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USE OF A MICRO-FREEZE DRYER FOR THE DEVELOPMENT OF A FREEZE-DRYING PROCESS

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Abstract

This paper deals with the use of a small-scale freeze-dryer where few vials are loaded, e.g. 19, each 10 mL, or 7, each 20 mL. The system has a metallic ring surrounding the batch of vials, in contact with the external ones: its temperature is manipulated independently from that of the shelf. Experiments were carried out using two sucrose solutions (5% and 10% w/w), aiming to verify the homogeneity of the batch, focusing on both product temperature and sublimation flux.

Keywords: *Micro freeze-dryer; freeze-drying; pharmaceuticals; mathematical modeling; processing.*

1. Introduction

The number of drugs requiring freeze-drying in the manufacturing process is ever-increasing as this allows preserving structure-function relationship and stability, avoiding aggregation, as well as physical and chemical degradation, during both manufacturing and storage.

A large number of experiments is typically required to identify the optimal values of the operating conditions of the process. These experiments require a lot of time, not only to carry out the freeze-drying process, but also for batch preparation, loading/unloading, condenser defrosting, etc. etc. Moreover, high amount of active pharmaceutical ingredient is needed.

There is thus a strong driving force to the development of systems that may be used for freeze-drying process development using a low amount of product. In this case the main challenge is represented by the fact that drying conditions are not uniform in a batch: radiation from chamber walls may affect the heat flux to the product in the external vials of the batch and, thus, the temperature and the drying duration (Pisano *et al.* 2011). When processing a small size batch, the number of vials at the edge of the batch can be even higher than that in the central positions, while in a large-scale batch they represent only a small fraction of the batch. This issue has thus to be taken into account when processing small size batch with the goal of obtaining results representative of the drying conditions in a large-scale unit.

This paper is focused on the investigation of the micro freeze-dryer, MicroFD[®] by Millrock Technology, Inc (Kingston, NY, USA) (Goldman *et al.* 2019). It consists of a small chamber where a temperature-controlled aluminum ring is in direct contact with the external vials of the batch. This aluminum ring mimics additional rows of vials and for this reason it has to be in contact with the vials of the batch. Its temperature is controlled on the basis of the product temperature in some vials of the batch, with the goal of maintaining a certain offset between the ring and the product temperature. Few



vials can be loaded, e.g. 7 each 20 mL, or 19 each 10 mL This paper reports results about (i) the homogeneity of drying conditions in this system as a function of the ring temperature, and (ii) the estimation of the values of model parameters K_v and R_p that can be used for in silico process simulation and design space calculation.

2. Materials and methods

Experiments were carried out in the MicroFD[®] by Millrock Technology, Inc (Kingston, NY, USA). All tests were carried out using sucrose aqueous solutions. The solid content was either 5% w/w or 10% w/w. Solutions poured into 6R tubing vials (Schott Pharmaceutical Packaging, Inc., Lebanon, USA), 3 mL per vial. Tests were carried out to investigate the effect of the temperature offset (defined as the difference between the temperature of the ring and that of the product) during the primary drying stage on both product temperature and on the sublimation rate. 4 values of the temperature offset were considered, namely -1°C, -3°C, -5°C and -7°C. The selected values of shelf temperature were -20°C and 0°C, while the values of chamber pressure were 80 µbar and 120 µbar. After 6 hours from the onset of the primary drying stage the run was stopped: weight loss in all the vials of the batch was then measured and recorded.

3. Results and discussion

First experiments were carried out with the 5% w/w sucrose solution at -20°C and 80 µbar, Moving from a temperature offset of -1°C to a value of -5°C the homogeneity of the batch is improved. In fact, while at -1°C the mean value of weight loss in the central vials was 0.81 g and that in the external vials was 0.86 g, with an offset of -5°C the weight loss in central and external vials is 0.8 g and 0.82 g respectively, that means about 1% difference in the amount of ice sublimated. Also the standard deviation is reduced, thus evidencing a greater homogeneity of the batch. For a temperature offset of -5°C the temperature evolution in the two groups of vials is almost overlapping, while for the offset value equal to -3°C the temperature of the edge vials is slightly higher, about 1°C, than that of the central vials.

With respect to the test carried out at 0°C and 80 µbar the optimal value of the offset appears to be -5°C: weight losses are in fact 1.58 g, 1.59 and 1.55 g, respectively, for a temperature offset of -1°C, -3°C and -5°C respectively, with a standard deviation of 5.13%, 4.52% and 3.57% respectively. For the test at 20°C and 120 µbar, if we focus on the difference between the mean values of weight loss in the two groups of vials it appears that the best choice is a temperature offset of -3°C: considering the batch as a whole, the minimum of the standard deviation, i.e. 5.88%, is obtained for this temperature offset (vs. 8.58% at -1°C and 9.52 % for -5°C). When considering a higher value of shelf temperature, namely 0°C, the temperature offsets of -5°C appears again to be the best choice, resulting in the minimum difference between the mean weight loss in the external and in the internal vials, and in the minimum value of the standard deviation of the weight loss in the vials (3.46%).

Results evidenced that the presence of the ring affects the heat flux to the vials and, when its temperature is properly selected, homogeneous drying conditions are obtained. By this way it becomes possible to replicate in this small-scale unit the evolution of the vials in a large-scale freeze-dryer, where most of the vials, i.e. the central ones, have a quite homogeneous behaviour.

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