Use of a multi-vial mathematical model to design freeze-drying cycles for pharmaceuticals at known risk of failure

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Abstract

Freeze-drying is a dehydration method suitable for the stabilization of heat-labile pharmaceutical products, such as vaccines. Due to the vial-to-vial variability of heat and mass transfer during the process, the value of the critical process parameters (e.g., product temperature, sublimation rate) may be different between vials and batches often present significant product quality heterogeneity. The aim of this work was the development of a dynamic, multi-vial mathematical model making it possible to predict risk of failure of the process, defined as the percentage of vials potentially rejected by quality inspection. This tool could assist the design of freeze-drying cycle.

***Keywords:** lyophilization; vaccines; heat and mass transfer; mathematical modeling; design space*

1. Introduction

Freeze-drying is a discontinuous process used to dry heat sensitive products by means of sublimation of the previously frozen product (primary drying), followed by desorption of the unfrozen water (secondary drying). Due to the use of low temperature, freeze-drying process is often the only solution to produce pharmaceutical and biological products (e.g., vaccines) with acceptable characteristics of stability, shelf-life, and potency. During the process design, two main constraints need to be taken into account in order to guarantee acceptable quality attributes of the final product, such as the visual aspect of the freeze-dried cake and the moisture content. Firstly, the product temperature has to be maintained below a critical value (namely collapse temperature) during the sublimation and desorption steps, to avoid the loss of the porous product structure. Furthermore, the desorption step should be carried out long enough to reach the target value of residual moisture content in the final product. However, due to the vial-to-vial variability of heat and mass transfer, the value of the critical process parameters (e.g., product temperature, sublimation rate and desorption rate) may be different between vials and the process can often result in vial batches presenting a significant heterogeneity in the product quality. Several mathematical models [1-5] were developed for the design of the primary drying and secondary drying steps. Most of these models were based on average values of the model parameters (e.g., product resistance, vial heat transfer coefficient, characteristic desorption time) over the vial batch and only few of them took into account the variability of the model parameters [2, 3] due to differences in heat and mass mechanisms between vials processed in the same or different batches. The understanding and quantification of the mechanisms responsible for product quality variability can lead to a better prediction of the process parameters distribution and consequently of the risk of failure associated to the process.

Our goal in the present study was to develop a multi-vial dynamic mathematical model for freeze-drying for the process design, taking into account sources responsible for heat and mass transfer variability among vials. The developed model was then used to propose a new quality risk-based approach for the design of the primary and secondary drying steps of the freeze-drying process, which includes the evaluation of the percentage of vials potentially rejected for specific combinations of operating variables.

2. Theory

2.1. Mathematical model

The heat flux received during the process by the vial is assumed to mainly serve for the ice sublimation during primary drying and for the water desorption in secondary drying, the difference being responsible for temperature variation of product and vial in transient regimes. The evolution of product temperature T_p (assumed to be the same as the vial) during primary and secondary drying can be determined as:

$$C_p \frac{dT_p}{dt} = \dot{Q}_{SV} - \Delta H_{sub} \dot{m}_{sub} - \Delta H_{des} \dot{m}_{des} \tag{1}$$

Heat transfer during primary drying

The heat transfer between the shelf and the vial $\dot{Q}_{SV}$ depends on the temperature difference between the shelf (T_S) and the product (T_p), and can be expressed in term of vial heat transfer coefficient K_V:

$$\dot{Q}_{SV} = \left(\frac{1}{K_V} + \frac{l_I(t)}{\lambda_{ice}} \right)^{-1} A_{BV} (T_S - T_p) \tag{2}$$

The term K_V depends on the vial bottom dimensions (vial–shelf contact area A_c and depth of bottom curvature l_{BV}) and the chamber pressure P_C and can be defined as:[6]

$$K_V = C_1 A_c + K_r + \frac{C_2 P_C}{1 + C_2 \frac{l_{BV}}{\lambda_v} P_C} \tag{3}$$

K_r being the radiation contribution of the top and bottom shelf.[6]

Mass transfer during primary drying

During primary drying the sublimation flux can be defined by the difference between the equilibrium pressure at the ice-vapour interface P_{v_i} and the partial vapour pressure in the chamber P_{v_C}:

$$\dot{m}_{sub} = \frac{A_i}{R_p} (P_{v_i} - P_{v_C}) \tag{4}$$

where R_p is the the mass transfer resistance of the dried layer, which depends linearly on the dried layer thickness for the considered product:[7]

$$R_p = R_{p_0} + l_d R_{p_1} \tag{5}$$

P_{v_i} can be calculated from the Clausius Clapeyron equation from the sublimation interface temperature,[6] and P_{v_C} is defined as in Trelea et al.[8] assuming ideal gas law for water vapour in the drying chamber:

$$\frac{dP_{v_C}}{dt} = \frac{R_g T_C}{V_C M_W} \left(\sum_1^{N_V} (\dot{m}_{sub} + \dot{m}_{des}) - \dot{m}_{CN} \right) \tag{6}$$

Finally, the fraction of ice f contained in the product evolves with time as a function of the sublimation rate $\dot{m}_{sub}$ as:

$$m_0 \frac{df}{dt} = -\dot{m}_{sub} \tag{7}$$

Mass transfer during secondary drying

The multilayer model developed by Trelea et al.[9] was used to describe the desorption kinetics in secondary drying.

2.2. Heat and mass transfer variability in freeze-drying

Four sources of inter-vial product quality variability were considered in this study:

➢ *Vial geometry*: K_V is influenced by the shelf-vial contact area A_c and the depth of bottom curvature l_{BV} (Equation 3). Thus, differences in these dimensions among the vials can results in variability of the heat transfer among the vials on the shelf. In the present study, the distributions of K_V at different chamber pressures over the vial batch were calculated based on the normal distributions of A_c and l_{BV}, as previously proposed by Scutellà et al.[6]

➢ *Edge vial effect*: It is well known that vials located at the periphery of the shelf receive an additional heat transfer by radiation from the wall and the rail and conduction through the gas between the chamber wall, the rail and the side wall of the vials. This phenomenon is known as edge vial effect. In the present study, the additional radiation heat flow rates from the wall and rail to the edge vials were calculated for edge vials using the Stefan-Boltzmann equation, as proposed in the 3D simplified radiation model developed by Scutellà et al. [10]

➢ *Mass transfer resistance*: The product resistance variability in a large batch of vials was previously quantified as normal distributions of R_{p_0} and R_{p_1} in Scutellà et al.[7]

➢ *Desorption kinetics*: The variability of the desorption kinetics was previously quantified as normal distributions of characteristics desorption times in Scutellà et al. [11]

2.3. Prediction of the risk of vial rejection

The developed mathematical model was used to propose a quality risk-based approach for the design of the primary and secondary drying steps of the freeze-drying process. The risk of failure of the primary drying step was calculated in terms of vials potentially rejected by considering two main constraints: (i) the product temperature had to be maintained at any time below a critical value (i.e., the glass transition temperature for amorphous products); (ii) the sublimation had to be completed at the end of primary drying (i.e., $f = 0$). For the design of the secondary drying step, the constraints were: (i) the final moisture content had to be equal or lower than the target moisture content (1.5 %) and (ii) the temperature at any moment had to be lower than the glass transition temperature of the dry product. The range of acceptable combinations of operating variables (i.e., T_s, P_C, operating time) was then identified based on the target level of risk. The capability of the pilot freeze-dryer was considered to be not limiting regardless of the operating conditions.

2.4. Numerical solution

The developed model was solved using Matlab R2014b software provided of the Statistics Toolbox (The MathWorks, Inc., Natick, MA). The analysis of the effect of the heat and mass

transfer variability on the critical process parameters during freeze-drying was performed using the Monte Carlo method. This method consisted in simulation of batches of 100 representative vials with random normal distributions of the considered model parameters (A_C, l_{BV}, R_{p_0}, R_{p_1}, τ_{ref_1} and τ_{ref_2}). Due to computer limitations, the number of simulated vials (100) was significantly smaller than the actual number of vials in the freeze-dryer (2310).

3. Simulated system

In the present work, the model was used to simulate freeze-drying process performed in the pilot freeze-dryer REVO (Millrock Technology, Kingston, United States). The equipment was composed of a drying chamber equipped with three shelves and a condenser running at temperature of -75 °C. A total of 770 glass tubing vials (Müller + Müller, Holzminden, Germany) were supposed to be loaded on each shelf. The vials had a total volume of 3 mL and were all filled with 1.8 mL of 5 % aqueous sucrose solution. Furthermore, the vial array was surrounded by a metallic rail (shielding 70 % of the lateral wall of the vials). The shelf was considered to be at a temperature of -50 °C at the beginning of primary drying.

4. Results

The developed model was used to predict the risk of failure of the process in terms of percentage of vials potentially rejected. Potential vial rejection of the primary and secondary drying steps were predicted for different combinations of operating variables (shelf temperature, chamber pressure, operating time) to select the best cycle at the maximum allowed risk (1 %). Figure 1A presents the percentage of vial rejection due to a product temperature higher than T'_g observed performing a primary drying of 84 hours in function of the chamber pressure and shelf temperature. Typical ranges of chamber pressure and shelf temperature used in the pharmaceutical industry were explored, respectively between 4 and 10 Pa, and -40 °C and -10 °C. The results shows that, if a value of shelf temperature higher than -27 °C is applied during primary drying, the percentage of vial rejection become higher than 1 % for most of the pressures tested. Furthermore, Figure 1B presents the percentage of vial rejection due to the sublimation not completed at the end of primary drying observed performing a primary drying step of 84 hours in function of the shelf temperature and chamber pressure. A shelf temperature higher than -30 °C has to be considered to avoid the presence of ice at the end of the primary drying time. Thus, the use of a shelf temperature of -27 °C and a chamber pressure between 4 and 9.3 Pa during primary drying step of 84 h results in a percentage of vial rejection lower than the maximum allowed one (1 %). Figure 2A presents the risk of vial rejection associated to the secondary drying step due to a product temperature higher than T_g. A range of shelf temperatures between 0 °C and 40 °C was explored, and the pressure was maintained constant at 6 Pa. The product temperature remains below the critical value regardless of the shelf temperature applied during the secondary

drying step, because the product dries enough during the shelf temperature ramp (1°C min⁻¹). Figure 2B presents the risk of vial rejection of associated to the secondary drying step due to a final moisture content in the product higher than the target value of 1.5 %. A shelf temperature higher than 4 °C will lead to no vial rejection if secondary drying is carried for at least 45 h. As product temperature remains below the critical value regardless the shelf temperature value used, the optimal operating conditions for secondary drying will be a shelf temperature of 40 °C and an operating time of 4 h, which leads to a vials rejection lower than 1 %.
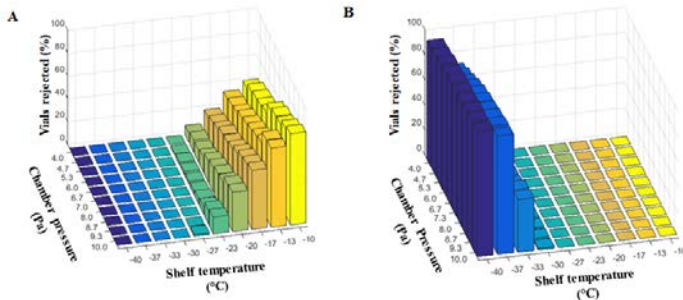
Fig. 1 Potential vial rejection (%) in primary drying performed at different chamber pressures and shelf temperatures due to (A) a product temperature higher than the critical value (T'_g) and (B) sublimation not completed after 84 h of primary drying.
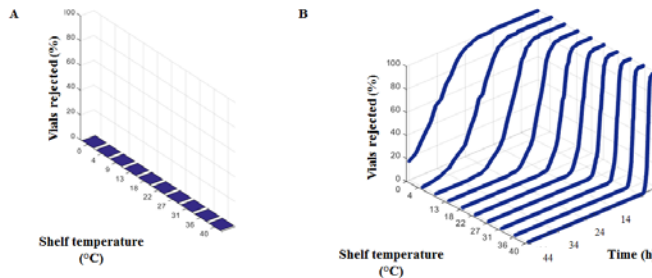
Fig. 2 Potential vial rejection (%) in secondary drying due to (A) a product temperature higher than the critical value (T_g) during the whole duration of the secondary drying step and (B) product moisture content higher than the target value (1.5 %) for different shelf temperatures and operating times.

5. Conclusions and perspectives

In this work, a multi-vial, dynamic mathematical model of the primary and secondary drying steps of the freeze-drying process was developed, including the heterogeneity of parameters such as the vial dimensions, the vial position on the shelf and the random nucleation process. The model was used to calculate the risk of failure of the primary and secondary drying steps for a 5 % sucrose solution processed in a pilot freeze-dryer, expressed in terms of percentage of vials potentially rejected. In the future, the proposed model will be experimentally

validated and used to calculate the design spaces of primary and secondary drying for the cycle transfer and scale-up of the process.

Nomenclature

A	Cross sectional area (m^2)	
C_1, C_2	Parameters of Equation 3 $(W\ m^{-4}K^{-1}), (W\ m^{-2}K^{-1}\ Pa^{-1})$	
C_p	Heat capacity $(J\ K^{-1})$	
ΔH	Latent heat $(J\ kg^{-1})$	
f	Mass fraction of ice in the product	
K	Heat transfer coefficient $(W\ m^{-2}K^{-1})$	
l	Layer thickness (m)	
$\dot{m}$	Water vapour flow rate $(kg\ s^{-1})$	
m	Mass (kg)	
M_W	Molecular mass of water $(g\ mol^{-1})$	
N	Number of vials	
P	Pressure (Pa)	
$\dot{Q}$	Heat flow rate (W)	
R_g	Ideal gas constant $(J\ K^{-1}kmol^{-1})$	
R_p	Product resistance $(Pa\ m^2\ s\ kg^{-1})$	
R_{p_0}, R_{p_1}	Parameter of Equation 5 $(Pa\ m^2s\ kg^{-1}), (Pa\ m\ s\ kg^{-1})$	
t	Time (s)	
T	Temperature (K)	
V	Volume (m^3)	

Greek

β	Mass transfer parameter $(s\ kg^{-1}\ K^{-1})$	
λ	Thermal conductivity $(W\ m^{-1}\ K^{-1})$	
τ_{ref}	Characteristic desorption time at reference temperature (s)	

Subscripts and Superscript

0	Initial
B	Bottom
C, c	Chamber and contact, respectively
CN	Condenser
d	Dried
des	Desorption
f	Frozen
i	Interface
ice	Ice
P	Product
r	Radiation
S, s	Shelf and solids, respectively

sub	Sublimation
T	Top
V, v	Vial and vapour, respectively
w	Water

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