Investing in the future of freeze-drying for biologic drugs

Retrofitting ControLyo technology to benefit all stages of development

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Abstract

Biologic drugs are the fastest-growing class of therapeutic products in the United States. They are complex structures which place many difficult demands on manufacturing. Structural integrity is critical to the drug's potency and preserving this during freeze-drying is challenging. Faithfully reproducing a freeze-drying cycle which stays within the design space for a given formulation is essential. Controlled nucleation using SP Scientific's ControLyo® technology enables more consistent cycles to be recreated improving homogeneity, reduce cycle times, improve cake consistency and increase product yield. As products move from development, the process of scale-up can be simplified by retrofitting ControLyo to existing units for a smooth transition to manufacturing. This article describes how a customer can benefit from retrofitting ControLyo to 'production' equipment thereby improving the development and manufacturing of their own biologic drug products, reducing the risk of batch failure, and providing closer adherence to the demands of the regulators.

Introduction

At the forefront of biomedical research, biologic drugs have the potential to treat many incurable diseases and to personalize medicine. According to EvaluatePharma[1] consensus forecasts, the pharmaceutical industry is set to grow at 6.3% per year reaching $1.12tr by 2022 with biologics contributing up to 50% of the top 100 product sales by this time. Better healthcare, globally, and growing technological advancements have driven this market growth, with increased geriatric populations and the rise of chronic diseases expecting to drive the future biologics market. It is also worth noting that due to patent expiration of many current drugs, it is expected that between $25-35 billion of the global market will be production of biosimiliar drugs[2]. There are currently over 5,000 new biologic drugs in the pipeline including 600 biosimilars and 500 biobetters. However, biologics are complex and need to be processed and stored under strict quality control guidelines, and often specialized conditions to preserve integrity of the drug's activity. This demands increased investment

and infrastructure and difficulties can be encountered in scaling up of early stage products to manufacture in larger quantities.

To stabilize, store and increase the shelf life of the compounds, drug products or conjugates can be freeze-dried (lyophilized). The process of lyophilization lowers the temperature of the product to below freezing before water or other solvent(s) are removed by sublimation using a deep controlled vacuum. At least 41% of biologic drug products are freeze-dried to retain their physical structure. In addition, almost all antibody-drug conjugates (ADCs) must be lyophilized to ensure the stability of the linker that joins the 'payload' to the antibody, during storage and transport. Freeze-dried biologics can be reconstituted quickly and easily (while retaining their biological activity), which is particularly valuable in the case of emergency vaccines and antibodies, which need to be administered as quickly as possible.

The critical process of freeze-drying

Batch consistency, within and between, is a major concern for manufacturers of all biological products, particularly when the drug is a parenteral product. Manufacturers need to achieve optimal consistency of the product and ensure sterility during all stages of the process including lyophilization while maintaining cost efficiency. Manufacturers must also consider future scale-up of a product during the early stages of its life to maximize investment and transition smoothly from small pilot production to larger manufacturing.

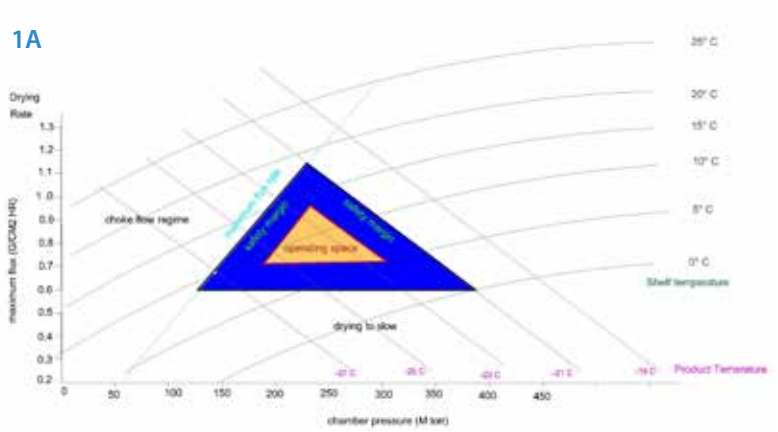
With the increase in new biologics on the market, technology has advanced in freeze-drying to increase shelf life of these products. Optimizing this process requires an understanding of the biological entities of the product and knowledge of the lyophilizing process.

Freeze-drying, or lyophilization occurs in four main stages (pretreatment, freezing, primary and secondary drying), all of which can be subjected to modifications to optimize the process according to a specific product's properties, the stability of the active pharmaceutical ingredients (API), reconstitution time, economics and clinical use. The critical freezing stage requires the biologic product to be gradually frozen below its triple point (the lowest temperature at which the compound coexists as a solid, liquid and gas phase) to form ice crystals (nucleation). Water is then removed from the product during the Primary and Secondary Drying stages using low pressure and enough heat for the ice to sublime. This phase can last several days to preserve the biologic drug product. The stochastic process of nucleation is random and can be highly variable – occurring over a number of hours - impacting greatly on the quality of the final product and batch consistency. In addition, structural integrity is reliant on a slow, gradual drying process which can take several days to complete.

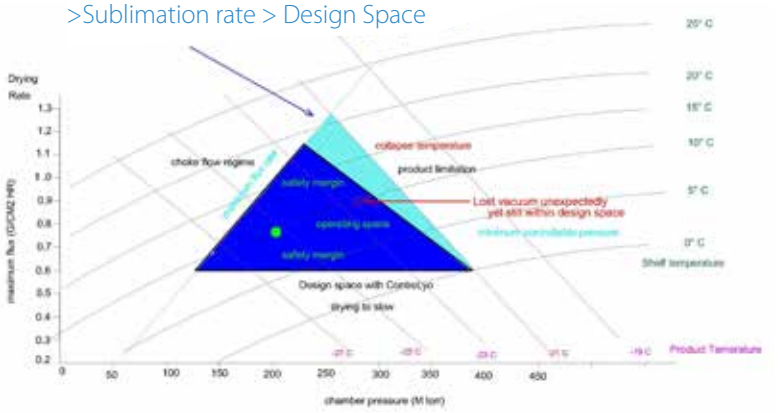
Quality by design (QbD) assure in vitro product performance which implies an assurance of in vivo product performance. As part of the QbD approach, a systematic methodology to development is applied beginning with predefined objectives and emphasizes product and process understanding. This is supported by scientific knowledge and quality risk management to establish a design space with defined sets of operating variables needed to maintain batch consistency. These are represented graphically as multi-dimensional points in relation to equipment limitation and critical product attributes (Fig 1A). It is common for an inner area of the design space to be designated as the nominal manufacturing conditions (operating space).

Operation within the design space will result in a product meeting a predefined quality. Having a larger design space or parameters in which to work increases the probability of executing a successful cycle, even in the face of potential problems occurring, including unplanned process excursions.

1A



1B Larger ice crystals reduces cake resistance >Sublimation rate > Design Space



1C

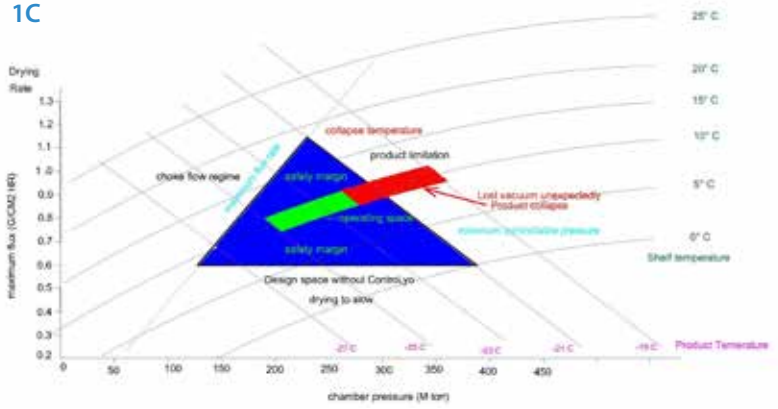


Fig 1. *The design space of the freeze-drying process. A) represents the triangular design space between the maximum sublimation rate of the freeze dryer (left side) and the product limitation defined by the collapse temperature (right side), B) Design space with ControLyo. Small green dot = operating space. Larger crystals reduce cake resistance which increases the sublimation rate and leads to a larger design space, C) Design space without ControLyo.*

Controlled nucleation and optimal drying times

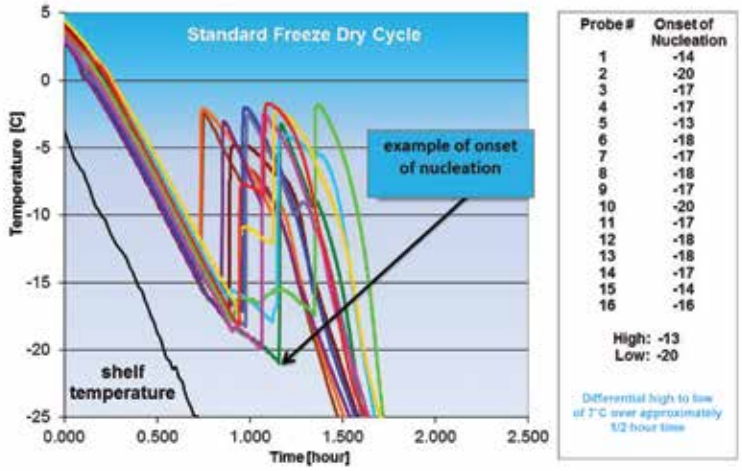
In general, uncontrolled nucleation occurs over a wide range of product temperatures, typically between -5°C and -15°C in the laboratory (and colder in a sterile production setting), over a period of up to several hours, and causes product variation (Fig. 2A and C). A high degree of supercooling leads to small ice crystals, which in turn results in small pores of high resistance in the product and slower freeze-drying times.

To overcome these limitations, various methods and technologies have been investigated to control nucleation and optimize the drying process.

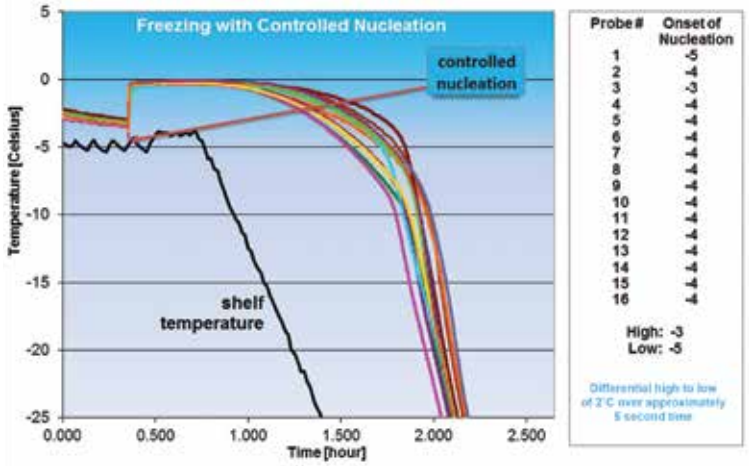
One such technology, ControLyo® from SP Scientific utilizes an inert gas and a series of pressurization and depressurization steps that creates instantaneous ice nucleation in all vials in the product chamber. The freeze dryer chamber is pressurized with sterile filtered inert gas and then quickly depressurized after a hold period. The quick depressurization causes all of the product that is slightly subcooled, to nucleate simultaneously at virtually the warmest possible temperature, thus yielding the largest possible ice crystals. The freeze-drying process starts at the surface of the product within the vial and over time the water or solvents are driven from the entire contents, resulting in a porous product that is easily reconstituted. Large crystals create larger cavities as the ice sublimes resulting in less resistance for subsequent drying of internal areas and the shortest potential drying time (Fig. 2B and D). Previous studies have shown that for every 1°C increase in nucleation temperature, the primary drying time is reduced by 3%[3]. In some instances, ControLyo has been shown to reduce the cycle time from 7.5 to 5.5 days which increases productivity and provides economic benefits.

Another important advantage of controlling the nucleation point is increased product homogeneity.

2A Uncontrolled Nucleation



2B Controlled Nucleation



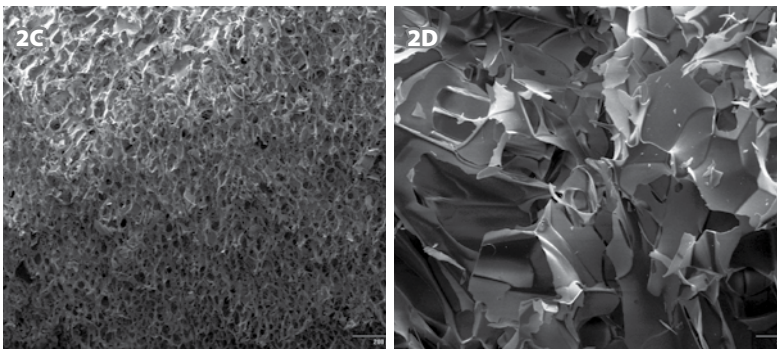


Fig 2. *Effects of controlled nucleation using ControLyo. A) Freezing temperatures of products during uncontrolled nucleation vary considerably, B) consistent freezing temperature of drug products during controlled nucleation with ControLyo, C) small, irregular crystals of sucrose (75 mg/mL) during uncontrolled nucleation using 1oC /min shelf cooling rate, D) larger, more consistent crystals of sucrose (75 mg/mL) during controlled nucleation with ControLyo at -3oC shelf cooling rate.*

Acceptable product is produced between the equipment limits and critical product temperature which normally define the design space for the product and freeze dryer. A safety margin is typically designed around the operating space to provide insurance against temporary component failures.

The variation among vials with ControLyo technology is very small because all vials freeze at the same product temperature (Fig 1B). Therefore, due to the benefits described earlier, there is less risk of losing the batch should an issue arise during the freeze-drying cycle. For example, if vacuum is unexpectedly lost, product quality will still be assured as it is still within the design space.
Uncontrolled freezing puts product loss at a higher risk as the operating space occupies a far greater portion of the design space thus decreasing the flexibility within the design space (Fig 1C). In this same example, unexpected loss of vacuum results in product collapse.

A complete lyophilization solution from early to late stage development

When setting up a freeze-drying system for research and development or initial pilot studies of biological drugs, smaller dryers are often the best economical choice. However, once a drug product becomes successful, additional equipment needs to be purchased (or dedicated) to provide the capacity required for scaling-up. Sometimes unexpected changes occur in the drug product due to variations in the lyophilization process of the new systems and this can be particularly true for biological products that are sensitive to minor changes in their structure. SP Scientific offers a complete, sustainable solution with a broad lyophilization range from small units that lyophilize as little as 7 vials (e.g. LyoCapsule™), to much larger systems with a capacity of >100,000 vials (e.g. Hull production lyophilizer) making the scaling-up transition more cost-effective and seamless. SP Scientific's LyoStar3 lyophilizer with ControLyo technology is specifically designed for formulation

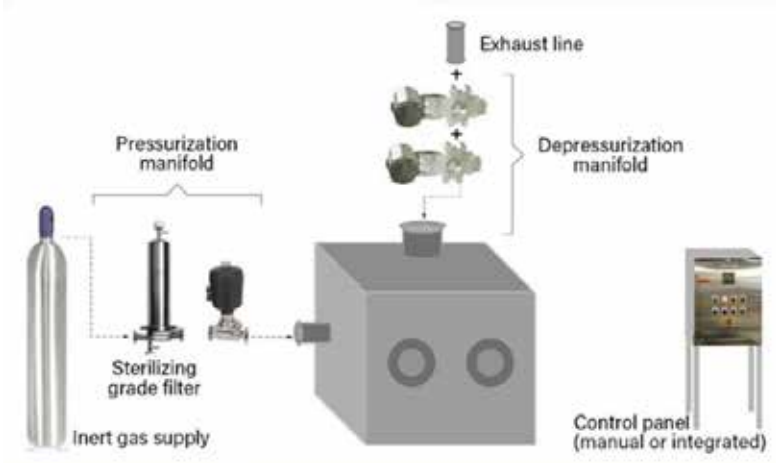


Fig 3. *Illustration of main components of the ControLyo retrofit.*

development of high-value pharmaceutical and biological products at a capacity of 1,800 vials (2 mL) and is the market leader for development of scalable freeze-drying processes.

This patented ControLyo technology overcomes freeze-drying scale-up challenges without introducing foreign particles into the vials (compromising sterility).

Alterations in the lyophilizing process during scale-up can be overcome by adhering to a freeze-drying technique even when new equipment is purchased. ControLyo technology can be utilized on SP Scientific's pilot, clinical and production freeze dryers, and has the option to be retrofitted onto qualified existing units from SP Scientific, and in specific cases, another manufacturer's equipment.

Retrofitting ControLyo to existing equipment to future-proof biologic production

Retrofitting ControLyo technology can repurpose existing production equipment to enable handling of products that were developed using control nucleation techniques. Repurposing existing freeze dryers will expand the capabilities of the freeze dryer. In addition, the time involved to retrofit is generally shorter than the manufacturing cycle for a new freeze dryer.

Adding ControLyo to an existing freeze dryer requires installation of large diameter exhaust valves to the chamber or use of multiple exhaust ports, to enable rapid depressurization of the system on demand, and an update to the controls system (Fig 3). The existing sterile nitrogen inlet is used to pressurize the chamber. An operator can manually trigger ControLyo when the correct product temperature is achieved. Alternatively, the freeze dryer program can be modified to activate these functions using dry contacts for communication between the software. The existing software can be paused at the appropriate times within the cycle and a signal sent to ControLyo controller, which recognizes the status inputs and initiates output commands to pressurize or exhaust the chamber, all with full traceability.

This solution allows the automation of the process within their freeze-drying recipe for each product and eliminates the need for operator intervention. The added advantage of the retrofit is that there is very little disruption to the existing system when implementing the technology - no significant addition of utilities or modification to chamber or condenser is needed, and it is also compatible with existing auto loading or unloading systems. Other cycles can still be run on the existing equipment by deselecting ControLyo functionality with no interference or need for requalification.

Showcasing lyophilization technologies

India is in a unique position to offer customers freeze-drying optimization on SP Scientific units at the Spinco Biotech's Center of Excellence for Process Technology in Chennai. Inaugurated in May 2018, the center houses SP Scientific's latest freeze dryers with ControLyo technology enabling product trials to be optimized at the initial stages of development. Valuable product data can be generated early on to address any challenges, and ease future scale-up.

Advanced regulations

The US Food & Drug Administration (FDA) has been investigating Process Analytical Technology (PAT) tools and emerging technology[4] for lyophilization. Lack of understanding and robustness in a process are critical deficiencies during audit review or inspection process. Controlling the freezing process will be instrumental in responding to regulatory agencies inquiries about individual processes and batch variation. Therefore, understanding the key process parameters, design space and failure points in relation to product quality is very important.

ControLyo is an emerging technology designed to conform to the QbD framework set out by the FDA to provide better process and design predictions. Studies have shown that ControLyo creates a better design space safety margin to scale up to commercial manufacturing levels. With respect to the retrofit of ControLyo, the proprietary software comes with 21 CFR 11 compliance to record the operator's signature as well as timing for each manual sequence of the process.

Increasing profitability with controlled nucleation

A scientific approach to change is necessary to improve the future of any process and benefit economically from it. There is robust evidence that ControLyo technology helps develop a larger design space, improves cycle time, cake morphology and enables higher sublimation temperatures to be used. These advantages have ultimate economic benefits especially when considering scaling up of biologic product manufacturing.

Profit loss from rejection of vials due to product collapse (complete or partial) and vial breakage can account for as much as 20% of overall production. By tightening the operating space utilizing ControLyo technology to induce simultaneous nucleation at a higher temperature, quality failure and vial breakage can be significantly reduced.

In collaboration with a large Pharmaceutical company, SP Scientific demonstrated that in a trial of a small molecule drug used in cancer, uncontrolled nucleation took place at -16°C to -19°C with 14% cracked vials. Using ControLyo controlled nucleation, the temperature was increased to between -4°C to -6°C and no vials were cracked. The cake appearance was also greatly improved and consistent.

Concluding remarks

Production of biological drug products (including biosimilars) is expensive but is also vulnerable to failure for many reasons. Biological materials are often labile. Stabilization by lyophilization is attractive and retaining their biological activity, structural integrity, homogenous quality is crucial. Investing in reliable equipment that can be used at early stages of development through larger scale manufacturing is costly, but the option of retrofitting ControLyo to existing equipment makes this a more affordable option while delivering all the benefits that the ControLyo technology can offer.

Realizing the value of controlled nucleation with ControLyo and the option to retrofit the technology to existing freeze dryers, it is hard to ignore, especially given the added protection it helps provide against batch failure, rendering it a worthwhile investment in any biological drug production facility.

References

1 EvaluatePharma World Preview 2016, Outlook to 2022 http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf

2 Biosimilar Market Trends 2018. Report from 3rd Congress Biosimilars India 2018 http://www.indiabiosimilars.com

3 J.A. Searles, J.F. Carpenter and T.W. Randolph. (2001) The ice nucleation temperature determines the primary drying rate of lyophilization for samples frozen on a temperature-controlled shelf. J. Pharm. Sci. https://doi.org/10.1002/jps.1039

4 Guidance for Industry - Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm478821.pdf

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