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Scale-up and process transfer of freeze-drying recipes

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Abstract

This paper proposes a simple and effective methodology for the scale-up and process transfer of freeze-drying recipes. Process modeling allows studying *in silico* product evolution in a given freeze-dryer, and calculating the operating conditions that results in the same product dynamics in a different equipment. Few experiments are necessary to determine model parameters and to characterize the two freeze-dryers. The problem of the batch non-uniformity and the effect of parameters uncertainty are also addressed. The effectiveness of this approach is demonstrated by means of various examples.

Key words

Freeze-drying; Heat and Mass Transfer; Mathematical Modeling; Pharmaceuticals; Scale-up; Process transfer.

Introduction

Freeze-drying is a crucial process technology in biotech manufacturing to avoid deterioration of temperature sensitive products like plasma, enzymes, vaccines, monoclonal antibodies and many others.^{[1],[2]} Despite it is widely used in bioproducts and biopharmaceuticals manufacturing, freeze-drying is still a costly, complex, and poorly understood process and various design, monitoring e control technological challenges need to be tackled.^[3]

The problems of recipe scale-up and process transfer are well known to every freeze-drying practitioner.

An extended experimental campaign is generally carried out at lab-scale to identify the values of the heating shelf temperature and of the drying chamber pressure that allow obtaining a product with acceptable quality. It is generally recognized that this result is achieved if product temperature is maintained below a limit value during primary drying, i.e. when the ice is removed from the frozen product by sublimation. Recently, model-based tools as the SMART™ Freeze-Dryer^{[4],[5]} and the LyoDriver^{[6],[7]} have been proposed in order to optimize the recipe by carrying out few experiments, thus shortening the step of recipe development.

The same recipe obtained in the lab-scale equipment cannot generally be used without modifications to freeze-dry the product in a pilot-scale or industrial-scale freeze-dryer, as it does not guarantee to obtain the same dynamics of product temperature and of the ice content (i.e. the same primary drying length). In fact, quite often product temperature could exceed the limit value, and/or the length of the process could be different. The same problems occur when transferring a process to a different equipment, even in case the scale is not modified. The reasons at the basis of this are numerous; some of them have been highlighted in various papers and have been recently discussed:^{[8]-[11]}

- *Environmental conditions in the manufacturing area*: they can affect the nucleation temperature and, thus, the distribution of the ice crystals size and the resistance of the dry layer to vapor flux during primary drying.^[12]
- *Shelf surface temperature*: it can be different in different machines, even when the set point of the heating/cooling fluid temperature is kept the same, due to differences in the apparatus design, in the temperature control strategy, and in the load. Moreover, there can be temperature variation across the shelves, particularly during heavy heat exchange requirement, and the temperature distribution is generally a function of equipment and load characteristics.^{[13],[14]}

- *Radiation effect*: radiation from the shelf and from chamber walls affects the heat transfer to the product. This contribution depends on the equipment characteristics, namely the distance between the shelves, the wall temperature, the proximity of the vials to the walls, and the emissivity of the surfaces.^[15]
- *Chamber pressure*: the local values of chamber pressure depend on the operating conditions and on the geometrical characteristics of the equipment, and they can affect both the heat flux to the product, and the mass transfer from the interface of sublimation to the chamber.^[16]
- *Heating and cooling rates*: their maximum values can depend on the type of equipment, and, thus, in certain cases it can be impossible to use the same recipe in two different freeze-dryers,^[14] besides, in case the freezing step is not carried out in the same way in both freeze-dryers (i.e. with the same evolution of product temperature vs. time), the structure of the cake obtained in the drying step can be significantly different, and this will affect product temperature during primary drying even when using the same operating conditions.

Moreover, it is generally assumed that the formulation and the containers are not modified in the scale-up of a recipe. With this respect it must be highlighted that small changes in the vial geometry, especially for what concerns the bottom shape, may have a significant impact. Finally, as a consequence of the effect that the chamber pressure can have on the process, it must be assured that the pressure control is similar and effective in both freeze-dryers: an higher impedance of the dryer can cause choked flow and, thus, uncontrolled and higher pressure in the chamber. Obviously "human errors" like the use of different types of pressure sensor, like a capacitance manometer and a Pirani gauge, with the same pressure set point, must be avoided.^[8]

Despite the relevance of the problem, few papers appeared in the literature dealing with recipe scale-up, and no simple and effective solutions were provided.

A first approach consists of designing a robust recipe that can be used both in the lab-scale and in the pilot-scale (or industrial-scale) freeze-dryer under the hypothesis that the two pieces of equipment are practically equivalent. This results is obtained by carrying out additional cycles in the lab-scale equipment using slightly different values of shelf temperature (e.g. $\pm 2^\circ\text{C}$ around the values of the original recipe) and of chamber pressure: if a product with acceptable quality is obtained, the recipe is considered to be sufficiently robust to be used in the pilot (or industrial) scale equipment.^[9]

A second approach to deal with the scale-up problem is to define a "robust" design

space of the primary drying step, i.e. the set of operating conditions that preserve product quality at the end of the lyophilization process in different freeze-dryers; statistical tools can be used to achieve this result.^[17]

Both when using a robust recipe or a robust design space no scale-up is carried out, as the same recipe is used in different freeze-dryers; obviously, the recipe that is used can be excessively conservative.

As an alternative, a trial-and-error approach is generally proposed to perform the scale-up of a recipe. Tsinontides et al.^[18] proposed to use a mathematical model to investigate product evolution in the large-scale freeze-dryer when the recipe developed in the small-scale equipment is used. Few experiments are required to determine the heat transfer coefficient to the product, and the resistance of the dry layer to vapor flow during primary drying is assumed to be not affected by the scale of the equipment if the same cooling rate is used in the freezing step. The goal of this study is to evaluate firstly the robustness of the recipe, and in case process simulation evidences that product temperature exceeds the limit value, a trial-and-error approach is required to determine the new recipe. Kuu et al.^[19] proposed a procedure to correlate some key parameters (the heat transfer coefficient between the shelf and the product, and the resistance of the dry product to vapor flow) between a laboratory and a production freeze-dryer, and used a mathematical model to investigate the effect of the selected recipe on maximum product temperature, thus pointing out the parameters that must be used in the large-scale equipment.

From this literature survey it comes out that the scale-up of a freeze-drying recipe is still an open problem. The Guidance for Industry PAT (Process Analytical Technology) released by US FDA in 2004 emphasizes the need for a deep understanding of biotech processes to improve manufacturing efficiency, with the goal to build product quality in the process.^{[20],[21]} In this framework, the possibility of performing a true scale-up of a freeze-drying recipe using mathematical modeling has been recently investigated by Kramer et al.^[22]: the pilot-scale shelf temperature was approximated using a steady-state value that was calculated using the values of model parameters obtained in the pilot-scale equipment, and neglecting the variation of product resistance during primary drying, as well as the variation of product resistance in different freeze-dryers.

This paper shows a simple and effective methodology for recipe-scale-up and process transfer that takes into account the variation of product resistance during the main drying, as well as the possibility that product resistance is not the same in different freeze-dryers. As it will become clearer in the following, such approach involves the use of mathematical

modeling to simulate product evolution for a selected recipe, and few experiments to determine model parameters and to characterize the different freeze-dryers. The effect of parameters uncertainty can be easily accounted for, as well as batch non-uniformity. We will refer to the equipment “1” as the freeze-dryer where the recipe has been obtained and, possibly, optimized (i.e. the lab-scale freeze-dryer): such recipe has to be transferred/scaled-up to the equipment “2” (i.e. the pilot or the industrial-scale freeze-dryer).

Methods and Materials

Process modeling

The scale-up procedure proposed in this paper is based on a mathematical model of the freeze-drying process. Among the various equations available in the Literature to describe product evolution in a freeze-drying process we focused on the model proposed by Velardi and Barresi.^[23] It is a one-dimensional model where the heat flux to the product and the solvent sublimation flux are calculated using the following equations:

$$J_q = K_v (T_{\text{fluid}} - T_B) \quad (1)$$

$$J_w = \frac{1}{R_p} (p_{w,i} - p_{w,c}) \quad (2)$$

The driving force for the heat flux is given by the difference between the heating fluid temperature (T_{fluid}) and the product temperature at the vial bottom. Generally, the shelf temperature is used instead of T_{fluid} : the reason for this will be discussed afterwards. The heat flux accounts for all the heat transferred to the product, e.g. for radiation from the chamber walls, and, thus, the coefficient K_v is an effective heat transfer coefficient.

The solvent flux from the interface of sublimation is calculated using eq. (2) as a function of the driving force and of a parameter, R_p , that can be determined with few experiments. Moreover, eq. (2) is simpler than the equation proposed by Pikal^[24] and Rambhatla et al.^[13] where all the contributions to mass transfer resistance (namely the dried layer, the stopper, and the chamber) appeared explicitly.

At the moving interface there is no heat accumulation, and the heat flux is used for ice sublimation:

$$\left(\frac{1}{K_v} + \frac{L_{\text{frozen}}}{k_{\text{frozen}}} \right)^{-1} (T_{\text{fluid}} - T_i) = \Delta H_s \frac{1}{R_p} (p_{w,i} - p_{w,c}) \quad (3)$$

The following equation gives product temperature at the vial bottom:

$$T_B = T_{\text{fluid}} - \frac{1}{K_v} \left(\frac{1}{K_v} + \frac{L_{\text{frozen}}}{k_{\text{frozen}}} \right)^{-1} (T_{\text{fluid}} - T_i) \quad (4)$$

Finally, the evolution of frozen product thickness is calculated by solving the following equation:

$$\frac{dL_{\text{frozen}}}{dt} = - \frac{1}{\rho_{\text{frozen}} - \rho_{\text{dried}}} \frac{1}{R_p} (p_{w,i} - p_{w,c}) \quad (5)$$

The vapor pressure at the sublimation interface ($p_{w,i}$) depends on the interface temperature (T_i): the Goff-Gratch equation is considered the reference equation, and the values obtained using this equation are in perfect agreement with those given by the International Association for the Properties of Steam.^{[25],[26]} Such equation can be simplified: in fact, the values of $p_{w,i}$ in the temperature range of interest for freeze-drying can be calculated, and then these values can be interpolated, thus obtaining:

$$p_{w,i} = e^{-\frac{6150.6}{T_i} + 28.932} \quad (6)$$

In the Literature about freeze-drying modeling it is possible to find various types of models for the primary drying step, taking into account various heat and mass transfer mechanisms, as well as the occurrence of radial gradients of temperature and composition^{[27]-[29]}. The main drawback of detailed and multidimensional models is that their equations involve a lot of parameters, whose value cannot be easily obtained by means of experiments with a small uncertainty; moreover, the calculation time can be really high. Thus, taking into account the goal of this paper, we focused on a simplified mono-dimensional model as it involves few parameters that can be easily measured (or estimated, as it will be discussed in the following); besides, the calculation time is short and, obviously, the model has been extensively validated.^{[23],[30]}

Determination of model parameters

The heat transfer coefficient is mainly a function of chamber pressure:

$$K_v = a_{K_v} + \frac{b_{K_v} P_c}{1 + c_{K_v} P_c} \quad (7)$$

Various expressions were provided in the past to calculate the coefficients a_{K_v} , b_{K_v} , and c_{K_v} ; nevertheless, experimental investigation is required to determine reliably these values.^{[31]-[33]}

A gravimetric method allows calculating K_v : it consists of preparing a batch with the vials filled with water and, then, to carry out the primary drying for a time interval (Δt) and to measure the weight loss (Δm) and the temperature of the ice at the vial bottom (T_B). The coefficient K_v is given by:

$$K_v = \frac{\Delta m \cdot \Delta H_s}{\Delta t \cdot (T_{\text{fluid}} - T_B) \cdot A_v} \quad (8)$$

The value of the sublimation flux (i.e. $\Delta m / (\Delta t \cdot A_v)$) can be obtained also using the Tunable Diode Laser Absorption Spectroscopy (TDLAS) if the vapor velocity in the duct between the chamber and the condenser is known. Also in this case K_v can be calculated if T_B is measured.^{[34]-[36]} Finally, K_v can be estimated using one of the algorithms proposed to monitor the process using the pressure rise test.^{[37]-[41]}

The value of the coefficient K_v is not the same for all the containers of the batch as a consequence of the different contributions of the various heat transfer mechanisms: as an example, the vials at the edges of the shelf receive also radiant heat from chamber walls, beside the heat flux from the heating fluid, while vials located in the central part of the batch are heated only from the heating fluid.^{[42],[43]} The gravimetric method allows to determine the distribution of K_v in the batch, while both the TDLAS sensor and the pressure rise test based methods allow to determine only a “mean” value of K_v for the batch. As the coefficient K_v is a function of chamber pressure, at least three measurements at three different values of P_c are required to calculate a_{K_v} , b_{K_v} , and c_{K_v} .

In the following we will assume that the batch is made up of various groups of vials, and the j -th group is characterized by the parameters $a_{K_v,j}$, $b_{K_v,j}$, and $c_{K_v,j}$. The parameters b_{K_v} and c_{K_v} are used to express the dependence of K_v on chamber pressure, and this is not expected to be influenced by the equipment characteristics or the position of the vial on the shelf: as a consequence only the parameter $a_{K_v,j}$ will be different according to the equipment and to the position of the vial over the shelf. This is a fair and useful assumption as it allows the User to do three gravimetric tests in a lab-scale equipment and only one test in the pilot-scale or industrial-scale equipment to calculate $a_{K_v,j}$.

It has to be pointed out that the driving force for heat transfer (eqs. (2) and (8)) is calculated using the heating fluid temperature. This allows accounting for the possible non-uniform shelf temperature in the equipment where the distribution of values of K_v is determined.

The resistance of the dry product to vapor flow (R_p) depends mainly on the cake thickness for a given product and freezing rate:

$$R_p = R_{p,0} + \frac{A_{R_p} L_{\text{dried}}}{1 + B_{R_p} L_{\text{dried}}} \quad (9)$$

The parameters $R_{p,0}$, A_{R_p} , and B_{R_p} can be calculated by looking for best fit between eq. (9) and the curve of R_p vs. L_{dried} that can be determined using the measurement of the solvent flux obtained with TDLAS sensor (with the measurement/estimation of product temperature):

$$R_p = \frac{P_{w,i} - P_{w,c}}{J_w} \quad (10)$$

or one of the algorithms used to interpret the pressure rise test. The value of R_p can also be calculated from the product specific surface area.^[13] Recently, Fissore et al.^[44] proposed to use a weighing device in the drying chamber to estimate R_p using the measurement of the weight loss and of product temperature in the weighed vials.

Method for recipe scale-up

A simple and effective method for recipe scale-up is proposed in this section. The original recipe is supposed to maintain product temperature below the limit value for the product considered. As the batch is non-uniform due to the distribution of K_v values, at first we need to select a group of vials and the new recipe is calculated so that the evolution of the product in that group is the same in the two pieces of equipment. To this purpose the heating fluid temperature is manipulated, while the values of chamber pressure vs. time are the same in the two freeze-dryers. We will first deal with the case with $R_{p,1} = R_{p,2}$, i.e. the values of resistance to vapor flow vs. cake thickness are the same in the two freeze-dryers, and then the case with $R_{p,1} \neq R_{p,2}$ will be analyzed. After this we will show how it is possible to account for parameters uncertainty.

Recipe scale-up in case $R_{p,1} = R_{p,2}$

When $R_{p,1} = R_{p,2}$ it is possible to scale-up a recipe so that both product temperature and the residual amount of ice vs. time are the same for the selected set of vials in the two pieces of equipment (labeled as 1 and 2). In this case the fundamental equation used to scale-up the recipe is obtained from eq. (3) that correlates T_{fluid} , T_i , T_B and L_{frozen} , and that can be written as:

$$T_{\text{fluid}} = \frac{K_v \left(\frac{1}{K_v} + \frac{L_{\text{frozen}}}{k_{\text{frozen}}} \right) T_B + T_i}{K_v \left(\frac{1}{K_v} + \frac{L_{\text{frozen}}}{k_{\text{frozen}}} \right) - 1} \quad (11)$$

The proposed method comprises the following steps:

- 1a. The product evolution in the first equipment can be calculated, given the values of T_{fluid} and P_c vs. time. At each time instant t , i.e. for each value of $T_{\text{fluid},1}$, the values of L_{frozen} , T_i and of T_B for the product in the equipment “1” (indicated as $L_{\text{frozen},1}$, $T_{i,1}$ and $T_{B,1}$) are thus known.
- 2a. At each time instant t the value of T_{fluid} in the equipment 2 ($T_{\text{fluid},2}$), characterized by a different value of the parameter K_v ($K_{v,2}$), can be calculated so that the product state ($L_{\text{frozen},2}$, $T_{i,2}$ and $T_{B,2}$) is equal to that obtained in the equipment 1 ($L_{\text{frozen},1}$, $T_{i,1}$ and $T_{B,1}$). Equation (11) can be used to this purpose, thus obtaining:

$$T_{\text{fluid},2} = \frac{K_{v,2} \left(\frac{1}{K_{v,2}} + \frac{L_{\text{frozen},1}}{k_{\text{frozen}}} \right) T_{B,1} + T_{i,1}}{K_{v,2} \left(\frac{1}{K_{v,2}} + \frac{L_{\text{frozen},1}}{k_{\text{frozen}}} \right) - 1} \quad (12)$$

- 3a. Previous calculations are repeated for all time instants, until the end of the main drying is reached, thus obtaining the new recipe ($T_{\text{fluid},2}$ vs. time).

In eqs. (11)-(12) the value of K_v in both equipment has to be that of the selected group of vials.

As the batch is non-uniform, mathematical simulation allows calculating product evolution in all the other groups of vials in the second equipment when the new recipe is used. The goal is to check if product temperature remains below the limit value in the whole batch, and to determine the drying time.

Recipe scale-up in case $R_{p,1} \neq R_{p,2}$

Cake resistance to vapor flow can be different in the two freeze-dryers for various reasons, e.g. for a different degree of subcooling, consequence of a different freezing rate, as well as for the occurrence of microcollapse during primary drying. When $R_{p,1} \neq R_{p,2}$ it is not possible to perfectly scale-up the recipe, i.e. to get the same dynamics of product temperature and of sublimation flux in the selected group of vials, as it is evidenced by eq. (3). The algorithm 1a-3a previously described has thus to be modified and it is required to decide if the goal of the scale-up is to get the same product temperature or the same sublimation flux vs. time in the

selected group of vials.

In case the purpose is to get in the equipment 2 the same evolution of T_i obtained in equipment 1, then the method comprises the following steps:

- 1b. Calculation of product evolution in the first equipment, given the values of T_{fluid} and P_c vs. time.
- 2b. At time $t = 0$ $T_{\text{fluid},2}$ is equal to $T_{\text{fluid},1}$ (and equal to the freezing temperature), and $L_{\text{frozen},2} = L_{\text{frozen},1} = L_0$ and the sublimation has not started yet.
- 3b. Let us assume that for a time interval Δt the fluid temperature is maintained constant, and equal to the initial value, in both pieces of equipment. Then, $L_{\text{frozen},2}$ at time $t = \Delta t$ can be calculated by solving model equations (3)-(5).
- 4b. At this point it is possible to use eq. (13), obtained from eq. (3), to determine $T_{\text{fluid},2}$ so that $T_{i,2} = T_{i,1}$:

$$T_{\text{fluid},2} = T_{i,1} + \Delta H_s \frac{1}{R_{p,2}} (p_{w,i,1} - p_{w,c}) \left(\frac{1}{K_{v,2}} + \frac{L_{\text{frozen},2}}{k_{\text{frozen}}} \right) \quad (13)$$

- 5b. Using the value of $T_{\text{fluid},2}$ determined at step 4b it is possible to integrate the model equations from $t = \Delta t$ to $t = 2\Delta t$, thus determining the new value of $L_{\text{frozen},2}$.
- 6b. Equation (13) allows calculating $T_{\text{fluid},2}$ so that $T_{i,2} = T_{i,1}$ when $t = 2\Delta t$.
- 7b. Previous steps have to be repeated until the end of the main drying thus obtaining the new recipe ($T_{\text{fluid},2}$ vs. time) that gives the same evolution of T_i vs. time in the two pieces of equipment.

The time interval Δt should be kept as low as possible (depending on the characteristics of the heating device) in order to get a perfect scale-up of the original recipe; in this work we assumed $\Delta t = 60$ s. Similar calculations are carried out in case the target of the scale-up procedure is to get the same evolution of T_B .

In case we desire to get the same drying time in the two freeze-dryers, then the evolution of $L_{\text{frozen},2}$ has to be the same of $L_{\text{frozen},1}$, but product temperature will be different. In this case the algorithm comprises the following steps:

- 1c. Calculation of product evolution in the first equipment, given the values of T_{fluid} and P_c vs. time.
- 2c. At each time instant $L_{\text{frozen},2} = L_{\text{frozen},1}$ and, thus, $J_{w,2} = J_{w,1}$ (but $R_{p,2} \neq R_{p,1}$ $T_{i,2} \neq T_{i,1}$) and $T_{\text{fluid},2}$ and $T_{i,2}$ can be calculated by solving the system of equations:

$$\begin{cases} J_{w,1} = \frac{1}{R_{p,2}} (p_{w,i,2} - p_{w,c}) \\ T_{\text{fluid},2} = T_{i,2} + \Delta H_s J_{w,1} \left(\frac{1}{K_{v,2}} + \frac{L_{\text{frozen},1}}{k_{\text{frozen}}} \right) \end{cases} \quad (14)$$

Using eq. (6), the solution of eqs. (14) is the following:

$$T_{\text{fluid},2} = \frac{6150.6}{28.932 - \ln(p_{w,c} + J_{w,1} R_{p,2})} + \Delta H_s J_{w,1} \left(\frac{1}{K_{v,2}} + \frac{L_{\text{frozen},1}}{k_{\text{frozen}}} \right) \quad (15)$$

3c. Previous steps have to be repeated until the end of the main drying thus obtaining the new recipe ($T_{\text{fluid},2}$ vs. time) that gives the same evolution of L_{frozen} vs. time in the two pieces of equipment.

Obviously, when the goal of the scale-up is to have the same sublimation flux in both freeze-dryers, in case the original recipe is not sufficiently robust with respect to variations of product temperature, it may occur that the maximum allowed temperature is exceeded in the equipment “2”. To this purpose, process simulation using the new recipe is required to determine if the constraint about product temperature is fulfilled.

Recipe scale-up in case of parameters uncertainty

In this case parameters uncertainty has to be modeled by means of a suitable probability density function. A Gaussian distribution characterized by the mean value of the parameter and by a standard deviation around the mean value can be assumed.^{[30],[45]} The previously described algorithms can be used, with the mean values of model parameters, to calculate the new recipe. Then, the probabilistic distributions of maximum product temperature at the interface of sublimation (T_{max}) and of drying time (t_d) in the second equipment have to be calculated. As the uncertainty of K_v and R_p in the two pieces of equipment is not expected to be significantly different, then the probabilistic distributions of T_{max} and of t_d in the two freeze-dryers will be close.

Case study

Examples of results obtained with the previously proposed algorithms are shown afterwards. The case study is the scale-up of the recipe for freeze-drying a 10% w/w sucrose aqueous solution in a *LyoBeta 25*TM freeze-dryer (Telstar, Spain), using a tubing vial ISO 8362-1 2R (internal diameter: 14±0.25 mm). The characteristics of the second equipment have been simulated using values obtained from various tests in industrial-scale freeze-dryers. Results

obtained in case of freeze-drying of a 5% w/w mannitol solution in the same vial/equipment system will also be discussed.

The parameters used to calculate the resistance to vapor flow for the 10% w/w sucrose aqueous solution are the followings:

$$R_{p,0} = 1.15 \cdot 10^4 \text{ m s}^{-1}, A_{R_p} = 2.65 \cdot 10^8 \text{ s}^{-1}, B_{R_p} = 2.5 \cdot 10^3 \text{ m}^{-1}. [30]$$

The parameters used for the 5% w/w mannitol solution are the followings:

$$R_{p,0} = 6.7 \cdot 10^4 \text{ m s}^{-1}, A_{R_p} = 7.7 \cdot 10^7 \text{ s}^{-1}, B_{R_p} = 0 \text{ m}^{-1}. [45]$$

When considering the scale-up to a different freeze-dryer we will firstly assume that the curve R_p vs. L_{dried} is not modified when changing the equipment, and, then, we will consider the case that $R_{p,0}$, A_{R_p} and B_{R_p} in the second equipment are 50% higher than the values obtained in the first equipment (in case of the scale-up to a real equipment, the curve R_p vs. L_{dried} in the second equipment has to be known).

With respect to the overall heat transfer K_v , the batch is not uniform and various groups of vials have been identified: while vials of the group 1 are placed in the central part of the shelf and, thus, they are not affected by radiation from chamber walls, vials of the other groups (2 and 3) are placed in the second and first rows of each side of the shelf and, thus, they are affected in different ways by radiation from chamber walls. The gravimetric method has been used to calculate the coefficients a_{K_v} , b_{K_v} , and c_{K_v} for the various families in the first equipment; their values are shown in Table 1, with the values assumed for the second equipment.

The recipe that has to be scaled-up is characterized by a variable fluid temperature according to the following steps:

- initial freezing at -40°C ;
- heating up to 0°C (heating rate = $0.6^\circ\text{C}/\text{min}$);
- permanence at 0°C for 30 minutes;
- cooling down to -10°C (cooling rate = $-0.15^\circ\text{C}/\text{min}$);
- permanence at -10°C until the end of primary drying.

Chamber pressure is maintained constant at 10 Pa.

Results and discussion

Let us consider firstly the freeze-drying of the 10% w/w sucrose solution, when $R_{p,1} = R_{p,2}$, and let us focus on the vials placed in the central position over the shelves (i.e. the group 1). Figure 1 shows the comparison between the evolution of T_i and L_{frozen} in the two freeze-dryers considered in this study when the same recipe is used: in this case maximum product temperature in equipment 2 is 1.5°C higher than the value obtained in equipment 1, and the drying time is reduced of about 2.5 h. When using the scale-up algorithm 1a-3a the same evolution of T_i and L_{frozen} is obtained in the two freeze-dryers: this result is obtained using a different recipe (shown in Figure 2), with lower values of T_{fluid} due to the higher value of K_v .

The batch non-uniformity has to be accounted for in the scale-up of a recipe. Thus, when the new recipe has been obtained, we need to calculate product evolution in all the groups of vials of the second equipment: this is required to evaluate if product temperature remains below the limit value in all the vials, and to calculate the length of the main drying in the second equipment. In case no scale-up is performed, the temperature in the vials of groups 2 and 3 is higher (of 1.6 and 2.2°C respectively) than that obtained in the first freeze-dryer, and the drying time for those vials is reduced (of 2.7 and 3 h respectively). In case the new recipe (shown in Figure 2) is used to carry out primary drying, the evolution of the temperature of the product at the interface of sublimation and of the thickness of the frozen layer is shown in Figure 3 for the three groups of vials in both pieces of equipment. As it can be expected the dynamics of the vials of group 1 in the second equipment (square symbols) is the same obtained in the first one, while the dynamics of the other two groups is different: in particular, maximum product temperature in vials of groups 2 and 3 is slightly higher than that obtained in the first equipment (of 0.1 and 0.5°C respectively), and the drying time is reduced (of 0.1 and 0.5 h respectively). This is a consequence of the lower shelf temperature required to maintain the temperature of the vials of group 1 in the second freeze-dryer at the same value obtained in the first one.

In order to maintain for the whole batch in the second equipment the maximum product temperature below the same value reached in the first equipment, we have to choose the dynamics of the group 3 of vials as the target for the scale-up procedure, as these vials exhibit the higher temperature due to radiation effect from chamber walls and, thus, the heat transfer coefficient is significantly higher: by this way the dynamics of the hottest vials is the same in both freeze-dryers. In this case the temperature of the heating shelf of the recipe calculated for the second freeze-dryer is shown in Figure 4, where it appears to be lower than that calculated

assuming the dynamics of the vials of group 1 as the target of the calculation: the temperature of the first heating step is decreased of 2.2°C , while the temperature of the second step is decreased of about 1.6°C . Figure 5 shows the dynamics of the product (T_i and L_{frozen}) in the various groups of vials in the first freeze-dryer, when the original recipe is used, and in the second one, when the new recipe is used. The dynamics of the product in the vials of group 3 is obviously the same in both freeze-dryers, and in the second freeze-dryer the temperature of the product in the vials of groups 1 and 2 is slightly decreased (of about 0.5°C) as a consequence of the lower shelf temperature; similarly, the drying time is increased (of 1.1 h for the product in the vials of group 1). Table 2 compares the differences between the maximum product temperature and the drying time obtained for the various groups of vials in equipment 2 with respect to the values obtained in equipment 1 in case the same recipe is used, and in case the original recipe has been scaled-up, taking the dynamics of the first and of the third group of vials as target. In case only the vials in the core of the batch in the first apparatus are considered, because the cycle has been developed only taking care of these ones, than the same procedure can be applied imposing that the product temperature evolution in the vials with the highest heat transfer coefficient (generally group 3 vials) in the second apparatus is the same of the central vials in the first apparatus; this may be the case when vials are shelved in the lab scale freeze-dryer, or metal frames are used to load the vials.

When the resistance of the dry product to vapor flow is different in the two freeze-dryers, it is no longer possible to “perfectly” scale-up the recipe, i.e. to have the same evolution of T_i and L_{frozen} in the two pieces of equipment. With the goal to test the algorithm 1b-7b we assumed that $R_{p,0}$, A_{R_p} and B_{R_p} in the second equipment are 50% higher than the values obtained in the first equipment, and we focused on the vials in the central position over the shelves. At first the target of the scale-up procedure was product temperature and eq. (13) was used to calculate the new recipe: results are shown in Figure 6 (circles), evidencing that a perfect agreement is obtained with respect to temperature values, but the drying time is increased (70 minutes). The other possibility is to use the sublimation flux as target for the scale-up: in this case eq. (15) has been used to calculate the new recipe, and results shown in Figure 6 (triangles) evidence the perfect agreement obtained with respect to the values of L_{frozen} , but the maximum product temperature at the interface of sublimation increases (of about 1°C).

A final test has been carried out considering parameters uncertainty. When measuring the values of K_v for the various groups of vials it is straightforward to determine the mean

values of a_{k_v} , one for each group of vials, and their standard deviation as the weight loss can be measured for all the vials on the shelves. Similarly, it is possible to repeat various times the test used to determine R_p , thus calculating both the mean value and the standard deviation of this parameter. As the goal of this work is to show the effectiveness of the proposed algorithms, we assumed that the standard deviation of a_{k_v} is equal to 10% of the mean value for each group, and that the standard deviation of $R_{p,0}$ is 10% of the mean value; the same standard deviation has been assumed in both freeze-dryers. As it has been previously discussed the new recipe can be calculated using the mean values of the parameters (using one of the previously proposed algorithms, depending on the values of R_p in the two freeze-dryers). Figure 7 shows the comparison between the cumulative distributions of the maximum product temperature at the interface of sublimation (upper graph) and of the drying time (lower graph) obtained in the first freeze-dryer (when using the original recipe) and in the second freeze-dryer (when using the new recipe). The same curve of R_p vs. L_{dried} has been used for the calculations, and only vials of group 1 have been considered for the scale-up of the recipe. With respect to the cumulative distribution of maximum product temperature, the same results are obtained in both freeze-dryers with respect to vials of group 1 (square symbols), whose dynamics was selected as target for the scale-up of the recipe, and only a slight difference in the cumulative distribution of the drying time is evidenced. The cumulative distributions of T_{max} and t_d has to be calculated also for the other groups of vials when the original recipe and when the new recipe is used, thus evidencing if the new recipe is adequate for the whole batch in the equipment 2.

A further test of the proposed algorithm has been carried out considering the 5% w/w mannitol solution, and results are shown in Figures 8 and 9. For this test we assumed that product resistance was the same in both freeze-dryers, and, thus, the target of the scale-up procedure was to reproduce the evolution of both sublimation flux and product temperature. Firstly we calculated the cumulative distributions of maximum product temperature and of drying time in the various group of vials in the first equipment and in the second equipment when the same recipe is used (Figure 8, upper graphs), pointing out that the maximum value of product temperature at the interface of sublimation can be significantly higher in the second freeze-dryer, e.g. about 3°C in the third group of vials, thus decreasing the duration of the main drying. The proposed algorithm has been used to scale-up the recipe, taking product dynamics in the third group of vials as the target of the calculation. The cumulative distributions of T_{max} and t_d are shown in Figure 8 (lower graphs), showing that also in this case

almost the same distributions are obtained in the target group of vials. The new recipe is given in Figure 9 (lower graph), while the upper graph of Figure 9 shows the evolution of the interface temperature in the third group of vials in the first equipment, and in the second equipment when using the original and the new recipe, thus confirming the effectiveness of the proposed algorithm.

Finally, this work has evidenced the following issues:

- When scaling-up a recipe, the target evolution of the product should be that of the vials characterized by the higher values of the heat transfer K_v , in order to guarantee that product temperature in the second equipment is not higher than the maximum value reached in the first equipment, but this can result in a higher drying time.
- In case the new recipe is too conservative, i.e. the drying time is increased to a value that is not considered suitable for the process, then the scale-up can be repeated using the dynamics of the vials in the central position over the shelves as target. Obviously, product temperature can exceed the limit value in the vials at the sides of the shelves and, thus, shrinkage or collapse are expected to occur in those vials.
- In case the resistance of the dry cake to the vapor flow is not the same in the two freeze-dryers, the target of the scale-up procedure should be the product temperature in order to avoid possible overheating: drying time can be increased or decreased depending on the value of K_v in the two freeze-dryers.
- The scale-up of the recipe can be based on the mean values of K_v and R_p , without taking into account parameters uncertainty. As the uncertainty about these values is not expected to be significantly different between two different freeze-dryers, than also the cumulative distributions of maximum product temperature and of the drying time will be not significantly affected.

Conclusion and final remarks

A simple and effective procedure for the scale-up and process transfer of a freeze-drying recipe has been proposed in this paper. The proposed algorithm can be used also in case the two freeze-dryers are not thermally equivalent. A mathematical model allows simulating product evolution given the operating conditions, and few experiments are needed to determine model parameters, namely:

- three gravimetric tests in the first equipment, to calculate the coefficient K_v for the

- various groups of vials, and their dependence on chamber pressure;
- one test in the second equipment to determine how the value of a_{K_v} is modified;
 - one test in the first equipment to determine the curve R_p vs. L_{dried} ;
 - one test in the second equipment to check if the same curve R_p vs. L_{dried} is obtained in this freeze-dryer.

It is not necessary to use any (expensive) device for process monitoring and model parameter estimations, and the calculations are very simple. Thus, we believe that the proposed approach is a really effective solution to the problem of recipe scale-up (and process transfer) that can motivate every freeze-dryer practitioner to abandon the (usual) trial and error procedure.

The previous approach can be extended also to the case where the container is changed: for this case, that will be investigated in a future work, a complete thermal characterization of the two containers must be carried out, and the influence on the R_p dependence on L_{dried} must also be investigated, but once model parameters in the second freeze-dryer are known, the same calculations previously described can be carried out to get the new recipe.

With a similar approach it would be also possible to estimate the design space for the new freeze-dryer, and thus transfer not only the recipe, but the whole design space, that contains more information, including the knowledge of the full set of conditions that allow to carry out successfully the drying step.^[46] This is very different from the use of a robust design space mentioned in the Introduction, and more efficient, because in this case the recipe would be optimized for the considered freeze-dryer. The knowledge of the safety margin incorporated in the recipe will also allow to evaluate if the increase in the maximum product temperature, consequence of the scale up criterion selected, may be acceptable, thus guiding in the choice of the best operating conditions; for example, in case of change in the cake resistance, it will allow to evaluate if it is possible to keep constant the drying time, as discussed in the test case presented.

List of Symbols

A_{R_p}	parameter used in eq. (9), s^{-1}
A_v	cross sectional area of the vial, m^2
a_{K_v}	parameter used in eq. (7), $J m^{-2} s^{-1} K^{-1}$
B_{R_p}	parameter used in eq. (9), m^{-1}
b_{K_v}	parameter used in eq. (7), $J m^{-2} s^{-1} K^{-1} Pa^{-1}$
c_{K_v}	parameter used in eq. (7), Pa^{-1}
ΔH_s	heat of sublimation, $J kg^{-1}$
J_q	heat flux to the product, $J s^{-1} K^{-1} m^{-2}$
J_w	sublimation flux of the solvent, $kg s^{-1} m^{-2}$
K_v	overall heat transfer coefficient between the heating fluid and the product, $J m^{-2} s^{-1} K^{-1}$
k_{frozen}	thermal conductivity of the frozen layer, $J K^{-1} s^{-1} m^{-1}$
L_0	thickness of the product after freezing, m
L_{dried}	thickness of the dried layer, m
L_{frozen}	thickness of the frozen layer, m
m	mass, kg
P_c	chamber pressure, Pa
$p_{w,c}$	water partial pressure in the drying chamber, Pa
$p_{w,i}$	water pressure at the interface of sublimation, Pa
R_p	resistance to vapor flow, $m s^{-1}$
$R_{p,0}$	parameter used in eq. (9), $m s^{-1}$
T_i	temperature of the product at the interface of sublimation, K
T_B	temperature of the product at the bottom of the vial, K
T_{max}	maximum product temperature at the interface of sublimation, K
T_{fluid}	temperature of the heating fluid, K
t	time, s
t_d	drying time, h

Greeks

ρ_{frozen}	density of the frozen product, $kg m^{-3}$
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ρ_{dried} apparent density of the dried product, kg m^{-3}

Abbreviations

PRT pressure rise test

TDLAS Tunable Diode Laser Absorption Spectroscopy

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List of Tables

Table 1 Values of the parameters used to calculate the coefficient K_v for the various groups of vials in the two pieces of equipment.

Table 2 Difference between the values of maximum product temperature and of drying time obtained for the various group of vials in equipment 2 with respect to the values obtained in equipment 1 in case the same recipe is used, and in case the original recipe has been scaled-up, taking the dynamics either of the first or of the third group of vials as target.

List of Figures

Figure 1 Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (lower graph) in a vial of the group 1 in the first equipment (solid lines), and in the second equipment, when the original recipe is used (dashed lines) and when the scaled-up recipe is used (symbols).

Figure 2 Comparison between the original recipe (dashed line) and the recipe calculate using the proposed scale-up algorithm (symbols).

Figure 3 Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (lower graph) in vials of the group 1 (solid line, \square), 2 (dashed line, Δ) and 3 (dotted line, \circ) in the first equipment (lines), when the original recipe is used, and in the second equipment (symbols), when using the new recipe calculated in order to get the same dynamics in the vials of group 1.

Figure 4 Comparison between the original recipe (dashed line) and the recipe calculated using the proposed scale-up algorithm in order to get the same dynamics in the vials of group 1 (\blacktriangle) and that obtained in case the target is the dynamics in vials of group 3 (\blacksquare).

Figure 5 Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (lower graph) in vials of the group 1 (solid line, \square), 2 (dashed line, Δ) and 3 (dotted line, \circ) in the first equipment (lines), when the original recipe is used, and in the second equipment (symbols), when using the new recipe calculated in order to get the same dynamics in the vials of group 3.

Figure 6 Evolution of the temperature at the interface of sublimation (upper graph) and of the thickness of the frozen layer (middle graph) in vials of the group 1 in the first equipment (lines), when the original recipe is used, and in the second equipment (symbols), when using the new recipes calculated in order to get the same evolution of the temperature at the interface of sublimation (\circ) or of the thickness of the frozen layer (Δ). The new recipes are shown in the lower graph.

Figure 7 Cumulative distribution of the maximum product temperature (upper graph) and of the drying time (lower graph) for the vials of group 1 (solid line, □), 2 (dashed line, Δ) and 3 (dotted line, ○) in the first equipment (lines), when the original recipe is used, and in the second equipment (symbols), when using the scaled-up recipe.

Figure 8 Cumulative distribution of the maximum product temperature (left hand graphs) and of the drying time (right hand graphs) for the vials of group 1 (solid line, □, ■), 2 (dashed line, Δ, ▲) and 3 (dotted line, ○, ●) in the first equipment (lines), when the original recipe is used, and in the second equipment, when the original recipe is used (filled symbols, upper graphs), and when using the scaled-up recipe (empty symbols, lower graphs) in case the target is the dynamics in vials of group 3. Results refer to freeze-drying of mannitol solution.

Figure 9 Upper graph: Evolution of the temperature at the interface of sublimation in vials of the group 3 in the first equipment when the original recipe is used (line), and in the second equipment when the original recipe is used (●), and when using the scaled-up recipe (○) in case the target is the dynamics in vials of group 3. Lower graph: Comparison between the original recipe (dashed line) and the scaled-up recipe (○). Results refer to freeze-drying of mannitol solution.

Table 1

		freeze-dryer 1	freeze-dryer 2
a_{K_v} , $\text{J m}^{-2}\text{s}^{-1}\text{K}^{-1}$	group 1	6.5	11.7
	group 2	9.4	16.1
	group 3	12.1	23.0
b_{K_v} , $\text{J m}^{-2}\text{s}^{-1}\text{K}^{-1}\text{Pa}^{-1}$		1.5	
c_{K_v} , Pa^{-1}		0.03	

Table 2

	no scale-up		scale-up (group 1)		scale-up (group 3)	
	ΔT_{\max} , °C	Δt_d , h	ΔT_{\max} , °C	Δt_d , h	ΔT_{\max} , °C	Δt_d , h
group 1	1.5	-2.5	0.0	0.0	-0.5	1.1
group 2	1.6	-2.7	0.1	-0.1	-0.5	0.9
group 3	2.2	-3.0	0.5	-0.9	0.0	0.0

Figure 1

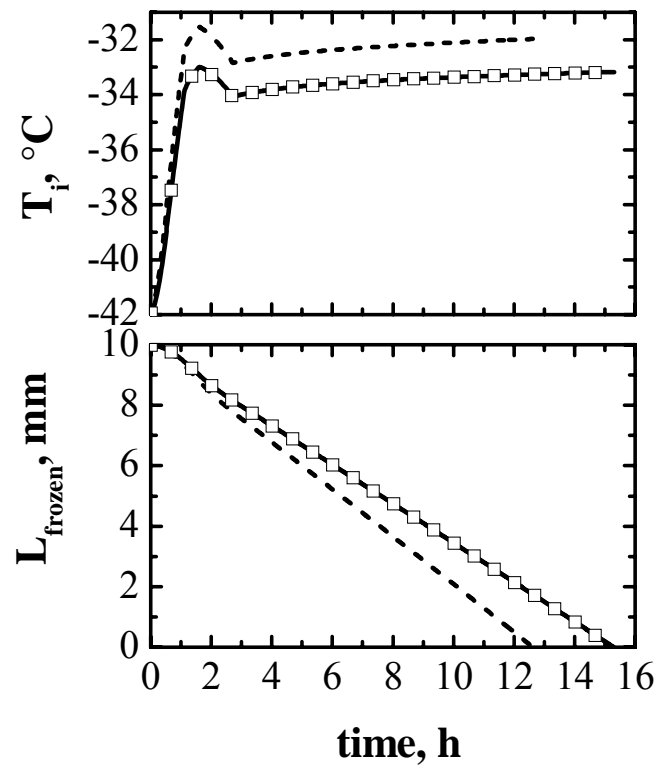


Figure 2

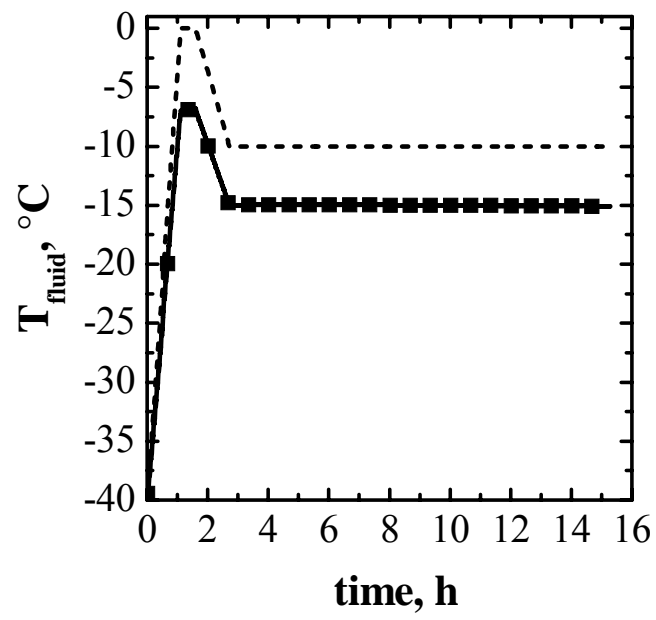


Figure 3

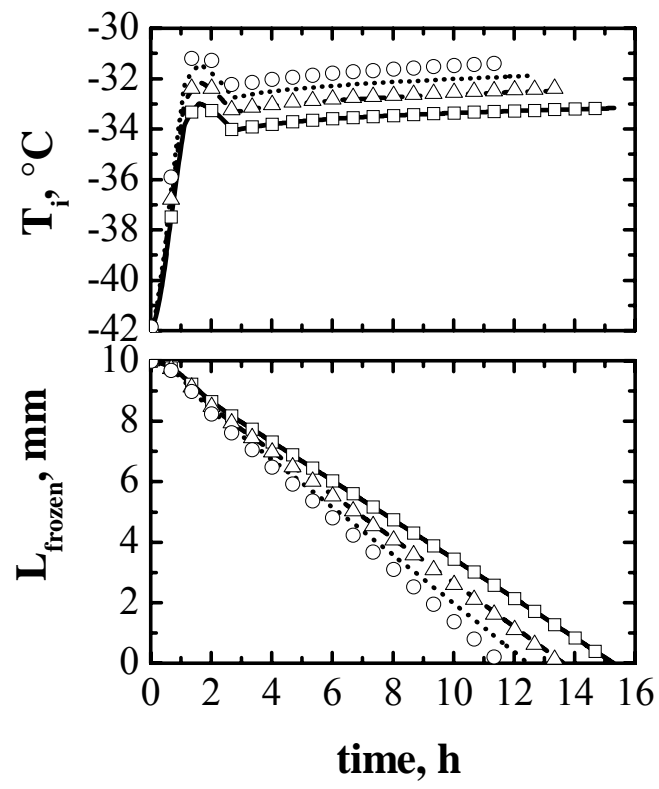


Figure 4

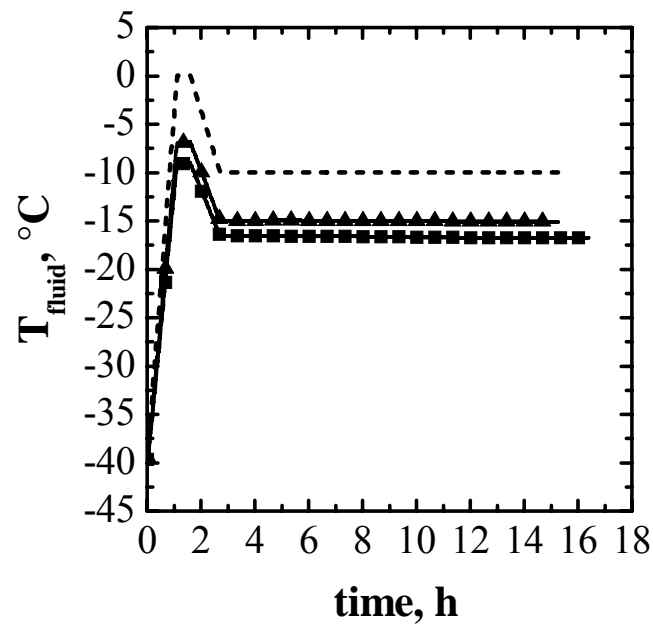


Figure 5

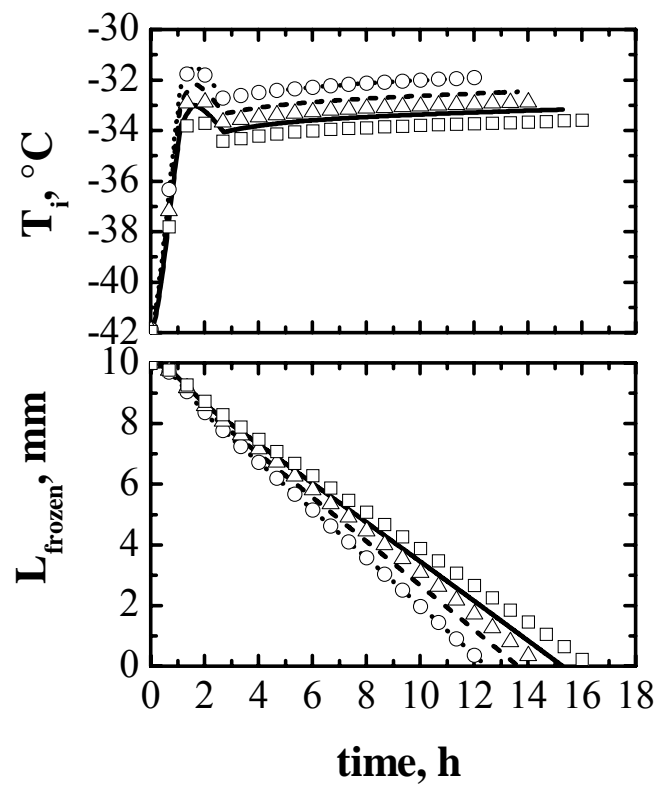


Figure 6

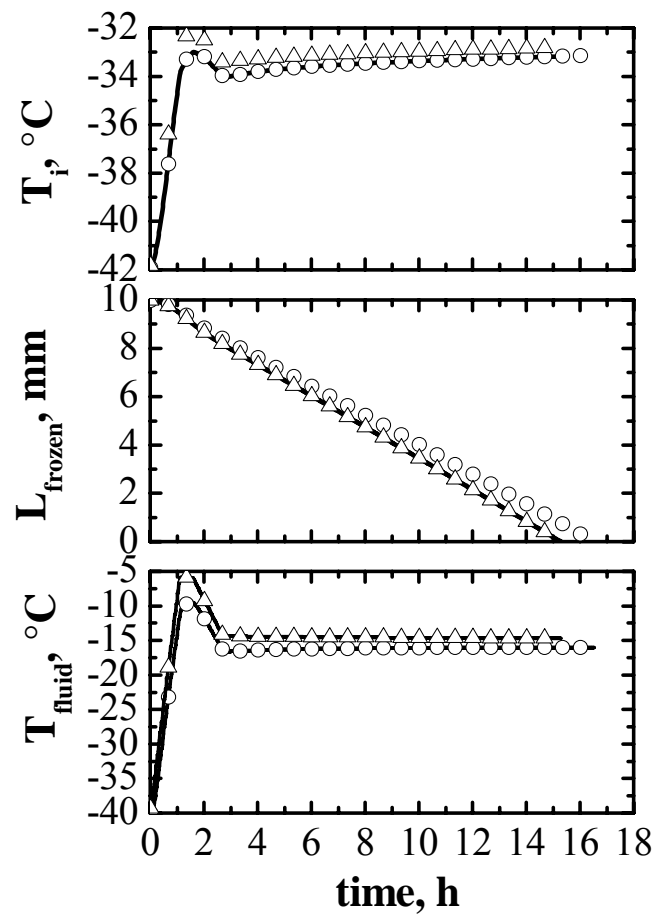


Figure 7

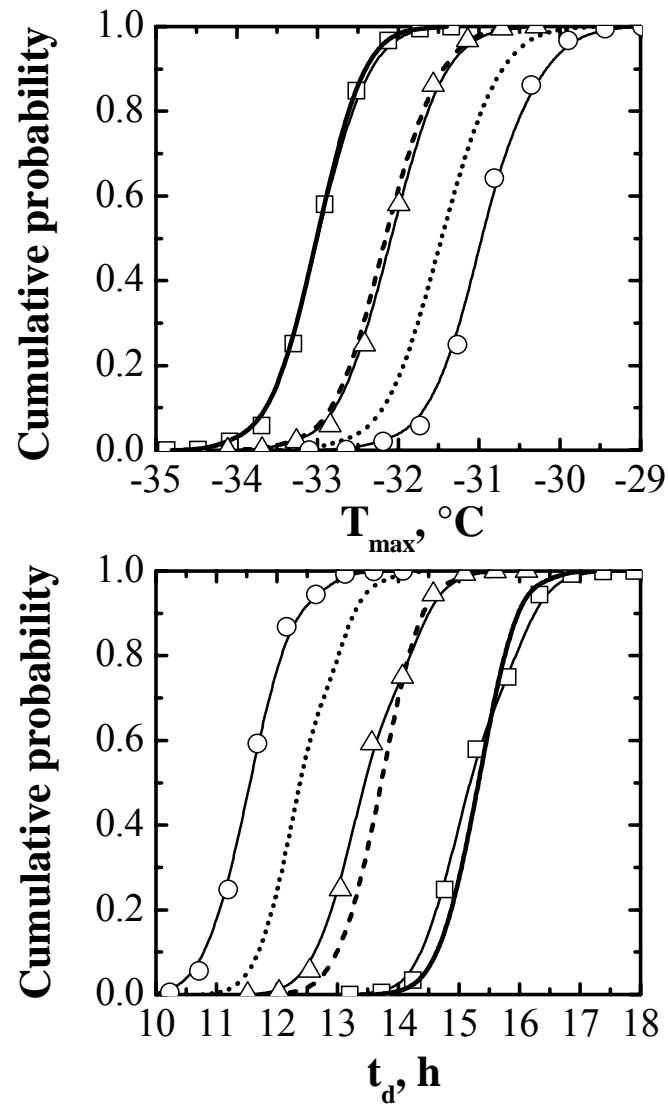


Figure 8

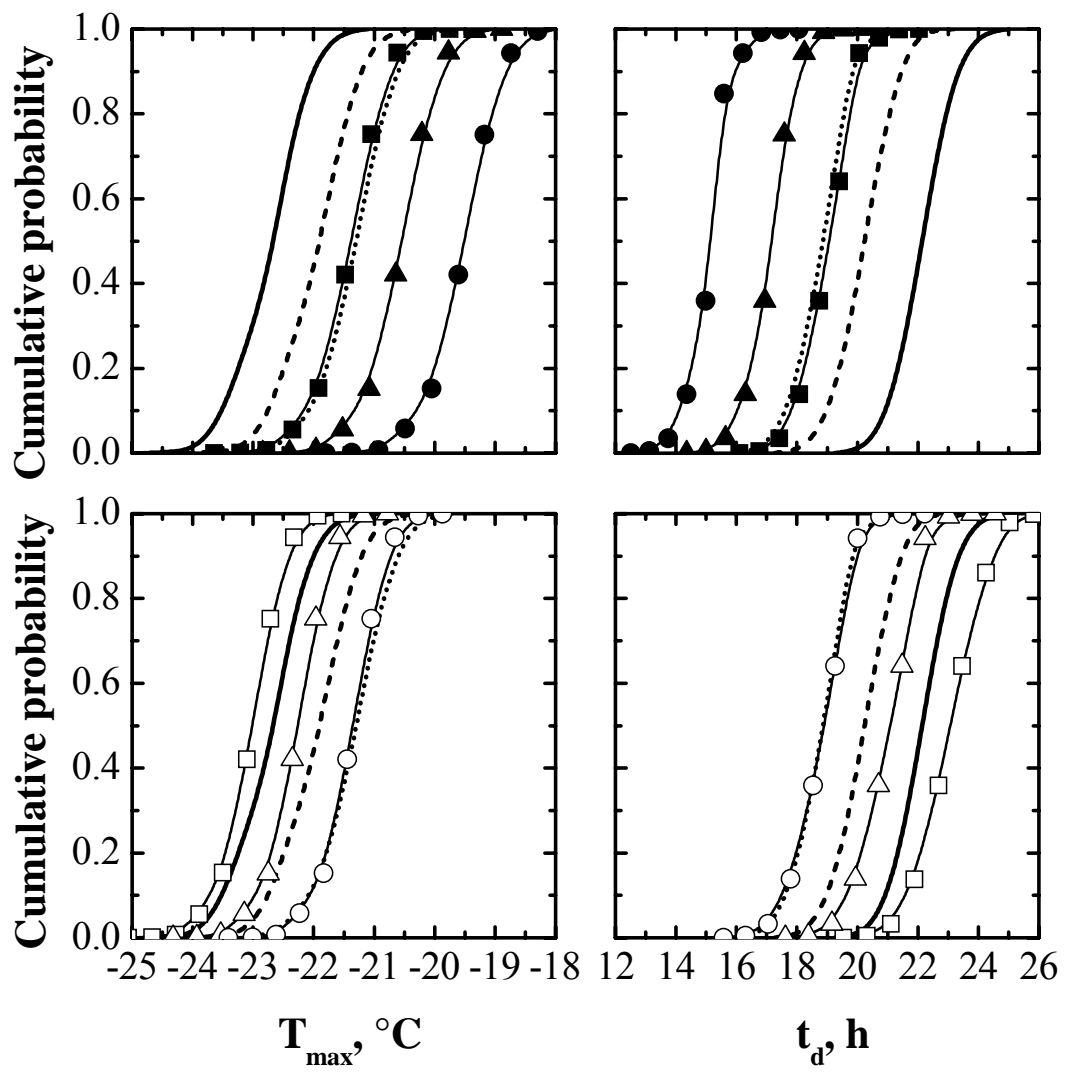


Figure 9

