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Research paper

Uncertainty analysis as essential step in the establishment of the dynamic Design Space of primary drying during freeze-drying

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ABSTRACT

Large molecules, such as biopharmaceuticals, are considered the key driver of growth for the pharmaceutical industry. Freeze-drying is the preferred way to stabilise these products when needed. However, it is an expensive, inefficient, time- and energy-consuming process. During freeze-drying, there are only two main process variables to be set, i.e. the shelf temperature and the chamber pressure, however preferably in a dynamic way. This manuscript focuses on the essential use of uncertainty analysis for the determination and experimental verification of the dynamic primary drying Design Space for pharmaceutical freeze-drying. Traditionally, the chamber pressure and shelf temperature are kept constant during primary drying, leading to less optimal process conditions. In this paper it is demonstrated how a mechanistic model of the primary drying step gives the opportunity to determine the optimal dynamic values for both process variables during processing, resulting in a dynamic Design Space with a well-known risk of failure. This allows running the primary drying process step as time efficient as possible, hereby guaranteeing that the temperature at the sublimation front does not exceed the collapse temperature. The Design Space is the multidimensional combination and interaction of input variables and process parameters leading to the expected product specifications with a controlled (i.e., high) probability. Therefore, inclusion of parameter uncertainty is an essential part in the definition of the Design Space, although it is often neglected. To quantitatively assess the inherent uncertainty on the parameters of the mechanistic model, an uncertainty analysis was performed to establish the borders of the dynamic Design Space, i.e. a time-varying shelf temperature and chamber pressure, associated with a specific risk of failure. A risk of failure acceptance level of 0.01%, i.e. a 'zero-failure' situation, results in an increased primary drying process time compared to the deterministic dynamic Design Space; however, the risk of failure is under control. Experimental verification revealed that only a risk of failure acceptance level of 0.01% yielded a guaranteed zero-defect quality end-product. The computed process settings with a risk of failure acceptance level of 0.01% resulted in a decrease of more than half of the primary drying time in comparison with a regular, conservative cycle with fixed settings.

1. Introduction

1.1. Freeze-drying

Nowadays large molecules receive more attention for their pharmacological properties and the interest in these molecules is growing. The list of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) with approved biopharmaceutical drug products (>300) contains approximately 50% freeze-dried products [1]. This indicates that freeze-drying (or lyophilisation) is the preferred way of stabilizing biopharmaceutical drug products that are unstable when formulated as an aqueous solution. However, the high cost and energy consumption as well as the long processing time are severe disadvantages [2,3]. Among the freeze-dried biopharmaceutical products the largest fraction are therapeutic protein formulations and vaccines [4].

Conventionally, freeze-drying is a batch process, consisting of three consecutive steps: freezing, primary drying and secondary

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drying [4]. At the start of the process, vials filled with the aqueous drug formulation are placed on temperature-controlled shelves in a drying chamber. The lyophilisation process starts with the chilling of these shelves to approximately −45 °C. During this freezing step most of the water crystallises to ice. The solutes gradually concentrate between these ice crystals, until they start crystallising (at the eutectic temperature T_e) or form an amorphous glass (at the glass transition temperature T'_g). In case of an amorphous product, the freeze-concentration is associated with an increase in viscosity until at a specific temperature further freezing no longer occurs. The temperature, characteristic for each formulation, where maximum freeze-concentration takes place, is referred to as T'_g [5]. Because freezing is interrupted before all water is converted into ice crystals, there is still a residual amount of unfrozen water present in the amorphous glass. In some cases the freezing step is immediately followed by an annealing step. During this annealing step, the shelf temperature is increased from the final freezing temperature to a temperature above T'_g, but below T_e of the formulation, and maintained for several hours. The purpose of annealing is to increase the uniformity of the size of ice crystals formed during the freezing step or to allow complete crystallisation of crystalline components. After complete solidification of the product, the primary drying step is started by decreasing the pressure, conventionally to a value between 5 and 30 Pa, in the drying chamber. Additionally, the temperature of the shelves is increased to provide energy necessary for ice sublimation. The sublimation front, the border between the ice crystals and ice-free dried product, gradually decreases in each vial during the progress of primary drying until ice sublimation is complete (Fig. 1). Finally, during the secondary drying step, the shelf temperature is further increased which allows the removal of the remaining unfrozen water by desorption until a dry cake is obtained.

Several Critical Quality Attribute (CQAs) are identified for freeze-dried biopharmaceuticals [5]. These product characteristics should be within appropriate limits to ensure product quality (ICH guidelines on Pharmaceutical Development (Q8)), e.g. the Active Pharmaceutical Ingredient (API) needs to stay stable throughout the lyophilisation process to guarantee optimal therapeutic activity (e.g. avoiding loss of protein conformation by adding lyo- and/or cryoprotectants) or the residual moisture level of the dried cake needs to be adequate to ensure product stability (e.g. water-mediated degradation pathways). Another important CQA is cake appearance. For aesthetic purposes and to ensure fast reconstitution of the drug product, loss of structure (cake collapse) should be avoided throughout the lyophilisation process [6]. Therefore the product temperature at the sublimation front T_i should during primary drying always be kept below the collapse temperature T_c and the eutectic temperature T_e for amorphous and crystalline materials respectively. T_c is generally a few degrees higher than the glass transition temperature T'_g because the high viscosity of the glass near T'_g limits molecular motion. Also during secondary drying loss of cake structure can occur. For this reason, to prevent viscous flow, T_i should not exceed the glass transition temperature T_g of the dried product. The T_g value is higher than the T'_g of the maximum freeze-concentrated formulation and is highly dependent on the moisture content because of the plasticizing effect of water. As a consequence, immediately after primary drying, the shelf temperature T_s should not be increased too fast, but progressively due to the high amount of residual moisture that is still present.

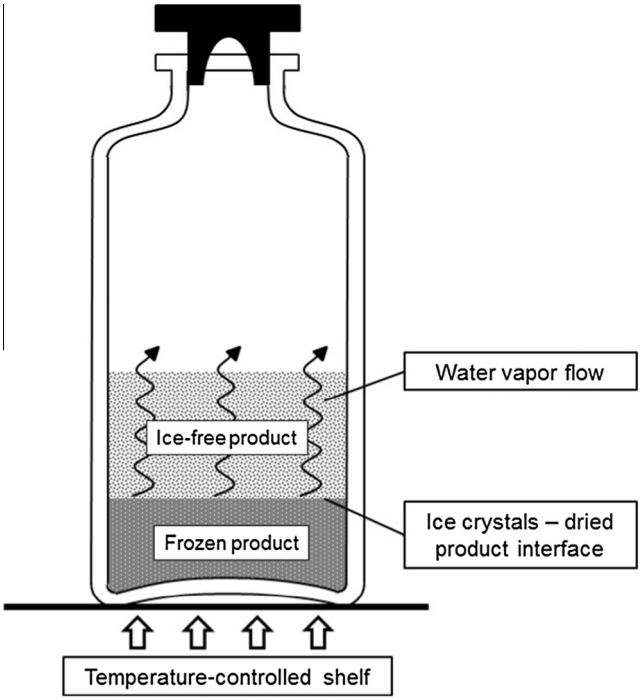

Fig. 1. Illustration of the progress of primary drying with the gradual decrease of the sublimation front.

To increase process efficiency, primary drying asks for T_i to be as high as possible. Therefore, the adaptable process variables, shelf temperature T_s and chamber pressure P_c, should not be chosen too conservative. Mechanistic modelling allows to determine the optimal combination of T_s and P_c keeping T_i below the critical temperature during primary drying [7,8]. In comparison with data-driven models, which are solely based on collected experimental data, mechanistic models are based on the underlying physical mechanisms and the fundamental understanding of the process under study is incorporated – to a certain extent – in the model. Therefore, mechanistic modelling is a powerful tool for both freeze-drying cycle development and optimisation. Based on the several combinations of T_s and P_c the primary drying Design Space can be constructed for a specific formulation. The limits of this Design Space are determined by the efficiency of primary drying, the equipment limitations and the CQAs identified for the specific biopharmaceutical drug product (e.g. the dried cake appearance) [9]. The target T_s and P_c settings should therefore be within these limits to acquire a good quality cake within an acceptable process time.

Since T_i depends on a wide range of changing parameters during sublimation, the optimal combination of T_s and P_c is dynamic rather than static during primary drying. For instance, along with the progress of primary drying the thickness of the dried product layer L_{dried} increases which leads to a simultaneous increase in dried product mass transfer resistance R_p and T_i. Because of these dynamics of the dependent parameters, the Design Space also becomes dynamic with the progression of the lyophilisation process; hence, we are dealing with a dynamic Design Space [10,11].

The Design Space is defined in ICH Q8 as the multidimensional combination and interaction of input variables and process parameters leading to the acceptable product quality with a controlled (i.e., high) probability [12]. Taking parameter uncertainty into account in the mechanistic model allows to quantitatively estimate the risk of collapse that is associated with a specific combination of T_s and P_c in the Design Space. Only few studies have focused on quantitative risk assessment, each via a different approach [7,13,14]. Bogner and Pikal [13] assessed the impact of varying input parameters on the product temperature by analysing the propagation of errors. Giordano et al. [7] and Bosca et al. [14]