Optimization of Primary Drying Time Using a Combination of *ControLyo™* Nucleation on Demand and SMART™ Freeze Dryer Technology

Author: Mark Shon, SP Scientific

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

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 the critical formulation temperature could lead to melting or collapse of the freeze dried cake which, in turn, compromises the quality attributes of the final drug product. Heat is generally added by shelf temperature adjustment and the process requires the development scientist to do the following: Make a small change to the shelf temperature and wait and watch the impact on product temperature. This process is repeated until the scientists finds a shelf temperature which results in a product temperature that is close to the critical formulation temperature, controlled typically about 3-5°C below this critical temperature boundary (safety margin). It is also important not to let this safety margin be too large since for each 1°C warmer you can run your freeze dryer, you can reduce primary drying by up to 13%.

In practice, work that we have done with some large pharmaceutical companies has shown that it can take 8-10 attempts (or more) and an average of 60 days to develop a cycle for one product. If a company produces 6-8 new drugs a year that

require freeze drying, that could require the development of as many as 100 cycles per year.

Fortunately, there is faster, less costly technology available to develop an optimized cycle. SP Scientific's Lyostar 3 development freeze dryer incorporates a technology called SMART™ freeze drying. SMART™ was developed by the University of Connecticut and Purdue University through the CPPR (Center for Pharmaceutical Processing Research) and licensed to SP[1]. 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 optimize 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 and they can get an optimized cycle without ever touching the dryer again. Collaborations with companies when SMART™ was developed showed the time to develop a cycle was reduced from an average of 60 days to an average of 13 days.

Another key cycle optimization technology was introduced by Praxair in 2011. This technology is called *ControLyo™* Nucleation on Demand Technology, and is also incorporated in SP Scientific's Lyostar 3 Freeze Dryer[2]. Its function is to control the nucleation of the product solution in the freeze dryer, i.e. the solution in all vials (or bulk, syringes, etc.) nucleates at the same time and the same temperature, which is predefined by the researcher. This is a key to reducing cycle

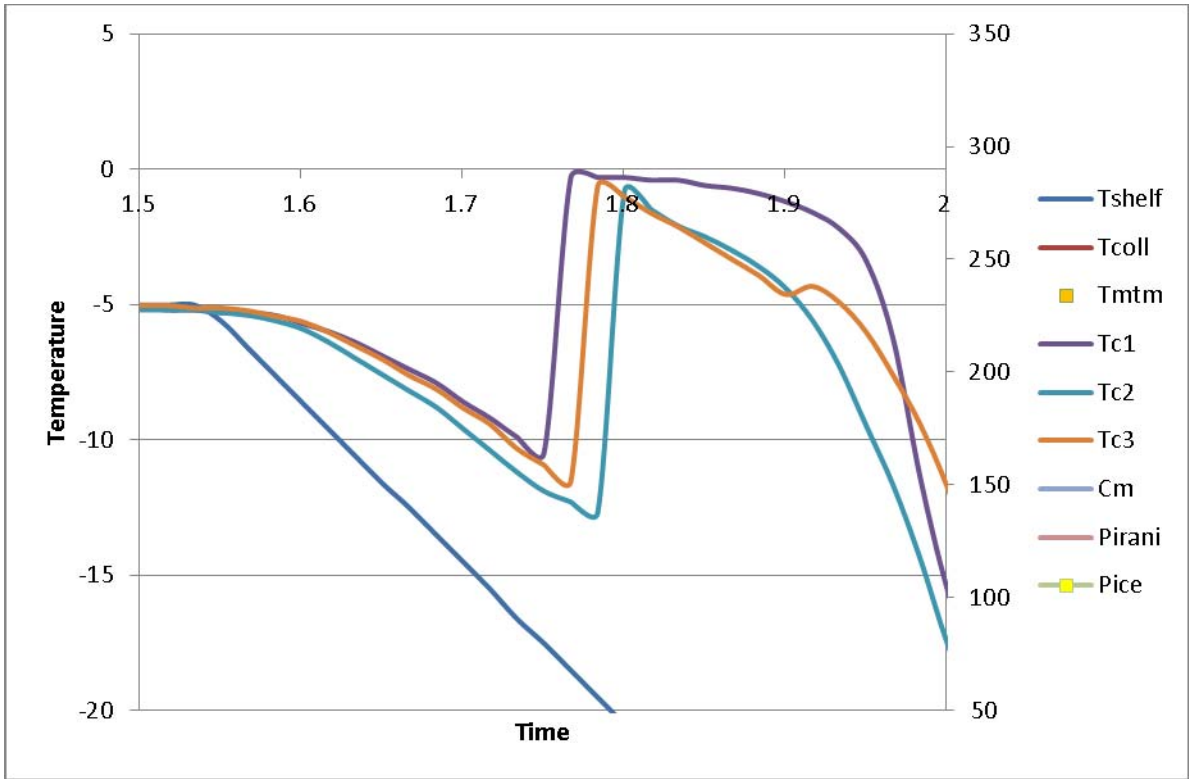
times since nucleation temperatures determine the ice / product morphology. Until the advent of the technology, all freeze dryers exhibited a phenomenon called “supercooling”. When a product supercools, it freezes at a temperature that is below its thermodynamic freezing point[3]. The greater the supercooling, the lower the temperature at which freezing begins (termed nucleation). In a development freeze dryer, nucleation commonly occurs in the temperature range between -10° and -15°. In a clean Class 100 cGMP environment, it may be as low as -40°C. Again, the inherent problem with supercooling is 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 get the sublimed water vapor out of the freeze dried cake, and the process of primary drying takes longer. It has been shown that for each 1°C warmer nucleation can take place; primary drying time can be reduced by 3%[4]. Another advantage of the Praxair technology is 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.

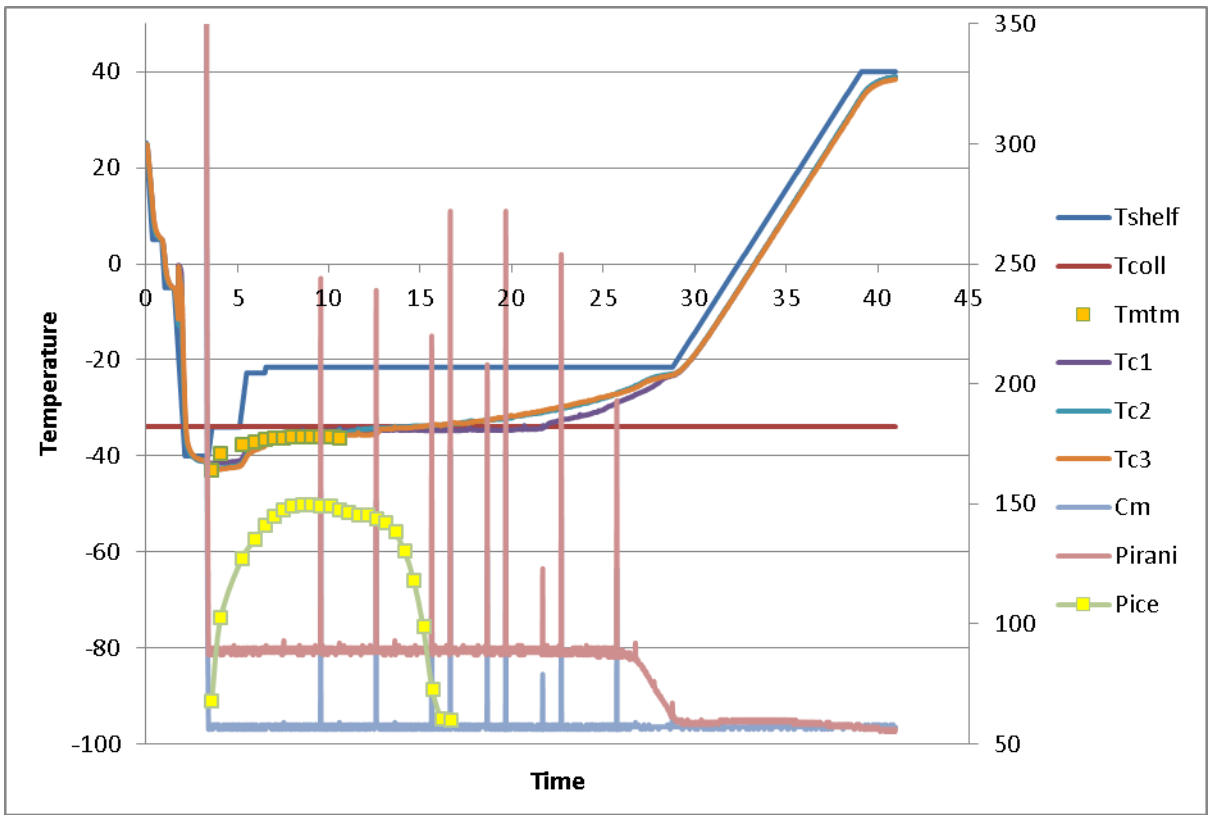
Given the availability of these two critical PAT (Process Analytical Technology) tools on one development freeze dryer, we ran a series of experiments where we controlled the nucleation temperature during the freezing phase and let SMART™ automatically optimize the primary drying cycle. We then compared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

Figure 1 illustrates the freezing phase in an uncontrolled nucleation of vials containing 5% sucrose. 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 the thermocouple itself from affecting the nucleation event. The subsequent SMART™ cycle is shown in Figure 2. Two points are worth noting. First, after the initial few shelf adjustments, SMART™ held the shelf temperature at -21.5°C throughout primary drying. Secondly, by using Capacitance Manometer/Pirani differential pressure control to determine the end of primary drying, the end of primary drying was delineated at about 27 hours.

Uncontrolled Nucleation (-10.5°C to -13°C)

Figure 1:





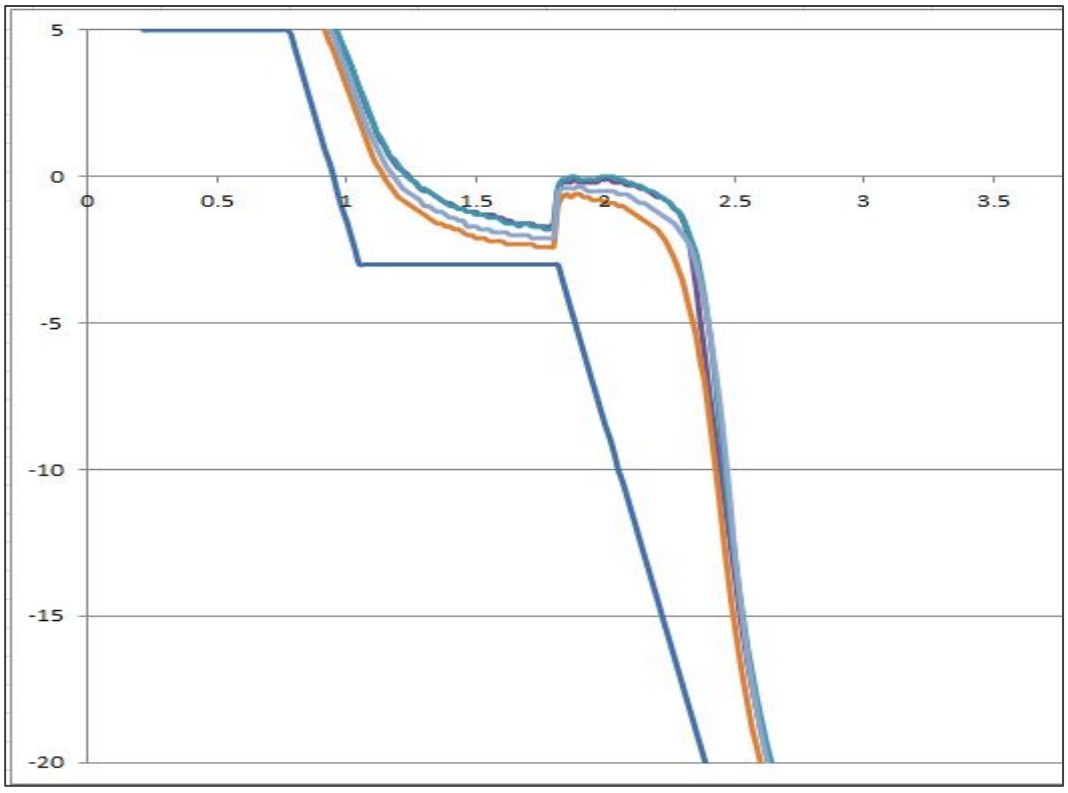
Uncontrolled Nucleation and SMART™ Cycle Optimization

Figure 2

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.

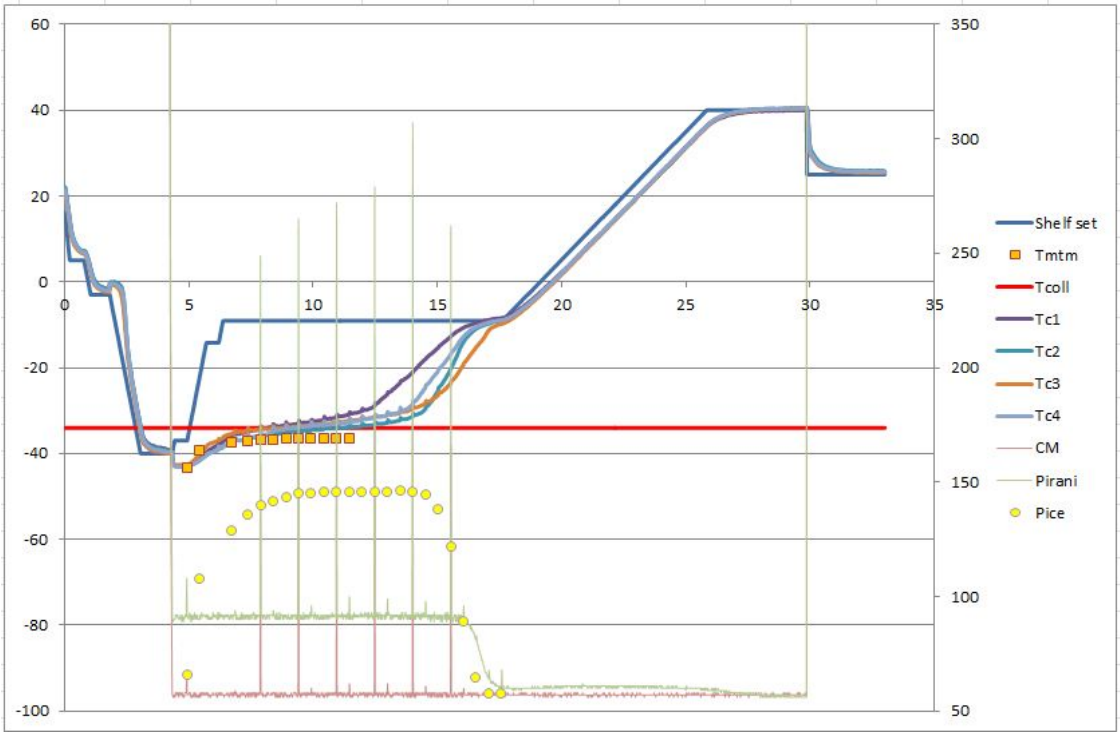
Controlled Nucleation at -3°C

Figure 3:



Controlled Nucleation at -3°C Followed by SMART™ Cycle Optimization

Figure 4:



The controlled nucleation cycle was greater than 40% shorter than the cycle run without controlling nucleation. The reduction in cycle time was the result of the following: 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 vapor flow, there is a greater "self-cooling" effect, 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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