

## Smart TDLAS-Based Freeze Dryer Technology: Application To Highly Concentrated Amorphous Systems

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Designing a freeze-drying process requires optimization and control of critical product parameters, such as the product temperature ( $T_p$ ) and residual moisture content. These parameters are controlled by the regulation of other process parameters including shelf temperature, chamber pressure, and drying times. The use of accurate process analytical technology to relate critical product parameters to controllable process parameters is essential to provide optimal cycle conditions for each product, some of which can be more challenging than others.

Recently, Ms. Emily Gong, Senior Research Scientist, Physical Sciences Inc., USA, presented a webinar describing how SMART TDLAS-based technology can be applied to any product formulation, including highly concentrated amorphous systems, to accurately control critical product parameters, such as  $T_p$ . This tech note summarizes the webinar and includes a selection of questions from the Q&A sessions.

### SMART Freeze-Drying Technology

Altering the process parameters controls the critical product parameters required for the optimization of freeze-drying cycle development. The relationship between these parameters is complex and is impacted by the type of product (due to product resistance to mass flow) and the freeze dryer (due to heat transfer to the vial and equipment limitations). If measurements of product resistance, vial heat transfer coefficients, and equipment capability limits are made, models can predict the freeze-drying cycles. However, models are not often used due to the level of expertise required to implement them. More commonly, process development occurs in an iterative trial-and-error approach which can be time consuming and costly.

SMART freeze-drying technology was created as a lyophilization cycle development tool based on a model of steady state heat and mass transfer in vials and decades of empirical observations.<sup>1,2</sup> In collaboration with leading academics at the University of Connecticut and Purdue University, the first commercial product available was based on Manometric Temperature Measurement

(MTM) to determine the  $T_p$  at the sublimation interface, during the freeze-drying cycle. Periodic determination of  $T_p$  combined with the model enables real-time prediction of how changing process conditions (shelf temperature,  $T_s$ , and drying chamber pressure,  $P_c$ ) affect future product temperatures. This eliminates the empirical nature of freeze-drying and enables scientists, possessing minimal knowledge of lyophilization, to successfully develop efficient process cycles.

### SMART Algorithm

The SMART algorithm works as a series of steps accelerating and streamlining the development of lyophilization cycles. It begins with determining the target  $T_p$  as a function of  $T_c$  or eutectic temperature ( $T_{eu}$ ), and setting the chamber pressure to ensure there is a driving force for sublimation. An initial conservative  $T_s$  is used until a steady state of sublimation is established. Further  $T_s$  set-points are determined using a heat and mass transfer model of freeze-drying to predict the resulting  $T_p$ . During the process of establishing the  $T_s$  set-point, the  $T_p$  is determined using measurements of the batch average water vapor mass flow rate in combination with the heat and mass transfer model of drying. A comparison is made between the measured  $T_p$  and the target  $T_p$ . If the measured  $T_p$  deviates too far from the target, an updated calculation of  $T_s$  is used as the shelf temperature set-point. This process only occurs after an appropriate equilibration time (~1 hour) in order to re-establish steady-state after process conditions are changed. This process is repeated until approximately two-thirds of the product cake has dried. After that point in drying, there is a risk of edge vials completing drying, leading to incorrect knowledge of the ice surface area undergoing sublimation and an inaccurate model predictions of  $T_p$ . Following that time-point the  $T_s$  remains constant.

The webinar compared two methods used for determining  $T_p$  and the resulting SMART freeze-drying cycles for drying two different formulations.

### MTM Technology

MTM is a pressure rise-based measurement technique mainly used to determine cake resistance and product temperature at the ice sublimation interface. The pressure rise results from the quick closure of the isolation valve between the product chamber



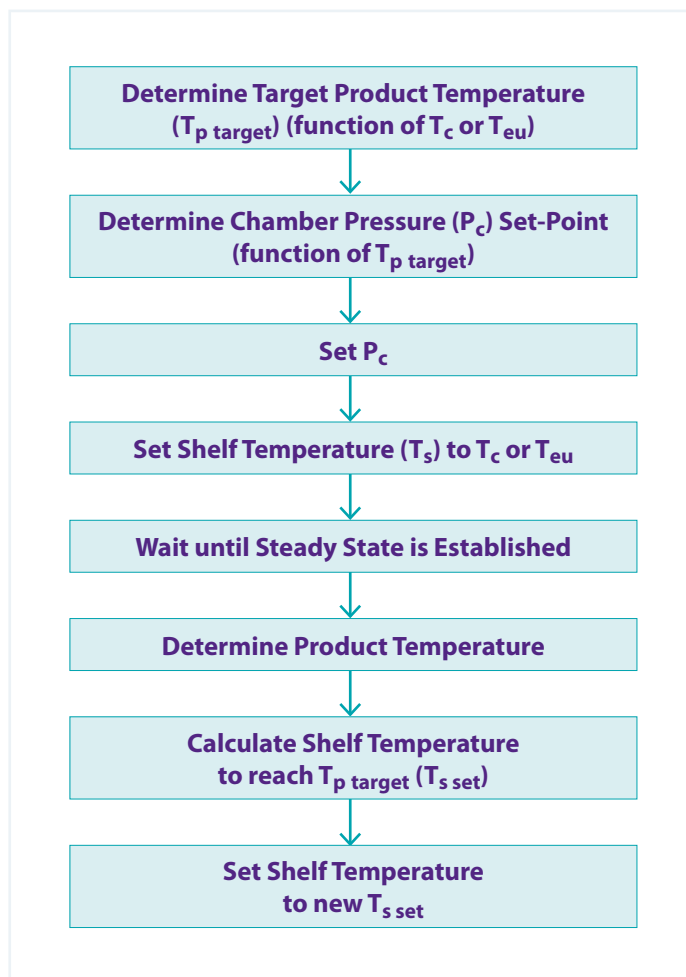


Figure 1. SMART Algorithm Overview

and freeze dryer condenser. The algorithm used to calculate  $T_p$  utilizes the vapor pressure of ice at the sublimation interface ( $P_{ice}$ ) and the product resistance ( $R_p$ ) to guide the choice of  $T_s$ .

There are several limitations of this method, one of which is the requirement for a fast-closing valve. This typically limits the application to smaller lyophilizers that utilize butterfly valves. Larger dryers tend to use mushroom valves to seal the large spool pieces that connect the chamber and condenser. These valves are not capable of achieving the <1 second closing times. Another limitation is the requirement for a lyophilizer leak rate of <30 mTorr/hour. In addition, the closing of the isolation valve disrupts the drying process resulting in a rise in the  $T_p$  which may be a risk for cycles with the  $T_p$  running close to  $T_c$  or  $T_{eu}$ .

Finally, another important factor to consider is that of product formulation. Amorphous formulations, common for many biopharmaceuticals, can reabsorb water in the dry layer when

the valve closes. This results in a failure of the pressure rise data processing algorithm and an under prediction of the  $T_p$ . The MTM SMART algorithm can then set the  $T_s$  too high and lead to a runaway process with collapse or eutectic melting of the product undergoing drying.

### TDLAS Integration

An alternative approach that circumvents these MTM limitations is the use of a Tunable Diode Laser Absorption Spectroscopy (TDLAS) water vapor mass flow rate monitor in combination with the freeze-drying SMART algorithm. The TDLAS sensor enables continuous, real-time measurements of near-IR absorption by water vapor at  $\sim 1.4$   $\mu\text{m}$ , eliminating the need for the pressure rise measurement. In the dryer, the optical measurement is made in the spool connecting the lyophilizer chamber and condenser. Water vapor flows through this duct and the light absorption along two line-of-sight measurement angles (45 and 135 degrees with respect to the gas flow) is detected using two laser beams originating from the same laser. The measurements made at angles to the flow path result in Doppler shifts of the absorption peaks (to higher and lower wavelengths) as a function of flow velocity.

Analysis of the resulting low-pressure absorption peaks enables the measurement of both the water vapor density (molecules/ $\text{cm}^3$ ) and flow velocity (m/s). This information is combined with the knowledge of the spool cross-sectional area enabling the determination of the water vapor mass flow rate,  $\text{dm}/\text{dt}$  (g/s). The  $\text{dm}/\text{dt}$  values are combined with the heat and mass transfer model of vial-based freeze-drying to enable the calculation of the batch average  $T_p$ , replacing the need for the MTM pressure rise measurements.

### Comparison Of MTM And TDLAS Method To Determine $T_p$

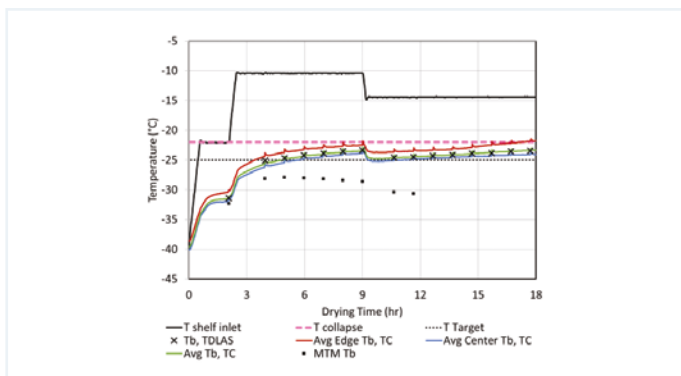
Previous evidence suggested that the MTM method provided inaccurate temperature determinations compared to thermocouple based measurements for hygroscopic formulations, such as PVP and highly concentrated amorphous formulations. In addition, it was previously shown that the TDLAS based sensor provided accurate determinations for all product formulations tested. During this R&D effort, several case studies were set up utilizing two excipients and in two different freeze dryers to determine if the development of the TDLAS SMART freeze dryer algorithm could be successfully used to develop drying cycles for all product formulations and could be applied to any size lyophilizer.

## Case Studies

The SMART freeze-drying model incorporated data from MTM or TDLAS to enable automated adjustments of  $T_s$  and vacuum set-points to build optimized recipes as the cycle progresses. During the webinar, Ms. Gong described the comparison of using SMART-TDLAS or MTM to determine  $T_p$  during primary drying of 5% sucrose or 10% sucrose/10% BSA in either a small lab-scale freeze dryer (LyoStar 3, 4.6 ft<sup>2</sup> shelf area, SP Scientific Products, USA) or in a pilot-scale freeze dryer (LyoConstellation, S20, 20 ft<sup>2</sup> shelf area, SP Scientific Products, USA).

During all experiments, the heat and mass transfer model broke down after approximately two-thirds of primary drying when the edge vials were nearly dry, resulting in inaccurate knowledge of the total ice surface area undergoing sublimation. Following this time-point the shelf temperature remained constant to the end of primary drying.

Both lab- and pilot-scale TDLAS- and MTM-SMART maintained the  $T_p$  below the  $T_c$  and accurately calculated the product temperature at the bottom of the vial ( $T_b$ ) during primary drying of 5% sucrose. However, for the more concentrated amorphous formulation (10% BSA, 10% sucrose), the TDLAS approach again accurately predicted the  $T_b$  but the MTM approach did not (Figure 2). After as little as 4 hours of primary drying, there was a noticeable difference between TDLAS and MTM determined value of the batch average  $T_b$  and resultant calculation of  $T_p$ . It is likely that this is due to water reabsorption by the dried product, leading to an overly aggressive cycle and the potential for product collapse.



**Figure 2.** Lab Scale TDLAS-based SMART Freeze-Drying Cycle for 10%BSA / 10% Sucrose showing the first two-thirds of primary drying.

Further studies provided evidence that TDLAS-SMART produced highly repeatable cycle with data output, such as product resistance and heat transfer coefficient that can guide future process development and aid in designing a robust design space for a product.

## Conclusions

The TDLAS-based SMART freeze dryer can accurately calculate  $T_p$ , generating cycles that maintain a  $T_p$  below the  $T_c$  for all vials. It is of particular interest that TDLAS can be applied to any formulation including high solid content formulations that fail using MTM SMART methods of calculation, and to any freeze dryer. One of the economic advantages is that TDLAS-SMART enables cycle development using a single experiment reducing time and money.

**To view the full webinar and download the slides, please go to the archived webinars on our website**

**<https://www.sp-scientificproducts.com/Webinars/Archives>**

## Q&A Session

### 1. What is the TDLAS experience in commercial lyophilizers, since your presentation is focused on the lab and pilot scale examples?

PSI and SP have implemented the TDLAS sensor on both the lab-scale LyoStar 3 and the pilot-scale LyoConstellation range of freeze dryers. The LyoConstellation goes up to an 130 ft<sup>2</sup> shelf area unit. The TDLAS sensor can be installed on production lyophilizers, but some design aspects must be considered for accurate TDLAS measurements. There must be a spool connecting the chamber and condenser with sufficient length to make the TDLAS measurement. Also, there cannot be any CIP/SIP piping disturbing the vapor flow both at the entrance to the spool as well as along the spool.

### 2. How is the data generated during a TDLAS-based SMART cycle used in Pikal's spreadsheet or the LyoModelling Calculator?

Pikal's spreadsheet and the LyoModelling Calculator require inputs for the vial heat transfer coefficient ( $K_v$ ) and for the product resistance parameters. For TDLAS-based SMART,  $K_v$  must be determined experimentally prior to the SMART cycle. The TDLAS sensor can allow you to determine  $K_v$  as a function of pressure in a single experiment. The TDLAS sensor will calculate product resistance as a function of dry layer thickness during the SMART cycle. This can be used to calculate the required resistance parameters. Additionally, TDLAS can be used to calculate the equipment capability limit (maximum mass flow as a function of pressure supported by the freeze dryer) in a single experiment.

### 3. How is the chamber pressure chosen by the SMART algorithm, and why are there multiple shelf temperature set-points during primary drying?

The chamber pressure is chosen based on the target product temperature selected by the SMART algorithm such that the chamber pressure is sufficiently lower than the vapor pressure of ice at the sublimation interface to provide a driving force for sublimation. The initial shelf temperature is set at the collapsed temperature to ensure the product does not exceed the collapsed temperature. The remaining shelf temperatures are chosen by the algorithm based on the product temperature measurements by TDLAS. The shelf temperature is adjusted throughout the first two-thirds of primary drying in order to keep the product at the target temperature. The shelf temperature may need to be lowered due to reduced sublimative cooling as the product resistance increases.

### 4. How accurate is the TDLAS sensor when at the end of primary drying with very low water vapor concentrations?

TDLAS is an extremely sensitive measurement for water vapor concentration. The signal to noise for the water vapor mass flow is generally limited by the velocity measurement. Sensor performance at the end of primary drying is dependent on the process and product. For example, an aggressive cycle with a product of low resistance will generally have higher signal to noise ratio at the end of primary drying than a conservative cycle with a product of high resistance due to sublimation rates. Experimentally, we have been able to accurately measure water removed from a single 20R vial dried at a shelf temperature of 0°C and a chamber pressure of 100 mTorr. In regards to TDLAS-based SMART, the algorithm does not make process changes past two-thirds of primary drying as determined by the dry layer thickness.

## References

1. Tang, X. C., Nail, S. L., & Pikal, M. J. (2005). Freeze-drying process design by manometric temperature measurement: design of a smart freeze dryer. *Pharmaceutical research*, 22(4), 685-700.
2. Gieseler, H., Kramer, T., & Pikal, M. J. (2007). Use of manometric temperature measurement (MTM) and SMART™ freeze dryer technology for development of an optimized freeze-drying cycle. *Journal of Pharmaceutical Sciences*, 96(12), 3402-3418.