Research Article

Finite Element Method (FEM) Modeling of Freeze-drying: Monitoring Pharmaceutical Product Robustness During Lyophilization

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Abstract. Lyophilization is an approach commonly undertaken to formulate drugs that are unstable to be commercialized as ready to use (RTU) solutions. One of the important aspects of commercializing a lyophilized product is to transfer the process parameters that are developed in lab scale lyophilizer to commercial scale without a loss in product quality. This process is often accomplished by costly engineering runs or through an iterative process at the commercial scale. Here, we are highlighting a combination of computational and experimental approach to predict commercial process parameters for the primary drying phase of lyophilization. Heat and mass transfer coefficients are determined experimentally either by manometric temperature measurement (MTM) or sublimation tests and used as inputs for the finite element model (FEM)-based software called PASSAGE, which computes various primary drying parameters such as primary drying time and product temperature. The heat and mass transfer coefficients will vary at different lyophilization scales; hence, we present an approach to use appropriate factors while scaling-up from lab scale to commercial scale. As a result, one can predict commercial scale primary drying time based on these parameters. Additionally, the model-based approach presented in this study provides a process to monitor pharmaceutical product robustness and accidental process deviations during Lyophilization to support commercial supply chain continuity. The approach presented here provides a robust lyophilization scale-up strategy; and because of the simple and minimalistic approach, it will also be less capital intensive path with minimal use of expensive drug substance/active material.

KEYWORDS: lyophilization; modeling; process deviation; robustness study; scale-up.

INTRODUCTION

Lyophilization or freeze-drying is a process commonly used in the pharmaceutical industry to stabilize bioproducts such as vaccines, proteins, biological materials, and microorganisms that are inherently unstable in solution form [1]. In solution, water may degrade the active pharmaceutical ingredient (API) over long periods of time [2]. Drying the product, however, greatly increases stability, enabling active ingredients to be stored for a much longer period of time [3]. Lyophilization consists of three primary stages: freezing, and primary and secondary drying. Freezing is primarily accomplished at atmospheric pressure and is intended to facilitate the formation of ice crystals that are amenable to sublimation. The goal of this step is to facilitate the formation of bigger ice crystals so that they sublime faster and hence result in a much shorter primary drying time, which is the next and most time/cost intensive phase of lyophilization. During the primary drying phase, the chamber pressure is reduced to a level that is much less than 1 Torr [4] and the

lyophilizer shelf temperature (T_s) is raised to facilitate sublimation. There are several ways to determine the end of primary drying and moving into the secondary drying stage [5], which we will elaborate later in this study. In the secondary drying phase, the shelf temperature is raised in order to remove the residual product bound moisture. Upon completion of secondary drying, the product contains very low moisture content, often less than 1% w/w [6].

Relative to primary drying, freezing and secondary drying steps are very short. Therefore, primary drying is the rate limiting step in lyophilization. Consequently, considerable research has been conducted in order to design an optimum primary drying cycle over the last few decades. An optimum cycle depends on the appropriate selection of process parameters such as shelf temperature (T_s), chamber pressure (P_c), and primary drying time (PDT). At high T_s , the water sublimates more quickly, and the solution dries faster. However, if the T_s is too high and the product temperature rises above its collapse temperature (T_c), the product may have micro/macro collapse leading to a lower quality of the product [7]. The combination of T_s and P_c primarily defines the sublimation rate of water and plays a vital role in developing a good quality drug product. As the lyophilization cycle goes longer, it decreases the manufacturing plant efficiency and leads to significant energy consumption. Therefore, identifying the optimal PDT is important to an efficient commercial process.

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Traditionally, a commercial scale lyophilization process is developed by an iterative method which consumes a large amount of time, money, and product. Several engineering runs are typically required to identify the optimal process parameters for a commercial cycle [4]. Several tools have been developed in order to assist in the design of a commercially viable lyophilization process. For example, a spectroscopy based method called tunable diode laser absorption spectroscopy (TDLAS) which allows detection and quantification of trace concentrations of moisture has been introduced for monitoring of freeze-drying cycles into commercial lyophilizers. This technology has been found useful for cycle development as well as scale-up of freeze-drying cycles [8, 9]. Another tool is the SMART Freeze dryer developed by FTS systems (Stone Ridge, NY). With the SMART equipped Lyostar II freeze dryer, an optimized freeze-drying run may be developed with a few laboratory scale lyophilization experiments. The SMART/Auto MTM mode conducts a pressure rise test [7, 10–14] based on user inputs at predefined time. Using the pressure rise data, the software predicts an optimum shelf temperature and chamber pressure for primary drying phase of lyophilization. In addition, critical product performance data, such as vial heat transfer coefficient (K_v) and mass transfer resistance (R_p) [7] are also outputs of the software. However, Tang [10, 12] noticed that MTM measurement is no longer accurate after about 60% of total primary drying time especially for conditions like low shelf temperature, low chamber pressure and low dry layer resistance. Further details on the SMART and Auto-MTM modes of the Lyostar II can be found in the methods section of this paper. Although the SMART technology could be used to predict the process parameters of a new compound entering development phase and reduce the number of trials needed to design a lyophilization process, it still uses costly active pharmaceutical ingredient and at least several experiments. In order to save active ingredient, cost, and experimental trials, along with gaining further understanding of the lyophilization process, several computational models have been developed. These models use a computational tool based on mass and heat transfer principles to predict primary drying time based on existing operation conditions and some additional experiments. The simplest way to model lyophilization is by assuming steady state in order to describe the physics using equations involving heat transfer and mass transfer. This assumption holds for much of the lyophilization process, as the shelf temperature remains constant for the entirety of primary drying and the energy transferred into the vial from heat transfer is absorbed through the endothermic process of sublimation. Assuming steady state simplifies the calculation of the heat transfer coefficient, K_v , which can be calculated with a simple energy balance [4]. The steady state assumption of this model, however, fails in several respects. While the majority of primary drying is a steady state process, the period immediately following a change in shelf temperature (such as the beginning of primary drying) is in a non-steady state [15, 16] and therefore this model does not apply for the entire primary drying phase. Pikal [16] states that the system does not reach steady state until 30 min after a change in shelf temperature. Furthermore, the steady state model will not yield information on the residual moisture content in the dry layer [15]. PASSAGE, a commercial software package from Technalysis (Indianapolis, IN,

USA), has been used to more accurately model the freeze-drying process [4, 15, 17]. PASSAGE uses a finite element method (FEM) to solve coupled heat and mass transfer equations in a two-dimensional axisymmetric space [17]. This model is much more complicated than the simple steady state model, but it is much more accurate. Since it is a semi-empirical model, several parameters must be characterized in order to solve the problem. These parameters include chamber pressure, shelf temperature, and various product and container properties such as the K_v and R_p . While previous work calculated the vial heat transfer coefficient with water sublimation tests [4, 17], this work performed sublimation tests with the specific formulation being tested. Upon the incorporation of these parameters into the PASSAGE model, it is capable of modeling the complete lyophilization cycle, including both primary drying and secondary drying. In doing so, the model is capable of tracking the position of the sublimation interface and product temperature throughout the process. The model also facilitates the prediction of primary drying time based on user inputs and sublimation profile over the duration of the lyophilization process. This information can drastically reduce the number of experiments necessary to optimize commercial scale lyophilization parameters.

This work describes a simplified process, which combines the capabilities of the SMART software, and the numerical algorithms of the PASSAGE software to develop a lyophilization cycle, with robust process parameters for the primary drying phase of lyophilization, that is optimal for commercial scale. The key model parameters such as heat transfer coefficient (K_v) and mass transfer resistance (R_p) are determined through manometric temperature measurement (MTM) and/or sublimation experiments. These along with other product-specific characteristics are then processed through a sequence of experiments and computational modeling, which computes primary drying time for various primary drying parameters such as shelf temperature and chamber pressure. The model also facilitates the prediction of the product temperature and moisture profiles over time. With the proposed process, the freeze-drying behavior of any drug product composition may be predicted with very few experiments.

Identifying a proven acceptable range for the critical process parameters of primary drying phase at commercial scale can be challenging due to lack of operational experience at batch sizes that are required for commercial supply. However, identification of a robust operating range for critical process parameters is vital to the efficient and successful transfer of a commercial lyophilization process. Rambhatla [18, 19] had investigated the heat and mass transfer scale-up issues during freeze-drying by conducting water sublimation experiments. They studied the edge vial heat transfer coefficient difference between laboratory scale and manufacturing scale at the same shelf temperature and chamber pressure. They found that a front vial in the laboratory lyophilizer received 1.8 times more heat than a front vial in a commercial freeze drying operation at a shelf temperature of -25°C and a chamber pressure of 150 mTorr during primary drying phase. Kramer *et al.* [4] had studied the scale-up optimization for the primary drying phase of lyophilization. They used pilot scale lyophilizer and water sublimation tests to get heat transfer coefficients, which were used as the input parameter for PASSAGE model. This is a great step towards the prediction

of primary drying time for commercial scale lyophilization. However, not much has been done to predict the primary drying time for commercial scale lyophilization using active pharmaceuticals because of their cost intensive nature. In addition, Koganti [17] also conducted studies on understanding the design space for freeze-drying at commercial scale, where the heat transfer coefficient used were from water sublimation experiments. The approach adapted by both authors utilizes water sublimation experiments which may not be truly representative, since the composition of the drug product, will have a big influence on the heat transfer coefficient and product resistance.

Heat and mass transfer coefficients will vary at different lyophilization scales and with different formulation compositions, and hence, we present an approach to use appropriate factors while scaling-up from lab scale to commercial scale. Using the approach presented here, one can create a design space/proven acceptable range and embrace quality by design (QbD) for the lyophilization process without conducting at scale experiments to gain similar knowledge and experience. Additionally, a well-designed process can greatly reduce risks, and increase product robustness and quality. In addition, several applications of the model will be discussed such as the lyophilization process robustness and investigations during process deviations using model predictions.

MATERIALS AND METHODS

Materials

A model protein (mAb A) was used throughout the investigation and was used in a concentration range 45–55 mg/mL. The drug product is lyophilized in a 20 cm³ vial, which had a composition that included sucrose and a surfactant in a buffered solution. The vials were filled to have drug content of X or Y mg/vial and were filled uniformly using a Watson Marlow 505 Digital Peristaltic Pump. The same materials were used for the sublimation tests as well as the SMART/Auto-MTM runs.

Freeze-drying Procedure

A volume equivalent to X or Y mg/vial of drug product solution was filled into 20-mL glass vials, where $X > Y$, and partially stoppered with 20 mm Lyo stoppers. Lyophilization cycles were performed in a LyoStar II freeze dryer (SP Industries, Stone Ridge, NY) in either SMART or auto-MTM mode. Calibrated 36-gauge thermocouples (OMEGA, Newport, CT) were placed at the bottom center of the vial (the tip touching the vial bottom) in both edge and center vials. The thermocouple probes (from LyoStar II) are calibrated once a year. Lyophilization cycles were conducted using the following initial freezing procedure: ramp from room temperature to -40°C (ramp rate, $0.5^{\circ}\text{C}/\text{min}$), hold for 2 h, ramp to -10°C ($0.5^{\circ}\text{C}/\text{min}$), and hold for 1 h (annealing step), return to -40°C , and maintaining shelf temperature for another 2 h. Primary drying was conducted at a chamber pressure (P_c) of 50–100 mTorr and shelf temperatures (T_s) were in range of -3 to -11°C . The chamber pressure and shelf temperature settings were maintained constantly during primary and secondary drying in a lyophilization cycle. In this manuscript,

maximum temperature during primary drying phase ($T_{p\text{max}}$) is considered to be the temperature reading or the inflection point of the product temperature probe when it starts its ascent towards the shelf temperature. The primary drying end point is the time at which the product temperature probe meets the shelf temperature. The primary drying time for the conservative cycle was set at 5400 min for mAb A. Secondary drying was performed at a shelf temperature of 25°C for 10 h ($0.5^{\circ}\text{C}/\text{min}$ ramp rate). SMART and Auto-MTM runs were done with a row of empty vials around the edge of the tray and in order to minimize heat transfer due to radiation from outside the lyophilizer, a heat shield of aluminum foil is placed in front of the lyophilizer door [12]. Eight thermocouple probes were used, where four were placed in the center vials, two were placed at the front and two were placed at the back of the shelf in the center of the load.

SMART/AUTOMTM Freeze Dryer Input Parameters

Lyostar II lyophilizer (FTS Systems, Stone Ridge, NY) equipped with SMART software can be operated in the SMART or Auto-MTM mode and the various input parameters that are needed for lyophilization experiments in these modes are described elsewhere [7]. Simplistically, SMART mode in our experiment setup was used to identify the initial process parameters for primary drying phase, and the process parameter optimization exercise was completed by execution of in the Auto-MTM mode. Irrespective of the mode the experiment was conducted, the output parameters that were used extensively in our downstream computational models are the heat transfer coefficient (K_s) and mass transfer resistance (R_p). In addition, the probe data which includes the product temperature and primary drying time is compared with simulation results to validate the computational model.

Finite Element Method-Based Model Description

PASSAGE is a semi-empirical numerical algorithm originally described by Pikal [15]. Then Technalysis (Indianapolis, IN, USA) developed a finite element method based GUI software based on the algorithm described by Pikal. Details such as governing equations, boundary conditions, assumptions, and validations are described elsewhere [15, 20]. In summary, the software uses an arbitrary Lagrangian-Eulerian method to accurately model the sublimation front of the freeze-drying process in two-dimensional axisymmetric space. Although both primary and secondary drying stages could be modeled, we mainly focus on the primary drying in this study because it is the most critical and longest stage between the two. It is capable of calculating product temperature at different interface locations by predicting the position and geometric shape of the moving interface. It is assumed that the interface thickness is infinitesimal; a binary mixture of water vapor and inert gas flows through the dried layer; the concentration of water vapor is in equilibrium with the ice at the interface; the moisture movement is slow in the porous region; the frozen region is considered to have uniform mass and heat transfer properties [20]. The assumptions are emphasized here again in order to clearly state the problem statement.

There are several kinds of critical input parameters in order to solve the coupled mass transfer and heat transfer equations embedded in PASSAGE. Some input parameters are straightforward and easy to obtain, such as, parameters for chamber pressure and shelf temperature. Another set of input parameters, which are generalized into material properties, can either be estimated from experiments or available in published material databases. Additionally, there are input parameters like heat and mass transfer coefficients which need to be determined experimentally for the composition of drug product and vial size as they have significant impact on model simulations.

In some previous studies, heat transfer coefficient was calculated by MTM measurement based on pressure rise data. However, this approach might not be accurate since the amount of water vapor during sublimation decreases during the progression of primary drying phase. The lack of adequate pressure rise will lead to erroneous heat transfer coefficient calculation [10]. As a result, sublimation tests [4, 17] were conducted using mAb A formulation to measure heat and mass transfer coefficient instead of MTM measurements, which greatly improved the accuracy of model predictions.

Sublimation Experiments

In this study, heat and Mass transfer coefficients were determined through gravimetric analysis using vial sublimation experiments in a laboratory scale Vertis Lyostar II lyophilizer. Each experiment consisted of 160–200 vials in two shelves of the lyophilizer. Vials were filled with the composition of interest and lyophilized under various process conditions to result in partial sublimation of the contents of the vials. Vials were weighed before and after sublimation test, and the overall heat transfer coefficient of the vial and drug product composition was calculated. The process parameters used for sublimation experiments were similar to the freeze-drying experiments described previously except that the experiment was stopped approximately 15 h into the primary drying phase in order to determine the sublimation rate. Vials were then stoppered, unloaded, and weighed to determine the water loss by sublimation. Knowing the amount of ice sublimed and heat of sublimation of the ice, the heat transfer coefficient (K_v) can be calculated using Eq. 1.

$$\frac{dm}{dt} \cdot \Delta H_s = K_v \cdot A_v (T_s - T_b) \quad (1)$$

where the rate of mass transfer (dm/dt) and product temperature (T_b) are measured experimentally at a defined shelf temperature (T_s). Additionally; heat of sublimation of ice (ΔH_s) and interfacial area of vial (A_v) are constants that are known.

The measured K_v from this sublimation experiment was used to determine K_c , which is a sum of radiation and contact heat transfer and is a constant for a particular combination of lyophilizer, vial, and drug product composition, using empirical Eqs. 2 and 3 [15].

$$K_v = K_c + \frac{K_p \times P}{1 + K_D \times P} \quad (2)$$

$$K_D = l_v \left(\frac{K_p}{\lambda_0} \right) \quad (3)$$

where K_p is a constant ($0.00332 \text{ cal/s} \cdot \text{cm}^2 \cdot \text{Torr}$) which defines the free molecular diffusivity of the gas at 0°C , l_v is the average gap distance between vial and shelf, which is dependent on the vial shape and λ_0 is conductivity of water vapor at ambient pressure ($0.025 \text{ W/m} \cdot \text{K}$). K_D varies depending on the vial type; however, it is a constant for the experiments in this manuscript because we only use one type of vial. The empirical Eq. 2 can be used to calculate the overall heat transfer coefficient at different chamber pressures once K_c is known. Procedure for inputting this measured heat transfer coefficient into the computational model is described elsewhere in the literature [15].

RESULTS AND DISCUSSION

Implementation and routine use of any computational model depends on its successful and robust validation. The model presented here is initially validated at the laboratory scale. Then, we present a pathway to apply it to commercial scale lyophilization. The computational model can predict primary drying time and product temperature irrespective of the scale of lyophilizer as it models a single vial and its sublimation profile. In addition to that, it is also capable of predicting product attributes such as interface temperature, ice thickness, *etc.*, which are difficult to measure using current tools available at commercial scale.

Figure 1a is a snapshot of freeze-drying sublimation front at different time steps during lyophilization. The blue area represents the frozen part, and the yellow area represents the dried material. The convex of the sublimation interface is formed due to the difference of heat transfer coefficients at the bottom of the vial, where the heat transfer coefficient of the direct conduction is slightly higher than the convection. Figure 1b is a representative snapshot of product temperature at the sublimation interface during lyophilization. The computational model is able to track both the sublimation front interface and product temperature at any time step during lyophilization, which facilitates better efficiency in monitoring the lyophilization process.

Validation of the Computational Model

Validation of the computational model can be accomplished by comparing primary drying time and product temperature profile between PASSAGE numerical simulations with experiment results. Primary drying time can be defined as the duration of the primary drying phase which is needed for the product temperature probes to reach the shelf temperature. We have primarily focused on the center vial primary drying time for this manuscript as it describes a worst case scenario by being the last vial to reach shelf temperature in any lyophilizer. Comparison of experimental (laboratory scale) vs. PASSAGE simulated primary drying time is shown in Fig. 2. It is observed that the PASSAGE simulation (68 h) agrees reasonably well with the experimental results (66.2 h). In addition, it also illustrates that the model is efficient in predicting the product temperature profiles, as they agree well with the thermocouple readings placed in the middle bottom of the central vial. The experimental thermocouple probe reading for the product temperature is a few centigrade degrees higher than the PASSAGE predicted temperature

Fig. 1. **a** Snapshots of freeze-drying sublimation front tracking at different time steps during lyophilization. **b** Snapshots of product temperature at the sublimation interface during lyophilization

profile, which can be attributed to the presence of temperature probes which traditionally have been known to provide nuclei for ice nucleation and create an ice crystal structure that is amenable for faster sublimation or higher probe reading, when compared to the drug product vials without probes. Additionally, the presence of probe in the vial will accelerate the drying process in the vial by providing additional pathways for vapor transport from the vial to the chamber, which will decrease the mass transfer resistance to vapor flow [17]. We notice that there is a sharp temperature increase in the predicted temperature profile compared to the experimental

results at the end of the primary drying, which may be attributed to the computational model ignoring the heat capacity of the glass vial wall and other factors discussed earlier [15].

Overall, the simulation predictions agree well with the experimental findings considering the complexity of the heat and mass transfer during lyophilization cycle, which lead us to apply the model for the following applications, where we explore the ability of the model to identify design space, predict primary drying time for commercial scale and identify implications of process deviations.

Model Application 1: Identification of Design Space through Computational Model-Based Parameter Variation

A robust commercially viable lyophilization cycle entails flexibility around the critical process parameters (CPP) and still maintains product quality attributes. In order to achieve this goal with minimal number of experiments, computational models were performed at different parameters as described earlier to identify a design space. The scope of this evaluation includes the identification of a design space through computational modeling by performing parameter variations. Based on the outcome of the design space, one can identify the acceptable variability in process parameters by conducting laboratory scale experiments. This approach will result in minimal number of laboratory experiments to be conducted, potentially identify the allowed range of variability for the CPP during primary drying phase and still result in an elegant cake which meets all product quality attributes. Traditionally, the design space is usually optimized by conducting numerous

Fig. 2. Validation: simulation results are compared with experimental results for the primary drying time and product temperature

Table I. Parameter Variation of the Lyophilization Cycle to Study Product Robustness for Both X mg/Vial and Y mg/Vial Drug Product

Chamber pressure (mTorr)	Shelf temperature (°C)				
	-13	-11	-8	-5	-3
50	A1	A2	A3	A4	A5
70	B1	B2	B3	B4	B5
100	C1	C2	C3	C4	C5
130	D1	D2	D3	D4	D5
150	E1	E2	E3	E4	E5

experiments [21, 22]. In this study, we have conducted computational modeling of primary drying CPP's with two targets which will be elaborated in details later, a product temperature of -20°C through two thirds of primary drying phase and a primary drying time of 75 h.

As demonstrated in Table I, shelf temperature was fixed within a range of -13 to -3°C , and chamber pressure was varied at each of these shelf temperatures, to determine the influence of chamber pressure on primary drying time and product temperature. For example, simulations from A1 to E1 were conducted with a fixed shelf temperature of -13°C , and chamber pressure in the range of 50–150 mTorr. These simulations will facilitate the determination of an acceptable range that can be experimentally proven/verified for acceptable quality attributes. We have used the model-based approach to examine what are the effects of shelf temperature and chamber pressure on the total primary drying time and product temperature (Table II).

Based on Fig. 3a–b, it is obvious to observe that the primary drying time decreases as the shelf temperature increases and that the chamber pressure influences primary drying time significantly. For example, with the increase of chamber pressure, the primary drying time decreases, this agrees with previous experimental observations [23], because sublimation rate will increase as the chamber pressure approaches the vapor pressure of the ice. The primary drying rate is directly dependent on chamber pressure; as a result, the heat transfer coefficient will also increase with the increase of chamber pressure. However, the heat transfer coefficient will become smaller if the chamber pressure is too low because there will be less heat convection during lyophilization. It will reduce ice sublimation and slows the primary drying process.

Freeze drying can only take place when the partial pressure of the vapor in the chamber is lower than the water vapor pressure. As shown by the simulation results, heat transfer coefficient can be controlled by chamber pressure during lyophilization. However, we should be reminded that there is a limitation that the chamber pressure can reduce to, in our case; we observe there is a significant increase of primary

drying time when the chamber pressure reaches 50 mTorr. As a result, we choose our operation chamber pressure between 70 and 130 mTorr.

The DOE experiments that we are conducting in this study are ensuring that the maximum critical product temperature never goes above the collapse temperature. The collapse temperature here in this case is -20°C , considering the PASS AGE product temperature prediction is always lower than the probes in the experiment, we set up the upper limit of the maximum critical product temperature to be lower than -20°C as shown below in the blue triangle zone. On the other hand, it is not necessary to mean that the lower the maximum critical product temperature, the better in the primary drying cycle. We also need to set up another boundary based on how many hours for the primary drying time. Here in this case, the upper boundary of primary drying time is set at 75 h. The primary drying time is too long if it is below the red triangle zone; the optimized primary drying time should be fall above the red zone.

As shown in Fig. 3c, the identified design space is the region in white between the red triangle and blue triangle for X mg/vial drug product presentation based on the criteria defined above. The identified design space fulfills both the objectives, which is, pharmaceutically elegant looking cake with no micro or macro collapse, no impact on stability indicating attributes such as moisture content, and a primary drying time that is not too long to become cumbersome for commercial operations. Finally, we selected the target shelf temperature and chamber pressure to be -8°C and 100 mTorr as the optimized operation setting for this case.

Thus, the model-based DOE provides a guidance to optimize the operation conditions with a minimum run of experiments. In addition to build our confidence about the model predicted design space, a process robustness experiment study was later conducted, where shelf temperature was varied at $\pm 3^{\circ}\text{C}$ within the target shelf temperature and the chamber pressure was varied at ± 30 mTorr within the target chamber pressure and the primary drying time was compared between model predictions and experiments. The primary drying times were in good agreement (within 2–3 h) and the quality attributes measured by SEC and CEX also showed that the model predicted design space is ideal for technology transfer to the commercial manufacturing site. The same procedure was repeated for Y mg/vial and identified the design space for Y mg vials as shown in Fig. 4c.

In summary, with the help of the computational model-based DOE, we are able to significantly reduce the experiment trials and provide a guidance for parameter variation before any experiments could be conducted.

Model Application 2: Scale-up

It is imperative that the optimized process parameters at laboratory scale be efficiently transferred to the commercial scale, and any such transfer should involve a successful transfer of the process parameters such as shelf temperature, chamber pressure, and phase durations with no impact on the product quality from laboratory to commercial scale. Historically, it is quite evident that the parameters such as shelf temperature and chamber pressure are well transferred to the commercial site. However, the phase durations for

Table II. Vial Heat Transfer Coefficient Calculated for Both Laboratory Scale Experiment and Commercial Scale Data

Vial location	Laboratory scale $\times 10^4$ cal/s cm^2K	Commercial scale $\times 10^4$ cal/s cm^2K
Edge	4.17	3.69
Center	2.59	1.86

Fig. 3. Design space for X mg vial of product A: **a** primary drying time contour plots for different shelf temperature and chamber pressure; **b** critical maximum shelf temperature contour plots for different shelf temperature and chamber pressure; **c** design space for primary drying process parameters, the dotted area are the optimized process conditions

primary drying and to some extent the secondary drying phase for commercial lyophilization cycle are accomplished through an iterative process of experiments including engineering runs. This exercise is laborious and cost intensive. It takes three to four lyophilization runs on the pilot scale to optimize primary drying *via* an iterative development cycle [4]. The process described below provides a methodology that is adapted for a commercial lyophilizer to identify a phase duration range by embarking on engineering or clinical/commercial lyophilization experiments. The methodology relies on the variability of product temperature values of edge vials measured experimentally at commercial scale and estimated primary drying time based on historical data, which are used to calculate both the center and edge vial heat transfer coefficient.

The configuration of the lyophilizers in laboratory scale and commercial scale is quite different. For example, the commercial lyophilizer has a steel door and the emissivity is much slower compared to the laboratory scale door [19]. As a result, the contribution of the radiation heat transfer to the overall heat transfer for the edge vials is very different in commercial scale compared to laboratory scale. In addition, there is much more shelf area (10~50 m²) for commercial scale lyophilizer than that in the laboratory scale lyophilizer (0.1~0.5 m²) [24], and the heat transfer characteristics are different for each shelf. The configuration of lyophilizers at

commercial scale also varies for different manufacturers. The current study is trying to find an empirical scale-up factor that can be utilized for various compounds using the same lyophilizer under the relatively similar operational conditions at our site. Therefore, a heat transfer coefficient scale-up factor (F_{Kv}) is defined as below for the specific lyophilizer used in this study. Again, the primary drying phase of the lyophilization cycle will be focused.

$$F_{Kv} = \frac{K_{v,commercial,edge}}{K_{v,commercial,center}} / \frac{K_{v,lab,edge}}{K_{v,lab,center}} \quad (4)$$

In Eq. 4, parameters such as heat transfer coefficient of center vials in the laboratory scale ($K_{v,lab,center}$), and heat transfer coefficient of edge vials in the laboratory scale ($K_{v,lab,edge}$) were determined from sublimation experiments at laboratory scale. The heat transfer coefficient of edge vials ($K_{v,commercial,edge}$) and center vials ($K_{v,commercial,center}$) at the commercial scale was back calculated with the PASSAGE model using product temperature profile data from edge vials and primary drying duration from center vials, respectively.

Here in this case, the average primary drying time of edge and center vials of mAb A is 51.6 and 88 h at commercial scale. Using PASSAGE, the heat transfer coefficient of edge vials and center vials was estimated to be 3.69×10^{-4} cal/s·

Fig. 4. Design space for Y mg vial of product A: **a** primary drying time contour plots for different shelf temperature and chamber pressure. **b** Critical maximum shelf temperature contour plots for different shelf temperature and chamber pressure. **c** Design space for primary drying process parameters, the dotted area are the optimized process conditions

$\text{cm}^2 \cdot \text{K}$ and $1.86 \times 10^{-4} \frac{\text{cal}}{\text{s}} \cdot \text{cm}^2 \cdot \text{K}$, respectively. The estimated heat transfer coefficients from commercial scale along with the laboratory scale heat transfer coefficients were plugged into Eq. 4 to get an empirical heat transfer coefficient scale-up factor of 1.23 for our specific lyophilizer. This number was also compared with previously published heat transfer coefficient measurements and based on the published values of sublimation tests at both laboratory scale and commercial scale [4, 17, 19], the scale-up factor calculated in this study falls into the range.

The product temperature profile at center vials is difficult to monitor in a GMP setting for aseptic products as product thermocouple probes are usually placed in the edge vials to avoid contamination of drug product vials due to manual operation at commercial scale. As shown in Fig. 5, the value of the FEM model becomes evident as one can plot the predicted product temperature profile of the center vial based on the calculated scale-up factor. The predicted product temperature profile and thermocouple readings for edge vials are also plotted in the figure. One of the advantages of this model is that with this semi-empirical approach, we could get an estimated heat transfer coefficient and primary drying time of center vials with a single engineering run for the same lyophilizer. Understandably, this effort is possible only if you have an edge vial product temperature profile from commercial scale, and hence, one can argue the benefit of the model. The premise of the model is such that once you have identified

the heat transfer coefficient scale-up factor from laboratory to commercial scale, you can reliably use that factor for that particular lyophilizer for any other product irrespective of the formulation composition, as long as you have the calculated heat transfer coefficient for both edge and center vial at laboratory scale and edge vial heat transfer coefficient at commercial scale for that particular composition. By using

Fig. 5. Commercial scale simulation of edge vs. center vials by PASSAGE

Table III. Shelf Temperature, Chamber Pressure and Time for Each Process Deviation

Parameter	Process deviation during primary drying phase step						
	1	2	3	4	5	6	7
Shelf temperature	-8 ⁰ C ^a	-3°C	-3°C	-8°C	-11°C	-11°C	-8°C
Chamber pressure (mTorr)	100 ^a	100	150	100	100	50	100
Hold time (hrs)	4	1	2	4	8	5	64

^a Process parameters and primary drying phase initiated at these parameters prior to process deviation

simulations instead of experimental trials to guide the design of a commercial scale lyophilization cycle, the cost of goods for technology transfer process is minimized. Furthermore, much more information may be gained from the output data of the model than that can be obtained experimentally. These data include a sublimation interface profile, product temperature profiles, and sublimation interface pressure distribution.

Based on the above principles, the capabilities of the model were further extended to identify the impact of minor process deviations on the product quality as described below.

Model Application 3: Process Deviations

Even though commercial lyophilization cycles are designed to operate within a proven acceptable range of process parameters, accidental process deviations due to instrument malfunction or power outage are routine during commercial drug product manufacturing process. A process deviation during a lyophilization cycle can be detrimental to the product if the deviation was to happen during the initial stages of primary drying phase of the lyophilization cycle, since this can result in a product temperature that is higher than the T_g resulting in micro/macrocollapse. Consequently, it may have a negative impact on product quality. Generating real time data and analysis of such deviations is an expensive and impractical approach. So, we explored the potential of computational model to predict the change in key product attributes such as product temperature due to the deviation and potentially use that information to conduct investigations in support of batch release. The result will help to make sure that the product temperature is always below the glass transition temperature as that would ensure drug product quality and stability.

An experiment was first conducted to determine the ability of the FEM model described above to predict product temperature profile of drug product in the vials subjected to a process deviation during the initial one thirds of a primary drying phase of lyophilization cycle. Briefly, shelf temperature and chamber pressure were varied from the optimized target primary drying cycle process parameters, *i.e.*, shelf temperature, -8°C and chamber pressure, 100 mTorr (step 1) for a predefined interval as shown in Table III, during steps 2–6, prior to bringing these back to the target cycle parameters for the remaining time of the primary drying phase at step 7. The experiment included a shelf temperature and a chamber pressure deviation of up to ~62 and 50%, respectively, to simulate a worst case scenario.

Results from experimental and model-based evaluation are plotted in Fig. 6. It is evident that the computational model was efficient in predicting the product temperature profile throughout the primary drying phase of the process deviation

experiment, as the model predicted values agreed well with the experimentally determined values. Model predicted product temperature values are a few degrees lower than the experimental values which are influenced by the presence of the probes as described earlier. The primary drying end point, as predicted by PASSAGE (70.2 h) due to the process deviation experiment also correlated well with the experimentally determined value (69.1 h).

Albeit, the validation for process deviation is demonstrated here at laboratory scale, it can be extended to the commercial scale by simply using the heat and mass transfer coefficients at the target commercial scale cycle parameters as that would give a good approximation of the product temperature profile during the process deviation, based on which the impact on product quality or CQA's can be addressed.

CONCLUSIONS

In this study, we have presented a coupling of computational model and experimental measurements to investigate the primary drying phase of lyophilization and provided an understanding of complex heat transfer and mass transfer processes. The model was validated with a good agreement between computational model prediction and experimental measurement of primary drying time and product temperature profiles during a typical lyophilization cycle. The viability of a heat transfer coefficient scale-up factor for a specific lyophilizer was proposed and implemented into the PASSAGE model, which was used to predict product temperature profiles. Several applications of the model such as the lyophilization design space, parameter variation, and process deviation study showed the powerful predication capability of the model

Fig. 6. Simulation of a process deviation experiment

once the accurate input parameters are provided either based on estimation or through small scale experimentation. Furthermore, the approach presented here provides a robust lyophilization scale-up strategy; it will also be less capital intensive path with minimum use of expensive active pharmaceutical ingredient because of the simple and minimalistic approach.

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