IDS 2020
22nd International Drying Synposium

IDS'2020 – 22nd International Drying Symposium
Worcester, Massachusetts, USA, June 28 – July 1, 2020
DOI: http://dx.doi.org/thisisa/placeholder/

Tunable Diode Laser Absorption Spectroscopy (TDLAS) Enabled SMART Freeze-Dryer Technology

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Abstract

Tunable Diode Laser Absorption Spectroscopy (TDLAS) measurements combined with SMART Freeze-Dryer Technology enabled automated pharmaceutical lyophilization process development. The sensor measured water vapor temperature, density and flow velocity to calculate water vapor mass flow rates (dm/dt). The dm/dt values were combined with a heat and mass transfer model of lyophilization and vial parameters to enable real-time determinations of product temperature during sublimation. The temperatures combined with a process development algorithm produced efficient freeze-drying cycles during a single lyophilization experiment. The TDLAS-enabled SMART Freeze-Dryer Technology was used to dry placebo formulations in laboratory and pilot-scale lyophilizers, demonstrating application at multiple scales.

Keywords: *TDLAS; SMART Freeze-drying; Process development; SMART-MTM; SMART-TDLAS*

1. Introduction

Many pharmaceutical products, most notably biopharmaceuticals, are lyophilized, or freeze-dried, to meet stability requirements for a commercializable product. During the lyophilization process, frozen water is removed through sublimation at low temperatures and pressures. [1] This results in a dried product that is stable and can be stored and reconstituted at the time of patient use. The process is typically designed to avoid the frozen product exceeding the formulation dependent critical temperature above which there will be viscous flow and adverse effects on the dried structure that may lead to increased residual moisture and reconstitution times as well as poor stability, [1] but overly conservative processes can add significant costs resulting in potential commercial failure. Generally, reducing the product temperature (T_p) by 1°C will increase the primary drying time, the longest portion of the process, by 13%. [2] Freeze-drying cycles are often days long, and non-optimized cycles can drastically increase production costs and lower processing capacity. Thus, there is substantial motivation to develop robust and efficient cycles.

The rapid growth of biopharmaceuticals has resulted in increased demand for freeze-drying; however, there is limited worldwide expertise in freeze-drying process design. The SMART Freeze-Dryer algorithm was developed by experts at the University of Connecticut and Purdue University to enable rapid process design, even for novice users. The SMART technology requires input parameters for product and vial characteristics and in-process T_p determinations to automatically develop a cycle. The algorithm incorporates a pseudo-steady state heat and mass transfer model of freeze-drying in vials and expert knowledge to determine appropriate shelf temperature (T_s) and process pressure set points. [3]

The SMART algorithm requires a process analytical technology (PAT) tool to determine T_p during freeze-drying. The original algorithm used Manometric Temperature Measurement (MTM) technology based on pressure rise measurements to determine T_p. [3] Using this method, the isolation valve between the lyophilizer chamber and condenser is quickly closed and the chamber pressure (P_c) is measured for 25 seconds. P_c rises due to on-going sublimation, and the pressure rise is fit to an equation to determine the vapor pressure of ice at the sublimation interface (P_{ice}) which is used to calculate T_p. [3] Limitations of MTM for calculating T_p include: 1) a requirement for a fast-closing valve (<1s) which is not feasible for larger dryers, 2) diminishing T_p measurement accuracy during the cycle due to reduced sublimation caused by increased product resistance to drying (Rp), and 3) some products, mainly high weight percent amorphous products, reabsorb water in the dried layer during the pressure rise test, leading to a reduced pressure rise and incorrect T_p determination. [4]

The limitations of MTM motivated the application of an alternate approach for determining T_p, using Tunable Diode Laser Absorption Spectroscopy (TDLAS). The TDLAS sensor measures water vapor absorption lineshapes at 1392.5 nm at two angles (45 and 135 degrees) with respect to the water vapor flow axis in the spool between the drying chamber and the condenser. [5] From the lineshapes, the gas temperature (K) can be determined using the full width at half maximum. The gas temperature is used to calculate the absorption linestrength, S(T). Using the Beer-Lambert law, the linestrength and the integrated area under the absorption lineshape are used to determine the water vapor concentration (molecules cm^{-3}). The gas flow velocity (m/s) is determined using the frequency or wavelength Doppler shift

between the lineshapes from the two measurement locations. The gas concentration, velocity and spool cross-sectional area are used to calculate the water vapor mass flow rate (g/s). The average rate is determined by real-time calculation of the flow development within the duct, assuming an axi-symmetric flow profile, to apply scaling factors to account for the variable gas temperature, density and velocity as a function of radial position across the duct. The TDLAS sensor can be implemented on any scale freeze-dryer, and its accuracy is not product dependent. Use of the TDLAS sensor to determine T_p in the SMART Freeze-Dryer eliminates the limitations of MTM and increases the applicability of SMART Freeze-Dryer algorithm.

2. Materials and Methods

2.1. Materials

Mannitol, sucrose, trehalose, glycine, polyvinylpyrrolidone (PVP), and bovine serum albumin (BSA) were purchased from MilliporeSigma (St. Louis, MO). Solutions were prepared using ultrapure deionized water and filtered using a 0.22 µm polyethersulfone filter (Thermo Fisher Scientific, Waltham, MA). Prior to final formulation, BSA solutions were dialyzed to remove salts then diluted to the final concentration. Two rounds of dialysis totaling 24 hours were performed using a cellulose membrane with a molecular weight cut off of 6-8 kDa (Spectrum Chemicals, Brunswick, NJ). The final BSA concentration was determined using UV slope spectroscopy (C Technologies, Bridgewater, NJ) with an extinction coefficient of 0.647. Vials used were 20cc glass tubing vials (either Schott, Lebanon, PA or Amcor, now Nippon Electric Glass, Shiga, Japan).

2.2. Equipment

Laboratory-scale experiments were conducted using a LyoStar 3 freeze-dryer (SP Scientific, Gardiner, NY) containing three shelves with a total shelf surface area of 0.43 m^2. Pilot-scale experiments were conducted in a LyoConstellation S20 (SP Scientific, Gardiner, NY) freeze-dryer containing five shelves with a total shelf surface area of 1.86 m^2. Both systems were equipped with a LyoFlux® (Physical Sciences Inc., Andover, MA) TDLAS sensor, the LyoS™ Software Control System (SP Scientific, Gardiner, NY) and the existing SMART MTM-based Freeze-Dryer technology, as well as the custom TDLAS-enabled SMART software. The TDLAS sensor and freeze dryer software were configured to enable communication and data transfer. The TDLAS sensor computer was connected by an Ethernet cable to the programmable logic controller (PLC) of the freeze-dryer via a separate network interface. The inter-machine communication was used to transfer status updates, alarms and system parameters between the freeze-dryer and the TDLAS sensor.

2.3. Experimental Setup

Vial heat transfer coefficients (K_v) were experimentally determined by subliming deionized water in vials under steady state conditions and calculated using Equation 1:

$$K_v = \left(\Delta H_s * {dm}/{dt}\right)/\left(A_v(T_s\text{-}T_b)\right) \quad (1)$$

where ΔH_s is the heat of sublimation of ice, dm/dt is the water vapor mass flow rate, A_v is the area of the bottom of the vial, T_s is the shelf temperature and T_b is the product temperature

at the bottom center of the vial. A_v was taken from engineering data for each vial type. The water vapor mass flow rates (dm/dt) during these experiments were determined using both TDLAS and gravimetric measurements. T_s and T_b were measured using 36 gauge bare lead thermocouple (TC) probes (Omega, Norwalk, CT). T_b was measured in a representative subset of vials using TC probes inserted into a standard lyophilization stopper and placed at the bottom center of the vial.. A heat of sublimation for ice of 670 cal/g was used.

3. Results and Discussion

3.1. TDLAS product temperature calculation accuracy

The SMART algorithm requires input of T_p to determine T_s set points required to maintain T_p below the product formulation critical temperature (collapse temperature, T_c, for amorphous formulations and eutectic melt, T_{eu}, for crystalline formulations). The TDLAS-enabled SMART Freeze-Dryer technology utilizes the batch average water vapor mass flow rate measured by the TDLAS sensor in conjunction with the pseudo steady-state heat and mass transfer model of freeze-drying to calculate T_p in real-time during freeze drying. TDLAS-determined T_p accuracy is dependent on the accuracy of the measured water vapor mass flow rate as well as the accuracy of the K_v used as a model input. Water vapor mass flow rate measurement accuracy was assessed using comparative experiments between TDLAS and gravimetric measurements of the integrated mass of water removed during ice slab experiments. During these experiments, ice slabs containing a known weight of water were formed in plastic lined frames placed directly on the lyophilizer shelves. Following sublimation experiments removing approximately 30% of the water used to form the ice slabs, comparisons of integrated amounts of water removed indicate that the TDLAS measurements had less than +/-5% error compared to gravimetric determinations.

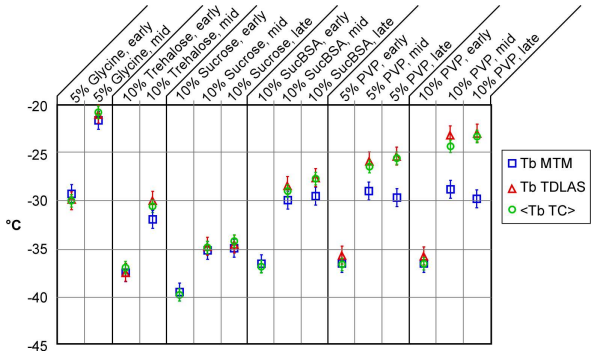

Fig. 1 Comparison of thermocouple, MTM and TDLAS measurements of T_b during freeze drying. Error bars: +1°C for MTM & TDLAS; 0.8°C for thermocouples.

Product temperature measurement accuracy was assessed during freeze-drying cycles. The product temperature at the bottom center (T_b) of a representative set of vials was measured using TCs and the batch average T_b was calculated using TDLAS and MTM. Fig. 1 shows a comparison of these three measurement techniques for a range of product formulations. A comparison between the TDLAS T_b and the thermocouple "gold standard" shows good agreement (within ±1°C) for all formulations. A comparison with the MTM technique shows that for some formulations MTM has good agreement, but for some amorphous formulations

(e.g. trehalose, sucrose/BSA and PVP) the MTM technique has unacceptable error, especially mid to late in the cycle due to water reabsorption.

3.2. SMART freeze drying of placebo formulations

Placebo formulations were used to test the TDLAS-enabled SMART Freeze-Dryer with relevant formulations. Sucrose is a common stabilizer and forms an amorphous product with a low T_c (-32°C). [6] Mannitol is a common bulking agent and forms a crystalline product with a high eutectic melt temperature that is dependent on the crystalline structure. [7] A formulation of BSA and sucrose was used as a model for a protein formulation. A high concentration, 20% total solids with 1:1 BSA to sucrose, was used to demonstrate the problems associated with MTM measurements and cycle development compared to the successful TDLAS measurements and control. Selected experiments were conducted in both a lab-scale freeze dryer (LyoStar 3) and a pilot-scale freeze dryer (LyoConstellation S20).

Fig. 2 shows the full cycle for 20% w/w sucrose generated by the TDLAS-enabled SMART Freeze-Dryer. During freezing and secondary drying, the cycle parameters are determined based on the nature of the drug product, amorphous or crystalline, and the fill depth. Freezing steps may be altered by the user based on the thermal response of the product (e.g. adding an annealing step). The P_c set point during primary and secondary drying was determined from the target T_p, and the T_s set points during primary drying were determined by the algorithm based on TDLAS-determined T_p. A secondary drying temperature of 40°C was used.

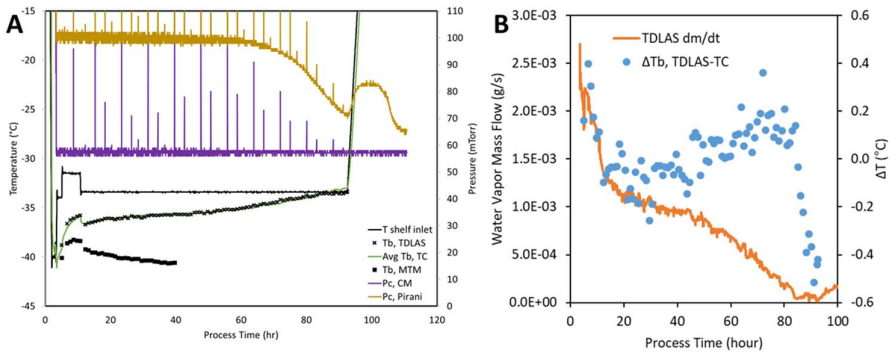

Fig. 2 A) Lab-scale TDLAS-enabled SMART Freeze- Dryer cycle developed for 20% w/w sucrose. B) TDLAS-determined water vapor mass flow and product temperature accuracy during primary drying. A single shelf of 160 20mL vials (Amcor) filled with 3mL of solution was dried.

For a sucrose concentration as high as 20%, it is expected that significant water reabsorption will occur in the dry product layer during the valve closure event for MTM-based T_p determinations. This is evident in T_b determined by MTM during the cycle where MTM under-predicts T_b compared to TC measurements, with errors greater than -4°C after only 1/3 of primary drying. MTM measurements end 2/3 through primary drying due to lower sublimation rates causing insufficient pressure rise for MTM measurements. However, TDLAS-determined T_p is accurate throughout the entire primary drying process. Fig. 2B indicates accurate TDLAS-based T_b determinations ($\leq \pm 1$°C error) throughout primary drying compared to TC based measurements. Pressure spikes in Fig. 2 and temperature spikes in Figs. 2 through 5 are a result of the isolation valve closures during MTM.

Experiments were conducted in lab-scale and pilot-scale dryers to demonstrate the application of TDLAS-enabled SMART Freeze-Dryer technology on multiple scales. Fig. 3. shows primary drying cycles determined by the SMART algorithm for 5% sucrose and 20% BSA:Sucrose at a 1:1 ratio in the lab-scale freeze-dryer. During sucrose drying, 112 vials were filled with 3 mL of solution, and a ring of empty (dummy) vials surrounded the product vials to lessen the radiation input from the warm walls. The input K_v reflected a batch average value determined using the same vial fill configuration. During drying of the BSA:sucrose formulation, all 160 vials were filled with product and a location dependent weighted average K_v was used.

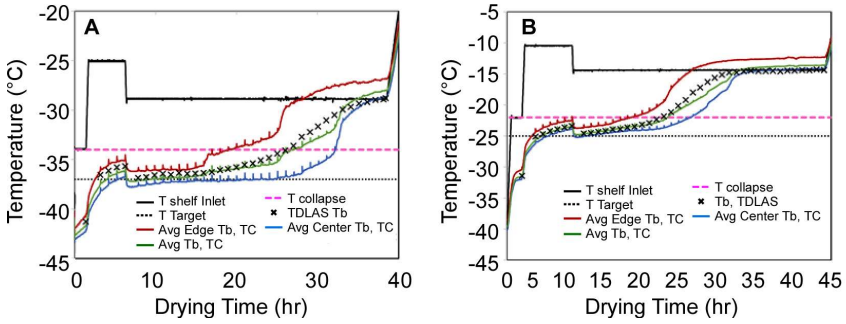

Fig. 3 Lab-scale primary drying recipes determined by the TDLAS-enabled SMART Freeze-Dryer for A) 5% w/w sucrose and B) 20% w/w BSA:Sucrose at a 1:1 ratio. For 5% sucrose, a single shelf of 112 glass tubing vials (Schott) filled with 3mL of solution was dried. For 20% BSA:Sucrose, a single shelf of 160 glass tubing vials (Schott) filled with 5mL of solution was dried.

Fig. 4 shows primary drying cycles for the same formulations in the pilot-scale freeze-dryer, without the use of "dummy" vials. The variation in number of vials was due to the vial configuration on the shelf. K_v was determined experimentally prior to each cycle using an identical configuration. For both the low and high solids content formulations at both scales, the TDLAS sensor accurately determined T_p as compared to thermocouple probes (within ±1°C for the first 2/3 of primary drying when all vials are undergoing drying).

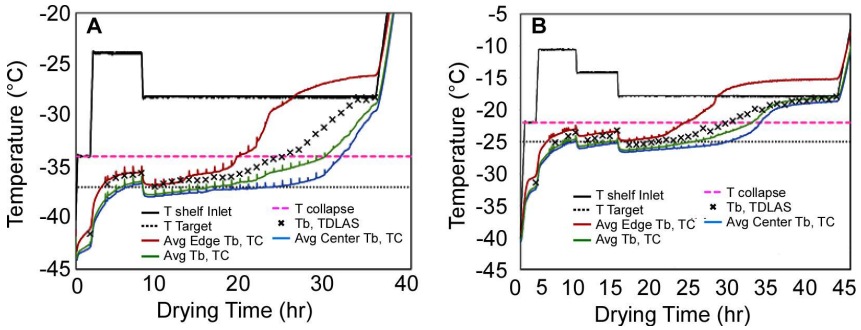

Fig. 4 Pilot-scale primary drying recipes determined by the TDLAS-enabled SMART Freeze-Dryer for A) 5% w/w sucrose and B) 20% w/w BSA:Sucrose, 1:1. For 5% sucrose, a single shelf of 382 glass tubing vials (Schott) filled with 3mL of solution was dried. For 20% BSA:Sucrose, a single shelf of 480 glass tubing vials (Schott) filled with 5mL of solution was dried.

In all cases, the T_s set points calculated by the SMART algorithm maintained the average T_p within ±2°C of the target T_p and below T_c. Critically, the edge vial temperatures, the warmest

vials due to radiative heat inputs from the dryer walls, were maintained below T_c while undergoing drying. The rise in T_p approximately midway through primary drying is due to edge vials completing drying and warming to at or above (due to radiation heat inputs) T_s. Once the ice is removed, the glass transition temperature of the dried product is raised. Therefore, these T_p increases are not detrimental to the product structure.

Experiments were conducted to determine reproducibility of the developed cycles. Two experiments were conducted for 5% sucrose (Fig. 5A) and 5% mannitol (Fig. 5B) in the lab-scale freeze-dryer. As shown in Fig. 5, T_s set points and T_p were consistent between the two cycles for both formulations.

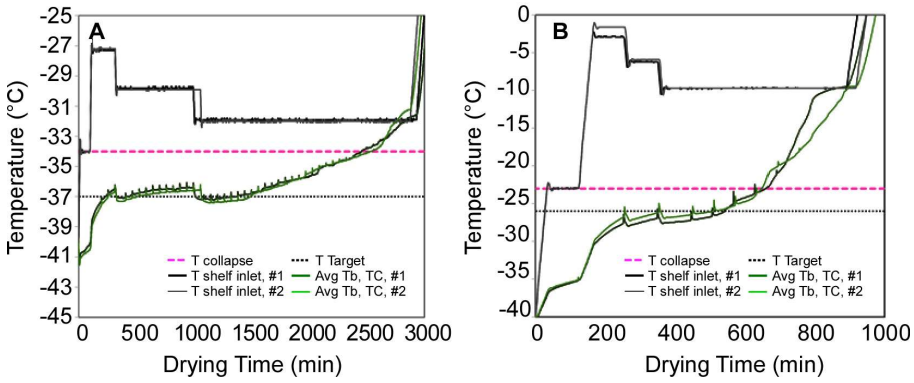

Fig. 5 Repeat lab-scale primary drying recipes determined by the TDLAS-enabled SMART Freeze-Dryer for A) 5% sucrose and B) 5% mannitol, a single shelf of 112 glass tubing vials (Amcor) filled with 3mL of solution was dried.

4. Conclusions

Replacement of the MTM T_p data with the TDLAS-based data enables application of the TDLAS-enabled SMART Freeze-Dryer technology to highly concentrated, amorphous, biopharmaceutical formulations not successfully handled using the MTM technique due to water reabsorption during the pressure rise measurements. The TDLAS measurement technology enables accurate determination of T_p for all formulations tested, providing a measurement accuracy of approximately +/-1°C for nearly all formulations throughout the first 2/3 of the primary drying phase of lyophilization when all vials are undergoing drying. [8] This measurement accuracy enables the SMART algorithm to automatically develop reproducible primary freeze-drying cycles for emerging high weight percent formulation biological products using a single experiment following experiments to determine K_v. Cycle development success was independent of amorphous or crystalline structure and solid weight percent in the formulation. This is a critical enabling technology for use by process engineers and scientists with limited freeze-drying experience.

Because the TDLAS-based measurement technique and the TDLAS-enabled SMART Freeze-Dryer technology are applicable for all scale lyophilizers, it will also enable rapid process scale-up from laboratory to pilot scale freeze-drying demonstrations. However, effective K_v scale-up methods will need to be explored for manufacturing freeze dryers where experimental K_v measurement is not feasible. Errors in K_v have a direct impact on accurate

T_p determinations. Incorporation of additional options for PAT tools to measure T_p including pressure decrease tests (PDT) which do not require valve closure and do not result in product temperature spikes [9] as well as wireless thermocouples could further expand the application of the SMART Freeze-dryer technology where retrofitting for a TDLAS instrument is not feasible. Nevertheless, the development of TDLAS-enabled SMART Freeze-Dryer technology is a significant step toward more efficient freeze-drying process development.

5. Acknowledgements

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R44CA200257. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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