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NON INVASIVE TEMPERATURE MONITORING: CONTROLLED NUCLEATION AS A CASE STUDY

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Introduction

Freeze-drying is employed in pharmaceutical industry to preserve thermo-sensitive products. It is a cost intensive process and, for its optimisation, it is important to maximise the ice sublimation rate during primary drying, thus reducing cycle duration. At this purpose, it is fundamental to monitor the product temperature and keep it at a value lower than that at which melting or collapse occurs. The temperature monitoring is also important during the freezing stage as it influences the two subsequent drying stages. In particular, the temperature of ice nucleation determines the size of ice crystals and the morphology of the frozen cake, thus impacting on the final properties of the product.[(1)] Moreover, as the nucleation of ice is a stochastic event and it is not certain that all the vials in the batch nucleate at the same temperature (allowing a non-homogeneous product structure and subsequent drying behaviour), several techniques have been proposed for inducing the nucleation at a certain temperature and time and make the process more cost efficient.[(2)]

The classical way to measure temperature in a freeze drying apparatus is by inserting miniature thermocouples (TCs) inside the solution to be frozen. However, this technique is not suitable for temperature monitoring as it results invasive and not representative for the entire volume of solution. In fact, miniature thermocouples act as preferential sites of nucleation, modifying the behaviour of the monitored vial during drying; furthermore, it can measure temperature in just a single point. To cover this gap in the research an innovative temperature sensor based on thin film technology is here presented.[(3,4,5)] This device was designed as an array of external thin film thermocouples able to perform non-invasive temperature measurements at different levels of the product. Both these characteristics are useful to better understand the nucleation event. In this paper thin film thermocouples were used to monitor the product temperature when the Vacuum Induced Nucleation method was used to control ice nucleation. The impact of this method on drying time and product structure was also shown.

Materials and methods

Vacuum Induced Nucleation method

The method for the control of nucleation here investigated is the Vacuum Induced Nucleation.[(6)] This method induces the freezing at the top of the product by a perturbation connected to a pressure decrease/ increase in the vacuum chamber. The original Vacuum Induced Nucleation[(6,7)] has been modified in order to avoid its typical problems (i.e., blow up and flake formation), and was proven to give high quality of the final product, cycle reduction and batch homogeneity. This method was here used to induce the nucleation at different temperatures of the product, while the final product structure obtained was analysed by means of a Scanning Electron Microscope (SEM).

Non-invasive temperature monitoring

The TC array was realised by depositing thin copper and constantan strips (T-type) on the external wall of the vial in a DC plasma sputtering reactor. The strips are 1-mm wide, while the vertical array of measuring junctions permits a mapping of the temperature (see Figure 1). The thickness of the metallic film is lower than 100 nm, so that the thermal distribution is not altered by the presence of the sensors. In Figure 1 an image of the TC array and of the measurement setup is shown. For the acquisition of cold junction resistance (Pt100) and of the thermocouple voltages a HP34970 DMM/scanner (connected to a PC via a GPIB bus) is used.

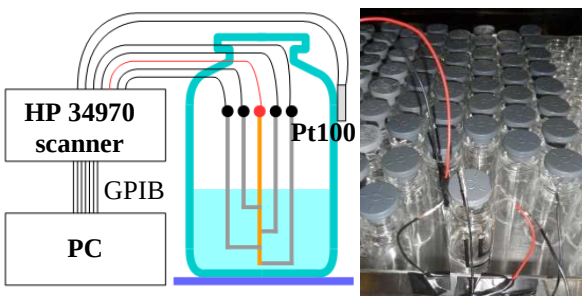

Figure 1: Scheme of the experimental measurement setup, where TC array is connected to the HP34970 scanner (left), and image of the vial with the TC array (right) are shown.

Experimental results

The case study here investigated regards a placebo solution of 1% mannitol and 4% dextrane freeze dried inside a freeze dryer of type LyoBeta 25 (Telstar, Terrassa, Spain) with freezing at –50 °C for 3 h for spontaneous nucleation, and by using the Vacuum Induced Nucleation method.[7] For both cycles, primary drying stage was carried out at 10 Pa and −18°C and secondary drying at 5 Pa and +20°C. As a first step thin film TC was compared with conventional thermocouples. It was found a fairly good agreement between the two types of thermocouples, in fact, the difference between the two temperatures was approximately 1.5°C, which was of the same order of magnitude of the sensor uncertainty. In Figure 2, the film thermocouples were used to monitor the temperature of the product (at various levels) when Vacuum Induced Nucleation was used to induce ice nucleation.

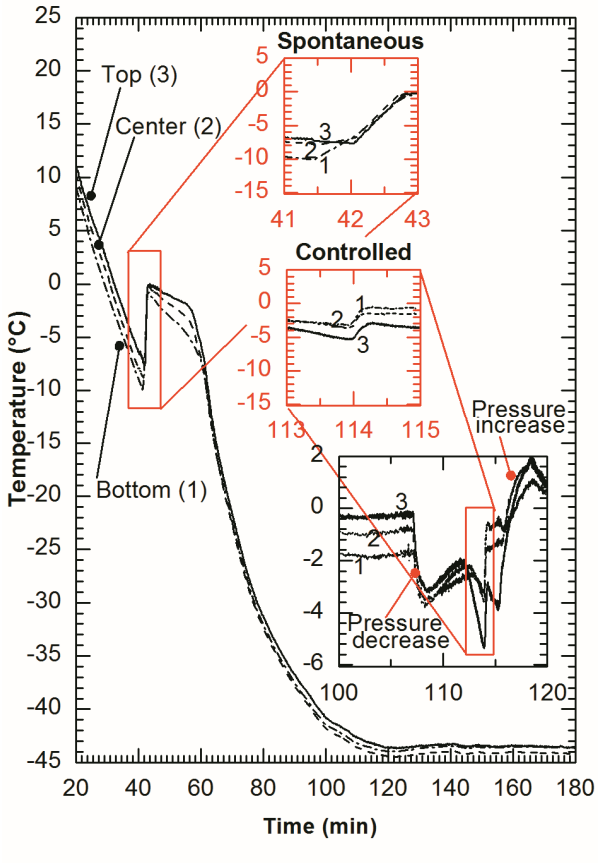

Figure 2: Evolution of temperature as measured through thin film thermocouples at various positions on the external wall of the vial. The evolution of the product temperature is shown in the case of spontaneous nucleation and controlled nucleation of 1% mannitol and 4% dextrane solution.

It can be observed that the nucleation event started from the top of the product and went down at bottom within 1 s; this behaviour was in contrast to what observed for the spontaneous nucleation where the freezing front moves from the bottom towards the top. This device was also able to detect the influence of the pressure decrease (during freezing) on the product temperature. In fact, decrease/increase of product temperature was observed in correspondence of decrease/increase of pressure in the vacuum chamber. This investigation was extended to different product temperatures and filling volumes. Also such tests were carried out with the help of the thin film thermocouples. The temperature of nucleation was found to have a dramatic impact on both drying time and product structure. As concerns product structure, high temperature of nucleation promotes the formation of a thin layer of ice at the top of the product, which resulted in a compact porous structure at the product top and in a dendritic one in the middle and bottom part of the cake (see Figure 3). On the contrary a uniform structure was observed when the nucleation was induced at -3/-10°C. Similarly we have observed that if the filling volume is small the dried structure was uniform, while for higher fill volume intra-vial heterogeneity was observed.

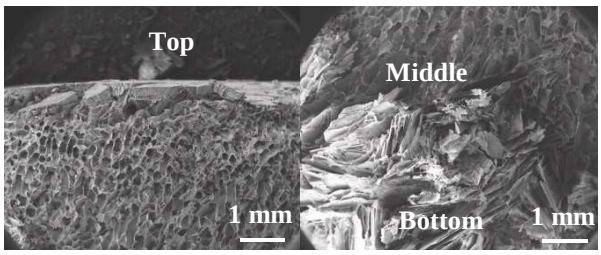

Figure 3: SEM image of a mannitol 5% solution freeze dried with control during freezing (temperature of nucleation of the product equal to -3°C and high fill volume).

Conclusions and future developments

In this study the effectiveness of the thin film technology for real-time and non-invasive monitoring of the nucleation event has been shown with success. A further improvement of this technology is the possibility to use a wireless thin film thermocouple array. This device presents advantageous prospects in the case of monitoring temperature of the product for the industrial scale freeze dryers.[8]

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