SPOTLIGHT feature

Incubators, Freezers & Cooling Equipment

Advancements in Freeze Drying Production & the Impacts on Scale, Sustainability and Compliance

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Freeze drying, also known as lyophilisation or simply 'lyo', is a drying process which consists of the sublimation of ice crystals into vapour. Rather than using a heat treatment, samples are frozen, then the pressure is decreased, and at that point sublimation occurs. As a process based on negative temperatures, the activity and stability of the product being freeze dried, along with any active ingredients, are better retained whilst limiting any damage to the product and avoiding degradation of the molecules. This is why freeze drying is especially popular in the pharmaceutical sector.

A strong factor that is driving the increased need for freeze drying in the pharmaceutical industry is because it stabilises a product and its ingredients for distribution, makes the product lighter, more compact and increases shelf life. This is a useful, cost effective and efficient way to optimise transport of large quantities of products, no matter the industry. In terms of pharmaceutical applications, it also allows products to be shipped to countries where temperature may affect the stability of a product and a cold chain is not available or where product may need to be stored for long periods.

Another strong factor underpinning the need for freeze drying for pharmaceutical applications is that freeze drying technology has adapted for scalability, allowing larger batches of products to be produced more quickly, more efficiently and more cost effectively, with much less error.

What Has Influenced Advancements in Freeze Drying Production?

Recent advancements in freeze drying over the past year have allowed for faster processing, scalable adaptability, optimised sustainability and legislation compliance within the sector. The Covid-19 pandemic has played a part in the advancements of newer technology for lyophilisation, due to the sheer scale of production requirements for vaccines and diagnostics alongside the extremely tight time scales to take products from conception to delivery.

Another trend to consider is how patient treatments have started to move away from broad population therapies in favour of targeted treatment of smaller and more personalised patient populations. For this reason, the biopharmaceutical industry has transitioned to smaller aseptic batch manufacturing. A potential reason for this shift toward small scale batches could be due to the fact that API can sometimes be scarce, so test quantities may be limited and very expensive. There are also new oncology drugs and live viruses needing to be handled carefully. This trend has become pronounced over the past decade, increasing the importance of freeze drying within biopharmaceutical research and development (R&D) and manufacturing environments, which continues to rise. Some key influences on this change are due to at least 41% of biological drug products requiring freeze drying/lyo processing and because continual growth is expected due to development and availability of more complex drugs. It is also because a high number of large molecule drugs, for example Antibody Drug Conjugates (ADCs), may be unstable unless freeze dried, driving forwards the necessity of freeze drying within the marketplace.

Formulation Considerations Can Affect Production

It is important to remember that when a formulation is developed for freeze drying, there are many factors which can affect the production and manufacturers will often see up to 20% of samples being rejected due to various things that can go wrong.

At the start of the lyo process, products must be formulated in such a way that they can be suitable for freeze drying. This involves the inclusion of cryo-protectants to protect against freezing injuries, and some lyo-protectants to protect against drying stresses, so having a well formulated product is essential. Depending on the application and the method chosen for freeze drying of the product such as liquid vials, well plates or lyo beads, having a bespoke, high-quality formulation can help to enhance the properties of the material and retain the activity and stability of the reagents, whilst ensuring that the formulation does not interfere with the product itself.

During the freeze drying process, vials can freeze at different rates and temperatures, moisture content is varied and some vials could even show evidence of collapse which means product homogeneity and yield can be inconsistent. This results in time lost, deviations or contaminated products which cannot be used, further time needed to correct the errors and all of this also costs money.

Not only is it now possible to ensure that a freeze dried product is of the highest quality, but the latest innovations have now made it possible to reduce room for error during the freeze drying process, which leads to higher efficiency, quicker production and higher cost savings.

By utilising the latest R&D insights from Biopharma Group such as ControLyo, SMART and TDLAS, which work on the principle that the more information and control one has over a process, the less likely issues are to occur with product moving beyond their design space and thus, needing to be rejected. ControLyo, for example, has many benefits whilst enabling scalability for manufacture for products such as sterile injectables. The product benefits include achieving improved inter and intra-batch product quality, with the QbD ('Quality by Design') approach ensuring that all vials have the same nucleation temperature and timestamp, including those with a thermal couple. In addition to this, manufacturers can now also reduce freeze drying stress on biologicals, work with larger ice crystal sizes to minimise dry layer resistance, have a shorter reconstitution time, reduced protein aggregation, reduced pH shift, better cake appearance and can often require no change to the users existing formulation.

The financial and operator benefits of utilising controlled nucleation include lower rejection rates due to no risk of foreign material entering the vials, enhanced quality, increased production capacity through shorter cycles, improved safety margin within the design space allowing a batch to be saved if the recipe is disturbed, and GMP compatibility meaning there will be no issues regarding compliance, unlike other technologies. It also allows for scalable technology, from R&D up to commercial scale equipment used for manufacturing, which is also easy to use and operator friendly.

How Has Demand Impacted Production?

To accommodate the trends and demand for lyo in pharmaceutical production, it is now imperative that operators are given the opportunity to utilise freeze drying equipment, designed for use at the R&D level, and capability of replicating process/ software controls in conjunction with fully scalable PAT technology - a necessity when facilitating a 'QbD' strategic approach to drug manufacture.

All of the above has lead to recent advancements in freeze drying technology such as the aforementioned ControLyo, SMART and TDLAS processes, as well as development of the Lyostar 4.0 freeze dryer that has been introduced to the UK, Ireland and France by Biopharma Group. This new freeze dryer has been developed to enhance R&D and process development, including scale-up, to improve speed to market of biopharmaceutical products, representing a significant advancement in freeze dryer engineering.

As a pilot-scale freeze dryer, the LyoStar 4.0 offers superior shelf mapping, rapid shelf freezing, process accuracy and reliability. It also includes an innovative suite of Process Analytical Technology (PAT) tools supplementing SP's Line of Sight™ technologies. Additionally, an eco-friendly refrigerant gas is used to help comply with sustainability and environmental impact legislation. This break-through technology incorporates the latest innovations in freeze drying to ensure precise process control and reliability. The flexibility to scale-up or down, is an important aspect in the process for developing pharmaceutical compounds. This equipment allows production to adapt to the demand because of the innovative technology it utilises to help overcome critical lyophilisation challenges during development, scale-up and manufacturing of biologicals, thus also enabling greater sustainability and regulatory compliance.

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.

What Does This Mean for the Pharmaceutical Industry?

The combination of advanced equipment, utilising the benefits of controlled nucleation and proven methods for improving the lyophilisation production process, ultimately enables the QP to consider whether the product has remained within its known 'design space' and safe limits for release, even in the event an issue occurrence during the cycle including unplanned process excursions. This is thanks to a higher level of data integrity becoming available within these advanced processes, highly desirable in the pharmaceutical industry due to the stringent regulations in place.

When also considering the costs associated with the material being processed, the difference between allowing a batch to be released, rather than it being quarantined and rejected, may be up to £1 million. The requirement to ensure as much data becomes available for consideration post-drying, potentially mitigating the risk of batches being rejected is highly sought after, due to minimising risks and yielding higher cost savings.

By being able to obtain the data that expands understanding of the equipment and process design space, when things go wrong (which they sometimes can), back-up information is available to prove batch integrity. Within the 'Line of Sight' technologies including ControLyo, other realised concepts such as SMART and TDLAS provide many benefits when used throughout lyo production.

SMART provides instant feedback on product resistance, heat flow, and product temperature at the sublimation interface. These attributes are critical to understanding long-term product stability. It determines and verifies your optimised primary drying cycle in three runs or less, whilst eliminating the trial-and-error approach normally involved in developing new lyophilised cycles. This allows researchers to spend more time on value added activities such as cycle optimisation with a QbD approach. It also improves ROI and provides a broader product understanding.

A TDLAS based sensor can be used to measure water vapour concentration and gas flow velocity during the freeze drying process. These measurements can be combined to calculate the instantaneous water vapour mass flow rate and the ice sublimation rate. This allows the user to assess freeze dryer equipment capability limits - very useful from a system validation perspective, monitor process and product parameters and develop freeze drying cycles based on QbD procedures. It is applicable to laboratory, pilot and production scale freeze dryers, using a continuous, non-intrusive monitoring of lyophilisation processes. It takes water vapour, concentration, flow velocity (V) and water mass flow (dm/dt) measurements, providing a continuous mass balance determination, as well as primary and secondary drying endpoints, average product temperature, average product resistance, vial heat transfer coefficients, and freeze dryer performance qualification - one particular area of growing popularity being the effective determination tool of vapour choke flow. This can be highly important when validating the capability of a machine and identification of this parameter, can support end users to conduct freeze drying cycles within the overall ability of the system, which in turn minimises the risk of batch failure.

The 'Line-of-Sight' technologies and latest equipment has enabled an increased understanding and control over the freeze drying process. Industry leading tools are now available that can characterise the freeze drying process from formulation through to full commercial production, providing successful scale-up and technology transfer as production requirements expand.

How Have the Latest Innovations in Freeze Drying Been Applied to Industry?

Throughout the Covid-19 pandemic, there was a huge demand for sterile injectables as well as other essential products such as In-Vitro Diagnostic (IVD) tests. To keep up with demand, increased capabilities and production capacity were applied within Biopharma Group, utilising these recently developed innovations to successfully meet the demand for the high volume of products required on a global scale.

In the near future, this experience combined with emerging equipment, R&D and innovative developments being made within the freeze drying industry, will have a wider impact on the treatment of many diseases and may even start to be utilised within other industry sectors such as nutraceuticals and even food production, in which freeze drying is commonly and frequently applied.

To discover more, contact the specialists at Biopharma Group