INTRODUCTION

Freeze-drying is a method of drying that is widely used for pharmaceutical formulations because of the low operating temperatures that allow preserving product quality. Nevertheless, each formulation is characterized by a limit temperature ($T_{\text{max}}$) that should not be trespassed during processing, and that is equal to the eutectic temperature in case of solutes that crystallize during freezing, or to the glass transition temperature when the frozen product is amorphous. In the first case the goal is to avoid melting of the product, and subsequent boiling, while in the second case the goal is to avoid the collapse of the dried cake. Thus, the values of the temperature of the heating fluid ($T_{\text{fluid}}$) and of the pressure in the drying chamber ($P_c$) have to be carefully designed in order to preserve product quality during manufacturing, and to avoid testing of final product quality, as recommended in the Guidance for Industry PAT (Process Analytical Technology) issued by US-FDA in 2004.

Various methods can be used to design in-line the freeze-drying recipe, namely:

i) expert systems, like the SMART™ Freeze-Dryer (Tang et al., 2005);

ii) control systems, like LyoDriver (Fissore et al., 2009; Pisano et al., 2010) or Model Predictive Control (MPC) algorithms (Daraoui et al., 2010; Pisano et al., 2011), that allow optimizing in-line the process.

Both the expert systems and the control systems require a device to monitor the state of the product.

As an alternative, it is possible to optimize off-line the recipe using a mathematical model of the process to build the Design Space of the formulation (Giordano et al., 2011; Fissore et al., 2011). To this purpose it is necessary a preliminary investigation to determine model parameters.

The goal of this paper is to compare the results that can be obtained when optimizing a recipe in-line, using a MPC system, and off-line, using the Design Space of the formulation.

MATERIALS AND METHODS

The case study that will be investigated is the freeze-drying of a placebo, constituted by a 5% w/w sucrose (or a 5% w/w mannitol) aqueous solution, processed in a pilot-scale freeze-dryer (LyoBeta 25 by Telstar, Spain) using ISO 8362-1 2R tubing vials filled with 1.5 ml of solution. Product temperature at the bottom of the vial is measured using T-type miniature thermocouples (by Tersid S.p.A., Milano, Italy). Product temperature at the interface of sublimation and the residual ice content are estimated using the pressure rise test (the valve placed in the duct connecting the drying chamber to the condenser is closed for a short time interval, causing chamber pressure increase) and DPE algorithm (Velardi et al., 2008). The end of primary drying is estimated using the ratio of Pirani and Baratron sensors (Barresi et al., 2009).

The dynamics of the product has been simulated using the simplified model of Velardi and Barresi (2008). The heat flux from the shelf to the product is described by the following equation:
\[ J_q = K_v (T_{\text{fluid}} - T_B) \]  

(1) 

where \( T_B \) is the temperature of the product at the bottom of the vial, and \( K_v \) is an overall heat transfer coefficient that takes into account the various mechanisms of heat transfer to the product and, thus, it can be used to take into account batch non-uniformity by grouping the vials into families characterized by a specific value of \( K_v \). The solvent flux from the interface of sublimation to the drying chamber is calculated using the following equation:

\[ J_w = \left( P_{w,c} - P_{w,c} \right) / R_p \]  

(2) 

The design space (DS) has been calculated using the method proposed by Fissore et al. (2011). Details about the methods used to determine \( K_v \) and \( R_p \) can be found in Giordano et al. (2011). With this approach it is possible to build a design space for each group of vials, thus identifying the optimal operating conditions for the whole batch. A contour plot, which displays isolines of \( J_w \) vs. operating conditions as calculated close to the end of the primary drying, can be used to select the optimal combination of \( T_{\text{fluid}} \) and \( P_c \) that maximizes \( J_w \).

The in-line optimization was carried out using a MPC algorithm (Pisano et al., 2011). We considered two configurations:

- **MPC1**: only \( T_{\text{fluid}} \) is manipulated, with the goal of minimizing the difference between product temperature and \( T_{\text{max}} \). The value of chamber pressure is here selected according to results obtained by off-line optimization.

- **MPC2**: both \( T_{\text{fluid}} \) and \( P_c \) are manipulated with the goal of minimizing the duration of primary drying (i.e. maximizing the sublimation flux). Various constraints (e.g. \( T_{\text{max}} \) and heating and cooling rates) were handled using penalty functions. The Internal Model Control strategy (Garcia and Morari, 1985) was used to take into account modeling errors. The pressure rise test coupled with DPE algorithm was used as sensing device and, thus, the average batch behavior is monitored (not taking into account for batch non-uniformity).

**RESULTS AND DISCUSSION**

Once the design space is built for the selected product (see Figure 1, where the case of sucrose solution is shown), operating conditions that provides assurance of quality can be easily identified. In particular, to determine the optimal combination of \( T_{\text{fluid}} \) and \( P_c \) that maximizes the sublimation flux, we used the contour plot of \( J_w \) calculated close to the end of the drying. According to Figure 1 a good combination of \( T_{\text{fluid}} \) and \( P_c \) which preserves product quality and maximizes \( J_w \), is \( T_{\text{fluid}} = 266 \) K and \( P_c = 5 \) Pa. A cycle was carried out with the constant values of \( T_{\text{fluid}} \) and \( P_c \) selected from the optimization procedure: the drying time resulted to be about 21 h.

Figure 2 shows the results obtained when using MPC1 and MPC2 algorithms to optimize in-line the recipe in case the 5% sucrose solution is freeze-dried. In both cases product temperature remains below \( T_{\text{max}} \) throughout primary drying, and a remarkable reduction of the drying time is obtained when optimizing both \( T_{\text{fluid}} \) and \( P_c \) (from about 20 h to about 15 h).

![Fig. 1. Design space for a sucrose solution (5% w/w). The dashed line identifies the limit operating conditions nearby the endpoint of the drying, while the symbol (■) corresponds to \( T_{\text{fluid}} = 266 \) K and \( P_c = 5 \) Pa. Isoflux curves (in kg h\(^{-1}\)m\(^{-2}\)) are shown.](image1)

![Fig. 2. Evolution of \( P_c \) (A), \( T_{\text{fluid}} \) (B) and \( T_B \) (C; solid lines: thermocouple measurements; symbols: DPE estimations; dashed line: \( T_{\text{max}} \)) when using MPC1 (l.h.s.) and MPC2 (r.h.s.) algorithms to design the freeze-drying recipe of the 5% sucrose solution. The vertical line evidences the end of the primary drying phase.](image2)
This comparison evidences that both MPC and DS are effective to maintain product temperature below $T_{\text{max}}$. Beside, MPC1 and DS give almost the same performance, and a significant reduction of drying time can be achieved only with the in-line optimization of $P_c$. Similar results were obtained when processing a 5% mannitol solution (Figure 3).

![Fig. 3. Comparison between drying time for the 5% sucrose and 5% mannitol solutions when the Design Space ( ) and the MPC algorithms (MPC1 ; MPC2 ) are used to design the recipe.](image)

**CONCLUSIONS**

The effectiveness of various model-based strategies to optimize a freeze-drying process has been demonstrated by means of experimental investigations. When using MPC system it is possible to get the optimal recipe in just one run, but an effective monitoring system is required. Moreover, potential disturbances affecting the dynamics of the process can be rejected. The DS provides much more information about the effect of the operating conditions ($T_{\text{fluid}}$ and $P_c$) on the product, but the recipe optimization can be less effective than that achieved using the MPC algorithm. Both approaches can be used both in small-scale and in large-scale freeze-dryers, thus avoiding the necessity to scale-up of the recipe.

**NOMENCLATURE**

- $J_q$: heat flux W m$^{-2}$
- $J_w$: sublimation flux kg s$^{-1}$m$^{-2}$
- $K_v$: heat transfer coefficient W m$^{-2}$K$^{-1}$
- $P_c$: drying chamber pressure Pa
- $P_{w,c}$: partial pressure of water in the drying chamber Pa
- $P_{w,i}$: partial pressure of water at the sublimation interface Pa
- $R_p$: resistance of the dried layer to vapor flow m s$^{-1}$
- $T_{B}$: product temperature at the vial bottom K
- $T_{\text{fluid}}$: temperature of the heating fluid K
- $T_{\text{max}}$: limit product temperature K

**REFERENCES**


