



Research paper

Quantitative risk assessment via uncertainty analysis in combination with error propagation for the determination of the dynamic Design Space of the primary drying step during freeze-drying



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ABSTRACT

Traditional pharmaceutical freeze-drying is an inefficient batch process often applied to improve the stability of biopharmaceutical drug products. The freeze-drying process is regulated by the (dynamic) settings of the adaptable process parameters shelf temperature T_s and chamber pressure P_c . Mechanistic modelling of the primary drying step allows the computation of the optimal combination of T_s and P_c in function of the primary drying time. In this study, an uncertainty analysis was performed on the mechanistic primary drying model to construct the dynamic Design Space for the primary drying step of a freeze-drying process, allowing to quantitatively estimate and control the risk of cake collapse (i.e., the Risk of Failure (RoF)). The propagation of the error on the estimation of the thickness of the dried layer L_{dried} as function of primary drying time was included in the uncertainty analysis. The constructed dynamic Design Space and the predicted primary drying endpoint were experimentally verified for different RoF acceptance levels (1%, 25%, 50% and 99% RoF), defined as the chance of macroscopic cake collapse in one or more vials. An acceptable cake structure was only obtained for the verification runs with a preset RoF of 1% and 25%. The run with the nominal values for the input variables (RoF of 50%) led to collapse in a significant number of vials. For each RoF acceptance level, the experimentally determined primary drying endpoint was situated below the computed endpoint, with a certainty of 99%, ensuring sublimation was finished before secondary drying was started. The uncertainty on the model input parameters demonstrates the need of the uncertainty analysis for the determination of the dynamic Design Space to quantitatively estimate the risk of batch rejection due to cake collapse.

1. Introduction

Pharmaceutical freeze-drying is a process often used to improve the stability of biopharmaceutical drug products with a limited stability when formulated as an aqueous solution [1]. Traditionally, freeze-drying is a batch-wise process during which all vials of each batch are processed through a sequence of consecutive steps (i.e., freezing, primary drying and secondary drying) until the dried end product is obtained [2]. Glass vials containing the aqueous drug formulation (i.e., unit doses) are loaded onto temperature-controlled shelves in the drying chamber. At the start of the freezing stage, these shelves are

gradually cooled until approximately $-45\text{ }^\circ\text{C}$, depending on the formulation characteristics. The temperature of the aqueous drug formulation decreases until ice nucleation takes place and part of the water is converted into ice. While ice crystal growth proceeds upon further cooling, the solutes gradually concentrate between these crystals (freeze-concentration) [3]. At the end of the freezing step, the shelf temperature reaches a value well below the eutectic temperature T_e or the glass transition temperature of the maximum freeze-concentrated formulation T_g^* for crystalline or amorphous products, respectively, resulting in complete solidification of the product. To allow full crystallization of crystalline components or to enhance the batch uniformity of

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Nomenclature

α	constant describing K_v in function of P_c ($J/(m^2 s K)$)	P_c	chamber pressure (Pa)
β	constant describing K_v in function of P_c ($J/(m^2 s K Pa)$)	$P_{w,c}$	partial water pressure in the drying chamber (Pa)
ΔH_{sub}	latent sublimation heat of ice (J/mol)	$P_{w,i}$	vapour pressure at the sublimation interface (Pa)
Δm	mass of sublimated ice (kg)	R	gas constant (8.3144621 J/(K mol))
Δt	primary drying time interval (s)	R_p	dried product mass transfer resistance (m/s)
$\dot{m}_{sub,chok,dryer}$	maximum sublimation rate avoiding choked flow at dryer level (kg/s)	r_d	equivalent radius corresponding to duct opening between chamber and condenser (m)
$\dot{m}_{sub,chok,vial}$	maximum sublimation rate avoiding choked flow at vial level (kg/s)	$R_{p,0}$	constant describing R_p in function of l (m/s)
\dot{m}_{sub}	sublimation rate (kg/s)	$r_{v,i}$	inner radius of the glass vial (m)
ϵ	volume fraction of ice (-)	$r_{v,n}$	equivalent radius corresponding to vial neck opening (m)
γ	constant describing K_v in function of P_c (1/Pa)	$r_{v,o}$	outer radius of the glass vial (m)
ρ_{ice}	density of ice (kg/m^3)	$S_{L^{dried}}$	uncertainty level on L^{dried} (m)
A_p	product area available for sublimation (m^2)	t	primary drying time (h)
A_v	outer vial area (m^2)	T_b	ice temperature at bottom of the vial (K)
A_{R_p}	constant describing R_p in function of l (1/s)	T_c	collapse temperature (K)
B_{R_p}	constant describing R_p in function of l (1/m)	T_e	eutectic temperature (K)
k	ratio of specific heats (-)	T_g	glass transition temperature of the freeze-dried product (K)
K_v	vial heat transfer coefficient ($J/(m^2 s K)$)	T'_g	glass transition temperature of the maximum freeze-concentrated formulation (K)
L^{dried}	dried layer thickness (m)	T_i	product temperature at sublimation front (K)
M	molecular weight (kg/mol)	T_r	temperature of the water vapour (K)
n_{vials}	amount of vials (-)	T_s	shelf fluid inlet temperature (K)
		$T_{i,crit}$	critical product temperature (K)
		V	filling volume (mL)

the ice crystal size, an annealing step can be added to the freezing stage [4–6]. Here, the shelf temperature at the end of the freezing step is raised to a temperature above T'_g , but below T_e . This shelf temperature is maintained for several hours before re-establishing the final freezing temperature, below T'_g . The primary drying step is initiated by lowering the chamber pressure, conventionally to a value between 5 and 30 Pa. When the desired pressure is reached, the shelf temperature is raised to promote ice sublimation. The sublimation front, i.e., the interface separating ice-free product from the ice crystal matrix, moves gradually downward with the progress of primary drying. When ice sublimation is completely finished, the shelf temperature is further raised during the secondary drying step supporting the desorption of unfrozen water in the amorphous matrix and/or the removal of hydrate water in crystalline material until the desired residual moisture content of the end product is obtained.

One of the Critical Quality Attributes (CQAs) of lyophilized biopharmaceutical products, defined as product properties or characteristics that should meet defined standards to ensure the desired quality (ICH Q8), is the cake appearance [7]. Loss of cake structure (collapse) should be avoided throughout the lyophilization process to ensure reconstitution of the drug product within an appropriate timing and for aesthetic purposes [1]. For this reason, the product temperature at the sublimation front T_i should be maintained below the critical product temperature $T_{i,crit}$ during the entire primary drying step. $T_{i,crit}$ is characteristic for each formulation and identified as the collapse temperature T_c or T_e for amorphous and crystalline products, respectively. In general, T_c lies a few degrees above T'_g because the viscosity near T'_g is sufficiently high to limit viscous flow [3]. During secondary drying, the product temperature should be kept below the glass transition temperature of the dried product T_g to avoid molecular motion and loss of cake structure. The value of T'_g is much higher compared to T_g of the freeze-concentrate and is highly influenced by the residual moisture content, due to the plasticizing effect of water [1]. In general, the shelf temperature ramp during the transition of the primary to secondary drying step is rather conservative, due to the potential high residual moisture content immediately after primary drying. However, several approaches have been developed to optimize this transition phase [8,9].

The freeze-drying process is characterized by two adaptable process

variables, i.e., the shelf fluid inlet temperature T_s and chamber pressure P_c . Combinations of both parameters are set in function of time, specific for each process step. During primary drying, the settings of T_s and P_c should result in a value for T_i associated with maximum sublimation efficiency, while maintaining an appropriate cake structure. Mechanistic models based on the fundamental understanding of the underlying physical mechanisms of the sublimation process, allow the determination of the optimal combination of T_s and P_c during primary drying and their calibration for a formulation to be freeze-dried [10,11]. The development of these mechanistic models only requires a limited amount of experiments, compared to data-driven empirical models associated with a high experimental load. Mechanistic modelling assists in cycle development and optimization by computing T_i for different combinations of T_s and P_c , eventually leading to the construction of the Design Space for primary drying [12–14]. The Design Space is defined as the multidimensional combination and interaction of input variables and process parameters leading to an acceptable product quality with a controlled probability (ICH Q8) [7]. For primary drying, the Design space is demarcated by the equipment limitations, the sublimation efficiency and the specific CQA for the lyophilized biopharmaceutical product, in this case the dried cake appearance [15–17]. All combinations of T_s and P_c within these limits lead to a lyophilized product with an appropriate cake appearance that is achieved within an acceptable time-frame. Model input variables can change with the progress of primary drying, such as the thickness of the dried product layer L^{dried} . Upon an increase in L^{dried} , the path of the water vapour originating from the sublimation interface through the pores of the above dried product layer becomes longer, associated with an increase in the dried product mass transfer resistance R_p . Therefore, the heat transfer to the product should be gradually lowered, to avoid an increase in T_i . As a consequence, the optimal combination of T_s and P_c changes in time to maintain T_i below $T_{i,crit}$, leading to a dynamic Design Space [12,13].

The mechanistic models are a mathematical approximation of the sublimation process during the primary drying stage. Inherent to model development, a few assumptions and simplifications are included in these primary drying models (e.g., a planar sublimation front and steady-state system are assumed). In addition, the model input variables and process parameters are in some cases an estimation of the real

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