Summary: Scale-Up of Freeze-Drying Cycles

Essential Factors and Transfer Strategies

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Differences in Freeze Dryer Construction and Control

Laboratory scale freeze dryers are used for lyophilization of small amounts of product, either for simple preparation of relatively robust materials or for cycle development and subsequent transfer to a larger scale. If the lyophilization process developed is to be scaled up later on, it is beneficial if the freeze dryers employed on the various scales are constructed similarly. The relevant structural features include 2-chamber vs. 1-chamber design, cooling and heating rates of the shelves, condenser temperature and radiation effects from chamber door and walls. If vastly different freeze dryer setups are applied on the different scales (e.g. freezing outside the lyophilizer and primary drying without proper temperature control), a rational transfer to a larger scale is extremely difficult, and major additional experiments and optimization is required on the manufacturing scale freeze dryer which is much more expensive.

However, if equivalent or similar equipment with good instrumentation is used, it is possible to design an optimized cycle including determination of process robustness in the laboratory, and save time and money during the scale-up process. This also applies to process control, for example use of identical sensor types for pressure control (Capacitance Manometer vs. Pirani vs. Thermocouple Vacuum Gauge) to ensure the same chamber pressure is used in all freeze dryers. Some major differences in freeze dryer construction cannot be avoided (i.e. ratio of vials in edge position to vials in center position, differences in radiation of walls and door, etc.), but can be compensated by process adaptations later on. In this context, environmental factors also play a large role, especially the particle-free conditions in a manufacturing environment compared to the laboratory scale.

Critical Parameters of the Formulation

The commonly accepted rational approach for the design of freeze drying processes is the initial characterization of the critical product parameters of the formulation, especially the collapse temperature, by thermal methods of freeze dry microscopy. Based on the information obtained, a process can be developed that ensures that the product temperature consistently remains below the critical formulation temperature throughout primary drying. Thermal characterization is also essential for optimal design of the freezing and annealing step. During primary drying, the development of the product resistance of the dried cake layer also plays a large role, as this strongly

influences the product temperature. Another important factor is the nucleation temperature and the extent of supercooling of the solution. If high supercooling is present (e.g. in sterile environments), a large number of small ice crystals is formed upon nucleation, leading to higher product resistance and product temperature and prolonged primary drying time compared to the larger ice crystals in small scale where a higher particle load is present.

Transfer Strategies

To ensure rapid and adequate transfer of freeze drying processes from one freeze dryer to another, especially on different scales, it is important not just to reproduce the process parameters such as shelf temperature and chamber pressure profile, and rely on similar product performance. In contrast, it is crucial to previously determine the critical product parameters and the range within which an acceptable product is obtained ("Design Space"), and to adapt the process parameters to retain the critical product parameters within this range.

In practice, this includes modifications of shelf temperature and chamber pressure to keep the product temperature within the desired range, and prolongation of primary drying time to account for the higher degree of supercooling. The reduced radiation effects from chamber door and walls and the lower ratio of edge vials result in higher homogeneity within the batch and in a more uniform drying process in manufacturing scale. It is also imperative to already consider equipment limitations in manufacturing scale lyophilizers during development of the process in small scale. Important aspects here are high mass flow rates in early primary drying which may exceed the heat removal capacity of the condenser, or rapid ramp rates of shelf temperature during freezing and primary drying. If the process that has been developed in the laboratory cannot be replicated in manufacturing, additional expensive development and optimization in the production equipment is required.

Experiments with Fractional Loads and Placebo

If the raw materials for the lyophilized product are scarce or very expensive, it may be useful to perform preliminary experiments with a fractional load, i.e. use only a part of the available freeze dryer shelf area, to minimize the financial risk in case of a failure. To make the results of this approach useful for future full load runs, some factors should be considered. First, the freeze drying equipment needs to be qualified and tested with higher load before, as no information on the sustainability of the full load process are gained (e.g. on handling of high mass flow rates and consequences for pressure control and condenser temperature). It is sensible to fill each shelf used completely with product vials so that the radiation effects encountered in a full load run can be recreated. Also, the performance most atypical shelves should be investigated to ensure satisfactory performance for all positions in the prospective full load run.

As an alternative, a placebo formulation can be used, either by itself or to fill up the remaining vials of the fractional load. For this purpose, the placebo formulation should be thoroughly investigated and chosen to imitate the original product. This is especially critical if the placebo is not just used for evaluation of system performance or batch heterogeneity, but to assess if the formulation parameters are satisfactory for all vials. The observations gained are only valuable if the critical product parameters of the placebo formulation are comparable to the API formulation, which is easier to achieve if low API content is present.

Conclusions

This webinar shows strategies for development of freeze drying processes in the laboratory scale under consideration of critical product parameters and equipment specifications. The developed cycle needs to be adapted to account for inherent differences between the freeze dryers and environmental factors. If this is successful, a rapid implementation of the process in large scale with only little additional optimization work is possible.

Literature

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See also Technical Briefs on the SP Scientific Lyolearn Archives Homepage regarding cycle development, characterization of the formulation, influence of nucleation temperature, …