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Abstract

Pharmaceutical batch freeze-drying is commonly used to improve the stability of biological therapeutics. The primary drying step is regulated by the dynamic settings of the adaptable process variables, shelf temperature T_s and chamber pressure P_c. Mechanistic modelling of the primary drying step leads to the optimal dynamic combination of these adaptable process variables in function of time. According to Good Modelling Practices, a Global Sensitivity Analysis (GSA) is essential for appropriate model building. In this study, both a regression-based and variance-based GSA were conducted on a validated mechanistic primary drying model to estimate the impact of several model input parameters on two output variables, the product temperature at the sublimation front T_i and the sublimation rate $\dot{m}_{sub}$. T_s was identified as most influential parameter on both T_i and $\dot{m}_{sub}$, followed by P_c and the dried product mass transfer resistance α_{Rp} for T_i and $\dot{m}_{sub}$, respectively. The GSA findings were experimentally validated for $\dot{m}_{sub}$ via a Design of Experiments (DoE) approach. The results indicated that GSA is a very useful tool for the evaluation of the impact of different process variables on the model outcome, leading to essential process knowledge, without the need for time-consuming experiments (e.g., DoE).

Keywords: Freeze-drying, Mathematical modelling, Global Sensitivity Analysis

1. Introduction

Biological drug products like therapeutic proteins and vaccines, gain more and more interest within the pharmaceutical industry [1]. However, the stability of these biopharmaceuticals in aqueous solution is often limited due to water-mediated degradation pathways. Freeze-drying (lyophilization) is a frequently applied drying process to improve the stability of these biopharmaceuticals during storage and distribution, despite the long processing time and high costs [2]. Approximately 50% of the biopharmaceutical drug products approved by the regulatory authorities (> 300) are freeze-dried formulations [3].
Conventional pharmaceutical freeze-drying of unit doses is a batch-wise process during which all vials of

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