting lyophilization right and are pursuing the innovations and expertise necessary to position themselves at the forefront of a fundamental shift in biopharmaceutical manufacturing.

UNDERSTANDING LYOPHILIZATION FOR BIOLOGICS

The stability of biologics increases markedly when frozen. However, because lyophilization has historically been difficult to achieve economically and efficiently, many biopharmas have chosen to forgo it in favor of more traditional liquid formulation.

But as innovations that streamline the lyophilization process continue to advance, and as CDMOs and other manufacturers continue to accrue expertise in the space, the advantages inherent to freeze-drying biologics will make it an integral competency for the biopharmaceutical industry. Lyophilization in drug manufacturing presents an important opportunity for developers to extend stability – by removing moisture from a formulation, which can be assessed by residual moisture assay, developers can markedly slow the degradation of a drug product. Yet despite the advantages of lyophilization, challenges related to selecting excipients, maintaining optimal temperatures, and preserving safety and efficacy make it an ambitious undertaking, one that requires broad expertise and attention to detail to get it right.

Balancing a formulation for salt content, tonicity, stability, pH, protein aggregation, and other key variables can be challenging for lyophilized products. But those challenges are rewarded by a number of benefits, not only for stability and shelf life, but for process efficiencies: after the secondary drying phase, vials of lyophilized product are crimped and sealed in a cleanroom setting, greatly reducing the potential for contamination. Additionally, lyophilization negates the need for extreme cold temperature storage, enabling companies to transport and store lyophilized products at refrigerated temperatures. In contrast, traditional formulation has necessitated cold chain shipments ranging from -20 to -80° C or lower, driving complex shipping paradigms that require careful management and the use of costly and volatile materials like dry ice or liquid nitrogen. While some remaining moisture is necessary – a maximum of ≤ 2% moisture is needed to avoid any friability form the cake during transportation – lyophilizing a product serves to markedly reduce its overall weight, a real benefit in shipping.

The COVID-19 pandemic illustrated the logistical intricacy of this reality with its initial vaccine rollouts, as manufacturers ran headlong into the lack of infrastructure surrounding super cold shipments at the scale needed to meet demand. While the industry has fomented around solving those issues in the near term, investment in alternatives that can reduce the need for frozen storage and transport will serve to create efficiencies for the entire biotherapeutic space.

EXCIPIENT AND BUFFER SELECTION

Because most viruses are stable in a hypertonic (highly concentrated) matrix, lyophilization of these viruses must be in an amorphous solution. But every virus is different – while many are hydrophobic, others thrive in isotonic solutions or solutions with higher concentrations of salt. Generally, salt is a developer's worst enemy during lyophilization, while its presence in liquid formulations is most often benign or even beneficial. Controlling for salt content during the lyophilization process is perhaps the most critical component to achieving success, and this equation ultimately hinges on the right excipient and buffer selection.

To ensure the successful lyophilization of enveloped viruses, expert knowledge is essential to optimize the appropriate buffer and excipients needed for a suitable matrix and to balance these considerations with safety and efficacy concerns. This paradigm exists in contrast to liquid formulation, which can accommodate varying amounts of salt, as long as the salt content is low enough that it avoids causing irritation upon administration. In a formulation with enough salt to cause discomfort, adding sucrose or other excipients capable of counteracting that salinity can also offer lyoprotection; understanding which excipients to add to a matrix in order to optimize it is integral to achieving a formulation, lyophilized

or liquid, that meets regulatory and patient care standards.

Choosing the correct buffers is another integral facet of optimizing a lyophilization process. Buffer materials should be chosen so that the buffer pKa is within ± 1pH unit of the desired formulation. The buffer capacity should be minimized, and the formulator should be conscious of the product and its route of administration, as certain excipients, administered subcutaneously with higher osmolality (tonicity level), can cause irritation or burning if not properly balanced in the solution. In lyophilization, the types of excipients used in a drug's formulation are limited, as most salts, commonly employed for liquid formulations, interfere with the freeze-drying process.

MAINTAINING OPTIMAL TEMPERATURES

Understanding how to balance bulking agents to address process changes is another critical component of formulation, as certain bulking agents can be affected by changes in the blast freezing temperatures. Conversely, balancing a formulation matrix (amorphous/crystalline) by adding sucrose, sorbitol, or mannitol, for example, may impact the material's glass transition temperature or its collapse temperature. Understanding the interplay between excipients and heating and freezing is crucial; determining the glass transition temperature to optimize the primary drying phase, as well as the collapse temperature to avoid cake collapse and inform both the primary and secondary drying phases. Using the correct excipients also ensures that manufacturers can avoid exceeding the triple point temperature during sublimation, which could cause cake collapse or melt-back.

On the whole, there are three primary characterizations that are important to codify when it comes to a lyophilized formulation's temperature – its eutectic, glass transition, and collapse temperatures. Pre-lyophilization characterization is critical to determining these temperatures and establishing whether a proposed lyophilization cycle is viable. Suboptimal lyo cycles can sometimes be made practicable by incorporating an annealing step. Annealing, a process modification that involves maintaining the product at a temperature above its final freezing point for a specific duration, is often employed in lyophilization to crystallize bulking agents and thereby prevent collapse/melt-back at higher drying temperatures.

While annealing can be useful for other formulation applications, it can cause undue stress in viruses when freezing. This can cause those particles to degrade, as most viruses exhibit signs of decay at temperatures above -20 C°, well below the typical temperatures employed during the annealing process. Even slight increases in temperature have the potential to destroy some sensitive proteins or viruses during the freezing process.

THE FUTURE OF LYO FOR BIOPHARMA

As these therapies continue to proliferate, addressing the challenges to lyophilizing certain therapeutics will require diverse expertise, a bespoke approach to formulation, and a focus on sterility and stability. For live agents, this expertise is critical: the potential for their contamination is higher, particularly during changeovers, as inactivation procedures are undertaken by exposing the product to various chemical or physical agents. To mitigate this potential, a CDMO may employ single-use equipment, including disposable mixing systems, in areas with potential contact.

Demand for lyophilizing viral products has only increased in the wake of the COVID-19 pandemic; CDMOs and biopharmas with experience lyophilizing live viruses are likely to encounter a growing demand for these capabilities as vaccines and other therapies derived from live viruses continue to proliferate. This is particularly important when it comes to scale-up – manufacturers with experience in vaccine production may be more equipped to engage in technical transfer of a live virus product from lab-scale through commercialization, and will have established the analytical methods, team, and process understanding necessary to optimize results.

For biopharmaceuticals, large and small molecules, execution of small-batch manufacturing and small-volume filling are critical to a project's success. Despite this, many companies may underestimate the time and resources needed to produce enough vials under GMP manufacturing conditions to smoothly transition through a study. Understanding the challenges inherent to small-volume fills, and finding a CDMO partner able to mitigate them, is crucial to avoiding unnecessary losses and delays.

Finding the right manufacturing partner to help optimize every part of a drug development process, from formulation to filling, requires a focus on a CDMO's capabilities, expertise, and facilities. It also necessitates an emphasis on the testing protocols, collaborative practices, and process understanding fundamental to early-phase research and development for these specialized therapies.

Ultimately, as drugs become more complex and present more challenges with regard to their stability, lyophilization can offer biopharmas a solution that helps advance a therapeutic while conferring it greater longevity. While many biopharmas may be reluctant to pursue lyophilization during product development due to its expense and time when compared to more well-understood liquid formulation, having a partner with expertise in lyo can help mitigate those issues.

ABOUT THE AUTHOR

Desline Barber serves as a Senior Scientist for Formulation Development at IDT Biologika. He has over 15 years of experience in developing liquid and solid drug product formulations for small molecules and large biologics.

ABOUT THE COMPANY

IDT Biologika is a global biopharmaceutical contract development and manufacturing organization that specializes in the production of innovative live viral vaccines, viral vectors for gene & immune therapeutics, oncolytic viruses, virus-like particles and other sterile liquid or lyophilized biologics to improve human health worldwide.