Continuous Freeze-Drying of Pharmaceuticals

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Continuous manufacturing is becoming increasingly important in pharmaceutical manufacturing. Lyophilization, as a downstream process in the pharma industry, also needs to move from batch to continuous.

In this Ph.D. thesis, a new concept for freeze-drying of pharmaceuticals in unit-doses is presented in response to the current trends in the pharmaceutical industry. The configuration studied in this work realizes a continuous freeze-drying process that produces a final product with similar characteristics to the parenteral products and biopharmaceuticals which are already commercialized, avoiding the backwards of the conventional, batch, freeze-drying. Moreover, this technology is also able to process other dosage forms, e.g., granular products, and alternate packaging, e.g., dual chamber cartridges/syringe and ampoules. This thesis is focused on liquid solutions and particle-based products in vials, which is a promises dosage form that is emerging in the last year for pulmonary and epidermal delivery.

The main idea behind this process is that a constant flow of vials enters and leaves the apparatus, passing through different, specialized, chambers (Figure 1).
The process starts out from the filling in continuous of vials, which, at that point, are suspended over a moving track and move into the conditioning module. Here, the flow of a cryogenic gas cools down the vial, bringing the product to the desired temperature. At the end of this module, the vial moves into a special chamber, the nucleation chamber, where the pressure is low enough to induce nucleation; VISF was extensively studied for the batch configuration, and here applied to continuous lyophilization. After that, the vial moves in the freezing module, where, again, a cryogenic gas cools down the vial, achieving the complete solidification of product. It is possible to create customizable freezing protocols by changing the gas velocity, and so, modulating the freezing rate. The vial is then transferred to the drying module by mean of a load-lock system, which allows the passage of the vial from a module at a higher pressure to another at lower pressure without breaking the vacuum. In the drying module, vials are suspended over a track and move in the module following "snake"-type path. The module is constituted of temperature-controlled walls that supply heat to the product via radiation. Changing wall temperature, it is possible to modulate heat transferred to the product, and, hence, to carry out both gentle and aggressive cycles. The last step of this process consists of the backfilling and vial stoppering. The entire process is carried out in continuous, without breaks between phase or manually intervention.

The concept proposed for performing freeze-drying in continuous is a completely new concept which needs to be deeply investigated to demonstrate its feasibility. In this sense, the experimental campaign was accompanied by modeling work. The experimental campaign was essential to give some insight into this new process, i.e., heat and mass transfer phenomena, product quality and cycle time. On the other hand, the modeling tools developed in this thesis have been essential to evaluate the pros and cons of this technology, such as to support the design of the apparatus.

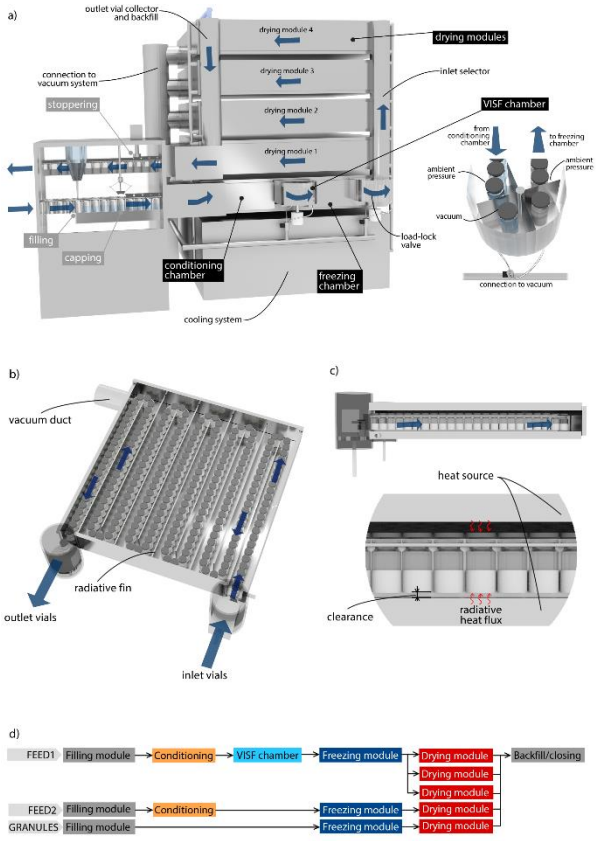

Figure 1. *(a) Schematic of the continuous freeze-dryer patented by the authors, (b) prospective view of a module, (c) side view of a module, (d) example of potential configurations for the continuous lyophilizer.*

As a first step, the feasibility of the continuous freeze-drying of suspended vials for pharmaceuticals in unit-doses is evaluated by replicating the condition of the continuous process in a functional prototype.

The suspended vial freezing led to a final product which had a larger and more uniform pore structure than that obtained with conventional freezing, which made the drying step faster. It is shown that the main advantages of this technology are the complete control of product structure, which can be reached using VISF, and the perfect control and uniformity of heat supplied to the product during drying. In fact, using VISF, nucleation temperature is the same for every sample, avoiding any differences in freezing history of the product, and, thus, in the final product structure. This technique allowed the production of freeze-dried products with the desired morphological attributes by changing cooling rate after nucleation had occurred. In recent year, VISF has become increasingly popular among researchers, and a wide literature already exists, making VISF a ready-to-use technique also in continuous.

A further advantage is the perfect control and uniformity of heat supplied to products during primary and secondary drying. In fact, no edge-vial effect can be identified any longer because every vial follows the same path and experiences identical conditions (Figure 2). Moreover, contrary to batch lyophilization, small variations in the geometry of the vials have no significant effect on the heat supplied by radiation. Moreover, heat by radiation is completely independent of chamber pressure, allowing to further reduce pressure and, hence, increasing sublimation rate.
The perfect control of product structure and heat supplied to the product by using the suspended-vial configuration had a beneficial impact on the uniformity of residual moisture at the end of primary drying, but also at the end of secondary drying, see Figure 2.

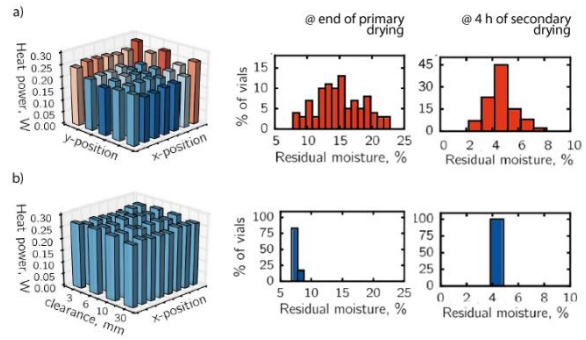

Figure 2. *Comparison of the heat power in batch and suspended-vial freeze-drying mode and residual moisture for the (a) batch and (b) suspended-vial configuration.*

A crucial requirement of continuous manufacturing is to reduce processing time and speed up the process. Both crystallizing (mannitol) and amorphous (sucrose) excipients were used to demonstrate the impact of the suspended-vial configuration on drying duration. Suspended-vial configuration was able to reduce primary drying duration from 3 to 4 times respect to batch configuration, and dramatically reduced the duration or eliminated the secondary drying, see Figure 3.

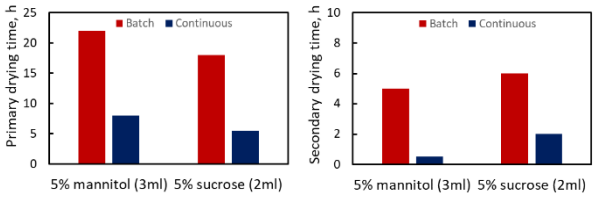

Figure 3. *Comparison of primary and secondary drying duration for the batch and suspended-vial configuration.*

Suspended-vial configuration coupled to VISF were able to produce products with a much lower specific surface area due to the larger pores. That had a beneficial impact on the activity recovery of the APIs which are sensitive to surface-induced denaturation. The activity recovery of LDH after freezing and freeze-drying have been studied for different formulations, i.e., sucrose 5%, trehalose 5%, sucrose/trehalose 2.5/2.5% and, finally, without excipients. In all those cases, LDH recovery activity was much higher in the case of suspended-vial configuration than in the batch.

From the perspective of developing a continuous technology, the control of freezing is fundamental to obtain products with uniform and specific characteristics, so as the control of the drying stages. In this thesis, a mathematical model of freezing of pharmaceutical solutions in a vial was, so, developed to estimate the average pore size and its distribution within the lyophilized product in the case of conventional, batch, freezing, and in the case of suspended-vial freezing. Moreover, a 2D and a simplified 1D model were developed for describing primary drying. As product quality is a key feature of continuous manufacturing, this thesis explores the possibility to look the product structure at a deeper level. For micro-particles, the discrete element method (DEM) and computational fluid dynamics (CFD) were used to estimate packing properties and coupled with a 2D model at the macro scale to describe the drying behavior of these products. For the frozen solutions, X-Ray micro-CT was used to analyzed samples and to reconstruct their product structure (Figure 4).

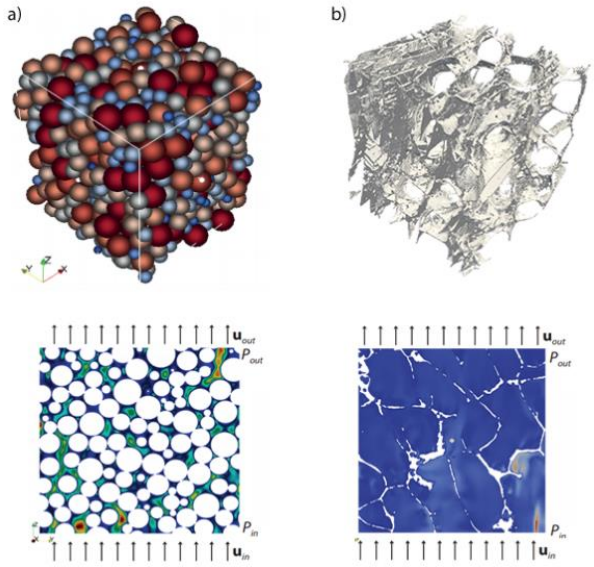

Figure 4. *Analysis of the product structure by using (a) DEM and (b) X-Ray micro-CT. Bottom figures refer to CDF simulations.*

This thesis demonstrated the feasibility of suspended-vial configuration for performing continuous freeze-drying and the advantages concerning processing speed-up, product quality and elimination of scale-up. The implementation of this technology at the pilot and industrial scale might be of interest to many pharmaceutical companies.