Telstar Lyometrics

Lyophilization (freeze-drying) is a well known drying technology especially suitable for many pharmaceuticals mainly because of the very low temperatures involved in the process, making it almost the unique available alternative for the long term stabilization of heat sensitive products.

During a freeze-drying process, the initial liquid solution is first frozen, and then water, (as the most common solvent) is separated by exposing it to a very low solvent partial pressure in the drying chamber, promoting the direct sublimation of the ice to vapor and leaving a porous dry structure with an apparent volume equal than the original solution. After a well performed cycle, the product exhibits long term stability and, at the time of use, can be reconstituted with a very fast re-hydration

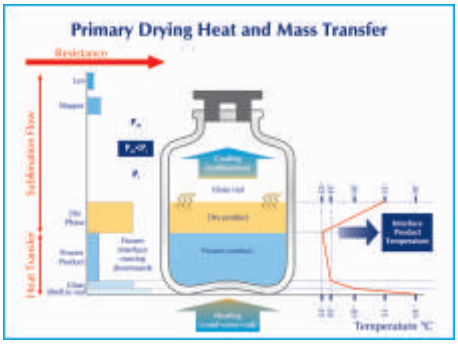
The drawbacks of this extremely gentle process are the high energy consumption and the long processing cycle time, due to the very low temperatures and low pressure involved. The ability of running this process under sterile conditions helps to make it also especially attractive to the Pharmaceutical Industry.

Process Challenges

The sublimation phase (primary drying) is the most risky stage of the process. In order to avoid the loss of morphology, that in turn would lead to loss of activity and difficulty of reconstitution, the primary drying must be performed maintaining the sublimation interface temperature below the formulation specific upper limit: the collapse temperature. But, from the other side, in order to minimize the duration of the process, the temperature should be maintained as high as possible.

.With the actual technology, it is impossible to obtain a direct measure of the parameters of interest –sublimation front interface temperature and sublimation mass flow- without interfering with the process dynamics or impairing the sterile conditions needed by some products.

An example of commonly used, but invasive, monitoring device is the insertion of a thin thermocouple or -a significantly more bulky- RTD inside the vial.



This method alters the elementary phenomena of nucleation and ice crystal growth, as well as the heat transfer to the product: as a consequence, the drying kinetics is faster in the monitored vial and the results are not representative of the whole system; nevertheless, this method is vastly used to monitor the primary drying and to detect the end-point of the primary drying stage. It is also impossible to place the temperature probe in a way that can monitor the ice temperature up to its complete disappearance, so it is common knowledge that "temperature probes only tell the truth during freezing, at the early phase of primary drying, and then one can trust them only during secondary drying", but, where the product is most at risk, its information can be totally non-meaningful.

Last, but not least, the probe insertion itself compromises the sterility of the product and it is also impossible to place them in a process with automatic loading and unloading.

QbD (Quality-by-Design): a change in mentality

In September 2004 the FDA released its Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.

This guidance was intended to describe a regulatory framework (Process Analytical Technology, PAT) that should encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance.

Citing the FDA: "the Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with the current drug quality system: quality cannot be tested into products; it should be built-in or should be by design".

This guidance can be understood as the trigger enabling the regulated pharmaceutical industries to embrace new technologies that can monitor the really process parameters of interest, that in turn will allow to manufacture better products increasing their quality, maximize the production and reduce the rejections.

Actual cycle definition

A set of steps defining the shelf temperature, chamber pressure and time are the independent parameters that nowadays define a lyophilization cycle, and it is not uncommon to read "that when these parameters are fixed, then the product temperature becomes also fixed". The main problem is the inability of predicting the product temperature because there are two main "resistances" in the kinetics of the drying process: the heat transfer resistance and the mass transfer resistance from the already dry phase.

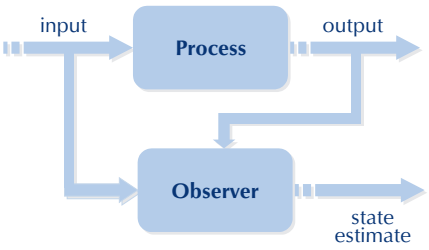
Heat transfer depends greatly on the different barriers between the product and the heat transfer shelf fluid. Pressure has a very important role in this heat transfer. Mass transfer depends basically of the morphology of the dry cake, so nucleation, product crystallinity, etc. are the key governing factors.

Additionally, these resistances are not constant along the primary drying, so

knowing which is the process limiting factor and when, is necessary to establish the optimum process parameters.

Lyometrics: the alternative

A non-invasive monitoring technique is proposed as a valuable alternative to the sensors previously mentioned. In many engineering applications it is desirable to have estimates of hard-to-measure or even non-measurable quantities. An observer combines a priori knowledge about the physical system (mathematical model) with experimental data (in-line measurements) to provide an in-line estimation of the sought quantities.

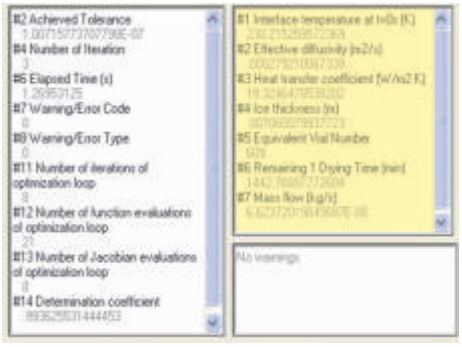


In this case the observer is the mechanistic model describing the heat and mass transfer both in the frozen phase and the already dry phase of a product being lyophilized.

The equations are transient state, so they are valid even if the process is not in steady state.

However, the parameters of these equations are not known, because they depend on the product properties and the specific conditions at which the process is run.

The way to overcome it is introducing a small perturbation in the process and acquiring the system response to this perturbation. The set of equations are then solved in order that can "reproduce" the system response.



The parameters found are the sought quantities: **sublimation interface temperature, mass transfer coefficient, heat transfer coefficient and sublimation mass flow.**

These parameters can be considered very robust explaining the process at this moment, but there is no guarantee of their accuracy after a certain time horizon. For this reason, this process is repeated in a timely manner along the whole primary drying step.

Lyometrics: the advantages

This system allows monitoring any production cycle. Its main advantages are:

- Detailed tracking of the whole primary drying process allow further improvements in order to maximize productivity without impairing product quality.
- Lyometrics provides also information of the completion of primary drying.
- The model is valid for both bulk and lyophilization in vials.
- Definition of the cycle design space coupling the product, its container and the lyophilizer capabilities extremely simplified.
- Lyometrics allows plant characterization, so scaling-up or simply transferring the production from one lyophilizer to another one, can be straight forward, helping to generate the documentation for full support of the transfer process.
- Much more robust process understanding has an inverse relationship with the risk of producing a poor quality product. Significantly less restrictive regulatory approaches and scrutiny can be expected.

Plant requirements

All Telstar Lyophilizers are already prepared to integrate as an option the Lyometrics. LyoSuite supervisory software is the perfect interface for parameters edition and variables recording:

- Sublimation interface temperature.
- Sublimation mass flow.
- Mass transfer coefficient.
- Heat transfer coefficient.

End of primary drying event.

Consult us for retrofitting this tool in an existing lyophilizer.

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