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Original
Intensification of the freeze drying process by the control of both freezing and primary drying steps / Oddone, I., Pisano, R., Barresi, A., Bullich, R.. - ELETTRONICO. - (2013). (EuroDrying 2013 Parigi October 2-4, 2013).

Availability:
This version is available at: 11583/2517541 since:

Publisher:
G. Almeida, F. Pierre, P. Lv and P. Perré, Eds.

Published
DOI:

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27 November 2026

Intensification of the freeze drying process by the control of both freezing and primary drying steps

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ABSTRACT. *The problem of optimization of freeze-drying cycles is addressed, with emphasis in both freezing and primary drying steps. In particular, this study shows that the control of the nucleation event produces more uniform batches (as ice nucleation is induced in all the vials of batch almost at the same time and temperature) and allows a marked reduction in the duration of the optimized cycle (if compared to cycles carried out with conventional stochastic nucleation).*

KEYWORDS: Freeze-Drying, Freezing, Primary Drying, Process intensification.

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1 Introduction

In pharmaceutical industry, freeze-drying is often used to transform instable liquid formulations into stable solid products under sterile conditions. As this transformation is carried out at low temperature and pressure, its energy consumption is very high. In the past, pharmaceutical companies paid little attention to this consumption, as it was justified by the high value of the end-to-use products. In these years, however, many drugs come off patent protection and thus branded manufactures have to face with a more competitive market. In this scenario, many companies strive to enhance their production in terms of increase in the production capacity within a given equipment volume, decrease in the energy consumption, reduction in wasted energy and in costs associated with waste product. In freeze-drying, all these objectives can be achieved if the drying time is reduced and the product temperature is accurately controlled. For this purpose, both the freezing and the drying processing steps have to be considered (Elia and Barresi, 1998).

Freezing is a crucial process step because it can modify product characteristics and improve process efficiency. In particular, various authors showed that control of the nucleation event can provide process benefits (Kasper and Friess, 2011). The earliest methods proposed were the electrofreezing (Rau 1951) and ultrasound technique (Inada *et al*., 2001; Zhang *et al*., 2001; Saclier *et al*., 2010; Nakagawa *et al*., 2006). However the additional equipment required by these two techniques is expensive and diminishes its applicability in manufacturing. Another technique is the depressurization method (Rampersad *et al*., 2010), which involves pressurization and subsequent depressurization inside the chamber to induce the nucleation. A limitation of this method is that it requires the modification of pre-existing freeze-dryers in order to support pressure higher than the atmospheric value. Rambhatla *et al.* (2004) describe the ice fog technique in which a flow of cold nitrogen is released and a suspension of small ice particles (ice fog) is generated due to the high humidity inside the chamber; the penetration of the ice fog into the vials induces the ice nucleation. The scale-up of this method is still under investigation, as it is not said that in industrial apparatus the whole batch of vials is reached by the ice particles.

In this study the vacuum induced nucleation described by Kramer *et al*. (2002) was investigated. In this method during freezing the pressure inside the drying chamber is reduced for a short time. This pressure reduction produces the partial evaporation of water, which causes the reduction of the surface temperature and in turns promotes the formation of a thin layer of ice on the top surface of the product. This method allows a precise control of the ice nucleation temperature for a batch of vials without requiring the installation of additional devices in the freeze-dryer.

As the vacuum-induced method produced defects in the cake structure due to boiling of the solution and blow up of the frozen product, a refined control technique has been investigated. The aim of this paper is to show the advantages in utilizing this method in terms of reduction in cycle time and elegance of the final product. In order to compare this method with conventional freezing, the temperature of the heat transfer fluid during drying was optimized by a model-based controller named *LyoDriver* (Fissore *et al*., 2009; Pisano *et al*., 2010, Pisano *et al.*, 2013), which maximizes the drying rate while the product temperature is maintained below its limit value. This controller coupled with the "vacuum-induced" method contributes to minimize the duration of the primary drying

step, thus having a further reduction in cycle time thanks to the optimization of both freezing and primary drying stages.

2 Materials and Methods

2.1 Materials and Instrumentation

The case study here investigated is the freeze-drying of placebo solutions, which are constituted by 5% and 10% w/w mannitol (Fagron, Terrassa, Spain) in deionized water (Wesel, Quimica Egara, Terrassa, Spain). The solution is processed in a pilot-scale freeze-dryer (LyoBeta 15 by Telstar, Spain) using a batch of 70 tubing vials (ISO 80426 6R) filled with 3 ml of solution and rubber stoppers (type 1319 4432/50/Westar, West Pharmaceutical Services, Terrassa, Spain), which is loaded directly on the shelf. The product temperature at the interface of sublimation (T_i) and the mass transfer resistance to the vapour flow through the dried layer (R_p) are estimated using the pressure rise test technique coupled with the modified Dynamic Parameters Estimation (DPE+) algorithm (Fissore *et al*., 2011). The R_p values estimated by DPE+ were analysed also taking into account the product structure observed by Scanning Electron Microscope analysis. Finally, the freeze-drying cycles are designed in-line using the *LyoDriver* control system. The duration of primary drying is estimated using the pressure ratio between Pirani and Baratron sensors (Barresi *et al*., 2009).

2.2 Methods

2.2.1 Freezing

The method for the control of nucleation consists in placing the vials onto pre-cooled shelves (+5°C) of the freeze dryer, and reducing the pressure. The pressure decrease depends on the formulation and solid concentration used. In this study, the vacuum is maintained for 1 min instead of 5 min utilized by Kramer technique. In order to prevent water loss because of boiling and inhibit melting of the ice film on the surface, the chamber pressure is released to atmospheric pressure as fast as possible, and the shelf temperature is simultaneously decreased to 3–4ºC below the eutectic melting temperature of the formulation. The shelf temperature is held for 1 h, and the shelf temperature is subsequently decreased to -45ºC to complete the freezing of the product. The control of pre-cooled shelf temperature and duration of the vacuum is fundamental to avoid aesthetic problems, which are detrimental for the elegance of the final product. For runs conducted with spontaneous nucleation, the temperature of the heat transfer fluid was held at -22°C for 3 hours , decreased to -45°C and held at this temperature for 1 hour.

2.2.2 Primary drying

The primary drying stage was optimized in-line using *LyoDriver*. This controller uses a mathematical model of the process to calculate the temperature of the heat transfer fluid that maintains product temperature close to the maximum allowable value, thus minimizing the duration of primary drying, and avoiding any temperature overshoot. This controller needs some input parameters, which are the maximum allowable fluid temperature ($T_{f,\max}$), set to 0°C, and the maximum product temperature ($T_{p,\max}$), which is

the collapse temperature lowered by a safety margin. DPE+ was used to monitor the process and estimate the input parameters required by the control system.

3 Results and discussion

Preliminary results showed that the refined method for the control of nucleation utilised here (see Fig. 1a) can effectively promote a more uniform drying behaviour, as all the vials of the batch are forced to nucleate within narrow temperature and time ranges. During the pressure decrease, the ice-nucleation is induced and a 1-3 mm thick-layer of ice was formed on the top surface of the sample (see Fig. 1b). After the induction of the ice-nucleation, the temperature of the heat transfer fluid was lowered and held at -10°C for 30 min in order to promote the production of larger ice crystals. As the ice nucleation was induced within 20 s for both formulations used and the vials are held at the same temperature before to pull down the pressure, it is possible to hypothesize uniform nucleation temperature for the batch, thus promoting a high uniformity of the freezing for the whole batch. This uniformity is fundamental to obtain a uniform behaviour during primary drying as well as to reduce the variance in residual moisture during secondary drying.

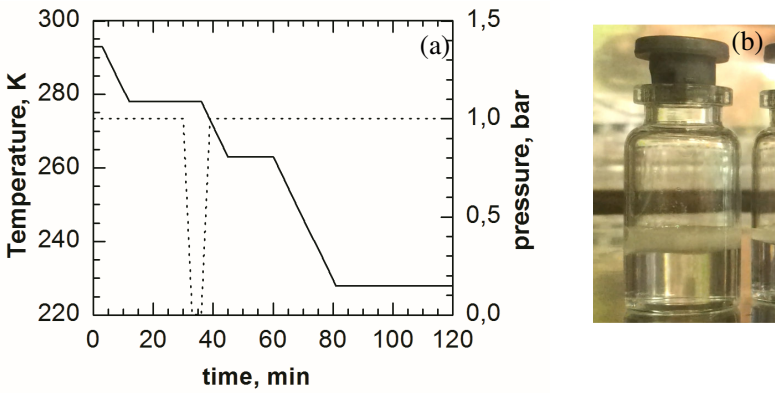


Fig. 1.(a) Evolution of pressure (--) and temperature (—) when the "vacuum-induced" method in used. (b) Picture of the vial after 10 s at 1.3 mbar during freezing.

Fig. 2 compares freeze-dried samples obtained using the "vacuum-induced" method as described by Kramer *et al.* (2002) and the method here proposed. The elegance of the final product was improved and the aesthetic problems, such as blow up of the frozen layer formed and flakes formation on the surface of samples, were avoided. In fact, when chamber pressure was decreased, we found that the thick-layer of ice on the top surface of the sample did not blow up nor stain the vial walls.

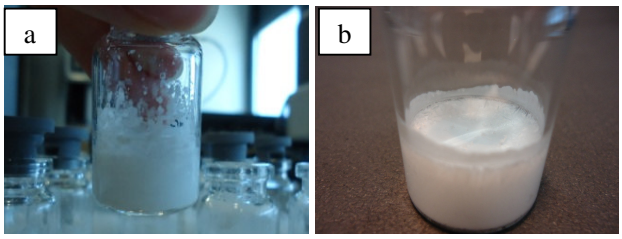


Fig. 2. Freeze drying product of mannitol 5% when forced nucleation is used: (a) Kramer method, (b) the "vacuum-induced" method as modified in this study.

Fig. 3 shows the trends of $T_{f,\max}$, T_i, $T_{p,\max}$ and pressure ratio for a cycle of 5% mannitol in case of spontaneous nucleation (left graph) and forced nucleation (right graph). As previously mentioned, the temperature of the heat transfer fluid was adjusted by using a model-based controller which maximizes the drying rate while the product temperature is maintained below its limit value. For the cycles presented, the limit temperature ($T_{p,\max}$) was set to -27°C. As can be seen from Fig. 3 freezing conditions impacted on the structure of the dried product resulting in different values for R_p vs L_{dried}. As a consequence, different cycles were obtained in terms of $T_{f,\max}$ and drying time, with the highest sublimation rate for the "vacuum induced" freezing.
In particular Fig. 4 shows that the reduction in drying time in case of controlled nucleation was 40% shorter with respect to the cycle conducted with spontaneous nucleation. A similar result was also observed for the freeze drying of mannitol 10 % (cycle graphs not shown). In Fig. 3 it is also possible to observe that the maximum product temperature was not overcome during the two cycles, in fact T_i (estimated by DPE+ algorithm) was always about 2-3°C below $T_{p,\max}$. Furthermore, *LyoDriver* takes into account the product temperature rise during the PRT when calculating the control actions. This explains why the steady-state value for the product temperature was lower than the target value. However, this temperature off-set was useful as it led to a robust cycle.

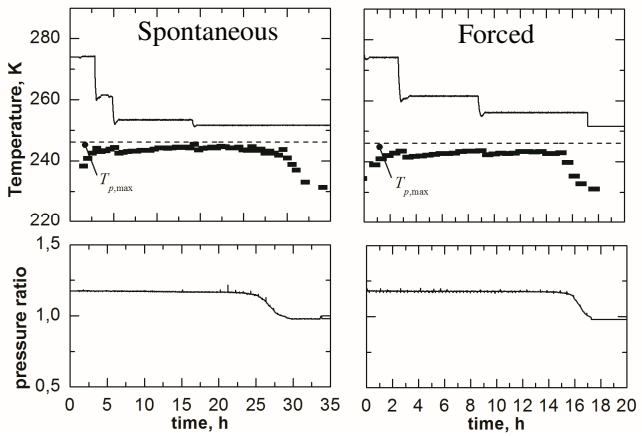


Fig. 3. Freeze-drying cycles for mannitol 5% in case of (left-graph) spontaneous nucleation and (right-graph) forced nucleation.(Top-graph) the evolution is shown for (—) the temperature of the heat transfer fluid and (■) the product temperature. (Bottom-graph) The evolution of the pressure ratio between Pirani and Baratron was also shown.

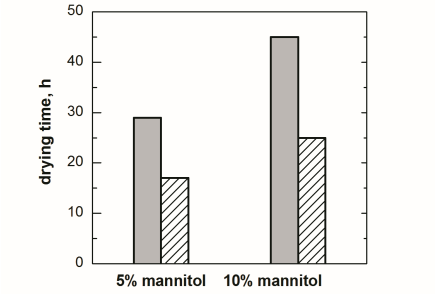


Fig. 4. Comparison between the drying time for 5% and 10% mannitol solutions when (□) spontaneous nucleation and (◪) forced nucleation are used.

The impact of the forced nucleation on the product structure was also investigated. As can be seen in Fig. 5c, the forced nucleation produced freeze-dried products with a more open structure than those observed for samples produced by spontaneous nucleation (Fig. 5b). In particular the release of vacuum and the reduction in the shelf temperature (see Fig. 1) promoted the growth of dendritic ice crystals, resulting in the formation of long, chimney-like and extremely large ice crystals. This structure modification impacted on the product resistance to vapour flow. Low values of R_p indicate high porosity of the material and high values for the sublimation mass flow and *vice-versa*. Fig. 5a confirms that forced nucleation significantly reduces the mass transfer resistance and thus allows the cycle to be carried out at the highest sublimation rate. By contrast the spontaneous nucleation produces a more compact structure, which is characterized by a markedly higher resistance to mass transfer. According to these results we found a dramatic reduction in drying time as previously shown in Fig. 3.

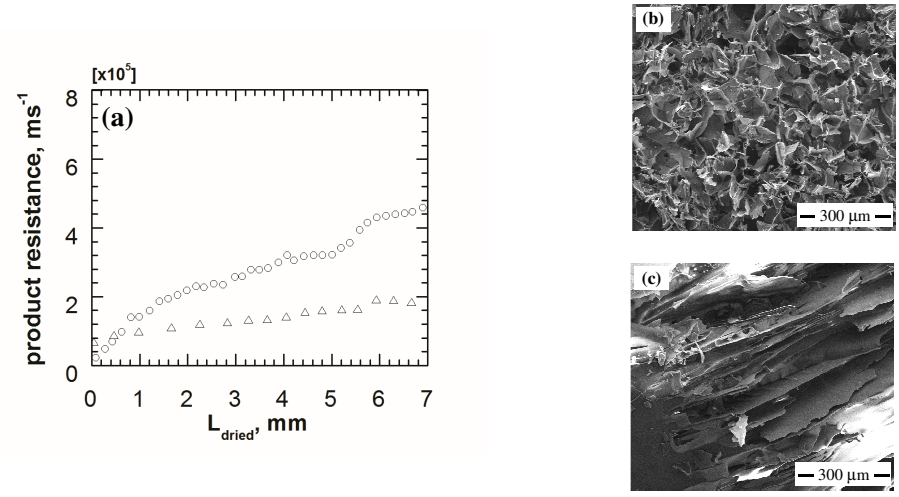


Fig. 5. (a) Product resistance to vapour flow for mannitol 5% in case of (○) spontaneous nucleation and (△) forced nucleation. Scanning Electron Microscope pictures of freeze-dried mannitol (metallized samples) in case of (b) spontaneous nucleation and (c) forced nucleation.

For the cycles conducted with controlled nucleation, we observed more uniform batches with respect to the cycle conducted with spontaneous nucleation. In fact, if we use the time between the onset and offset of the pressure ratio curve as indication of the batch uniformity, it can be noted that vacuum-induced nucleation gave a shorter time, i. e., a more uniform batch with respect the run carried out using conventional freezing, 1.5 h vs 4 h. Similar result were found for the mannitol 10% solution.

4 Conclusions

This study showed that the optimization of the freeze-drying cycle has to involve the control of both freezing and primary drying. In particular, it has been demonstrated that the control of the nucleation event not only produces more uniform batches, as confirmed by on-set and off-set time, but also allows a dramatic reduction in the drying time. Moreover, the controlled nucleation method used in this study does not produce problems on the cake structure of the product, which are usually observed when the vacuum-induced nucleation is carried using the conditions suggested by Kramer *et al*.

NOTATION

R_p	resistance of the dried layer to vapour flow	m s^{-1}
$T_{f,\max}$	maximum temperature of the heating fluid	K
T_i	product temperature at the sublimation interface	K
$T_{p,\max}$	limit product temperature	K

Abbreviation

DPE+	Dynamic Parameters Estimation
PRT	Pressure Rise Test

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