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Optimization of Primary Drying in Lyophilization During Early-Phase Drug Development Using a Definitive Screening Design With Formulation and Process Factors

Johnathan M. Goldman*, Haresh T. More, Olga Yee, Elizabeth Borgeson, Brenda Remy, Jasmine Rowe, Vikram Sadineni

Drug Product Science and Technology, Bristol-Myers Squibb, New Brunswick, New Jersey 08901

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ABSTRACT

Development of optimal drug product (DP) lyophilization cycles is typically accomplished via multiple engineering runs to determine appropriate process parameters. These runs require significant time and product investments, which are especially costly during early phase development when the DP formulation and lyophilization process are often defined simultaneously. Even small changes in the formulation may require a new set of engineering runs to define lyophilization process parameters. To overcome these development difficulties, an 8 factor definitive screening design, including both formulation and process parameters, was executed on a fully human monoclonal antibody DP. The definitive screening design enables evaluation of several interdependent factors to define critical parameters that affect primary drying time and product temperature. From these parameters, a lyophilization development model is defined where near optimal process parameters can be derived for many different DP formulations. This concept is demonstrated on a monoclonal antibody DP where statistically predicted cycle responses agree well with those measured experimentally. This design of experiments approach for early phase lyophilization cycle development offers a workflow that significantly decreases the development time of clinically and potentially commercially viable lyophilization cycles for a platform formulation that still has variable range of compositions.

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Introduction

Freeze-drying, or lyophilization, is a common practice for parenteral pharmaceuticals to improve long-term product stability and simplify product shipping and handling. It is a 3 stage process that consists of freezing, primary drying (ice sublimation), and secondary drying (unfrozen water desorption) steps. It is a time and energy intensive process that may require days or even weeks to complete, where the bulk of the cycle time is spent during primary drying. Consequently, optimization of the primary drying step has become a large focus for process development scientists to reduce operating costs and increase manufacturing throughput.[1-7]

The goal during primary drying is to minimize drying time (*PDT*) while maintaining the product temperature (T_P) below the formulation's critical product temperature, such as the collapse temperature (T_c) for amorphous systems or the eutectic temperature (T_e) for crystalline systems. The formulation defines the critical product temperature as the maximum primary drying T_P, which is then used as an upper boundary to define process parameters that produce a primary drying temperature typically 1°C-2°C below this critical product temperature.[8,9] When T_P exceeds the critical product temperature, defects in cake structure may occur. These structural changes not only result in poor cake appearance but may also affect other lyophilized product CQAs such as reconstitution time, final moisture content, and protein stability.[10-13]

Over the past few decades, many different process analytical technologies (PATs) and mathematical models have been implemented to help optimize primary drying cycles.[1,6,14-16] Most PATs and mechanistic primary drying models are focused on process optimization for a product that has a predefined dose and

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The authors Johnathan M. Goldman, Haresh T. More, and Olga Yee contributed equally to this manuscript.

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* *Correspondence to:* Johnathan M. Goldman (Telephone: +1 732-227-7027).
E-mail address: johnathan.goldman@bms.com (J.M. Goldman).

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Nomenclature

CQA	Critical quality attribute
DoE	Design of experiments
DP	Drug product
[*DP*]	Drug product concentration
DSD	Definitive screening design
mAb	Monoclonal antibody
PAT	Process analytical technology
P_C	Chamber pressure
PDT	Primary drying time
R_F	Freezing rate
RMSE	Root mean square error
T_C	Collapse temperature
T_P	Average primary drying product temperature
T_S	Primary drying shelf temperature
[*Suc*]	Sucrose concentration
V_F	Fill volume

formulation. Although these tools and models excel at late-phase process optimization and scale-up, they may not be ideal during early-phase development where the dose selection for first in human (FIH) trials may vary dramatically based on toxicological data. In addition, there may only be small quantities of DP available during early-phase development, which makes high material demand lyophilization developmental batches difficult to perform.

To overcome the challenges of early-phase lyophilization cycle development, extremely conservative process conditions are selected for FIH manufacturing to minimize any risk on DP CQAs. These conservative conditions lead to long and expensive cycle times, as well as providing minimal information to process development teams for later phase development. A recent study by Hay et al.[17] reported that approximately 70% of monocloncal antibody (mAb) drug products (DPs) successfully transitioned from phase I to phase II trials from 2003 to 2011. Given the high success rate of transition to later stage development, there exists an opportunity to introduce a robust early phase lyophilization cycle development strategy while being flexible to changes in clinical dosage in a material sparing manner. This strategy should also provide direction for later stage development upon trial success when conventional PAT and modeling tools become more applicable.

To address these challenges during early phase lyophilization development, an 8-factor design of experiment (DoE) that includes both formulation and process parameters was performed on a fully human mAb DP. By utilizing a definitive screening design (DSD) for the study, only 20 lyophilization experiments were needed to fully characterize all linear and some higher order effects between the 8 parameters. A conventional sequential DoE approach would typically require a screening design, such as fractional factorial or custom design, followed by a response surface design, and would be prohibitive in resources required for execution. Definitive screening is a fairly new class of designs that allows investigating screening and optimization in a single step without compromising ability to fit nonlinear models. This becomes especially important when significant 2-factor interactions between the process and formulation parameters are expected, as well as nonlinear effects for process parameters.[18,19] The models for *PDT* and T_P were used to build a near optimal design and formulation space with respect to both formulation and process parameters. All of which are carried out without performing a single experimental batch using the formulation parameters and critical product temperature as model inputs. Although mathematical models inform optimal lyophilization process parameters in fewer runs, unique cycle development for many different DPs under a fast to FIH approach would create a time challenge. Thus, the DoE approach for lyophilization cycle development in the early phase offers a workflow that significantly decreases the development time of potentially clinically viable lyophilization cycles for a formulation that is generally platform but still has variable ranges of compositions.

Experimental

Materials

A model BMS mAb, mAb1, was used for all lyophilization DoE experiments. A second BMS mAb, mAb2, was used to verify the DoE model predictions in a separate lyophilization run. All solutions were prepared in a platform buffer containing a single buffer species, surfactant, chelator, and sucrose. The type and concentration of the buffer species, surfactant, and chelator were constant for all solutions. They are present at low concentration and assumed to have minimal impact on the model responses and critical product temperature. The sucrose and DP concentration would have a significant effect on primary drying responses and, thus, were included as DoE parameters. Solutions were lyophilized in 20 cc glass tubing vials (SCHOTT North America, Inc., Lebanon, PA) using a laboratory scale Lyostar II or VirTis Genesis freeze dryer (SP Scientific, Warminster, PA). The lyophilizers were of similar size and design. Product temperatures were monitored during lyophilization using calibrated 30-gauge T-type thermocouples (Omega, Norwalk, CT). A 150 kDa dextran polymer (Sigma-Aldrich, St. Louis, MO) was used to prepare a placebo solution in the same buffer at a dextran concentration equal to the mAb DP. The sucrose concentration was kept at 7.5% w/v in all placebo formulations. Measurement of the collapse temperature for each mAb formulation was completed on a FDCS196 freeze-drying cyrostage (Linkam Scientific, Tadworth, UK) attached to a polarized light microscope (Olympus, Waltham, MA).

Lyophilization Procedure

Each lyophilization cycle used a total of 30 vials filled with mAb1 DP at a DoE formulation defined concentration, sucrose wt%, and fill volume (see Table 1). An additional 274 vials were filled with the dextran placebo solution at the same fill volume. The placebo vials provided similar product temperature profiles as the DP to enable loading of 2 full trays without sacrificing extensive amounts of DP material. The placebo vials are not expected to influence the drying behavior of the DP vials since they were found to have the same product temperature profile and similar collapse temperature as the DP (data not shown).

The DP vials were distributed between center, front, and rear positions on each tray to examine edge vial effects, as depicted in Supplementary Figure 1. The trays were loaded into either a Lyostar II or VirTis Genesis freeze dryer according to the DoE. Both lyophilizers have a clear acrylic front door. An aluminum foil shield was placed inside each unit in front of the trays to reduce effects of radiation through the acrylic door. In addition, DP vials were positioned to ensure they did not contact the metal ring holding the vials in place, which can greatly influence the drying performance of vials and impact the ability to detect significant parameters from the DoE. Thermocouples were placed in the center-bottom of the vial at different positions along the trays according to Supplementary Figure 1. Ten thermocouples were used for the