CASE STUDY

Non-invasive product temperature monitoring as a recipe design and scaling up tool

The impact of a Lyometrics PAT tool to monitor the temperature of product during primary drying to assist the final user in the design and scaling up of freeze-drying recipes

ABSTRACT

A new non-invasive monitoring technique enables measurement of product interface temperature during primary drying under developmental or full production conditions, collecting more accurate, complete and reliable information, rather than physical probes. The new development utilizes a soft sensor technology that provides on-line monitoring of the global batch temperature which serves as a useful tool to design a freeze drying recipe and to perform the scaling up. This case study shows the results after implementing a continuous monitoring of product interface temperature during the lyophilization process of a high valued formulation product.

Customer issue

The customer product is a very high value formulation, with substantial associated production costs. Therefore, a continuous monitoring of one of the critical parameters during lyophilization is required. There were two main factors leading the customer towards a non-invasive product temperature monitoring tool, minimizing the product loss and the process representativeness.

Solution

Telstar develops the freeze-drying recipe of this product at its process laboratory through the monitoring of the product temperature during sublimation using the non-invasive tool, Lyometrics. The same software tool can monitor the product thermal behaviour during the scaling up in the industrial freeze dryer, dramatically improving the industrialization of the freeze-drying process.

Concepts

Lyophilization process is a high added value drying process directly related with the conservation and the quality of the dried pharmaceutical and biological products, among others.

The main phases of this process are freezing, primary drying and secondary drying. The sublimation is the longest phase and achieves the solvent transformation from the solid phase to gas phase (without passing through liquid phase). The sublimation is a surface process which moves downwards, and it is usually the longest step of the freeze-drying process. The sublimation front is where phase changing is taking place, and therefore, the lowest product temperature during primary drying phase.

The product temperature at the sublimation front should never exceed the critical temperature of the product (eutectic or collapse temperature depending on whether the product is crystalline of amorphous). When this is guaranteed, a good drying and preservation of the product quality would be achieved. If this temperature is overcome, the product will be damaged and could lose its critical quality attributes (CQAs).

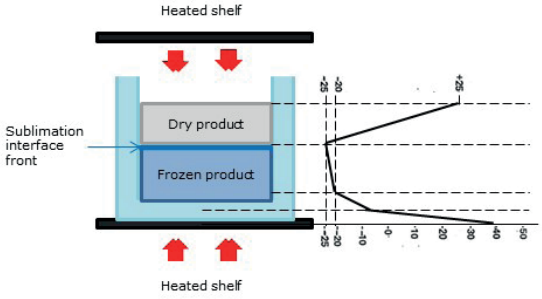
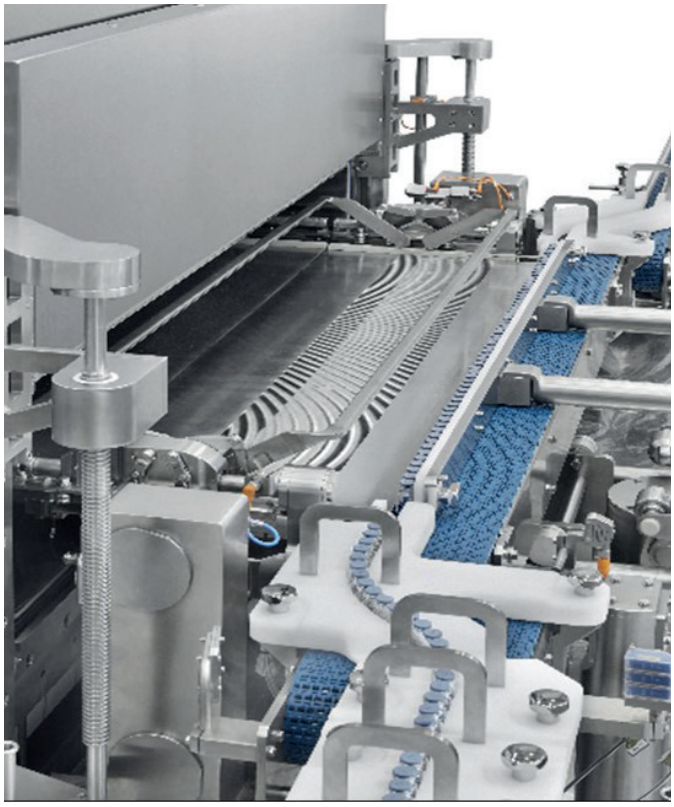


Figure 1. Product temperature profile during primary drying

Physical probes are not capable of monitoring and measuring the sublimation front temperature due to the downward movement. Physical probes cannot be moved inside the containers. In addition, they cannot be handled at the more frequently used automatic loading-unloading systems.



Lyometrics is a software sensor which can calculate this temperature through a small perturbation in the chamber's pressure. Throughout the use of physic-chemical calculations, the Lyometrics allows the final user to monitor the product's sublimation front temperature. It is fully compatible with automatic loading-unloading systems.

Results

Telstar has performed a differential scanning calorimetry (DSC) and a freeze- drying cryogenic microscope (FDM) in which the critical temperatures of the product results is -10ºC, so the product temperature at the sublimation front must not exceed this temperature.

The study has included up to six freeze drying cycles. The optimal critical process parameters (CPPs) of the freeze-drying process are defined in functions of the lyophilisation cycle duration and the following CQAs: final residual moisture, product aesthetics and reconstitution time.

Finally, the optimal freeze-drying cycle has been executed twice and the Lyometrics effect and results has been analysed. The product temperature is monitored by an internal thermocouple in one cycle, and the second cycle is monitored by an internal thermocouple and by the Lyometrics software.

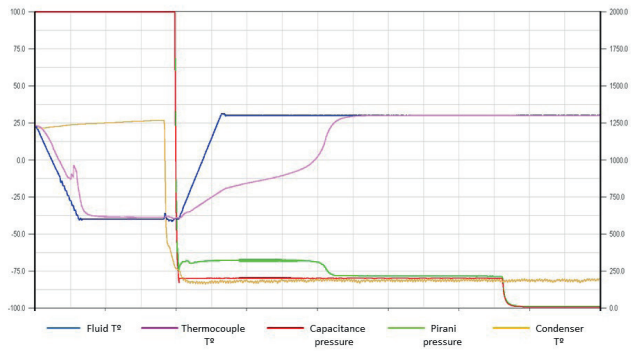


Figure 2. Freeze drying cycle monitored by a physical internal thermocouple

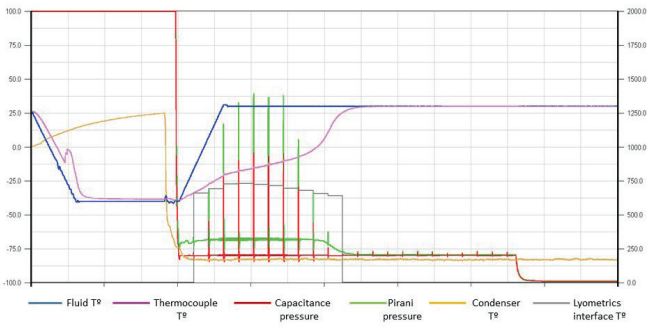


Figure 3. Freeze drying cycle monitored by a physical internal thermocouple and Lyometrics software

The obtained results have been the same in both cycles. The product temperature measurement throughout thermocouple is the same in both cycles, and higher than the calculated sublimation front temperature measured by Lyometrics (pink and grey trend lines Figure 2 and 3). The sublimation front temperature calculated by Lyometrics is lower than the critical product temperature of -10ºC, so the product is not degraded.

The minimum time to reach a full product sublimation has been the same in both cycles (comparative values between pirani and capacitive probes).

The Lyometrics is representative of the whole batch sublimation end, as well as the comparative probes tool. However, Lyometrics allows us to optimise the primary drying duration if there is only one pressure probe to control the process. Therefore, the extra time of primary drying step (blue mark in figure 3) is eliminated, and cycle duration optimized. This benefit can be used in any equipment size.

There are no differences in product aesthetic results (see figure 4), residual moisture and reconstitution times.

Figure 4. Product aesthetics. Standard freeze-drying cycle (top figure); Lyometrics freeze-drying cycle (bottom figure)

Final added value

The Lyometrics software offered three very well differentiated benefits in this case:

1)Recipe development

- Telstar's process laboratory has offered the possibility of developing the recipe with less product quantities. The investment to develop the freeze-drying recipe has been reduced to the minimum.
- Telstar proved the equivalence in between the product and process quality, using or not using the non-invasive temperature measurement tool, Lyometrics.
- The recipe development has been done without a physical sensor. Therefore, no product is lost during this process.

2)Recipe scaling up to industrial manufacturing

- No product loss for temperature monitoring
- Monitoring of product behaviour at the sublimation interface front.
- Minimizing product losses by adjusting the scaling up recipe. Possibility to adjust the CPPs in the industrial equipment looking for the sublimation front temperature (Lyometrics) equivalence with the laboratory study.
- The investment to develop the freeze-drying recipe scale up has been reduced to the minimum.
- Good adjustment of primary drying duration without any extra probe, just Lyometrics software.

3)Industrial production

- This tool could be also used during production to monitor and/or validate the thermal process that the product is withstanding in each batch.

The author

Maria Santafé Villarroya holds a MEng in Chemical Engineering from the "Universitat Autònoma de Barcelona (UAB)", Spain. After more than six years of studying Lyophilization technology as a Process Laboratory Engineer, she is now head of Process Laboratory at Telstar thus leading all customer projects in this field. In addition, and as part of the R&D team, she actively contributes with her expertise in all R&D process related projects. Her active involvement in the development area gave Telstar the opportunity to launch one of the most innovative methods to control the nucleation process into the market.

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.