CASE STUDY

Controlled Nucleation:
more than just a homogenization tool

Optimizing the freeze-drying pharmaceutical process
**ABSTRACT**

The vacuum-induced nucleation system controls and affects ice crystal size and distribution. In addition, it manages to homogenize the moment when the freezing starts so that all the vials nucleate at the same time, in a few seconds, compared to the spontaneous nucleation that takes at least 30-45 minutes. Developed by Telstar under “Lyonuc” brand, this method based on controlling the temperature and pressure to induce the first ice crystals generation (nucleation) at the freezing phase, also ensures the uniformity and homogenization of the vials in all the batches, respecting the product’s physico-chemical properties. It is particularly advantageous for long duration freeze-drying cycles where the benefit of reducing the drying time is much greater. This case study shows the results after implementing an induced nucleation process on an industrial freeze dryer.

**Customer issue**

In freeze drying, the complexity is not just related to the high-end technology of the machine but also to the process itself. The development of a freeze-drying cycle is a critical step towards an efficient and repetitive batch.

With this particular customer, after stabilizing the machine during a thorough validation and maintenance plan and apparently having developed a proper recipe for the freeze-drying cycle, several batches appeared with aesthetical defects and mainly a random product loss within batch and from batch to batch.

There was not a clear pattern in the product loss. In addition, the machine complied with every critical process parameter previously defined. Therefore, focusing on the process itself and after a detailed root cause analysis together with Telstar, the non-uniformity of the frozen product was proposed as the most likely cause of the issue encountered. The hypothesis was based on a proven fact; the nucleation is a stochastic process. This random process could be leading to a heterogeneous batch, having a certain amount of product “suffering” conditions not prepared for.

This article intends to describe and quantify the success that a customer has experienced after implementing an induced nucleation process on an industrial freeze dryer (6 m² freeze dryer operating at a load of 13000 vials).

**Solution**

Telstar developed a recipe focusing the efforts on the step responsible for both the within-batch and the within product variability, the most important event in the freezing step, the nucleation. The Telstar vacuum induced nucleation, Lyonuc, was included in the parameters to be considered in the recipe development.

**Basic concepts**

Inducing the nucleation enables controlling the ice nucleation temperature which dictates the ice crystal morphology, size distribution and consequently the final properties of the freeze-dried product (1,2). Controlling nucleation at higher temperatures produces substantially larger ice crystals than stochastic nucleation (2). Larger ice crystals provide less resistance to water vapour flow during sublimation because they leave behind larger pores (3) reducing the internal pressure at sublimation front and preserving the cake structure at whole batch.

Controlled nucleation by Telstar, commercially named Lyonuc®, is based on vacuum induced nucleation. Vacuum promotes a decrease of the

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**Figure 1. Non controlled nucleation defect**

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liquid surface temperature by solvent evaporation, creating the first ice crystal (seeding) followed by the freezing phase.

It is important to remark, that this process is product dependant and requires an intensive study for every case to determine the required vacuum, stabilization time and other process parameters.

Results

The project was divided in two phases:

1) Laboratory proof of concept
2) Industrial validation

Laboratory testing

In order to design the best conditions of the nucleation process, several tests were performed in the Telstar laboratory. Batches ranging from 50 to 500 were tested and a recipe was developed in a laboratory, scalable to freeze-drying equipment.

The frozen product nucleated at high temperature obtaining larger ice crystals than in the spontaneous freeze-drying cycle. This resulted in a robust structure which allowed an easier output of water vapour at the sublimation front, without any collapse within the vials.

Industrial validation

Once the recipe was developed, the process set points are transferred to the industrial machine.

Currently, at the customer freeze drying unit, the whole batch is nucleated in less than three minutes offering a high homogeneous batch that is able to withstand the same conditions with no product loss at all.

In addition, due to the lower subcooling (higher freezing temperature), there was a 20% reduction of the total batch time for the same product and machine. The customer did not just increase efficiency due to the reduction of product loss but they were also able to shorten the cycles, increasing the availability of the production line.

Final added value

The added value can be divided into two categories:

1) Product quality assurance:
   - Absence of aesthetics cake “defects” (big shrinkage, half-collapsed bottom cake).
   - Batch homogeneity, ensuring that there are not differences within the bath and between batch to batch.

2) Production efficiency:
   - Optimised duration of the cycle to achieve the proper product results.
   - Absence of product loss increasing productivity.

Bibliography


Telstar Lyonuc

Lyonuc is a new vacuum induced nucleation method in the freeze-drying process suitable for any freeze-dryer without modifying its main components or adding external substances to the product that has been developed. Created by Telstar, this method reduces the duration of the primary drying cycle and ensures the homogenization of the batches of vials.

This method based on controlling the temperature and pressure to induce the first ice crystals generation at the freezing phase, also ensures the uniformity and homogenization of the vials in all the batches, respecting the product’s physiochemical properties.

About Telstar

Telstar, part of the azbil Group, is a company specialized in the development of engineering & construction projects, integrated process equipment and GMP consultancy solutions, including turnkey projects and critical installations, for companies associated with Life & Health Sciences (pharmaceutical & biotechnology, healthcare, cosmetic, veterinary and food & beverage industries, hospitals, laboratories & research centers). Acknowledged as one of the 10 major suppliers for the pharmaceutical industry, Telstar is one of the few international manufacturers able to offer integrated process solutions for the biopharmaceutical industry with in-house sterilization, freeze drying, containment, process water & waste treatment, clean air and cold storage technologies.