Doctoral Dissertation
Doctoral Program in Chemical Engineering (36th Cycle)

Continuous Freeze-Drying for Pharmaceutical Applications: Design, Prototyping and Process Development

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Summary

The pharmaceutical industry has undergone a profound transformation in recent decades, transitioning from conventional chemically synthesized drugs to biopharmaceuticals. However, biopharmaceutical products often face stability challenges in liquid solution, and are sensitive to the high temperatures associated with conventional drying methods. Freeze-drying constitutes the optimal approach, increasing the shelf life of pharmaceutical drugs while involving gentle drying conditions. Unfortunately, freeze-drying largely relies on batch production, limiting its potential toward such a dynamic and evolving environment.

This thesis addresses the pressing need for continuous freeze-drying in the biopharmaceutical production sphere, proposing a novel concept for a continuous freeze-dryer for unit doses and presenting significant advancements achieved in the construction of a working prototype. The project involved a collaborative effort with a research group from the Massachusetts Institute of Technology (MIT).

Following an introductory section, providing a comprehensive overview of continuous freeze-drying, the concept of the prototype discussed in this thesis is presented, emphasizing the challenges encountered during the design phase and the solutions implemented to address them. The introduction is completed by an in-depth economical evaluation of a batch freeze-drying cycle, focusing on process bottlenecks and energy consumption. The discussion then progresses on the design of the continuous freeze-dryer prototype, analyzing in depth various aspects of the machine using both computational and empirical approaches.

Firstly, the discussion focuses on the freezing section, delving into the optimization of chamber geometry, vial arrangement, and process conditions to achieve uniform cooling among all vials using a stream of refrigerated nitrogen. Moreover, the feasibility of a new method to induce nucleation in supercooled solutions contained in vials is evaluated. The method utilizes a jet of extremely cold and fast nitrogen to facilitate the formation of a stable nucleus, while maintaining the majority of the solution at a predetermined temperature. Additionally, the energy requirements of the freezing section are estimated to inform the design of the cryogenic system and the concept of a bubble pump is explored to allow the safe and contaminant-free injection of liquid nitrogen for refrigeration purposes.

Secondly, the attention shifts toward the drying section of the continuous freeze-dryer. Computational simulations and experimental analyses are employed to evaluate radiative heat transfer as the primary energy source for the vials,

analyzing various chamber geometries and vials arrangements over a wide range of process conditions to determine optimal designs that maximize heat transfer uniformity. Additionally, the design of the vacuum system is discussed proposing a computational framework to model the building blocks connecting the drying chamber to the condenser and allow the design of modular solutions for a wide variety of chamber configurations and process conditions.

Completing the design of the machine, a novel mass inference system for determining the primary drying endpoint during continuous operations is presented. The new sensors overcome the impracticality of the conventional methods, translating a change in mass into a motion in the horizontal plane, detectable through the use of fiducial systems.

Following the discussion on the continuous freeze-dryer prototype, the thesis explores alternative continuous freeze-drying processes and more fundamental aspects. Specifically, the discussion focuses on spray freeze-drying (SFD), presenting a new multiscale model addressing the drying of packed beds of spray-frozen particles, on an extensive study on the ice nucleation temperature distribution and its dependence on the water self-diffusion kinetics, and, lastly, on the role of silicon stoppers on the freeze-drying cycle of pharmaceutical products.

In conclusion, this thesis represents a comprehensive exploration of the development of a continuous freeze-drying prototype and the freeze-drying process in its entirety. While the construction of the actual machine is an ongoing endeavor, significant strides have been made in advancing a technology that has been attempted by many but achieved successfully by few. The integration of the machine at the MIT facilities is nearing completion, and the prototype is poised to commence the production of lyophilized products, accumulating valuable experimental results. This thesis marks a significant step forward in the continued advancement of this technology, promising exciting prospects for the future of freeze-drying.