Using SMART™ Freeze Drying Technology to Understand the Impact of Controlled Nucleation Temperature on Product Resistance

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The ability to control nucleation in freeze drying is now available by using the novel, patented *ControLyo*™ Nucleation on Demand Technology from Praxair[1]. As the shelf temperature is lowered during the freezing step, the ControLyo™ process induces nucleation by pressurizing the freeze dryer chamber and then rapidly depressurizing the chamber when the temperature reaches the desired nucleation temperature. Figure 1 shows the impact of controlled nucleation on the primary drying phase of freeze drying. The higher (i.e., warmer) the nucleation temperature, the less super-cooling takes place. A high degree of super-cooling leads to small ice crystals, which in turn results in product morphology of small pores during and after sublimation. These small pores create a high resistance (R_p) to mass flow (water vapor leaving product via sublimation). Because of the high resistance, primary freeze drying is relatively slow[2,3]. When nucleation is forced at higher temperatures (less super-cooling) with the *ControLyo*™ Technology, larger ice crystals are formed, which result in larger pore structure. This morphology of larger pores allows for lower resistance to mass flow and faster primary drying time. The *ControLyo*™ Technology is available on the SP Scientific Lyostar 3 research & development freeze dryer.

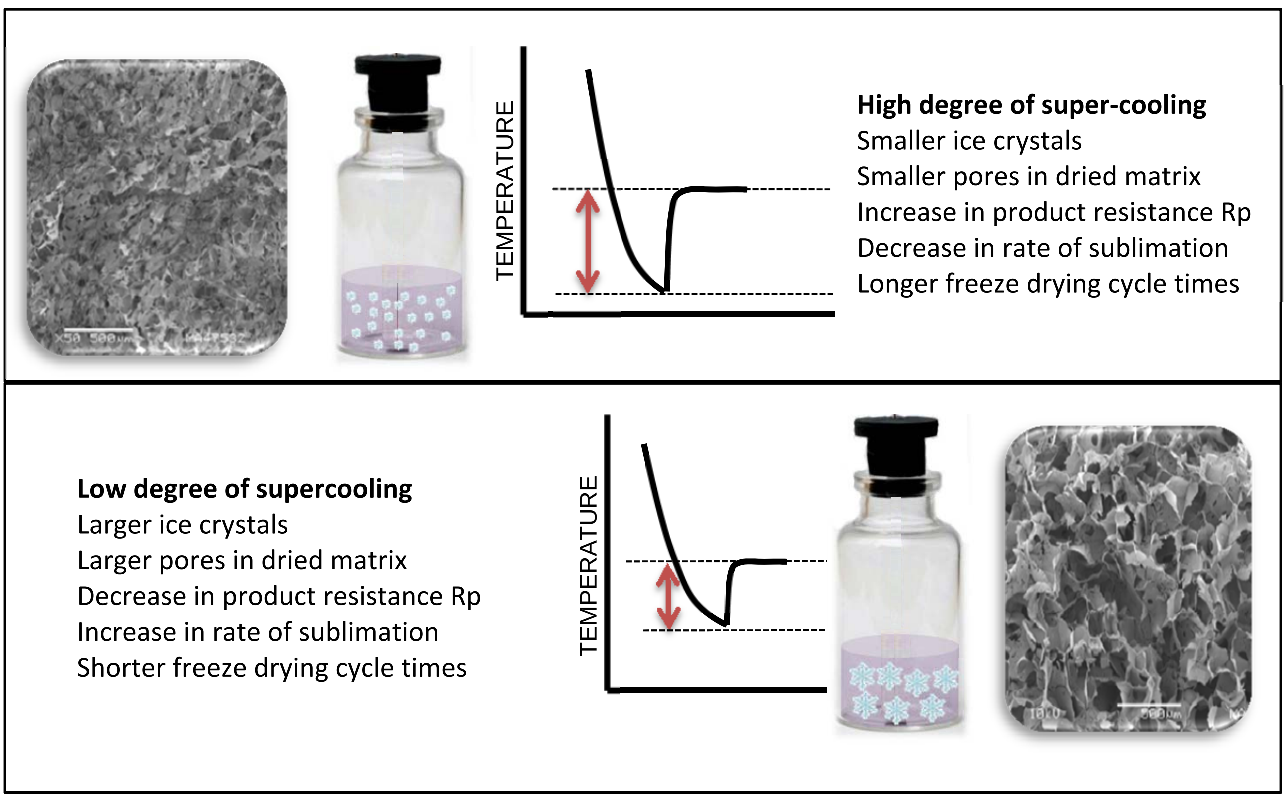

Figure 1. *Illustration of the effect of the degree of supercooling*

The Lyostar 3 incorporates SMART™ technology, which utilizes manometric temperature measurement (MTM) techniques to identify and control important process parameters during the primary drying phase of freeze drying. In addition to the well described use of SMART™ to optimize a freeze drying cycle, it also calculates and reports a number of critical process and product parameters, including product resistance (R_p), sublimation rate (dm/dt) and dry layer thickness (L_{dry}) during primary drying.

During primary drying, a valve between the chamber and condenser closes periodically for a period of 30 seconds. During this time, the pressure rise in the product chamber is recorded and data is subsequently fitted to the MTM equation by non-linear regression analysis. This automatic procedure conducted by SMART™ allows the direct assessment and reporting of the product resistance, and the vapor pressure of ice at the sublimation interface. Other parameters, such as sublimation rate and L_{dry}, are calculated by the SMART™ software using a series of well understood heat and mass transfer equations[4].

While other methods have been described to measure product resistance[5], the simplicity and versatility of SMART™ make it the technology of choice to collect these measurements. Other techniques typically involve more complex manual calculations and/or non-standard solutions. SMART™ reports the product resistance as one of the product and process parameters in an excel file that is saved at the end of a run.

Since the SP Scientific Lyostar 3 research and development freeze dryer has both the *ControLyo*™ Nucleation On-Demand Technology and SMART™, there is a unique opportunity to implement controlled nucleation as part of a cycle optimization as calculated and performed by SMART™. The advantage is that the product related properties can be instantly linked to important process performance attributes.

In the first series of experiments, the impact of nucleation temperature on product resistance was explored using a 5% sucrose solution. In two cycles, nucleation was not controlled and SMART™ cycles were run. Subsequently, we nucleated the same solution at -2°C, -3°C and -5°C and SMART™ was utilized to determine and complete the cycles. Figure 2 shows product resistance (R_p) plotted against dry layer thickness (L_{dry} - also calculated by SMART™) for each of the experimental runs. It can be observed that there is an inverse relationship between nucleation temperature and resistance: The higher the temperature at which nucleation is activated, the lower the product resistance. This is in agreement with the description of nucleation previously described. Two points are worth noting in the graph:

1. The reproducibility of the data as evidenced by the overlap of the two separate runs nucleated at-3°C .
2. The ability to discern differences in resistance with only a 1°C change in nucleation temperature.

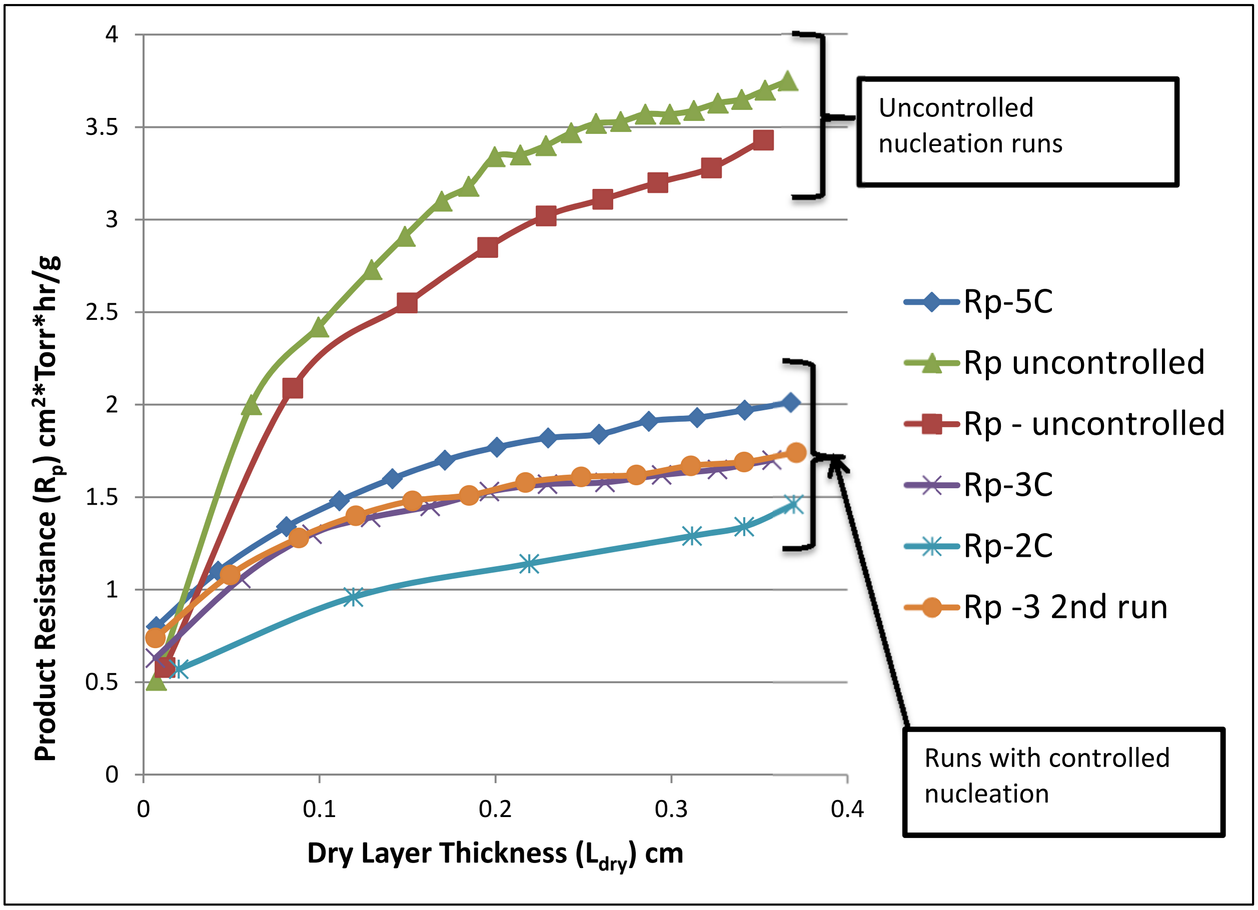

Figure 2. *Product resistance vs. dry layer thickness*

As mentioned above, product resistance is one of the most important critical product parameters in freeze drying[6]. It gives an instantaneous picture at the time of measurement of changes in the cake morphology as a function of the applied cycle conditions. Besides cake shrinkage, collapse and cracking, even subtle changes in the cake inner morphology (micro-collapse) can be examined by the product resistance data[7]. The complementary use of product interface temperature ($T_{p\text{-}mtm}$) and product resistance (R_p) provides a direct link between temperature during primary drying and product quality. This is clearly illustrated in the example in Figure 3[8].

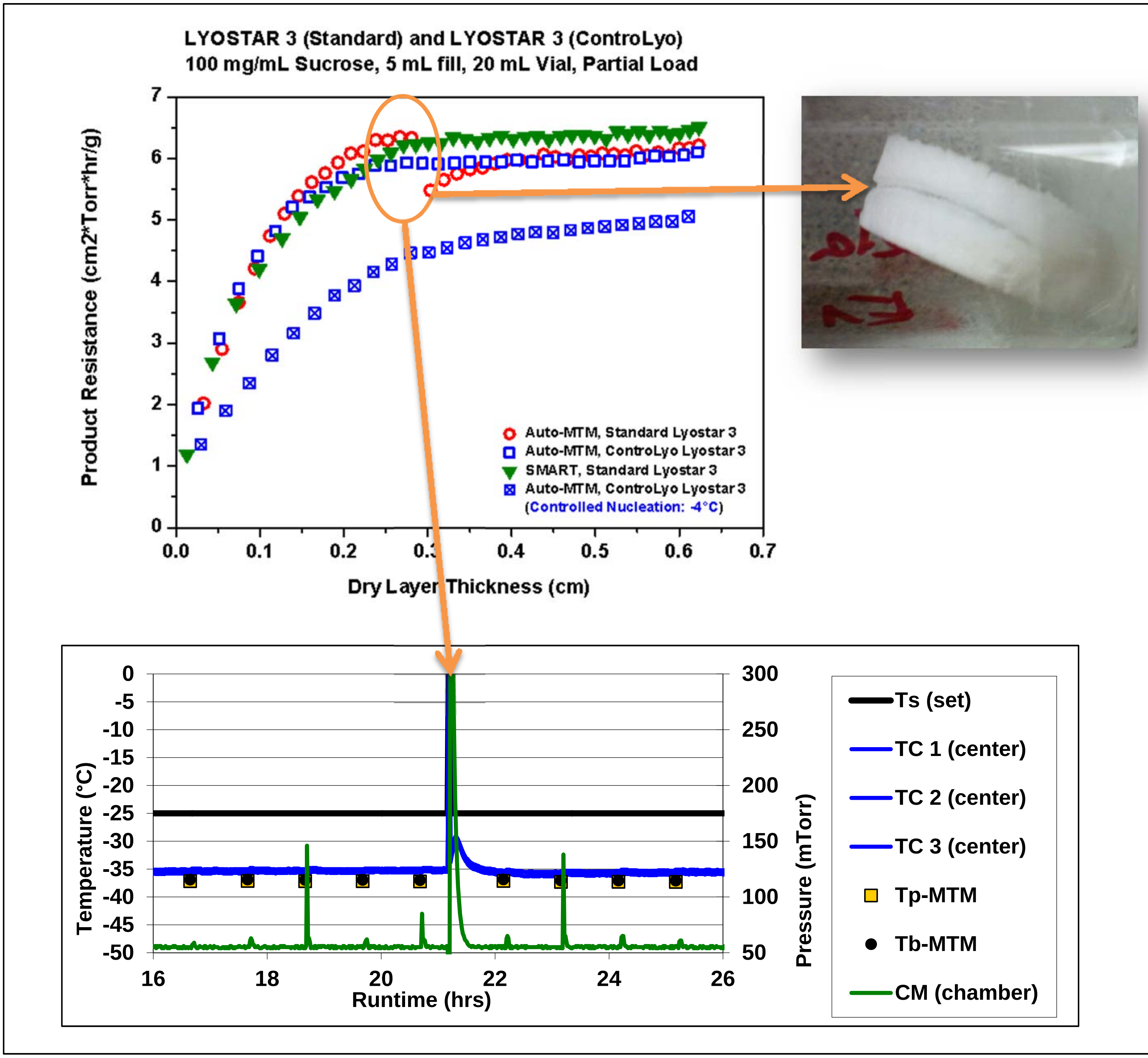

Figure 3. *Illustration of relationship between product resistance measurement and cake morphology Courtesy of Dr. Henning Gieseler, GiLyos*

In this example, three (3) separate runs were performed in the Lyostar 3 freeze dryer, without controlling nucleation. At the end of the runs, R_p was plotted against L_{dry}. The run with the green triangles (▼ and the run with the open blue squares (□) are classic resistance plots that one would expect to see. The run with the open red circles (○) reveals an anomaly that occurs about half way through the primary drying. The resistance of the product drops significantly for a short time period and then continues its normal course, similar to the others. During this short time interval, the pressure in the chamber increased. As a result, product temperature at the ice-sublimation interface increased, as well, and resulted in structural loss (collapse) in this particular region of the cake. Once the pressure control was regained, the product temperature decreased to below the collapse temperature and the cycle was completed. When the freeze dried cake was examined, the increase in temperature and subsequent collapse that occurred during the pressure loss can be seen as a layer of decreased structural integrity in the cake.

While the data that is generated by SMART™ is saved in a file and graphed at the end of the run, this example offers opportunity to use product resistance as a process analytical technology (PAT) tool to perform "In-Process" analytical analysis. If R_p vs. L_{dry} was reported and visible in real time, the anomaly that occurred would have been seen during the run, and would have predicted that the cake would likely have morphological anomalies.

ControLyo™ Nucleation On-Demand Technology is a Trademark of Praxair Inc.

SMART™ is a Trademark of SP Scientific

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