MODEL PREDICTIVE CONTROL FOR THE PRIMARY DRYING STAGE OF LYOPHILIZATION

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Lyophilization, commonly referred to as freeze-drying, is a widely used method of preserving biomaterials and pharmaceuticals. The longest and most time-consuming stage of lyophilization, primary drying, sublimates ice from the frozen product to produce a dry and stable product. The dynamics of the drying process are complex, making it difficult to control and optimize while being essential for the output's quality and stability. In this work, we investigate the application of nonlinear model predictive control (MPC) in the first drying stage of lyophilization. The MPC control approach uses a mathematical model of the primary drying process to forecast future behavior and optimize the operation (significantly reducing the primary drying time while maintaining product quality). In this paper, we demonstrate how MPC improves the efficiency of the lyophilization process.

The nonlinear model predictive control (MPC) technique [1] developed in the GEKKO environment [2] was used to regulate the product temperature and reduce the main drying time. In our situation, the method is based on the outputs of the model (LyoPRONTO primary drying calculator [3]), which predicts the product temperature across the particular prediction horizon at every time step of the process. Based on these predictions, the computer alters the controlled variables (shelf temperature, chamber pressure, or mixed) to make the product temperature match the projected trajectory as closely as possible. To show the efficacy of the MPC control strategy, the experiments were carried out on a Millrock REVO lyophilizer for two formulations: 3 ml of 5% sucrose and 5% mannitol in SCHOTT 6R vials. The temperature was measured using conventional thermocouples inserted into the vial. When the drying procedure was over, the cake's visual quality was demonstrated.

The nonlinear MPC control method has been incorporated into the Millrock REVO lyophilizer as a control technique. The Python OpenOPC module is utilized to bypass the control software and directly connect with the Programmable Logic Controller (PLC). All read and write operations can be queued and done asynchronously due to the multithreaded design of the control system. Directly from the lyophilizer, the model-predictive controller receives product temperature information. Here, the optimal chamber pressure and shelf temperature are determined (while adhering to equipment capability restrictions) and returned to the PLC as setpoints. The controller computes and writes setpoint data at 30-second intervals in order to maintain the product's temperature at its critical temperature during the period of primary drying. However, extra resilience is still required to accommodate both anticipated (e.g., loss of thermocouple contact with ice) and unforeseen events.

Figure 1 depicts the chamber pressure control of the primary drying process for 5% mannitol to illustrate the performance of the algorithm. In this instance, the temperature of the shelf is held constant at 25 °C, but the chamber pressure is varied. After 50 minutes of primary drying, the product temperature approaches the critical threshold of -5 °C. In the following 3 hours, the nonlinear control algorithm manipulates the chamber press to maintain the product temperature within 0.1 °C of the critical value. Four hours after the start of the primary drying process, the pressure rapidly decreases to zero in an attempt to accomplish the control objective, but the product temperature continues to rise. This means that the sublimation front reached the tip of the thermocouple and the sublimation process in the vial is close to the end. At this point, the control algorithm brings the chamber pressure back to where it started and keeps it there until the primary drying step is done. **Figure 2** demonstrates the mannitol 5% in a vial after the PD cycle was finished. No visible signs of collapse were observed.

Other control strategies: shelf temperature control and mixed control (chamber pressure plus shelf temperature control), were also applied to mannitol 5% and sucrose 5% solutions, and the absence of product collapse was demonstrated after visual inspection of the samples.

References:

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[3] Shivkumar, G., Kazarin, P. S., Strongrich, A. D., & Alexeenko, A. A. (2019). LyoPRONTO: an open-source Lyophilization process optimization tool. AAPS PharmSciTech, 20(8), 1-17.

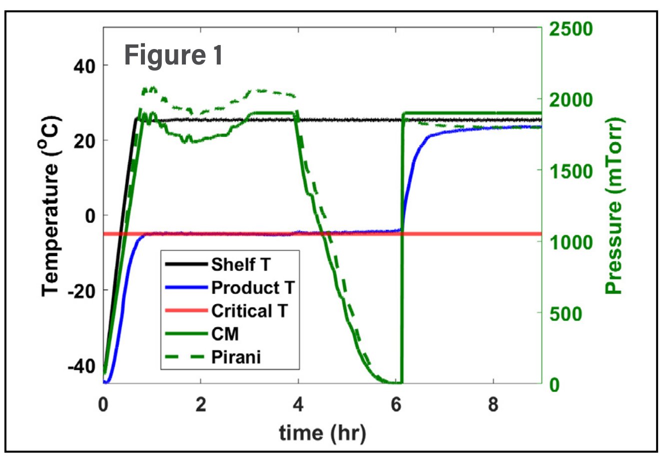

Figure 2