A NEW CONCEPT FOR THE CONTINUOUS FREEZE-DRYING OF PHARMACEUTICAL PRODUCTS IN UNIT DOSES

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The new paradigm of pharmaceutical industry is to move from batch to continuous processes so as to satisfy the stringent requirements of quality, safety and efficiency set by regulatory authorities and reduce production costs. In this perspective, freeze-drying needs to be completely rethought, making it more integrated in the chain of production of drugs and more flexible to respond to variations in market needs. The future of freeze-drying, as a downstream process, is therefore to move from batch to continuous. Over the past decades many ideas regarding continuous freeze-drying has been proposed, but none of them has been successfully applied. The objective of this work is to demonstrate the feasibility of an innovative concept to produce lyophilized unit-dose drugs using a continuous process. This novel strategy was demonstrated to improve both yield and vial-to-vial uniformity, giving all those advantages that are typical of continuous technology such as flexibility and elimination of process scale-up from laboratory to industrial scale.

A schematic of the continuous technology is shown in Figure 1. The basic idea is the realization of a continuous flow of vials that experience the same identical processing conditions. This result is achieved by suspending vials over a track and moving them through a plurality of modules.

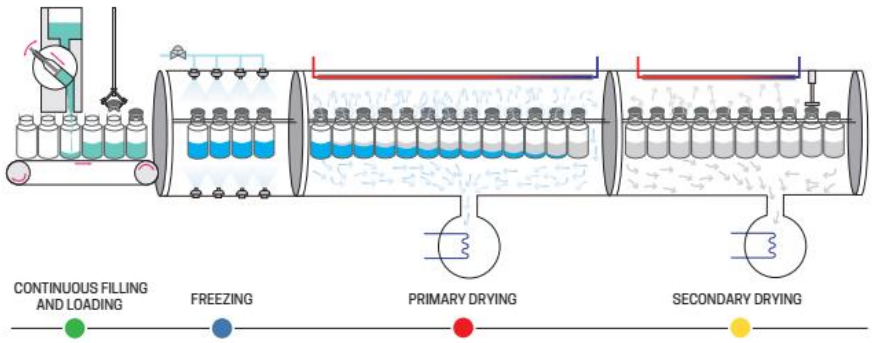

Figure 1 – Schematic of the continuous lyophilizer proposed in this work.

The feasibility of the continuous freeze-drying technology has been studied simulating the process using a functional version of the continuous freeze-dryer. Heat transfer during freezing and primary drying was studied reproducing the same conditions occurring in the continuous process. Various process conditions and formulations (containing both amorphous and crystallizing excipients) were investigated in order to better understand the range of applicability of this new process. It has been demonstrated that the cycle duration of the continuous freeze-drying was comparable to that of a conventional batch process, and the aesthetic acceptability of the product was achieved. The continuous freeze-drying technology also impacted positively on inter- and intra-vial heterogeneity. The internal structure of the products, as analyzed by SEM, showed that the continuous freeze-drying led to a structure with larger pores, homogeneously distributed within the product. In addition to these advantages, we have found that the continuous technology can reduce processing time up to 5 times with respect to the batch technology, and the equipment size up to 10 times.