CONTINUOUS FREEZE-DRYING AND ITS RELEVANCE TO THE PHARMA/BIO TECH INDUSTRY

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The new paradigm of pharmaceutical industry is to move from batch to continuous processes in order 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 in order to be more integrated in the chain of production of drugs, more flexible to respond to variations in market needs and allowing the monitoring of product quality. 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.

The feasibility of continuous freeze-drying 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 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. As can be seen Figure 1, the continuous technology gave the most narrow distribution of residual moisture at the end of primary drying.

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 15 times.

Figure 1 – Statistical distribution of residual moisture as observed at the end of primary drying.