Looking inside the 'black box': freezing engineering to ensure the quality of freeze-dried biopharmaceuticals

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Looking inside the 'black box': freezing engineering to ensure the quality of freeze-dried biopharmaceuticals

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Abstract

The freezing step plays a central role in reaching the most stringent requirements of quality, homogeneity and standardization of freeze-dried products. In this paper, a systematic procedure has been proposed to obtain a quantitative estimation of the pore-size variability of lyophilized products resulting from uncontrollable variations of the nucleation temperature. This procedure consisted in collecting the nucleation temperature from a statistically significant number of samples and correlating each nucleation temperature to the corresponding product morphology, using a mathematical model, to obtain a statistical description of the lyophilized product structure. This approach can also be used to obtain an estimation of the variability of the mass transfer resistance to vapor flow and, finally, of the drying time. Two different freezing configurations, i.e., conventional and suspended-vial freezing, have been used as case studies since they can produce significantly different freezing rates.

Keywords: Freeze-Drying, Freezing, Lyophilization, Ice Nucleation, Mass Transfer Resistance, Uncertainty

1. Introduction

The pharmaceutical industry is at a turning point, as it is shifting from a mass production of patented drugs to a more competitive, innovative and highly regulated market. In fact, the last few years have witnessed the rapid

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