Time-scale modelling and optimal control of freeze-drying

Estefania Lopez-Quiroga^a, Luis T. Antelo^a, Antonio A. Alonso^{a,*}

^a*Process Engineering Group, Marine Research Institute, IIM-CSIC, Eduardo Cabello 6, Vigo, Spain*

Abstract

Freeze-drying is considered to be an attractive dehydration method of preserving the quality of high value foods products. Unfortunately, it is an expensive operation, which calls for efficient tools capable of minimizing time and/or energy while preserving product quality.

In this work, time-scale analysis has been applied to a detailed first-principle based model. From such analysis a simplified model, capable of describing freeze-drying at the time scales relevant to quality, has been proposed. The model has been solved by the Finite Element method, showing good agreement with the results in literature. Likewise, the efforts associated with the computation of optimal operation policies have been reduced.

In this regard, different operational scenarios that take into account shelf temperature (T_L) and chamber pressure (P_c) have been considered on a simulation basis. In all cases the resulting optimal control profiles obtained led to significant reductions of cycle time while ensuring product quality.

Keywords: Freeze-drying dynamics, Time-scale separation, Mathematical modelling, Optimal control, Minimum process time

1. Introduction

Freeze-drying (lyophilisation) is a dehydration process well known in food industries as it is an operation which preserves the biological activity of thermosensitive components, as well as the organoleptic and nutritional proper-

*Corresponding author. Tel.: +34 986 231 930; fax: +34 986 292 762
Email address: antonio@iim.csic.es (Antonio A. Alonso)

ties of the material. It must be also mentioned that freeze-drying extends products shelf life, while making goods easier to transport and to store.

However, the slow drying rates and the working conditions (close to low absolute) constitute the main disadvantage of lyophilisation. This translates into an expensive process in terms of time and energy, and so economics. Thus, industrial uses of freeze-drying have been restricted to dehydration of high value products (Litchfield & Liapis, 1979; Pikal et al., 1983; Pikal, 2000; Trelea et al., 2007).

Three stages can be identified in the complete freeze-drying process (Song et al., 2002; Trelea et al., 2007), during which different physical phenomena take place, as depicted in Figure 1:

1. The first stage (*freezing*) involves a quick decrease of the sample temperature (reaching values below water triple point) in order to control the ice crystals size growth and to avoid possible damage to the material can be caused.
2. The second step, the so called *primary drying*, consists of heating of the sample under partial vacuum conditions (always below the triple point) to force ice sublimation. This leads to an interconnected porous structure which can be later rehydrated very effectively while preserving the organoleptic and nutritional properties of the product. During this stage (the longest one of the cycle), which conditions most of the quality properties of the product, almost all frozen water is sublimated.
3. Finally, the last step, the *secondary drying*, is an ordinary drying process where the water still bounded to the porous matrix is desorbed by increasing the temperature. Typical figures for final moisture levels in the product are around 0.5% w/w.

The efficiency of the freeze-drying process in terms of productivity and product quality (obtaining of the highest quality in the shortest cycle time), is defined by various process variables (Trelea et al., 2007), being the product temperature the most determinant one. Although sublimation phenomenon is faster when temperature is increased, an overheating of the product could result into the collapse of the pore structure (Pikal & Shah, 1990) and the loss of the quality properties. This collapse phenomenon is usually associated with the glass transition temperature of the maximally freeze-concentrated phase. Thus, the proper handling of the product temperature will allow not only the maintenance of quality under market standard requirements but also to reduce process cycle time.

42 In this framework, theoretical modelling has been revealed as a very useful
43 tool to achieve a better understanding of process dynamics and their influence
44 on cycle time and product temperature history.

45 Classical freeze-drying references (Litchfield & Liapis, 1979; Millman et al.,
46 1984; Pikal et al., 1983) offer an exhaustive description of the process dynam-
47 ics, involving a high number of parameters. Still accurate, these models and
48 their subsequent improvements e.g. (Boss et al., 2004; Bruttini et al., 1991;
49 Mascarenhas et al., 1997), are computationally involved and time consuming,
50 so unsuitable for on-line/real time control purposes. More recent publications
51 echoed the need of developing simplified and control-oriented models. (Trelea
52 et al., 2007) proposed a lumped model for optimizing process performance.
53 The inherent loss of dynamical information, which could affect the quality
54 requirements of the final product, might be the main disadvantage of this
55 model. The same motivation appears in (Velardi & Barresi, 2008), where
56 two simplified models are developed for on-line applications. Although both
57 models are based on the separation of slow and fast dynamics of the sys-
58 tem in order to obtain the desired simplifications, no theoretical basis, and
59 therefore systematics, is provided.

60 The present work is aimed at going one step further. A first principle-
61 based model, describing primary and secondary drying dynamics, is pre-
62 sented. By considering the corresponding thermophysical properties of the
63 material, different characteristic times for freeze-drying dynamics are defined.
64 Associated to these, the diverse time scales in which the involved physical
65 phenomena take place are also revealed. From this rigorous time-scale anal-
66 ysis, a simplified distributed model is launched as a suitable tool not only to
67 provide an accurate description of the freeze-drying dynamics but also to be
68 used as the core for computing optimal operation policies.

69 Aiming the establishment of such optimal operations conditions, a num-
70 ber of methodologies have been describe in literature. The objective is to
71 determine the operating conditions over the control variables, namely, the
72 shelf temperature and the chamber pressure, which are the most intuitive
73 controls. The purpose of these contributions is minimizing the drying time
74 while satisfying the glass transition constraint (Gan et al., 2004; Rene et al.,
75 1993). The suitable shelf temperature and chamber pressure conditions are
76 frequently established on a trial-and-error basis (Alves & Roos, 2006). Thus,
77 considering constant values for these variables arises as the simplest approach
78 to determine optimal operation policies. Such approach normally results into
79 non-optimal conditions for the primary drying (Liapis et al., 1996).

Since significant advantages can be obtained if shelf temperature and chamber pressure are varied during the process time (Pisano et al., 2010), the definition of a procedure to optimally determine time-varying operating profiles has become one of the scopes of recent research on freeze-drying (Pisano et al., 2010; Boss et al., 2004; Velardi & Barresi, 2008). The aim of the approach presented in this paper is to easily and systematically determine optimal operation policies for freeze-drying processes, while trying to overcome disadvantages presented in previous literature. Drawbacks are mainly related, as previously mentioned, to the use of computationally expensive dynamics models, parameter uncertainty (Litchfield & Liapis, 1982) or policies established on case-by-case basis (Alves & Roos, 2006; Sadikoglu et al., 1998).

In this work, the optimal control problem associated to the complete freeze-drying process is simultaneously solved for primary and secondary drying stages. The time-scale based model here proposed is defined as the core of the stated problem. It must be considered that if the mathematical model is not properly defined, this could lead once again to non-optimal process operation, which could result in a loss of product quality (Sadikoglu et al., 1998; Sadikoglu, 2005). Thus, the importance of a low dimensional control-oriented model, as the one here proposed by the authors.

Finally, it must be mentioned that, in order to obtain a low dimensional non linear programming (NLP) problem, a Control Vector Parameterization (CVP) approach is employed. The resulting NLP problem is then efficiently solved by using a novel optimization tool based on scatter-search (SSm).

The paper is organized as follows: In Section 2, the time-scale analysis is introduced, and the resulting first principle based model describing freeze-drying dynamics is presented. The dynamic validation of the proposed dimensional reduced model is presented in Section 3. Finally, in Section 4, this novel time-scale based model will be employed to compute optimal policies for freeze-drying process.

2. Materials and Methods

Porous media are defined as a permeated material constituted by an interconnected network of pores throughout which the vapour flux can circulate (Roth, 2007). Its importance is well known in many mass transfer applications, including freeze-drying of foods, where the process depends on the vapour water transport through a porous layer of dried solids (Bird et al.,

2007). As a consequence, heat and mass transfer mechanisms will be considered in order to obtain a dynamic description of the freeze-drying process. In this paper, skim milk is selected as reference material. The physical parameters used to define the different work cases developed in this paper have been taken from literature (Liapis & Bruttini, 1994; Mascarenhas et al., 1997; Millman et al., 1984).

2.1. Assumptions

For modelling purposes the following standard assumptions are made (Mascarenhas et al., 1997; Millman et al., 1985; Trelea et al., 2007):

1. The frozen region has uniform heat and mass transfer properties.
2. There is a continuous interface (sublimation front) between the dried and the frozen region, with infinitesimal thickness.
3. At the interface, the concentration of water vapour is in equilibrium with ice.
4. The structure of the porous matrix is rigid provided that its temperature is below that of glass transition.
5. The solid matrix is permeable, thus allowing the circulation of vapour fluxes.

2.2. Geometry

In this work, we approximate a generic system to be freeze-dried, as the one depicted in Figure 2, by a 1D slab. Initially, the thickness of the dried region (and therefore the position of the front) is considered to be the 2% of the total length (Mascarenhas et al., 1997). The porous dried media and a frozen region coexist separated by the sublimation front. Note that the existence of both regions will be needed for the boundary conditions to hold, avoiding discontinuities at $x = 0$ instants after the heat begins to be supplied.

2.3. Time scale approach to model simplification

As commented in Section 1, freeze-drying dynamics has been extensively analyzed in literature (Bruttini et al., 1991; Litchfield & Liapis, 1979; Mascarenhas et al., 1997; Millman et al., 1985; Pikal et al., 2005; Ratti, 2001; Sadikoglu & Liapis, 1997). Relying on these references, a first principle based model describing the primary drying (stage which determines the product quality) and secondary drying is here presented. The main difference with

respect to those other models is related to the treatment of the heat transfer phenomena in the dried layer. It must be remarked that separated energy transfer mechanisms for vapour and porous matrix in the dried region are considered. In order to both achieve a better comprehension of the process as well as to identify its leading roles, the coupled mass and energy balances are described by taking into account the inherent thermophysical properties of the system. Thermal diffusivities, desorption rate and the mass flux velocity, define a set of characteristic times in which the different physical phenomena take place (see Table 1). Please, check Appendix A for more detailed information on the time-scale approach.

Based on this time scale analysis, a simplification of the governing equations is performed. This approach will allow us to focus just on the phenomenon of interest and to neglect mechanisms occurring at different time scales. For the freeze-drying case, the relevant time scale is the one related to the temperature distribution within the porous matrix. This will define a model we will refer to as *the matrix scale model*. For the 1D case it is described as follows.

2.3.1. Heat transfer equations

Heat transfer is governed by Fourier's equation in both regions:

$$\frac{\partial T_I}{\partial t}(x, t) = \alpha_I \frac{\partial^2 T_I}{\partial x^2}(x, t), \quad \forall x \in (0, S(t)) \quad (1)$$

$$\frac{\partial T_{II}}{\partial t}(x, t) = \alpha_{II} \frac{\partial^2 T_{II}}{\partial x^2}(x, t), \quad \forall x \in (S(t), L) \quad (2)$$

where T_I and T_{II} are the temperatures of the dried and the frozen layer, respectively, and $S(t)$ denotes the position of the sublimation front. Over the product top ($x = 0$), radiation is the main heat transfer mechanism while at the bottom ($x = L$) convection must be considered (Bruttini et al., 1991). This leads to the following Neumann-type boundary conditions:

$$k_I \frac{\partial T_I}{\partial x}(x, t) = \sigma e_p f_p (T_c^4 - T_I^4), \quad x = 0 \quad (3)$$

$$k_{II} \frac{\partial T_{II}}{\partial x}(x, t) = h_L (T_L - T_{II}), \quad x = L \quad (4)$$

where T_L is the shelf temperature and the convective heat transfer coefficient, h_L , depends on the chamber pressure P_c (Bruttini et al., 1991; Sadikoglu &

177 Liapis, 1997) as:

$$h_L = 1.5358P_c \quad (5)$$

178 Continuity of temperature across the front is also imposed:

$$T_I = T_{II} = T_s, \quad x = S(t) \quad (6)$$

179 It must be noted that the sublimation front constitutes a moving boundary,
180 which calls for an extra boundary condition, the Stefan condition (Crank,
181 1984) at $x = S(t)$, of the form:

$$k_{II} \frac{\partial T_{II}}{\partial x}(x, t) - k_I \frac{\partial T_I}{\partial x}(x, t) = \Delta H_s(\rho_{II} - \rho_I) \frac{\partial S(t)}{\partial t} \quad (7)$$

182 2.3.2. Mass transfer equations

183 Due to the fact that heat and mass transfer mechanisms are strongly
184 coupled, the continuity equation must be also defined in the dried region.
185 For porous materials, the vapour velocity will be computed by Darcy's law:

$$\frac{\partial}{\partial x} \left(-\rho_v(x, t) \frac{K_m}{\mu} \frac{\partial P_v}{\partial x}(x, t) \right) = 0, \quad \forall x \in (0, S(t)) \quad (8)$$

186 where P_v is the vapour pressure and ρ_v its density, which is assumed to obey
187 the Ideal Gas condition. In this way, vapour density can be calculated from
188 P_v and T_I data directly. The other two parameters associated to Darcy's
189 equation are the matrix permeability, K_m , and the vapour viscosity, μ .

190 Pressure value is fixed in the freeze-dryer chamber, while the sublimation
191 phenomena origins a vapour flux from the front. This translates into the
192 following Dirichlet and Neumann boundary conditions defined at $x = 0$ and
193 $x = S(t)$, respectively:

$$P_v = P_c, \quad x = 0 \quad (9)$$

194

$$-\rho_v(x, t) \frac{K_m}{\mu} \frac{\partial P_v}{\partial x}(x, t) = \frac{\partial S(t)}{\partial t} (\rho_{II} - \rho_I), \quad x = S(t) \quad (10)$$

195 Since ice and vapour are in equilibrium at the moving front, once T_s is
196 obtained by solving Equations (1)-(7), the Clausius-Clapeyron equation is
197 employed to obtain $P_v(S(t))$, what closes the coupled mass transport prob-
198 lem. It should be remarked proportionality between gradient pressure and
199 vapour flux in Equation (10), from which it is easy to see that, the driving
200 force of the sublimation rate, and therefore drying, is the gradient pressure.

201 Despite the fact that the classical definition of freeze-drying distinguishes
 202 between primary and secondary drying as two consecutive stages, bounded
 203 water begins to be desorbed locally when the sublimation front passes by,
 204 creating a new portion of dried layer (Bruttini et al., 1991), what results into
 205 a coupled phenomenon. The evolution of water desorption in the product
 206 can be obtained from the vapour pressure in the dried region by solving
 207 the following Initial Value Problem (IVP), being the time dependence of the
 208 moisture content of the form (Mascarenhas et al., 1997; Millman et al., 1985;
 209 Pikal et al., 2005):

$$\frac{dC_b}{dt}(t) = K_g (C_{b_{eq}} - C_b(t)), \quad \forall x \in [0, S(t)) \quad (11)$$

$$C_{b_{ini}} = C_b(x, 0) \quad (12)$$

211 where C_b represents the product water content (in *kg water/kg solids*) while
 212 $C_{b_{eq}}$ and $C_{b_{ini}}$ are the equilibrium and initial water contents of the sample,
 213 respectively. The equilibrium concentration for the sorbed water, $C_{b_{eq}}$, is
 214 given by the GAB equation (van den Berg & Bruin, 1981):

$$C_{b_{eq}} = \frac{m_m a_w C_G K_{GAB}}{(1 - a_w K_{GAB}) [1 + (C_g - 1) a_w K_{GAB}]} \quad (13)$$

215 The water content of the monolayer capacity m_m is expressed in grams of
 216 water per 100 grams of solid. The water activity a_w is here defined as the
 217 quotient between the vapour pressure in the dried layer, P_v , and the equilib-
 218 rium vapour pressure at the considered temperature, given by the Clasi-
 219 us-Clapeyron equation, $P_{v_{eq}}$. The values m_m , K_{GAB} and C_G for the skim milk
 220 are taken from (Furmaniak et al., 2009).

221 3. Results and Discussion

222 3.1. Validation and numerical simulation of the matrix scale model

223 In order to verify the goodness of the simplified *matrix scale model*, a case
 224 study has been defined, consisting of the freeze-drying of a 3 mm and a 6 mm
 225 thickness skim-milk slabs. The governing equations for the matrix time scale
 226 were implemented in the commercial software COMSOL Multiphysics[®] and
 227 solved by the Finite Element method (FEM) together with an Arbitrary
 228 Lagrangian-Eulerian method (ALE) (Donea et al., 2004) in order to track
 229 the moving front (Mascarenhas et al., 1997). The results obtained for the 3

mm thickness slab are presented in Figure 3, where trends for the product temperature distribution along the sample for the sublimation stage show good agreement with those reported in (Mascarenhas et al., 1997) when the same boundary conditions are chosen. Differences might be attributed to the unlike initial conditions employed and to the use of inert gas in the literature case. In addition, final times for primary drying for both sample longitudes are compared in Table 3 to those reported in (Mascarenhas et al., 1997; Millman et al., 1985), showing also good agreement with literature.

Once stated the proper dynamic response of the developed matrix-scale model, it has been used to analyze the freeze-drying process of a 10 mm thick sample. For this new case, both sublimation and secondary drying stages have been simulated. The drying stage starts at the end of the sublimation phenomena. During this stage the whole sample can be considered dried. This new scenario is entirely governed by the heat transfer mechanism corresponding to the dried material, so it can be described by Equation (1) and boundary conditions defined by Equations (3)-(4). The same numerical procedure employed in the validation case has been used to solve the 10 mm sample thickness case study, by using the data and parameters shown in Table 2.

The product temperature profiles at different times can be seen in Figure 4. Both regions (dried and frozen) are well defined in the plot, being the lowest temperature point the one corresponding to the sublimation front. During the first 5-6 hours of the process a quick rise of temperature is detected, while a softer evolution follows next. Under conditions defined for this case (Table 2), the time needed to complete the primary drying was around 23.9 hours, being the secondary drying time of 6 hours.

Figure 5 shows the evolution in time for the temperature and position of the sublimation front during the primary drying stage. The behavior of the front temperature follows the same trend as the whole product: an initial high increase, followed by a smooth evolution. The water content profiles for different sample positions during the complete freeze-drying cycle are depicted in Figure 6.

As reported in (Furmaniak et al., 2009; Jouppila & Roos, 1994; Jouppila et al., 1997), Equation (13) is limited to a certain range of a_w values. Numerically, this requires the adjustment of the water activities also in the simulations. From the results obtained, it is possible to determine the required freeze-drying cycle time required to fulfill a given quality specification for the product. In this case, an average moisture content (C_b^{ave}) below 0.02

268 *kg water/kg solids* at the end of the process has been selected, which cor-
 269 responds to an average of 2% of water content. To attain such a product
 270 quality requirement, the process takes about 30 hours.

271 3.2. Optimal Control

272 Based on the *matrix scale model* previously developed, different scenarios
 273 have been devised (i.e. different pressure and temperature configurations in
 274 the equipment). These alternatives can be evaluated as a function of the
 275 moisture content in the product.

276 Such assessment has been formulated as a dynamic optimization problem.
 277 The aim is to minimize the freeze-drying cycle time t_f , while satisfying both
 278 product stability specifications (C_b^{ave}) as well as process dynamics. Stabil-
 279 ity conditions are related to the product temperature (T), which must be
 280 lower than the glass transition temperature (T_g) at any point of the sample
 281 during the whole freeze-drying cycle. Process dynamics is that described
 282 by equations (1)-(13) discussed in Section 2 which we formally represent as
 283 $f(\dot{x}, x, u, p, t) = 0$. Mathematically, the problem can be stated as follows:

$$\min_u t_f \quad (14)$$

284 subject to:

$$f(\dot{z}, z, u, p, t) = 0 \quad (15)$$

$$C_b^{ave}(t_f) = 0.02 \text{ kg water/kg solid} \quad (16)$$

$$T(x, t) \leq T_g \quad (17)$$

$$223K \leq T_L \leq 323K \quad (18)$$

$$10 \text{ Pa} \leq P_c \leq 60 \text{ Pa} \quad (19)$$

289 where $z \in \mathbb{R}^\alpha$ are the states, $\dot{z}$ are their derivatives, $u \in \mathbb{R}^{nu}$ is the control
 290 vector that includes shelf temperature T_L and chamber pressure P_c , and p
 291 $\in \mathbb{R}^{np}$ are a given set of parameters. The target average moisture content
 292 (C_b^{ave}) is considered as an end point constraint while the quality requirements
 293 ($T \leq T_g$) are taken into account as path constraints. As such, the latter will
 294 be introduced as penalties in the objective function. The upper and lower
 295 bounds for the considered controls have been chosen based on operational
 296 limitations of freeze-drying equipments.

297 It must be mentioned that the values of T_g during the complete cycle were
 298 obtained by using the Gordon-Taylor equation (Gordon & Taylor, 1952):

$$T_g = \frac{w_1 T_{g1} + k_{GT} w_2 T_{g2}}{w_1 + k_{GT} w_2} \quad (20)$$

299 Here, T_g is the glass transition temperature of the sample, $w_1 = 1 - C_b$ and
 300 $w_2 = C_b$ are the weight fractions of matrix and water respectively. T_{g1} and
 301 T_{g2} are the glass transition temperatures of skim milk and water, and k_{GT}
 302 is a constant¹. Parameter values corresponding to skim milk are taken from
 303 (Jouppila et al., 1997). For this system a constant shelf temperature and
 304 chamber pressure profile which leads to a cycle time (t_f) = 29.888 *h* and sat-
 305 isfies a final average moisture content not larger than 0.02 *kg water/kg solids*
 306 is presented in Figure 7. For this case, it is shown that at the beginning of the
 307 secondary drying, the product temperature is above that of glass transition.
 308 Such dynamic behavior could lead to a collapsing phenomenon of the dried
 309 porous matrix and therefore, to rejection of the batch.

310 In order to overcome the drawbacks related to operate close to or over the
 311 collapse conditions, we propose the optimal control problem (14-19). As a
 312 first approximation, we consider the case of solving a simple NLP problem to
 313 determine optimal constant profiles along the whole operation time horizon
 314 for the decision variables (T_L and P_c). Mathematically, this scenario is anal-
 315 ogous to Problem (14-19), with $u = [T_L, P_c]$ and $T_{chamb} = 298$ *K*. For this
 316 case, the value obtained for the optimal freeze-drying cycle time is $t_f = 38.45$
 317 *h*. This value is a 28.6% higher than the base case considered with T_L and
 318 P_c defined by the values referred to in Table 2. Such significant increase in
 319 operation time is the price to pay to avoid any violation of the temperature
 320 constraint (17) at any point of the sample and at any time. This behavior is
 321 shown in Figure 8, where the product and the glass transition temperature
 322 evolutions are represented at different sample positions. As a result, quality
 323 requirements for the final product are ensured but through penalizing the to-
 324 tal process time. For this operational scenario, the associated water contents
 325 at different sample positions are depicted in Figure 9.

326 Next, variable control profiles will be considered to reduce the process
 327 time needed while preserving product stability and quality. A Control Vector
 328 Parameterization approach (Vassiliadis, 1993; Vassiliadis et al., 1994) has been

¹The temperature in this equation must be given in degrees Celsius

employed to transform (14-19) into a non-linear optimization problem (NLP) of low dimension. To that purpose, the selected operation time horizon is divided into ρ time intervals and, the controls (T_L, P_c) are approximated by piece-wise constant functions in each interval. Practical considerations regarding the operation of freeze-dryers on real food and biotechnological processing plants suggest such a kind of approximation.

Different optimization algorithms can be used to solve the resulting NLP problem. Based on previous work developed by the Process Engineering Group of IIM-CSIC (Egea et al., 2007, 2009), eSS-SSm *Enhanced Scatter Search* solver (Egea et al., 2009) has been selected. This method, recently developed for solving nonlinear dynamic optimization problems, shares some features of the scatter search meta-heuristic. This algorithm is simpler and quite effective in helping to overcome typical difficulties of nonlinear dynamic systems optimization such as noise, flat areas, non-smoothness, and/or discontinuities. It provides a good balance between robustness and efficiency between the global and local search, outperforming other state-of-the-art methods.

3.2.1. One Control Variable Optimization (shelf temperature T_L)

In this subsection, the same scenario analyzed in previous works on freeze-drying optimization (Trelea et al., 2007) is considered. The aim is to solve the NLP problem (14-19) when only one control variable (shelf temperature, T_L) is taken into account. Moreover, the operation time horizon is now unfixed, becoming the duration of the sublimation and drying stages two new decision variables. The associated optimization problem is defined as follows:

$$\min_u t_f (\equiv t_{sub} + t_{dry}) \quad (21)$$

subject to:

$$f(\dot{z}, z, u, p, t) = 0 \quad (22)$$

$$C_b^{ave}(t_f) = 0.02 \text{ kg water/kg solid} \quad (23)$$

$$T(x, t) \leq T_g \quad (24)$$

$$223K \leq T_L \leq 323K \quad (25)$$

where now $u = [T_L, t_{sub}, t_{dry}] \in \mathbb{R}^{2\rho+2}$ and $P_c = 10 \text{ Pa}$ and $T_{chamb} = 298 \text{ K}$ are constant along the five intervals ($\rho = 5$) in which the sublimation and drying time horizons have been divided. In this case, the value obtained for

the optimal cycle time is $t_f = 31.64 \text{ h}$, which supposes a decrease of up to 17.71% when compared to the one attained for the optimal constant control variables case ($t_f = 38.45 \text{ h}$). Note that no violations of the temperature constraint were detected (as shown in Figure 10), fulfilling the desired quality properties of the final product.

The water content evolutions at different sample positions and the optimal control profile for T_L are presented in Figure 11 and Figure 12, respectively. It must be noted that an increase of control discretization (ρ) would improve the freeze-drying operation time. However, such refinement could lead to a significant increase of the computational requirements to solve the problem. Consequently, a compromise between ρ and computation costs must be achieved. In this work, and based on several tests performed, it was concluded that the selected level of discretization $\rho = 5$ is enough to clearly improve process time without the need of intensive computational efforts.

3.2.2. Two Control Variables Optimization (T_L and P_c)

The influence of changes in chamber pressure over the freeze-drying cycle and its duration is analyzed next. To that purpose, two control variables, T_L and P_c , are considered. The NLP problem (14-19) is now defined as:

$$\min_u t_f (\equiv t_{sub} + t_{dry}) \quad (26)$$

subject to:

$$f(\dot{z}, z, u, p, t) = 0 \quad (27)$$

$$C_b^{ave}(t_f) = 0.02 \text{ kg water/kg solid} \quad (28)$$

$$T(x, t) \leq T_g \quad (29)$$

$$223K \leq T_L \leq 323K \quad (30)$$

$$10 \text{ Pa} \leq P_c \leq 60 \text{ Pa} \quad (31)$$

where $u = [T_L, P_c, t_{sub}, t_{dry}] \in \mathbb{R}^{4\rho+2}$.

Practical considerations regarding the operation of freeze-dryers on real food and biotechnological processing plants suggest to use step changes (piece-wise constant intervals for control discretization) over the chamber pressure (P_c). By comparing the water contents of the sample at different positions for the current case (Figure 13) with the ones obtained for the optimal constant controls ($T_L=251.75 \text{ K}$ and $P_c=25.398 \text{ Pa}$) scenario (Figure 9), a notable gain is obtained in terms of operation time. The cycle time for this optimal

391 two control variables scenario is $t_f = 28.667 h$, which represents a significant
 392 reduction of $9.783 h$ ($\approx 25.5 \%$) and $2.973 h$ ($\approx 9.40 \%$) when compared to op-
 393 timal constant profiles and one control variable (T_L) cases, respectively. Shelf
 394 temperature profile (Figure 14) diminished due to self-cooling effect (Trelea
 395 et al., 2007) since ice sublimation rate decreases when the mass transfer resis-
 396 tance through the dry layer increases. During secondary drying, the moisture
 397 content of the product reduces, thus increasing the glass transition tempera-
 398 ture in the product. As a consequence of those combined effects, the risk of
 399 collapse disappears since product temperature will be below T_g , leading to
 400 the possibility of increasing significantly the shelf temperature. As expected,
 401 the profiles shown in Figure 14 and Figure 15 are quite smooth during the
 402 primary drying, as compared with the secondary drying stage. This results
 403 into an easier implementation of those profiles into freeze-dryers. Regarding
 404 temperature constraint violations no problems have been detected as shown
 405 in Figure 16. As a consequence, the porous structure and, therefore, quality
 406 of the final product is ensured while drastically reducing process time.

407 4. Conclusions

408 A novel low-dimensional model based on a time-scale simplification ap-
 409 proach (the *matrix-scale model*) has been presented and its performance con-
 410 fronted with literature data. This model constitutes the core of the proposed
 411 optimal control approach, which defines the operation conditions for mini-
 412 mizing freeze-drying cycle time while preserving product quality (final water
 413 content) through the solution of a dynamic NLP.

414 For the case study considered, various control scenarios have been ana-
 415 lyzed. First, constant optimal control profiles for T_L and P_c along the process
 416 time horizon were considered, overcoming temperature constraint violations
 417 that could lead to collapse of the product porous structure. For this scenario,
 418 final product quality is ensured at the expenses of an increase of about the
 419 29% of the cycle time as compared with a standard non-optimal constant
 420 profile ($T_L = 263 K$ and $P_c = 10 Pa$). After that, variable control profiles
 421 were proved to be successful in reducing process time while satisfying product
 422 quality standards. The resulting optimal profiles for (T_L, P_c) led to reduc-
 423 tions of up to an 17.71% (one control variable case - T_L) and 25.5% (two
 424 control variable case - T_L and P_c) of the cycle time when compared with the
 425 case under optimal constant controls ($T_L = 251.75 K$ and $P_c = 25.398 Pa$).

The implementation on a freeze-drying pilot plant of the optimal profiles obtained is the purpose of future work to be performed by authors. As it might be expected such optimal operation practices will ensure product quality with a significant reduction of process time.

Acknowledgements

The authors acknowledge the financial support received from the 7th Framework Programme of the European Union (CAFE Project - Large Collaborative Project: KBBE-2007-2-3-01), the Spanish Government (MICINN Project AGL2008-05267-C03-01) and Xunta de Galicia (IDECOP 08DPI007402PR). Author Estefania Lopez-Quiroga also acknowledges the financial support of FPI programme (Spanish Government, MICINN).

Appendix A. Time-scale analysis for model reduction

Mass transfer equations

The evolution of water desorption in the product is obtained from the vapor pressure in the dried region by solving the following Initial Value Problem (IVP):

$$\frac{dC_b}{dt}(t) = K_g (C_{b_{eq}} - C_b(t)), \forall x \in [0, S(t)) \quad (\text{A.1})$$

$$C_{b_{eq}} = \frac{m_m C_G K_{GAB} a_w}{(1 - a_w K_{GAB}) [1 + (C_g - 1) a_w K_{GAB}]} \quad (\text{A.2})$$

$$C_{b_{ini}} = C_b(x, 0) \quad (\text{A.3})$$

Mass vapor transport through the dried region is described by a modified continuity equation which includes a desorption term. This is written as follows:

$$\varepsilon \frac{\partial \rho_v}{\partial t} = -\varepsilon \frac{\partial (\rho_v \vartheta)}{\partial x} - \rho_M \frac{dC_b}{dt}, \forall x \in (0, S(t)) \quad (\text{A.4})$$

where ε is the void volume fraction in the dried layer. Darcy's law is used to compute the vapour flux velocity:

$$\vartheta = -\frac{K_m}{\mu} \left(\frac{\partial P_v}{\partial x} \right) \quad (\text{A.5})$$

450 Substituting (A.5) into (A.4) we get:

$$\varepsilon \frac{\partial \rho_v}{\partial t} = -\varepsilon \frac{\partial}{\partial x} \left(-\rho_v \frac{K_m}{\mu} \frac{\partial P_v}{\partial x} \right) + \rho_m \frac{dC_b}{dt}, \quad \forall x \in (0, S(t)) \quad (\text{A.6})$$

451 This equation describes the motion of the vapor in the porous matrix.

452

453 Heat transfer equations in the dried region

454 For the porous material, transfer mechanisms comprise heat conduction,
455 bounded water sublimation heat and heat transfer between solid matrix and
456 vapor:

$$\frac{\partial T_M}{\partial t} = \alpha_M \frac{\partial^2 T_M}{\partial x^2} + \frac{\Delta H_s}{C_{pM}} \frac{dC_b}{dt} - \frac{h_{mv} S_{mv}}{\rho_M C_{pM}} (T_M - T_V), \quad \forall x \in (0, S(t)) \quad (\text{A.7})$$

457 with T_M being the temperature of the porous matrix and h_{mv} the heat trans-
458 fer coefficient. Denoting the characteristic diameter by d_p , the contact surface
459 between matrix and vapor can be defined as $S_{mv} = \frac{6(1-\varepsilon)}{d_p}$ (Mhimid et al.,
460 2000).

461 For the vapor flux, heat transfer comprises conduction, advection, bounded
462 water sublimation heat, and heat transfer between solid matrix and vapor:

$$\begin{aligned} \varepsilon \frac{\partial T_V}{\partial t} + \varepsilon \vartheta \frac{\partial}{\partial x} (T_V) = & \varepsilon \alpha_v \frac{\partial^2 T_V}{\partial x^2} + \frac{\varepsilon h_{mv} S_{mv}}{C_{pv} \rho_v} (T_M - T_V) - \\ & - \frac{\rho_M f_D \Delta H_s}{C_{pv} \rho_v} + \frac{\rho_M f_D T_v}{\rho_v}, \quad \forall x \in (0, S(t)) \end{aligned} \quad (\text{A.8})$$

463 with T_V being the vapor temperature.

464 For the frozen region, heat is assumed to be transferred only by conduc-
465 tion from the bottom shelf, so that:

$$\frac{\partial T_{II}}{\partial t} = \alpha_{II} \frac{\partial^2 T_{II}}{\partial x^2}, \quad \forall x \in (S(t), L) \quad (\text{A.9})$$

466

467

468 Time-scale analysis of freeze-drying

469 The analysis makes use of dimensionless field variables (Table A.2), char-
470 acteristic times and time-scales (Table A.1) and a dimensionless space vari-
471 able:

$$\xi = \frac{x}{L} \quad (\text{A.10})$$

At the relevant time scale of the process ($\Theta_M = \frac{t\alpha_M}{L^2}$), which is in the order of the characteristic time corresponding to the porous material, and after assuming local thermal equilibrium (LTE), the process dynamics reduces to the following equations:

$$\frac{d\hat{C}_b}{d\Theta_M} = -\frac{K_g L^2}{\alpha_M} (\hat{C}_{b_{eq}} - \hat{C}_b) \quad (\text{A.11})$$

$$\frac{\partial \hat{\rho}_v}{\partial \Theta_M} = \frac{-L\vartheta^{ref}}{\varepsilon\alpha_M} \frac{\partial}{\partial \xi} (\hat{\rho}_v \hat{\vartheta}) - \frac{K_g L^2 \rho_M C_b^{ref}}{\alpha_M \varepsilon \rho_v^{ref}} (\hat{C}_{b_{eq}} - \hat{C}_b) \quad (\text{A.12})$$

$$\frac{\partial \hat{T}_{II}}{\partial \Theta_M} = \frac{\alpha_{II}}{\alpha_M} \frac{\partial^2 \hat{T}_{II}}{\partial \xi^2} \quad (\text{A.13})$$

$$\frac{\partial \hat{T}_M}{\partial \Theta_M} = \frac{\partial^2 \hat{T}_M}{\partial \xi^2} - \frac{C_b^{ref} K_g L^2 \Delta H_s}{\alpha_M C_{pM} (T_{ini} - T_L)} (\hat{C}_{b_{eq}} - \hat{C}_b) \quad (\text{A.14})$$

where the dimensionless vapour flux velocity is defined as:

$$\hat{\vartheta} = \frac{-P_v^{ref} K_m}{\vartheta^{ref} L \mu} \frac{\partial \hat{P}_v}{\partial \xi} \quad (\text{A.15})$$

For the reference values given in Table A.3, some of the terms in the RHS of Equations A.11-A.14 can be neglected, what leads to the following simplified description:

$$\begin{aligned} \frac{d\hat{C}_b}{d\Theta_M} &\simeq 0 \\ \frac{\partial(\hat{\rho}_v \hat{\vartheta})}{\partial \xi} &\simeq 0 \\ \frac{\partial \hat{T}_{II}}{\partial \Theta_M} &\simeq \frac{\alpha_{II}}{\alpha_M} \frac{\partial^2 \hat{T}_{II}}{\partial \xi^2} \\ \frac{\partial \hat{T}_M}{\partial \Theta_M} &\simeq \frac{\partial^2 \hat{T}_M}{\partial \xi^2} \end{aligned} \quad (\text{A.16})$$

- 480 System A.16 (together with the corresponding boundary conditions), when
 481 re-written back in the original variables, is the model we referred to as *the*
 482 *matrix scale model* in Section 2.
- 483 Alves, O., & Roos, Y. H. (2006). Advances in multi-purpose drying opera-
 484 tions with phase and state transitions. *Drying Technology*, *24*, 383–396.
- 485 van den Berg, C., & Bruin, S. (1981). Water activity and its estimation in
 486 foods systems:theoretical aspects. New York, NY: Academic Press volume
 487 Water activity: Influences on Food Quality pp 1-61.
- 488 Bird, R. B., Stewart, W. E., & Lightfoot, E. N. (2007). *Transport Phenom-*
 489 *ena*. (2nd ed.). John Wiley and Sons Inc.
- 490 Boss, E. A., Filho, R. M., & de Toledo, E. C. V. (2004). Freeze-drying
 491 process: real time model and optimization. *Chemical Engineering and*
 492 *Processing*, *43*, 1475–1485.
- 493 Bruttini, R., Rovero, G., & Baldi, G. (1991). Experimentation and mod-
 494 elling of pharmaceutical lyophilization using a pilot plant. *The Chemical*
 495 *Engineering Journal*, *45*, B67–B77.
- 496 Crank, J. (1984). *Free and moving boundary problems*. Oxford, UK: Claren-
 497 don Press.
- 498 Donea, J., Huerta, A., Ponthot, J.-P., & Rodriguez-Ferran, A. (2004). Arbi-
 499 trary lagrangian-eulerian methods. In E. Stein, R. de Borst, & T. J. Hughes
 500 (Eds.), *Encyclopedia of Computational Mechanics* chapter 14. John Wiley
 501 & Sons.
- 502 Egea, J., Rodríguez-Fernández, M., Banga, J., & Martí, R. (2007). Scat-
 503 ter search for chemical and bio-process optimization. *Journal of Global*
 504 *Optimization*, *37*, 481–503.
- 505 Egea, J. A., Balsa-Canto, E., Garcia, M. S., & Banga, J. R. (2009). Dynamic
 506 optimization of non linear processes with an enhanced scattered search
 507 method. *Industrial & Engineering Chemistry Research*, *48*, 4388–4401.
- 508 Furmaniak, S., Terzyk, A. P., Golembiewski, R., Gauden, P. A., & Czepirski,
 509 L. (2009). Searching the most optimal model of water sorption on foodstuffs
 510 in the whole range of relative humidity. *Food Research International*, *42*,
 511 1203–1214.

- 512 Gan, K. H., Bruttini, R., & Crosser, O. K. (2004). Heating policies during the
513 primary and secondary drying stages of the lyophilization in vials: Effects
514 of the arrangement of vials in clusters of square and hexagonal arrays on
515 trays. *Drying Technology*, 22, 1539–1575.
- 516 Gordon, M., & Taylor, J. S. (1952). Ideal copolymers and the second-order
517 transitions of synthetic rubbers. *Journal of Applied Chemistry*, 2, 493–500.
- 518 Jouppila, K., Kansikas, J., & Roos, Y. H. (1997). Glass transition , water
519 plasticization, and lactose crystallization in skim milk powder. *Journal of*
520 *Dairy Science*, 80, 3152–3160.
- 521 Jouppila, K., & Roos, Y. H. (1994). Water sorption and time-dependent
522 phenomena of milk powders. *Journal of Dairy Science*, 77, 1798–1808.
- 523 Liapis, A., & Bruttini, R. (1994). A theory for the primary and secondary
524 drying stages of the freeze-drying of pharmaceutical crystalline and amor-
525 phous solutes: comparison between experimental data and theory. *Sepa-*
526 *ration Science and Technology*, 4, 144–154.
- 527 Liapis, A. I., Pikal, M. J., & Bruttini, R. (1996). Research and development
528 needs and opportunities in freeze-drying. *Drying Technology*, 14, 1265–
529 1300.
- 530 Litchfield, R. J., & Liapis, A. I. (1979). An adsorption-sublimation model
531 for a freeze-dryer. *Chemical Engineering Science*, 34, 1085–1090.
- 532 Litchfield, R. J., & Liapis, A. I. (1982). Optimal control of a freeze-dryer ii:
533 dynamic analysis. *Chemical Engineering Science*, 37, 45–55.
- 534 Mascarenhas, W. J., Akay, H. U., & Pikal, M. J. (1997). A computational
535 model for for finite element analysis of the freeze-drying process. *Computer*
536 *Methods on Applied Mechanics and Engineering*, 148, 105–124.
- 537 Mhimid, A., Nasrallah, S. B., & Fohr, J. P. (2000). Heat and mass trans-
538 fer during drying of granular products- simulation with convective and
539 conductive boundary conditions. *International Journal of Heat and Mass*
540 *Transfer*, 43, 2779–2791.
- 541 Millman, M. J., Liapis, A. I., & Marchello, J. M. (1984). Guidelines for the
542 desirable operation of batch freeze dryers during removal of free water.
543 *Journal of Food Technology*, 19, 725–738.

- 544 Millman, M. J., Liapis, A. I., & Marchello, J. M. (1985). An analysis of
545 the lyophilization process using a sorption-sublimation model and various
546 operational policies. *AIChE Journal*, *31*, 1594–1604.
- 547 Pikal, M. J. (2000). Heat and mass transfer in low pressure gases: ap-
548 plications to freeze-drying. chapter 16. volume Transport Processes in
549 Pharmaceutical Systems of *Drugs and the Pharmaceutical Science*.
- 550 Pikal, M. J., Cardon, S., Bhugra, C., Jameel, F., & Rambhatla, S. (2005).
551 Non steady state modeling of freeze-drying: in-process product temper-
552 ature and moisture content mapping and pharmaceutical product quality
553 applications. *Pharmaceutical Development and Technology*, *1*, 17–32.
- 554 Pikal, M. J., Roy, M. L., & Shah, S. (1983). Mass and heat transfer in vial
555 freeze-drying of pharmaceuticals: role of the vial. *Journal of Pharmaceu-
556 tical Sciences*, *73*, 1224–1237.
- 557 Pikal, M. J., & Shah, S. (1990). The collapse temperature in freeze-drying:
558 Dependence on measurement methodology and rate of water removal from
559 the glassy state. *International Journal of Pharmacy*, *62*, 165–186.
- 560 Pisano, R., Fissore, D., Velardi, S. A., & A. Barresi, A. (2010). In-line opti-
561 mization and control of an industrial freeze-drying process for pharmaceu-
562 ticals. *Journal of Pharmaceutical Sciences*, *99*, 4691–4709.
- 563 Ratti, C. (2001). Hot air and freeze-drying of high value foods: a review.
564 *Journal of Food Engineering*, *49*, 311–319.
- 565 Rene, F., Wolff, E., & Rodolphe, F. (1993). Vacuum freeze-drying of a
566 liquid in a vial: determination of heat and mass transfer coefficients and
567 optimisation of operating pressure. *Chemical Engineering and Processing*,
568 *32*, 245–251.
- 569 Roth, K. (2007). Soil physics lecture notes v1.2.
570 [http://www.iup.uniheidelberg.de/institut/forschung/groups/ts/
571 soil_physics/students/lecture_notes05](http://www.iup.uniheidelberg.de/institut/forschung/groups/ts/soil_physics/students/lecture_notes05).
- 572 Sadikoglu, H. (2005). Optimal control of the secondary drying stage of solu-
573 tions in vials using variational calculus. *Drying Technology*, *23*, 33–57.

- 574 Sadikoglu, H., & Liapis, A. I. (1997). Mathematical modelling of the pri-
 575 mary and secondary drying stages of bulk solution freeze-drying in trays:
 576 parameter estimation and model discrimination by comparison of theoret-
 577 ical results with experimental data. *Drying Technology*, 15, 791–810.
- 578 Sadikoglu, H., Liapis, A. I., & Crosser, O. K. (1998). Optimal control of
 579 the primary and secondary drying stages of bulk solution freeze-drying in
 580 trays. *Drying Technology*, 16, 399–431.
- 581 Song, C., Nam, J. H., Kim, C.-J., & Ro, S. T. (2002). A finite volume analysis
 582 of vacuum freeze-drying processes of skim milk in trays and vials. *Drying*
 583 *Technology*, 20, 283–305.
- 584 Trelea, I. C., Passot, S., Fonseca, F., & Michele, M. (2007). An interactive
 585 tool for the optimization of freeze-drying cycles based on quality criteria.
 586 *Drying Technology*, 25, 741–751.
- 587 Vassiliadis, V. S. (1993). *Computational solutions of dynamic optimization*
 588 *problems with general differential-algebraic constraints*. Ph.D. thesis Im-
 589 perial College, University of London.
- 590 Vassiliadis, V. S., Pantelides, C. C., & Sargent, R. W. H. (1994). Solution of a
 591 class of multistage dynamic optimization problems. *Engineering Chemistry*
 592 *Research*, 33, 2111–2122.
- 593 Velardi, S. A., & Barresi, A. A. (2008). Development of simplified mod-
 594 els for freeze-drying processes and investigation of the optimal operating
 595 conditions. *Chemical Engineering Research and Design*, 86, 9–22.
- 596 Wang, W., & Chen, G. (2005). Heat and mass transfer model of dielectric-
 597 material-assisted microwave freeze-drying of skim milk with hygroscopic
 598 effect. *Chemical Engineering Science*, 60, 6542–6550.

List of figures

Figure 1: Freeze-drying physical phenomena represented on the water phase diagram.

Figure 2: Scheme of the freeze-drying process.

Figure 3: Profiles for the product temperature evolution in time at different sample positions: (A) Matrix scale results vs (B) (Mascarenhas et al., 1997).

Figure 4: Product temperature profiles at different times for the skim-milk freeze-drying case during the primary drying.

Figure 5: (A) Sublimation front position evolution during primary drying for the skim-milk case: a quasi linear behaviour for the evolution of the sublimation front position can be seen. (B) Front temperature profile during the primary drying: fast increasing of the front temperature during the first hours while smoother evolution is observed in the final part of the process.

Figure 6: Profiles for the sample water content at different positions during the complete freeze-drying cycle. The horizontal straight line represent the final moisture requirement $C_b = 0.02 \text{ kg water/kg solid}$.

Figure 7: Product temperature (solid line) and glass transition temperature (dotted line) at different positions during the complete freeze-drying cycle with constant $T_L = 263 \text{ K}$ (for primary drying), $T_L = 283 \text{ K}$ (for secondary drying) and $P_c = 10 \text{ Pa}$ profiles. The shelf temperature profile considered is represented on the upper left figure (dash-dotted line). The final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$) is attained for a final cycle time of 29.888 h.

Figure 8: Product temperature (solid line) and glass transition temperature (dotted line) at different positions during the complete freeze-drying cycle with constant optimal control profiles for $T_L = 251.75 \text{ K}$ and $P_c = 25.398 \text{ Pa}$. The final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$) is attained for a final cycle time of 38.45 h.

Figure 9: Profiles for the sample water content at different positions during

the complete freeze-drying cycle with constant optimal control profile for $T_L = 251.75 \text{ K}$ and $P_c = 25.398 \text{ Pa}$. The horizontal straight line represent the final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$).

Figure 10: Product temperature (solid line) and glass transition temperature (dotted line) at different positions during the complete freeze-drying cycle with optimal control profile for T_L and constant $P_c = 10 \text{ Pa}$. The shelf temperature profile considered is represented on the upper left figure (dash-dotted line). The final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$) is attained for a final cycle time of 31.64 h .

Figure 11: Profiles for the sample water content at different positions during the complete freeze-drying cycle with optimal control profile for T_L and constant $P_c = 10 \text{ Pa}$. The horizontal straight line represents the final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$).

Figure 12: Optimal T_L profile for the scenario of one control variable.

Figure 13: Profiles for the sample water content at different positions during the complete freeze-drying cycle with optimal control profiles for T_L and P_c . The horizontal straight line represents the final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$).

Figure 14: Optimum temperature control profile obtained with SSm for the dynamic optimization of a freeze-drying cycle for a skim-milk sample. Two control variables considered: T_L and P_c .

Figure 15: Optimum pressure control profile obtained with SSm for the dynamic optimization of a freeze-drying cycle for a skim-milk sample. Two control variables considered: T_L and P_c .

Figure 16: Product temperature (solid line) and glass transition temperature (dotted line) at different positions during the complete freeze-drying cycle with optimal control profiles for T_L and P_c . The shelf temperature profile considered is represented on the upper left figure (dash-dotted line). The final moisture requirement ($C_b^{ave} = 0.02 \text{ kg water/kg solids}$) is attained for a final cycle time of 28.667 h .

Figure 1:

Figure 2:

Figure 3:

Figure 4:

Figure 5:

Figure 6:

Figure 7:

Figure 8:

Figure 9:

Figure 10:

Figure 11:

Figure 12:

Figure 13:

Figure 14:

Figure 15:

Figure 16:

675 ***List of tables***

676

677 **Nomenclature.**

678

679 **Table 1:** Characteristic times of the freeze-drying phenomena.

680

681 **Table 2:** Input data and parameters. PD = primary drying; SD = secondary
682 drying. All temperatures are in Kelvin, pressure is in Pascal.

683

684 **Table 3:** Primary drying times (in minutes): comparison with literature.

685

686 **Table A.1:** Characteristic times and dimensionless time scales of the freeze-
687 drying phenomena.

688

689 **Table A.2:** Dimensionless field variables.

690

691 **Table A.3:** Reference values.

692

Nomenclature

α_I	Dried layer thermal diffusivity [m^2/s]
α_{II}	Frozen layer thermal diffusivity [m^2/s]
α_v	Vapour thermal diffusivity [m^2/s]
k_I	Dried layer heat conductivity [W/mK]
k_{II}	Frozen layer heat conductivity [W/mK]
ρ_I	Dried layer density [kg/m^3]
ρ_{II}	Frozen layer density [kg/m^3]
ρ_v	Vapour density [kg/m^3]
K_m	Dried material permeability [m^2]
μ	Vapour viscosity [$Pa\ s$]
v_{ref}	Vapour reference velocity [m/s]
σ	Stefan-Boltzmann constant [W/m^2K^4]
e_p	Vapour chamber emissivity
f_p	View factor for the shelf radiation flux
h_L	Convective heat coefficient [W/m^2K]
ΔH_s	Sublimation enthalpy [J/kg]
L	Sample length [m]
K_g	Desorption coefficient [$1/s$]

Phenomena	Characteristic times	Order of magnitude
Desorption	$\tau_b = \frac{1}{K^g}$	hours
Heat transfer in the porous dried matrix	$\tau_I = \frac{L^2}{\alpha_I}$	minutes
Heat transfer in the frozen region	$\tau_{II} = \frac{L^2}{\alpha_{II}}$	seconds
Heat transfer in the vapour phase	$\tau_{v\alpha} = \frac{L^2}{\alpha_v}$	milliseconds
Mass transfer in the vapour phase	$\tau_{vc} = \frac{L}{v_{ref}}$	milliseconds

Table 1:

Parameter	Value	Reference
C_{pI}	2595	(Mascarenhas et al., 1997)
ρ_I	145	(Mascarenhas et al., 1997)
C_{pII}	1967.8	(Mascarenhas et al., 1997)
ρ_{II}	1058	(Mascarenhas et al., 1997)
k_I	$8.826 \times 10^{-5} P_v$ $+2.706 \times 10^{-2}$	(Mascarenhas et al., 1997)
k_{II}	2.4	(Mascarenhas et al., 1997)
K_g	11.08×10^{-5}	(Mascarenhas et al., 1997)
K_m	3.62×10^{-10}	(Liapis & Bruttini, 1994)
μ	8.36×10^{-6}	(Wang & Chen, 2005)
f_p	0.99	(Pikal, 2000)
e_p	0.94	(Pikal et al., 1983)
ΔH_s	2.79×10^6	(Mascarenhas et al., 1997)
$m_m(\%)$	5.123	(Furmaniak et al., 2009)
K_{GAB}	0.9394	(Furmaniak et al., 2009)
C_G	5.512	(Furmaniak et al., 2009)
T_{g1}	370	(Jouppila et al., 1997)
T_{g2}	138	(Jouppila et al., 1997)
k_{GT}	6.7	(Jouppila et al., 1997)
σ	5.6704×10^{-8}	
T_{ini}	227	
T_c	298	
T_L	263 (PD) 283 (SD)	
P_c	10	

Table 2:

Sample length	Authors	Mascarenhas et al. (1997)	Millman et al. (1985)
$L = 3 \text{ mm}$	13.66 <i>min</i>	13.77 <i>min</i>	13.47 <i>min</i>
$L = 6 \text{ mm}$	54.83 <i>min</i>	55.26 <i>min</i>	54.07 <i>min</i>

Table 3:

Phenomena	Characteristic Times	Dimensionless Time Scale
Desorption	$\tau_b = \frac{1}{K_g}$	$\Theta_b = tK_g$
Heat transfer in the porous dried matrix	$\tau_M = \frac{L^2}{\alpha_I}$	$\Theta_M = \frac{t\alpha_M}{L^2}$
Heat transfer in the frozen region	$\tau_{II} = \frac{L^2}{\alpha_{II}}$	$\Theta_{II} = \frac{t\alpha_{II}}{L^2}$
Heat transfer in the vapor phase	$\tau_{v\alpha} = \frac{L^2}{\alpha_v}$	$\Theta_{v\alpha} = \frac{t\alpha_v}{L^2}$
Mass transfer in the vapor phase	$\tau_{vc} = \frac{L}{n^{ref}}$	$\Theta_{vc} = \frac{tv}{L}$

Table A.1:

Variables	Dimensionless fields
Temperature in the frozen region	$\hat{T}_{II} = \frac{T_{II} - T_{ini}}{T_L - T_{ini}}$
Temperature of the water vapour	$\hat{T}_v = \frac{T_v - T_{ini}}{T_L - T_{ini}}$
Temperature of the porous matrix	$\hat{T}_M = \frac{T_M - T_{ini}}{T_L - T_{ini}}$
Temperature of the sublimation front	$\hat{T}_s = \frac{T_s - T_{ini}}{T_L - T_{ini}}$
Density of the vapour	$\hat{\rho}_v = \frac{\rho_v}{\rho_v^{ref}}$
Thermal conductivity of the vapor	$\hat{k}_v = \frac{k_v}{k_v^{ref}}$
Heat capacity of the vapour	$\hat{C}_{pv} = \frac{C_{pv}}{C_{pv}^{ref}}$
Concentration of bounded water	$\hat{C}_b = \frac{C_b}{C_b^{ref}}$
Vapour flux velocity	$\hat{\vartheta} = \frac{\vartheta}{\vartheta^{ref}}$
Front position	$\hat{X} = \frac{X}{L}$
Vapour pressure	$\hat{P}_v = \frac{P_v}{P_v^{ref}}$

Table A.2:

Parameters of reference	Values
$C_{p_v}^{ref}$	1674.7 [J/kgK]
ρ_v^{ref}	$1.54e^{-3}$ [kg/m^3]
k_v^{ref}	0.016 [W/mK]
C_b^{ref}	0.22 [$kg\ water/kg\ solids$]
ϑ^{ref}	2.05 [m/s]
L	3[mm]

Table A.3: