

A reduced variable neighborhood search for the just in time job shop scheduling problem with sequence dependent setup times

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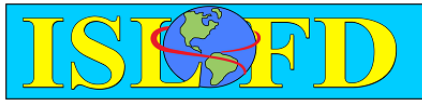
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Modernizing lyophilization of pharmaceuticals in unit doses via continuous manufacturing

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Abstract

This work shows an alternative pharmaceutical freeze-drying concept, which makes it possible to move from batch to continuous manufacturing. The continuous flow of vials is achieved by suspending them over a moving track. The vials move through chambers which have different pressure and temperature conditions and are separated by a load-lock system. Uniformity in freezing conditions is demonstrated by combining the Vacuum Induced Surface Freezing method and convective freezing.

Introduction

In response to the current trend in the pharmaceutical industry [1], a new concept for the lyophilization of pharmaceuticals in unit-doses is presented: the continuous freeze-drying/lyophilisation of suspended vials. This configuration makes it possible to set up a continuous lyophilization process that produces a final product with similar characteristics to those traditionally obtained by means of the batch process, but which avoids the drawbacks of conventional, batch freeze-drying [2]. The feasibility and advantages of this new concept are presented in this work.

Methods

The continuous flow of vials is achieved by suspending them over a moving track. The uniformity in freezing conditions resulted from the combination of convective freezing and Vacuum Induced Surface Freezing method, while heat is transferred substantially through radiation during drying. The vials move through chambers which have different pressure and temperature conditions and are separated by a sluice-gate system. A schematic of the concept is shown in Fig. 1.

Results

In order to obtain a quantitative estimation of the advantages of the proposed continuous strategy, with respect to the batch one, a functional version of the continuous plant has been set up, adapting a batch freeze-dryer. This plant allowed us to simulate the same heat and mass transfer conditions to which vials would be exposed in a continuous freeze-dryer. The performances of the batch and continuous configurations were evaluated in terms of processing time and vial-to-vial variability.

Continuous lyophilization has been found to improve heat transfer uniformity, and a dramatic reduction in the process time (up to 5 times) has been observed. This last result makes it possible to lower the production costs by 50-70%. As far as the structure of lyophilized products is concerned, this technology improves vial-to-vial and intra-vial homogeneity. Overall, this technology results in higher productivities and yields of improved product quality. Additionally, equipment size is greatly reduced (up to 10-15 times) compared to batch lyophilization for the same mass per time throughput.

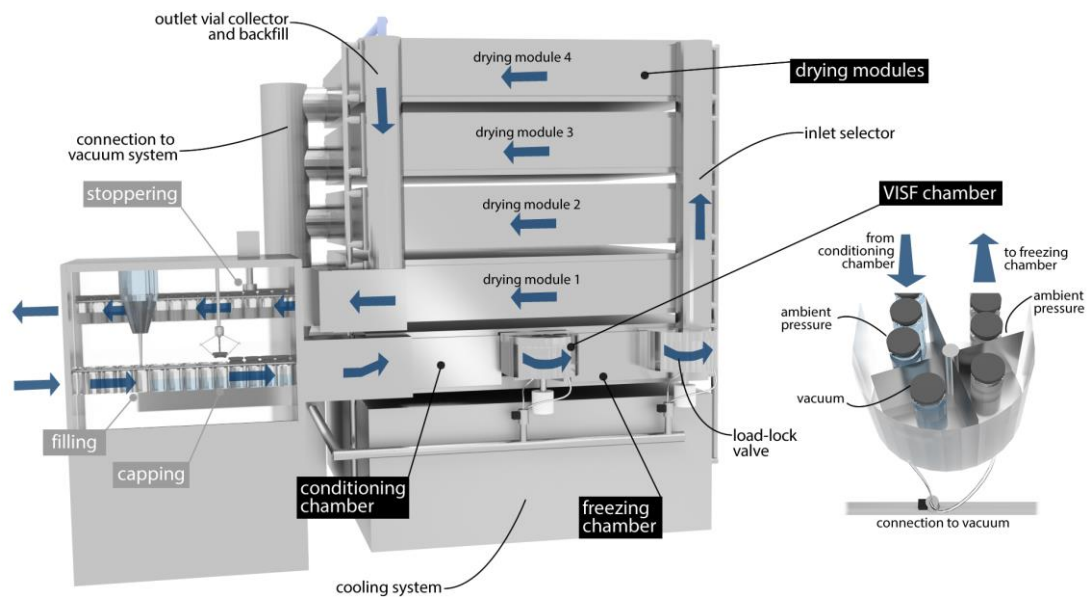


Fig. 1 Schematic of the continuous lyophilizer

Conclusions

The obtained results have demonstrated the feasibility of our concept as a valid alternative to conventional batch lyophilisation, which may open up new perspectives and opportunities to completely re-think the production of parenteral products and make freeze-drying more efficient and versatile.

References

- [1] R. Pisano, A. Arsiccio, L.C. Capozzi, B.L. Trout, Achieving continuous manufacturing in lyophilization: Technologies and approaches, *Eur. J. Pharm. Biopharm.* 142 (2019):265-279.
- L.C. Capozzi, B.L. Trout, R. Pisano, From batch to continuous: freeze-drying of suspended vials for pharmaceuticals in unit-doses, *Ind. Eng. Chem. Res.* 58(2019):1635-1649.