The availability of two technologies – one that enables the optimisation of freeze-drying cycles and a second that controls nucleation of the product solution – is helping to drive down freeze-drying costs and reduce cycle development times.

**Optimisation of Primary Freeze-Drying Cycle Times**

Given the significant costs of producing a freeze-dried product (equipment, utilities and so on), and the desire to reduce cycle development times to get product to the market faster, the ability to both reduce cycle development times and shorten drying cycles are two significant drivers of lower costs and faster product development times in the industry today.

**The Trial-and-Error Approach**

Conventional cycle development in the industry today still consists of a trial-and-error methodology. Based on knowledge of the critical temperature of a formulation (glass transition, T_g, or collapse temperature, T_c), the goal is to narrowly control heat flow into the product to avoid a situation where the product temperature exceeds this critical formulation temperature. Exceeding this temperature could lead to melting or collapse of the freeze-dried cake which, in turn, would compromise the quality attributes of the final drug product.

Heat is generally added by shelf temperature adjustment, and the process requires the development scientist to make a small change to the shelf temperature, and then wait and watch the impact on product temperature. This process is repeated until the scientist finds a shelf temperature that results in a product temperature that is close to the critical formulation temperature, controlled typically to about 3 to 5°C below this critical temperature boundary as a safety margin. It is also important not to let this safety margin become too large since, for each 1°C warmer that you can run your freeze dryer, primary drying can be reduced by up to 13 per cent.

In practice, our experience with some large pharmaceutical companies has shown that it can take eight to 10 attempts (or even more) and an average of 60 days to develop a freeze-drying cycle for just one product. If a company produces six to eight new drugs a year that require freeze drying, then this could require the development of as many as 100 cycles per year.

**Cycle Optimisation Technology**

Fortunately, there is a faster, less costly technology (SMART) available to develop an optimised cycle. SMART was developed by the University of Connecticut and Purdue University through the Center for Pharmaceutical Processing Research (CPPR); the technology is licensed to SP Scientific (1) and incorporated into their Lyostar 3 development freeze dryer. Given some information that is readily available – such as the number of vials, fill volume, fill weight, freeze-dryer chamber volume and, most importantly, the critical formulation temperature – SMART does the following to optimise a cycle:

1. Selects an optimum freezing cycle based on whether the formulation is crystalline or amorphous. For crystalline products, it will automatically run a predefined annealing step
2. Selects the optimum chamber pressure
3. Automatically determines the target temperature of the product (between 3 to 5°C below T_c)
4. Dynamically adjusts the shelf temperature during primary drying to keep the product at the pre-determined target temperature

Simply put, all the researcher has to do is load the dryer and click the SMART icon on the software; they can then obtain an optimised cycle without ever touching the dryer again. Collaborations with companies when the SMART technology was first developed showed the time required to develop a cycle was reduced from an average of 60 days to an average of 13 days.
Another key cycle optimisation technology (ControlLyo Nucleation on Demand Technology) was introduced by Praxair in 2011 and is also incorporated into SP Scientific’s Lyostar 3 freeze dryer (2). Its function is to control the nucleation of the product solution in the freeze dryer – that is, the solution in all vials (or bulk, syringes, and so on) nucleates at the same time and the same temperature, as predefined by the researcher. This is a key to reducing cycle times since nucleation temperatures determine the ice/product morphology. Until the advent of this technology, all freeze dryers exhibited a phenomenon called ‘supercooling’.

When a product supercools, it freezes at a temperature that is below its thermodynamic freezing point (3). The greater the supercooling, the lower the temperature at which freezing begins (termed nucleation). In a development freeze dryer, nucleation commonly occurs in the temperature range between -10°C and -15°C. In a clean Class 100 cGMP environment, it may be as low as -40°C. Again, the inherent problem with supercooling is that the greater the supercooling, the smaller the ice crystals that form during freezing. As the drying progresses, small ice crystals lead to small pores and greater resistance to mass flow. Therefore, it is more difficult to remove the sublimed water vapour from the freeze-dried cake, and the process of primary drying takes longer.

It has been shown that for each 1°C warmer that nucleation can take place, primary drying time can be reduced by 3 per cent (4). Another advantage of the Praxair technology is that it eliminates the random nature of typical uncontrolled nucleation, where vials nucleate at different times and temperatures as the temperature is ramping during the freezing phase. This can lead to a variety of process and product problems and, in an industry where vial-to-vial uniformity and product homogeneity is critical, uncontrolled, random nucleation leads to vial-to-vial differences.

**PAT Considerations**

Given the availability of these two critical Process Analytical Technology (PAT) tools on one development freeze dryer, we ran a series of experiments where we controlled the nucleation temperature during the freezing phase and let the SMART technology automatically optimise the primary drying cycle. We then compared these results with a run where nucleation was uncontrolled and SMART optimised the primary drying cycle.

The freezing phase in an uncontrolled nucleation of vials containing 5 per cent sucrose is illustrated in Figure 1. Due to the effect of supercooling, nucleation temperatures ranged from -10.5°C to -13°C. Self-adhesive thermocouples were attached to the outside of the vials to prevent
by using capacitance manometer/Pirani differential pressure control, the end of primary drying was determined to be about 27 hours.

Figure 3 shows a graph of the freezing phase in a run where nucleation was controlled at -3°C. All vials nucleated at exactly the same time and temperature.

Figure 4 shows the subsequent SMART cycle. There are two significant differences between this and the SMART cycle in the uncontrolled nucleation run. The final shelf set-point determined by SMART was -9°C, which is 12.5°C warmer than the uncontrolled run. The end-point of primary drying, (again determined by capacitance manometer/Pirani gauge convergence) was approximately 17 hours.

The controlled nucleation cycle was more than 40 per cent shorter than the cycle run without controlling nucleation. This reduction in cycle time was due to the fact that in the controlled nucleation run, larger ice crystals were formed that resulted in larger pores, less resistance to mass flow, and higher sublimation rates during the freeze drying process. Additionally, because of the higher vapour flow, there is a greater ‘self-cooling’ effect, and so more heat can be put into the product without collapse; hence, the higher shelf set-point that was automatically determined and set by SMART.

References

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