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Model based-monitoring of a non-uniform batch in a freeze-drying process

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Abstract

This paper deals with the freeze-drying of pharmaceuticals in vials and assesses the importance of model-based monitoring of the process; in fact, the vials in the chamber of the freeze-drier can exhibit different behaviors due to radiation effects and fluid-dynamics as it has been evidenced by CFD simulations. The curves obtained by traditional Pressure Rise Test (PRT) provide mean values of the parameters of the batch and thus can be misleading. To this purpose a new monitoring tool is proposed.

Keywords: freeze-drying, monitoring, Pressure Rise Test, CFD.

1. Introduction

Freeze-drying is the process where water or another solvent is removed from a frozen product by sublimation, operating under low pressure, thus leaving a porous matrix of the dried material (primary drying). The residual moisture is then reduced to a lower level (secondary drying), thus ensuring long term product preservation at room temperature. The vapour originated at the interface of sublimation flows through the dried material, goes into the lyophilization chamber and is removed by a condenser connected to the chamber; a heated shelf supplies the heat required by the sublimation. This work is focused on the primary drying phase of the lyophilization process as this is generally the longest and the most risky step of the whole process.

Poor process control is a limitation of the current technology as the parameters of interest, namely product temperature and residual water content, cannot be measured in-line. According to PAT (Process Analytical Technology) guidelines of the FDA, issued in 2004, there is the need to develop in-line tools allowing for monitoring and control. PAT is considered to be a system for designing, analyzing and controlling the manufacturing process through timely measurements (i.e., during processing) with the goal of ensuring the final product quality. It is thus necessary to design non-invasive sensors able to estimate those parameters that are not directly measurable (interface position, heat and mass transfer coefficients, product temperature), thus allowing for a tighter control of the process and for a reduction of the variance between the samples in the same batch and between different production lots. Three variables should be monitored:

1. the frozen product temperature, that has to be maintained below the collapse (or the melting) temperature to avoid the loose of the macroscopic structure, with irreversible damages of the product;
2. the sublimation mass flow, which has to be maximized in order to minimize the time required to complete the cycle;
3. the position of the sublimating interface, the evolution of which gives the state of progression of the primary drying.

With classical monitoring tools (e.g. thermocouples) these variables cannot be monitored; moreover, the insertion of a thermocouple in a vial is invasive and can alter

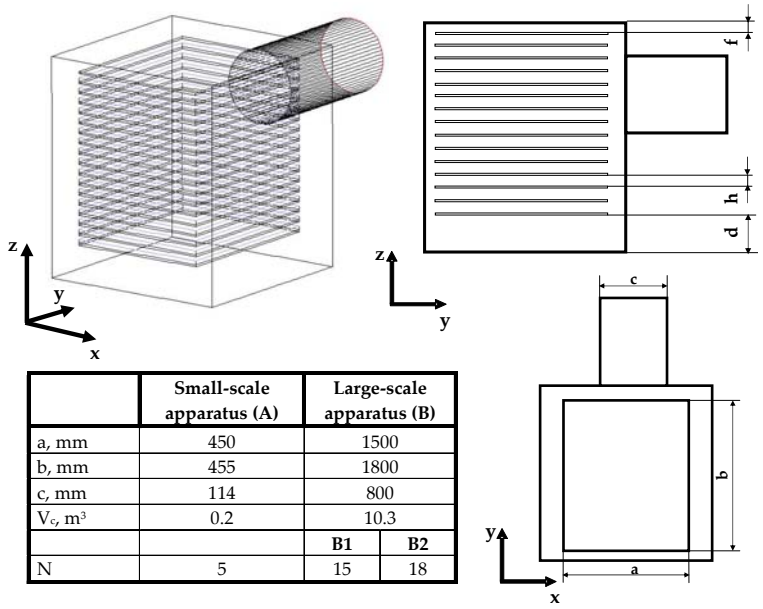
the physical structure of the product. Non-invasive monitoring techniques have been recently proposed, most of them based on the measure of the pressure rise generated by closing the valve placed between the drying chamber and the condenser for a short time interval, typically up to 30 seconds: chamber pressure values are collected during the test and related to the temperature of the product by means of a mathematical model (see for example the Manometric Temperature Measurement by Milton et al., 1997). Performing some tests throughout all the primary drying phase it is possible to monitor the evolution of the product temperature and of the other variables of interest.

These methods generally give quite reliable estimations up to about 2/3 of the time required to complete the primary drying but can fail (or give inaccurate results) toward the end of this step. Moreover they provide information about the product temperature and interface position assuming that the behavior of all the vials is the same. Nevertheless, it is well known that inter-vial variance can be relevant, mainly due to radiation effects from the chamber wall (Gan et al., 2005a, 2005b); Kobayashi et al. (1991), as well as Oetjen (2004), in fact, investigated the possibility of acting on the wall temperature in order to achieve higher uniformity. Beside radiation effects, another significant cause of inter-vial variance is the fluid-dynamics inside the lyophilization chamber. This issue has not been yet investigated in the Literature and it will be studied in the followings by using CFD (Computational Fluid Dynamics) calculations. Moreover the effect of these two heterogeneity causes on the results that can be obtained from the PRT will be investigated and thus a new monitoring tool is proposed.

2. Batch heterogeneity caused by fluid-dynamics and radiation

CFD is a useful tool to investigate the fluid-dynamics of the vapour in the chamber of the freeze-dryer. The commercial software FLUENT 6.2.16 has been used for the calculations: even if the values of pressure are very low during the operation, the Knudsen number is less than 0.01 for the cases investigated in this work, thus allowing to consider the fluid as a continuous phase. Simulations have been carried out at steady-state: the flow of the vapour is laminar and radiation has been taken into account by means of the P-1 radiation model (Siegel and Howell, 1992). The kinetic theory of gases has been used to evaluate the transport properties of the vapour. Figure 1 gives a sketch of the systems investigated; both a small-scale (with different values of the free space from the last shelf and the top of the chamber, f, and on the free space from the bottom of the chamber and the first shelf, d, being constant the number N of shelves) and a large-scale freeze-dryer (indicated as B1 and B2, according to the number of shelves, being d and f constant) have been simulated. The shelf at the top of the chamber is only used during the stoppering of the vials, so that the shelves available for the vials are N-1. The calculation grids were created using GAMBIT, with about 500,000 cells for both configurations. Figures 2 and 3 show an example of the pressure profiles obtained in the space over the vials in different conditions: it is possible to see that in the large scale apparatus the pressure over the tray (a layer of 43 mm has been considered occupied by the vials with the stopper in all cases) can vary from 15.6 up to 19 Pa. In fact, the pressure gradient is influenced by the number of shelves inserted in the chamber (if this number is decreased, i.e. the clearance, h, and thus the free-space is increased, the pressure gradient is reduced) as well as by the scale of the apparatus, and in particular by the length of the shelf. In the small scale freeze-dryer a more uniform pressure profile is obtained over the tray as the shelves are smaller than those of the large scale apparatus; see also Figure 6, where a more symmetric distribution of overpressure with smaller clearance is observed. The maximum variance of the pressure

is obtained on the trays near the duct and is also strongly affected by the duct position.



	Small-scale apparatus (A)	Large-scale apparatus (B)	
a, mm	450	1500	
b, mm	455	1800	
c, mm	114	800	
V_c, m³	0.2	10.3	
		B1	B2
N	5	15	18

Figure 1. Main geometric characteristics and chamber volume (V_c) of the freeze-dryers investigated with a duct at straight angle on the back.

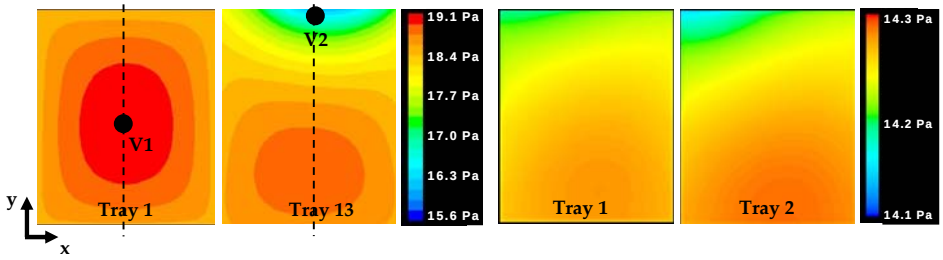


Figure 2. Contour plot of the pressure over some plates in the large-scale (B2 with *h* equal to 85 mm, on the left) and in the small-scale (with *h* equal to 100 mm, on the right) freeze-dryer. Operating pressure 10 Pa, wall temperature 283 K, shelf temperature 258 K, product temperature 239 K and mass flux 1 kg m^2 K^{-1}.

Figure 4 shows what happens in a vial (V1 filled up to 10 mm) placed in the center of the 1st tray of the freeze-dryer B2 (where the pressure has the maximum value) and in a vial (V2) placed on the border of the 13th tray (where the pressure has one of the lowest value): different evolutions of the interface temperature and position are obtained as a consequence of the different pressure. If also radiation effects from the chamber wall and from the surfaces of the shelves are considered (according to the model of Gan et al., 2005b) the behaviour is very different: when vials located at the border have completed their drying in the other vials a significant amount of ice is still present. An effective monitoring system has to take into account this heterogeneity.

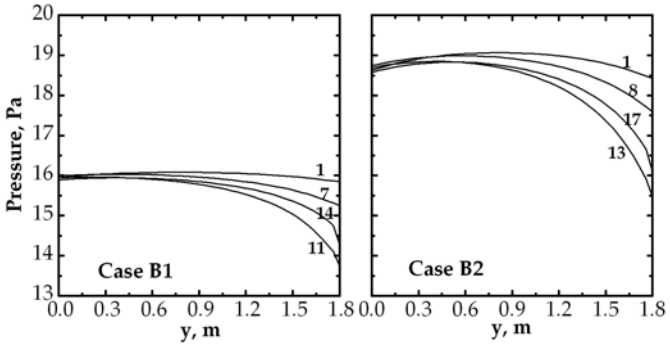


Figure 3. Pressure profiles over some plates in the large-scale apparatus along the mean *x*-position (evidenced by the dashed line in Figure 2); the numbers identify the tray, starting from the bottom (h = 110 mm in case B1 and h = 85 mm in case B2).

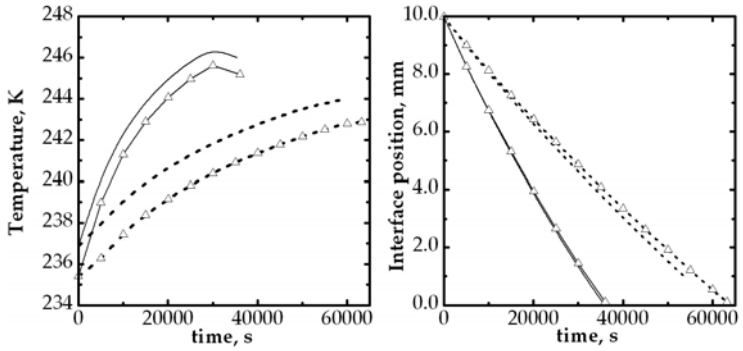


Figure 4. Time evolution of the interface temperature and position for the vials in position V1 (bare line) and V2 (line with symbols), when radiation is taken into account (solid lines) or is absent (dashed lines). [See Figure 2 for vials location.]

3. Use of a modified DPE algorithm for model based monitoring

The DPE (Dynamic Parameters Estimation) is an advanced monitoring approach based on the pressure rise data and on a rigorous unsteady-state model. During the PRT the dynamics of the pressure in the chamber of volume V_c is given by:

$$p_c = p_w + p_{in} = p_w + F_{leak}t + p_{in0}\text{, for } t \geq 0 \quad (1)$$

where F_{leak} is the leakage rate, and *w* and *in* refer to water and inert respectively. The dynamics of the partial pressure of water in the generic *j*-th vial of section *A* is given by:

$$\frac{dp_{w,j}}{dt} = \frac{1}{V_c} A \frac{k_{1,j}}{L - L_{frozen,j}} \left(p_i\left(T_{i,j}\right) - p_w \right), \text{ for } t > 0 \quad (2)$$

with adequate boundary and initial conditions; k_1 is the mass transfer coefficient and L the product thickness. Traditional approaches (see details in Galan et al., 2007) consider that the batch is homogeneous; in this case eq. (2) holds for all the N_v vials, thus giving:

$$\frac{dp_w}{dt} = \sum_{j=1}^{N_v} \frac{dp_{w,j}}{dt} = N_v \frac{1}{V_c} A \frac{k_1}{L - L_{frozen}} \left(p_i\left(T_i\right) - p_w \right), \text{ for } t > 0 \quad (3)$$

In practice, the average value of A, L_{frozen}, T_i and k_1 are considered. The values of these parameters are thus calculated in order to have a best fit between the simulated chamber

pressure and the measured data: the Levenberg-Marquardt method is used to minimize a cost function given by the difference between the simulated values of the chamber pressure and the values measured during the PRT. The most important results made available by the DPE estimator, when the computation has been performed, are the product temperature of the ice front at the beginning of the test, the actual thickness of the frozen portion of the product and the mass sublimation flux. These results averaged over all the vials of the batch; actually, vials placed in different positions have different behaviors because of the fluid-dynamics and radiation. Figure 5 (left hand graph) compares the actual curve obtained from a pressure rise test (estimated) with those expected if the conditions over the plates were those corresponding to the different zones shown in the first plot of Figure 2, where the pressure is different as an effect of the fluid-dynamics. Figure 5 (right hand graph) shows a similar comparison when radiation effect is taken into account: in this case only two zones have been considered, namely one along the edge of the plate and the other inside, where most of the vials are located. The values of the parameters that can be obtained are representative of the average pressure value or, in case of radiation present, of the largest part of the vials which are shielded.

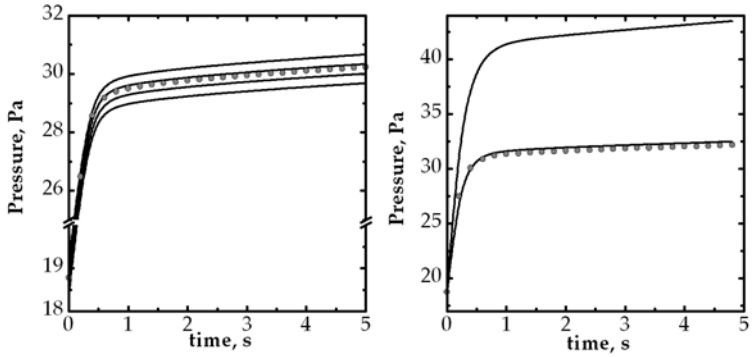


Figure 5. Estimated pressure evolution in a PRT in the large-scale freeze-dryer where either fluid-dynamics effects (left hand graphs) or radiation effects (right hand graph) are taken into account. The one resulting from the heterogeneous batch (symbols) and those expected in case of uniform distribution corresponding to the different zones (solid lines) are shown.

In large-scale apparatus the effect of fluid-dynamics is more relevant than that caused by radiation. The situation in the small-scale apparatus is quite different, as it is evidenced by Figure 6. In this case the pressure gradients are negligible, while radiation effects are more important: the contribution of the vials positioned on the side of the plate to the PRT curve is significant. This different behaviour must be taken into account when transferring the results from small to large scale apparatus.

This analysis evidenced that the simplification at the basis of eq. (3) can have serious drawbacks on the predictions of the parameters and this is of outmost importance as the values obtained from the PRT are used for monitoring and control purposes. Thus a different approach has to be implemented: eq. (3) can be developed in series around the effective value of the interface temperature (T_i), of the height of the frozen layer (L_{frozen}) and of the mass transfer coefficient (k_1), thus obtaining:

$$\frac{dp_w}{dt} = \frac{N_v A k_1}{L - L_{\text{frozen}}} \frac{\left(p_{\text{i}}(T_i) - p_{\text{w}}\right)}{V_c}\left(1 + f^*\right), \text{ for } t > 0 \qquad (4)$$

where N_V is the number of vials f^* is a global variance parameters, depending on the variance of the variance of the various parameters (Ti, L and p) that in principle could

be estimated with the other parameters by the best fitting of the experimental data.

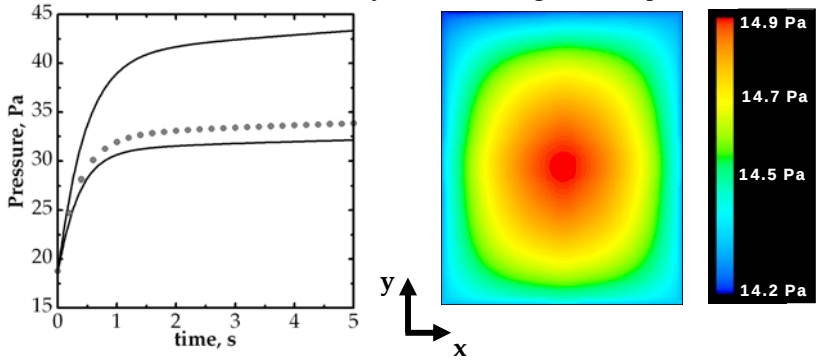


Figure 6. Estimated pressure evolution in a PRT (l.h.s symbols as in Figure 5) in the small scale apparatus with radiation effects; pressure contour plot (r.h.s) over a plate with *h* equal to 60 mm.

4. Conclusions

In order to obtain a high quality product, during a vial freeze-drying process, all the vials must undergo the same freeze-drying history but it is very difficult to achieve this result, not only because of the well known radiation effect, but also because of the flow field inside the freeze-dryer chamber. CFD has been used to show that the geometrical parameters of the device strongly influences the vapor fluid-dynamics, and thus the results of the process. Moreover the effect of these two heterogeneity causes on the performance of the monitoring tools based on pressure rise tests has been investigated.

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