PhD program in Chemical Engineering XXXII cycle
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Abstract

Freeze-drying is a low temperature drying process, the most reliable technology for the stabilization of a liquid pharmaceutical formulations. The process consists of three steps: freezing, primary drying and secondary drying. During the first phase the product, in most cases a liquid solution containing the drug and some excipients, is poured into single dose containers and placed on the shelves of the equipment. A cold fluid, flowing into the shelves, is used to remove heat from the product and promote the conversion of the liquid solvent, usually water, into ice. When the product is completely frozen the pressure in the drying chamber is reduced below the triple point of water and heat is supplied to induce the sublimation of the ice crystals. Finally, the temperature is increased, to further reduce the residual moisture level, through the desorption of the liquid water bounded to the solid structure. In recent years, both the number of formulations that require a freeze-drying step and the requirements in terms of efficiency, quality and safety of the products have increased. To take the challenge, the right equipment and Process Analytical Technologies are required.

All the three steps of a freeze-drying process are characterized, from the physical point of view, by a heat transfer process intimately coupled with a mass transfer process. Thus, from the thermal evolution of the process, coupled with a mathematical model of the process, it is possible to infer all the parameters required for process monitoring, control and/or optimization. This idea has been proved and validated in many works presented in the Literature. The main limitation of the state-of-the-art technologies used for this purpose, thermocouples and thermistors, is the need to have their tip inserted inside the liquid solution. The introduction of an external object inside the solution has been proved to trigger the nucleation of the solution, thus resulting in drying kinetics not representative of those of the other samples of the batch. For this reason, infrared cameras, have being proposed in the past as an alternative technology able to overcome this problem.

In this Thesis an infrared (IR) imaging sensor for the real time monitoring of the freeze-drying process was designed and the pros and cons of this technology investigated in detail. Being based on an imaging technology, the sensor does not have to be in contact with the sample. Besides, the large quantity of data provided by the thermal images contains also a large amount of information that makes possible a wider range of applications. This work aims to deepen the potential benefits deriving from the application of an infrared camera to the monitoring of a vacuum freeze-drying process of pharmaceuticals and biopharmaceutical products in unit doses. Figure 1 graphically summarizes the contents of this Thesis.

At first, the many aspects that must be considered to properly design and implement the sensor and obtain reliable readouts are discussed. In fact, the

prototype was developed in order to be placed inside the drying chamber, despite of the harsh environmental conditions, and image pretreatment and analysis is a mandatory step in order to maximize the quality and quantity of information extracted.

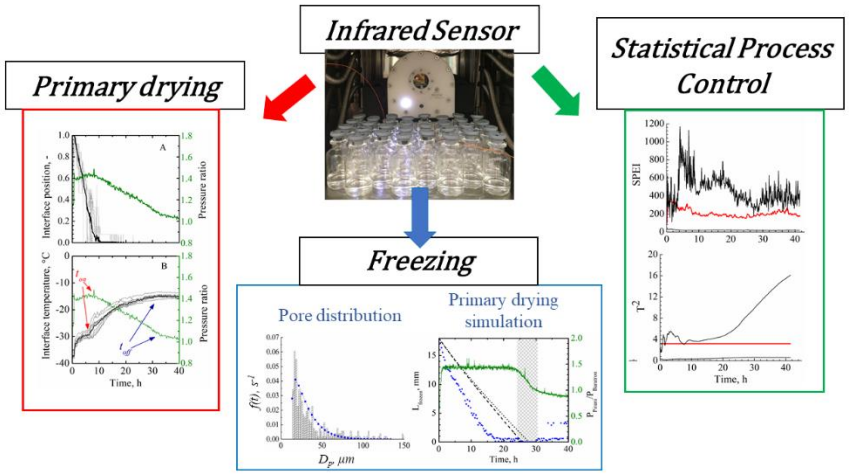

Figure1. Graphical abstract of the Thesis work.

The thermal images obtained during the primary drying phase can provide information on both the heat and mass transfer inside the vial allowing for its full description. Both the maximum temperature of the product, the residual amount of ice into each sample and identify the ending time of the process, despite of the heterogeneity of the system. Besides, both the heat and mass transfer coefficients of the mathematical model currently used for process optimization, control, scale-up and monitoring can be estimated.

When applied to the monitoring of the freezing step, the infrared technology can be used to characterize the thermal evolution of the product and infer the parameters required to infer the resulting crystals size distribution inside the frozen product. The prediction of the resulting crystals size distribution from the characterization of the thermal evolution of the process is usually performed using a mathematical model of the process. Thus, after proving the concept on some models already available in Literature, a new mathematical model for the estimation of the crystals size distribution was presented and validated. The proposed model provides a more physically grounded description of the process and provides additional and more accurate results. Besides, an analytical solution was derived, making it suitable for real time application.

Finally, two algorithms for multivariate statistical process control were derived, using both the features extracted from the thermal images and other variables obtained from other PAT or from the PLC of the equipment. The idea is to model a set of batches obtained under normal operating conditions and obtain a reference trajectory describing the evolution and variability of the process. Every incoming batch will be compared against this ideal *fingerprint* to check whether it is still under control or not. The possible applications of these techniques include: fault detection, process supervision and optimization, batch validation and quality assurance.