Advances in Freeze Drying Technology

A review of recent developments in freeze drying technology from the standpoint of the improvements in equipment needed to address regulatory, legislative and process requirements.

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From its earliest applications in the stabilisation of blood plasma, freeze drying has been in use in the life sciences for over 50 years. During this period, the freeze dryer – or ‘lyophiliser’ – has evolved from a simple device for vacuum drying at low temperature to an extremely sophisticated integrated system that orchestrates a number of processes to ensure that a product is consistently delivered to technical and biological specifications, while considering economic, safety and environmental issues. This article reviews the development of freeze drying technology from the standpoint of the improvements in equipment needed to address regulatory, legislative and process requirements.

PLANT LAYOUT

In the past, the equipment modules of a freeze dryer tended to be installed on one or two skids which were situated on a single floor level. While this remains convenient for small machines, there is a growing tendency for larger freeze dryers to be installed across two or three floor levels: the freeze dryer chamber is installed at the production level, while the ice condenser and all ancillary equipment is installed on the floor below. Sometimes a third or ‘mezzanine’ level above the freeze dryer accommodates air-handling equipment and affords access to valves, sensors and gauges mounted on top of the chamber. All controls and utilities are routed to the equipment level. Although a more costly installation, there are several benefits to this configuration:

- Minimum intervention is required at the production level
- Access for maintenance, validation and calibration is improved at the equipment level
- A ‘pass-through’ process path or rear chamber door for maintenance can readily be provided without compromising equipment layout or maintenance space

SUB-SYSTEMS

Refrigeration, vacuum and control systems have all undergone significant changes in recent times.

Refrigeration Systems

Since the Montreal Protocol was established in 1990, refrigerants used in freeze dryers have progressed from CFCs, through HCFCs to the present HFCs, which have zero ‘Ozone Depletion Potential’. The higher level of mechanical stress imposed on compressors by modern refrigerant gases has resulted in screw compressors being favoured over reciprocating compressors – especially in 60Hz regions of the world where rotational speeds are higher. Although the cost of a single screw compressor can be up to three times that of a reciprocating compressor, the lifetime of a screw machine is much longer and mechanical maintenance is virtually eliminated. Furthermore, since screw compressors are readily available in larger capacities, and the installation and circuit are simpler, the cost of the entire skid is
Innovations in Pharmaceutical Technology

When automated loading systems first began to emerge in the 1980s, potential users looked at the economics in terms of a reduction in the cost of personnel. It is now clear that the benefits of the technology are derived from elsewhere: from a safety standpoint, loading systems help keep products remote from operators, and from a regulatory perspective, they help keep operators remote from products. Early loading systems were not sufficiently reliable and, in solving this issue, suppliers were insufficiently sensitive to requirements for cleanliness and ease of cleaning. Modern systems, however, are acceptable from both reliability and pharmaceutical viewpoints.

Automated Loading/Unloading Systems (1, 2)

Figure 1: The Shelf of a Freeze Dryer is Unloaded by a ‘Fixed’ Load/Unload System
Each freeze dryer shelf is in turn brought to a loading/unloading level. Vials are marshalled on and off the shelves by a front pusher (in foreground, with gate raised) and a rear pusher (seen moving the pack of vials onto the conveyor system). The filling and the capping lines are out of frame on the left and right respectively.

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Automated loading systems tend to be categorised into ‘fixed’ systems of hard automation, which offer limited logistical flexibility or expansion capability (Figure 1), and ‘flexible’ systems, which use a robot vehicle to service a variable number of stations in a reconfigurable sequence (Figure 2, page 58). Choice of ‘fixed’ or ‘flexible’ is dependent upon a number of parameters. Fixed systems are most cost-effective in applications requiring one or two freeze dryers of less than 20sq.m in shelf area processing a few products with relatively long cycle-times. As the size and quantity of freeze dryers increase, and product and cycle diversity broaden, a flexible configuration becomes more suitable.
Furthermore, with a little foresight, freeze dryers can be incrementally added to a flexible configuration with relatively little disruption. Fixed and flexible systems can be supplied suitable for use under laminar air flow or with isolation technology.

Loading systems can offer validation challenges, since it is not practical to insert thermocouples into vials for process monitoring. However, this problem is generally addressed by correlating product temperature against shelf temperature during the validation stage. Confidence in the uniformity of shelf temperature between validation intervals is increased by continuously monitoring the temperature of the heat transfer fluid at a common inlet and at each individual shelf outlet. Process capability studies also increase confidence that control loops are adequate and that cycles have appropriate tolerance bands (3).

CLEANING AND STERILISATION (4)

Most modern freeze dryers are fitted with cleaning-in-place (CIP) systems; these work by spraying water over all parts of the shelves and chamber through a multitude of fixed and rotating nozzles, so that the momentum of the water spray removes any insoluble particles present. In some applications, such as the dairy industry, detergents are often added during spraying, but this is unusual in pharmaceutical aseptic production because lyophilised products are essentially soluble. Additives are therefore normally limited to applications where neutralisation of the product is performed during CIP.

For final rinsing, very pure water must be used – normally water for injection (WFI).

The most recent developments have focused on reducing the consumption of expensive WFI, resulting in the following typical CIP cycle:

- A three- to five-minute once-through rinse with purified water (such as that produced by reverse osmosis) to remove the heaviest contamination. If detergents or neutralisers are required, they can be added at this stage.
- A 10- to 15-minute recirculated rinse with purified water, using the base of the chamber or condenser as a reservoir.
- A three- to five-minute once-through rinse with WFI

Improvements in mechanical components and design have made routine steam-in-place (SIP) sterilisation under pressure a practical proposition. Sterilisation by pressure steam has become the preferred method for all regulatory authorities.

The high levels of pressure and temperature reached with pressurised steam subject the freeze dryer to considerable stress, especially on seals and valve seats. For this reason, there is still interest in sterilisation at lower temperatures and pressures using vapours or gases. These methods tend to be limited to pilot or retrofit applications, since the most commonly used vapour (hydrogen peroxide, \( \text{H}_2\text{O}_2 \)) presents difficulties in monitoring and control, and the most commonly used gas (chlorine dioxide, \( \text{ClO}_2 \)) has the disadvantage of encouraging stress corrosion cracking in stainless steel.

The filters through which sterile air or nitrogen gas is admitted during drying and aeration are also normally sterilised in place. The preferred method of integrity testing is by the water intrusion test (WIT), whereby the filter cartridge is flooded with water and a known pressure is applied to the known gas volume upstream of the water; this is then isolated, and the change in pressure over time (or alternatively the mass flow) is measured. The filter manufacturers supply validation documentation showing good correlation with the HIMA (Health Industry Manufacturers Association) Bacterial Challenge Test. Diffusive flow testing using a water/alcohol solution to wet the filter membrane is also a validated method; however, it is less favoured as removal of the residual solution involves an extra step. Furthermore, this method cannot be used after...
sterilisation, since the downstream side of the filter membrane would become non-sterile. Integrity testing systems are available as discrete instruments from filter manufacturers, but more recently, collaboration between filter manufacturers and producers of freeze dryers has resulted in integrity test functionality being fully integrated with the freeze drying control system.

HAZARDOUS ENVIRONMENTS

There are four main hazardous conditions that can occur in freeze drying applications and need to be addressed through specific design procedures and construction details:

1) The product being freeze dried is hazardous to personnel or the environment
2) The gas being used for aeration prior to stoppering is hazardous to personnel or the environment
3) The solvent in the liquid product is flammable
4) The fluids present in the freeze dryer can become flammable under certain operating conditions

In each of these situations, a risk assessment should be used as the basis for a hazard analysis; this will identify individual hazard elements and demonstrate how the associated risk is mitigated by design and process conditions.

A matrix of risks and technical approaches to be considered when assessing the four hazardous conditions is presented in Table 1.

With respect to potentially explosive atmospheres, guidelines such as those in the EU ATEX Directive (5) are very valuable in assessing risks from both a supplier and user perspective.

FUTURE DIRECTIONS

One major area of freeze drying technology that requires attention is control of the process. Indeed, it is questionable whether existing techniques actually 'control' the process at all, since they are neither scalable nor transferable, and rely on the ability of a specific piece of equipment to replicate a set of conditions which are known to produce the desired result. Initiatives such as PAT (Process Analytical Technology) from the FDA only serve to exacerbate this observation. As a result, research is ongoing into methods by which the process of freeze drying can be more directly monitored and controlled, for example by observing the mass flow of vapour (6).

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References