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In-line control of a freeze-drying process in vial

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Abstract

This paper deals with the control of a freeze-drying process in vials. Firstly, the results that can be obtained when the operation is carried out at constant chamber pressure and shelf temperature are predicted by means of mathematical simulation, using a previously validated detailed model, thus allowing to optimise off-line the process.

Further improvements can be obtained if the shelf temperature is varied during the process in such a way that the product temperature is always maintained at the maximum allowable value. This strategy for the in-line control of the process allows to minimise the time required for the primary drying, beside satisfying the process constraints. The possibility of manipulating the chamber pressure for control purposes is also discussed.

An alternative strategy based on a simple feedback controller, with proportional-integral action, is also investigated: it is able to control the product temperature at a pre-determined value, giving stable and fast responses. The controller uses a soft-sensor to get in-line a reliable estimate of the controlled variable, i.e. of the maximum temperature of the product

Keywords

Freeze-drying control, Primary drying, Model-based control, Feedback control

Introduction

Freeze-drying is the process that removes water (or another solvent) from a frozen solution by sublimation. The process consists of three steps;

1. *freezing*, when the solution containing the product to be dried is frozen;
2. *primary drying*, when the ice is sublimated, operating under low pressure (heat is continuously supplied through an heating shelf as the sublimation process is endothermic);
3. *secondary drying*, when the residual moisture, which is strongly bounded to the partially dried cake, is reduced to a low level, thus ensuring the long term preservation of the product (this step is usually carried out at high vacuum and moderate temperature, from +20 to +60°C).

This paper is focused on the control of the primary drying phase of a freeze-drying process of pharmaceuticals in vials: primary drying is generally the longest and the most expensive step of the whole process.

Currently, even the most advanced industrial freeze-dryers have control systems that are no more than data acquisition systems for certain key variables (Liapis et al., 1996). Monitored data and information obtained in previous runs, carried out with the same formulation, are used to manage the process. In some cases the working temperature is selected by the operator, as well as the temperature ramp required to reach the working temperature: this, however, may not guarantee repeatable conditions for the freezing and sublimation steps. In some other cases the working temperature is obtained from the mathematical simulation of the process, with the goal to optimise the process, using either semi-empirical models, that do not properly account for the heat and mass transfer mechanisms occurring during the process, or detailed models (Rene et al., 1993; Lombraña et al., 1993a and 1993b; Boss et al., 2004; Velardi and Barresi, 2007). The influence of the arrangement of the vials on the tray and of the tray side on the heating policy has also been investigated using detailed multidimensional models (Gan et al., 2004; Gan et al. 2005).

Poor process control is a consequence of the limitation of the current technology, mainly due to the impossibility, in a production process, of measuring the parameters of interest, namely the product temperature and the residual moisture content. Moreover, regulatory guidance, up to now, imposed to operate the manufacturing process in open loop, so that only an activity of monitoring is allowed during production. Nevertheless, at least during the phase of process development carried out at laboratory or pilot scale, it would be very useful to have an in-line control system to minimise the drying time, taking into account the final quality of the product: process development can be expensive and highly time consuming, but no regulatory restrictions apply during this phase and thus the use of an efficient control system can give significant advantages.

PAT (Process Analytical Technology) guidelines issued by the US FDA (Food and Drug Administration) in September 2004 describe a regulatory framework encouraging the voluntary design and implementation of innovative pharmaceutical development, manufacturing, and quality assurance to support innovation and efficiency to have safe, effective, and affordable medicines. PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality: quality cannot be tested into products, but it should be built-in or should be by design. The benefits that can be achieved by an optimal control and monitoring policy have been recently discussed by Sadikoglu et al. (2006).

The PAT guideline is at the basis of this paper, whose goal is to show how it is possible to control effectively the primary drying of a freeze-drying process in vials, thus minimising the total duration of the operation, beside maintaining the product temperature below a maximum value:

1. in case of solutes that crystallise the temperature has to be maintained below the eutectic point of the system in order to avoid the formation of a liquid phase (melting);

2. in case of solutes, such as proteins, that do not crystallise during the freezing, a glass is obtained: this can be beneficial for the preservation of the activity, but it makes the drying process more demanding in terms of process time and physical conditions, because the primary drying must be carried out below the glass transition temperature to avoid the collapse of the cake structure.

The chamber pressure and the temperature of the heating shelf are the two variables that can be used for control purposes as the mass and heat transfer strictly depend upon these variables: a change in the operating conditions to improve heat transfer may hinder mass transfer. The pressure, for example, can have an opposite effect on the two phenomena. Sandall and Wilke (1967) found experimentally and theoretically that an optimal pressure exists which maximises the drying rate. Nail (1980) and Pikal et al. (1984) showed that even if sometimes mass transfer may be the rate limiting factor, heat transfer from the heat source to the sublimation front is usually the rate limiting process due to the low pressure which reduces the gas thermal conductivity, thus increasing the heat transfer resistance in the air gaps between the vials and the tray and between the tray and the heating shelf. However, the situation seemed to be controversial since Jennings (1986), by measuring the sublimation rate of ice, found that decreasing pressure has a positive effect on the sublimation rate. Livesey and Rowe (1987) considered different situations in order to discriminate between the various effects. They pointed out that even if from a theoretical point of view the sublimation rate is expected to decrease while increasing the chamber pressure, the enhancement of the heat transfer has a more significant effect. Nevertheless, an optimum in the operating conditions can be found in order to minimise the primary drying time: Franks (1998) calculated the values of the chamber pressure and of the shelf temperature that allow to maintain a certain value of the maximum product temperature; similar results were given by Oetjen (1999) using a simplified model for the main drying. Trelea et al. (2007) used a detailed mathematical method to calculate the value of the shelf temperature that minimise the drying time, beside maintaining the product temperature below the maximum

allowable value, thus ensuring quality preservation. Velardi and Barresi (2007) used a similar approach, but included in the optimisation procedure also the chamber pressure.

Few papers appeared in the Literature about the in-line control of a freeze-drying process. Among the others, Liapis and Litchfield (1979) proposed to manipulate the radiator energy output and the total pressure in the drying chamber in order to minimise the time required to get a fixed amount of residual water in the product at the end of the primary drying step; constraints are placed on the scorch temperature of the dried product and on the melting point of the frozen interface. The application of this control strategy to secondary drying was investigated by Sadikoglu et al. (1998). In both papers a quasi steady-state model of the process is used and the temperature profile in the vial is assumed to be fully known, thus allowing to discriminate between a process whose dynamics is controlled by the heat transfer (for which the manipulation of the shelf temperature is effective) and a process whose dynamics is controlled by the mass transfer (for which the manipulation of the chamber pressure is effective). As the temperature profile is hardly known, the proposed control policies should be interpreted with caution, as it is highlighted in the conclusions of the paper of Liapis and Litchfield (1979), and in the paper of Litchfield and Liapis (1982). A similar approach was proposed by Lombraña and Diaz (1987a, 1987b), who compared two different strategies: in the first the heating is constant and the chamber pressure is varied, while in the second the chamber pressure is constant and the heating is controlled. Also in this case the temperature profile in the vial is assumed to be known and the algorithm determines if the process is under mass or heat transfer control, thus activating the most suitable controller. Variational calculus involving a detailed multidimensional model of the process has been recently used by Sadikoglu et al. (2003) and by Sadikoglu (2005) to optimise both the primary and the secondary drying stage of a vial freeze-drying process. Tang et al. (2005) and Pikal et al. (2005) proposed, and patented, an "expert system" for manipulating the shelf temperature and the chamber pressure using a

simplified model and the results obtained by means of the Manometric Temperature Measurement (see, for example, Milton et al., 1997, for details about the MTM). A similar approach, named Thermodynamic Lyophilisation Control, was proposed by Oetjen (1999) and by Oetjen and Haseley (2004): it is based on the results of the barometric temperature measurement (based on the same principle of the MTM) and on a set of heuristics for the calculation of the control actions.

In this work a mathematical model of the process is used in the control algorithm in such a way that the control action is no longer based on “rules of thumb”, but a truly optimisation of the process can be achieved. The proposed algorithm continuously changes the shelf temperature in order to minimise the time required to complete the primary drying, beside maintaining the product temperature below a maximum value. The chamber pressure is optimised as a function of the product characteristics, i.e. of the heat and mass transfer resistance; the possibility of manipulating the pressure for control purposes is also discussed. This model-based approach has some limitations: it requires that the model perfectly describes the dynamics of the process and that all the parameters and all the variables of the process are known. Due to the technical difficulties in the measurement of the temperature profile in the vial, i.e. of the controlled variable, a soft-sensor (observer) can be used to get a reliable estimation of the temperature profile. Thus, a simple feedback PI controller that uses an observer is proposed and its effectiveness is shown by means of mathematical simulations.

Two case studies are used to test the proposed control algorithms, namely a 5% solution of Bovine Serum Albumin (BSA) and skim milk; the main parameters corresponding to these two samples are given in Table 1.

Model-based control

Firstly, the case of a constant values for the chamber pressure and for the

temperature of the heating shelf for the main drying (after an initial ramp of 3 hr from the starting value) has been considered. A detailed mono-dimensional model has been used to simulate the primary drying in a vial placed in the centre of the shelf, for which radiation can be neglected (Velardi and Barresi, 2007). The time required to carry out the primary drying has been calculated for various values of the operating parameters and the results are shown in Figure 1 (upper graph): for a given T_{shelf} it is possible to find an optimum value of the chamber pressure that minimises the drying time. In fact, when operating at very low vacuum, a pressure increase leads to a diminution of the drying time because heat transfer is improved; however, if the pressure is raised beyond a certain value, the time required to complete the primary drying starts increasing because the driving force for mass transfer becomes too small and sublimation takes place slowly. The optimum condition is visible in Figure 1 (upper graph, dotted line) for the curves calculated using values of T_{shelf} lower than 260 K, while it is shifted at pressures higher than 60 Pa if T_{shelf} is higher than 260 K. The calculated couple of values of T_{shelf} and of chamber pressure that minimise the primary drying step does not take into account the presence of the constraint given by the maximum temperature that allows a safe operation without any denaturation (collapse or melting) of the product. If the maximum product temperature is taken into account (240 K in this example) the optimal pressure can become, as in this case, the minimum that can be obtained in the apparatus (dashed line).

Some advantages can be obtained if the operation is carried out with a variable T_{shelf} . For this reason a new model-based control strategy for the heating shelf is proposed: it continuously adjusts T_{shelf} during primary drying in order to maintain the product temperature at the maximum allowable value. The control law is thus expressed as:

$$T_{shelf}(t) = f(T_{p,max}, t) \quad (1)$$

In practice this corresponds to adopt an ideal control strategy since we assume to

perfectly know the process and thus to be able to calculate at any instant the value of the shelf temperature that sets the maximum product temperature ($T_{p,max}$) at the maximum allowable value ($T_{p,max}^*$) without any feedback from the system.

An example of the results that can be obtained using this approach is given in Figure 2 (l.h.s), in which again it has been assumed a maximum allowable temperature of 240 K for the product. At the beginning of the drying phase T_{shelf} is raised at a 0.5°C/min constant rate; after about 2 h of drying, when the shelf temperature reaches a value of 281 K, the maximum product temperature is approached and the control logic overrides the initial heating program (straight lines): the temperature of the shelf starts being regulated in such a way that $T_{p,max}$ remains constant and below $T_{p,max}^*$. By this way the primary drying is completed in 13.5 h, as it can be seen from the time evolution of the position of the sublimation front (Figure 2, r.h.s). If the shelf temperature is maintained constant, the product temperature is free to vary (dashed lines); thus, T_{shelf} must be fixed at a lower constant value in order not to exceed the maximum allowable temperature that is approached only at the end of the drying phase: a longer primary drying time is thus obtained (the moving front reaches the bottom of the vial after 22 h).

Various simulations of the primary drying have been carried out for different values of the pressure in the chamber and using the previously described control strategy. The results are given in Figure 1 (lower graph). In these simulations the shelf temperature is initially ramped at 0.5°C/min up to the set-point value of T_{shelf} , which parameterises the curves. Then T_{shelf} is maintained constant until the maximum product temperature reaches the value $T_{p,max}^*$ (set equal to 240 K in this example). At this point the previously described control strategy is taken. It is possible to individuate also in this case a curve (dotted line) which represents the locus of the values of chamber pressure and initial set-point shelf temperature that ensure to minimise the time required to complete the primary drying and to compare this locus with the analogous obtained in case of constant T_{shelf} . For example, if T_{shelf} is

maintained constant at 280 K and the constraint on the maximum product temperature is active, the minimum drying time (11.1 h) is obtained at a pressure of 3.3 Pa, while, when the optimal heat input strategy is adopted, a lower minimum drying time is found (10.25 h) with a higher chamber pressure (6.75 Pa), thus with minor energy consumption. Figure 3 shows the time variation of $T_{p,max}$ and T_{shelf} in both cases.

Concerning the case of constant shelf temperature (Figure 1, upper graph), it can be observed that the best operating conditions are those with $T_{shelf} \cong 300$ K and with a value of chamber pressure as low as possible, resulting in a minimum time of 10.5 h. In the case of a variable heating strategy, the pressure should be also as low as possible, but with an initial set-point $T_{shelf} \cong 320$ K the main drying ends after 9 h. Thus, it can be concluded that the proposed control strategy allows to carry out the process faster, under the constraint given by the maximum allowable temperature of the product.

These results are mainly influenced by the values of the heat and mass transfer coefficients; according to Velardi and Barresi (2007) the mass fluxes inside the pores of the dried layer are calculated using the equations of the Dusty Gas Model (Mason et al., 1967; Kast and Hohenthanner, 2000) and the heat transfer resistance between the shelf and the vial is calculated as the sum of the resistance in the glass at the bottom of the vial and of the external heat transfer resistance, that can be calculated as the sum of a convective and of a radiation contribution (Nail, 1980; Pikal, 1985; Brülls and Rasmuson, 2002). Using the result of Figure 1, i.e. that the minimum in the drying time can be obtained with the proposed temperature control, starting the operation with a shelf temperature of 320 K, we have investigated the role played by the heat and mass transfer resistance on the results. Figure 4 (upper graph) shows the time required to complete the main drying as a function of the chamber pressure for various values of the overall heat transfer coefficient (the "*" indicates the base case): it is possible to see that the higher is the overall heat transfer coefficient the lower is the value of the pressure that minimise the time required by the primary drying.

Figure 4 (lower graph) shows the influence of the mass transfer resistance: in this case the volume of the solution is varied; it is possible to see that the higher is L , i.e. the higher is the mass transfer resistance, the lower is the optimal pressure. These results are obviously dependent on the maximum temperature allowed by the product.

Figure 5 shows the optimal values of the chamber pressure as a function of the maximum temperature allowed by the product when the model-based controller is used with an initial shelf temperature of 320 K. The values of the chamber pressure calculated using the correlation of Tang et al. (2005) are also shown for comparison: if the maximum temperature allowed by the product is higher than 247 K the value of the optimal chamber pressure calculated using our approach is higher than that suggested by Tang et al. (2005), who posed a limit in the chamber pressure for $T_{p,\max}^*$ higher than -15°C .

In the proposed control algorithm the pressure is maintained constant at a value chosen in such a way that the manipulation of the shelf temperature minimise the time required to complete the main drying. A little improvement could be obtained by manipulating simultaneously the shelf temperature and the pressure; in this case the control system becomes multivariable and the calculation of the control actions becomes very complicate, due to the interaction effect. Thus, we prefer to operate with a simple control system, where only the heat supply is manipulated, and we propose to vary the pressure in the chamber only in case of emergence, when, due to errors in the off-line optimisation or to malfunctioning of the control system, the maximum temperature of the product increases beyond the limit value (Rey and May, 2004): in such a situation pulling the vacuum down immediately works as a real thermal switch with an instantaneous result, whereas cooling the shelves requires a longer time.

Figure 6 shows the results obtained for the mathematical simulation of the solution of BSA with an initial shelf temperature of 290 K: without any control action, the maximum temperature would approach 244 K. If the pressure in the chamber is

increased, the maximum product temperature increases and so, in order to reduce this value, the chamber pressure has to be decreased. In Figure 6 it is possible to see that the response of the system is very fast: a few minutes are sufficient to decrease the temperature of the product; moreover, the lower is the chamber pressure, the lower is the temperature of the product that can be obtained. Obviously, when the pressure is changed from the initial value of 6.75 Pa the operating conditions are no longer the optimal ones, and thus the time required to complete the primary drying increases. Figure 6 points out also that firstly the temperature of the product decreases (due to the lower equilibrium value), but then it starts increasing again if the temperature of the heating shelf is not modified.

Feedback control

The control strategy proposed in the previous paragraph calculates the control action using only the mathematical model of the process: this requires the perfect knowledge of all the parameters and all the variables of the process in order to have an effective control action.

Moreover, also the value of the maximum product temperature can be hardly known. In fact, if the maximum product temperature is that at the bottom of the vial it could be possible to measure it by using a thermocouple; anyway, this procedure produces a modification of the elementary phenomena of nucleation and of ice crystal growth as the tip of the thermocouple acts as an heterogeneous nucleation site: this can result in an increase of the average crystal size of the ice that leads to a lower mass transfer resistance. Furthermore, a preferential path for the vapour molecules is created by the presence of the body of the probe, and this also causes a reduction of the mass transfer resistance in the dried layer. All these effects can lead to a significant faster drying kinetics for the monitored vials which, as a consequence, can not be considered representative of the whole batch. Moreover, when dealing

with pharmaceutical products, the insertion of probes can create some problems concerning the sterility of the product. In some cases, in particular when radiation effect from the upper tray is relevant, the maximum product temperature can be that at the sublimating interface, that cannot be measured by any thermocouples as the position of the sublimation front is moving during the main drying. In this case the MTM (Milton et al., 1997) can be an effective system to estimate the interface temperature.

Inferential systems can also be used to overcome this problem. Among the others, the observer (or soft sensor) is a very powerful instrument: it combines a priori knowledge about the physical system (a mathematical model, even simplified, of the process) with some experimental data (in-line measurements, like the external temperature of the vial wall or the temperature of the product inside the vial) to provide a real-time estimation of the state of the system (temperature and concentration profiles) and of the unknown (or poorly known) parameters of the process (heat and mass transfer coefficients).

Let us consider a non-linear system:

$$\dot{x} = f(x, u) \quad (2)$$

with observations given by

$$y = c^T x \quad (3)$$

where x is the state of the system, u is the input (manipulated) and y is the output of the system (i.e the measured variables); f is a non-linear vector of functions and c is a constant vector that allows to extract the output variables y from the state x . In order to estimate the unknown state x using y and u , we can build the following non-linear observer:

$$\dot{\hat{x}} = f(\hat{x}, u) + K(\hat{x}, u)(y - \hat{y}) \quad (4)$$

The observer is thus derived from the model equation by adding a term given by the difference between the measured and the observed states multiplied by the gain K , which is a matrix, whose coefficients are non-linear functions with respect to the state

and to the input of the observer. Let us define the observation error:

$$e = x - \hat{x} \quad (5)$$

The following differential equation results after subtraction of eq. (4) from eq. (2):

$$\dot{e} = \dot{x} - \dot{\hat{x}} = f(x, u) - f(\hat{x}, u) - K(\hat{x}, u)c^T e \quad (6)$$

and describes the dynamics of the observation error. The gain K has to be calculated in order to drive asymptotically the observation error to zero, thus ensuring the convergence of the estimated state \hat{x} to the real one x .

The synthesis of an observer, i.e. the calculation of the gain K , is a complex task and a lot of methods have been proposed in the past. A Kalman filter and a High Gain observer were proposed to estimate the dynamics of the temperature of the product at any time during primary drying, as well as the effective diffusion coefficient in the dried layer, that affects mass transfer, and the heat transfer coefficient between the shelf and the vial bottom. Both observers use the measurements of the temperature at the bottom of the frozen product (Barresi et al., 2006, 2008; Velardi et al., 2007), but also the external temperature at the bottom of the vial glass can be used to this purpose (Velardi et al., 2005; Galan et al., 2007).

The control system we propose is thus based on a feedback logic that manipulates the temperature of the heating shelf T_{shelf} in order to maintain the product temperature at the maximum allowable value; an observer is used to estimate the full temperature profile in the product using the temperature measurement at the bottom of the vial. The control law corresponds to a conventional proportional-integral compensator:

$$T_{shelf}(t) = -K_p e_{PI}(t) - K_I \int_{t_0}^t e_{PI}(\tau) d\tau + T_{shelf,0} \quad (7)$$

$$e_{PI}(t) = T_{p,max,observer}(t) - T_{p,max}^* \quad (8)$$

The control action is taken when the temperature estimated by the observer, $T_{p,max,observer}$, approaches the limit value $T_{p,max}^*$, which represents the controller set-point; $e_{PI}(t)$ gives the error between the actual value of $T_{p,max,observer}$ at time t and $T_{p,max}^*$, t_0 is the starting time of the control action and $T_{shelf,0}$ is the value of the manipulated variable

at time t_0 . The proportional mode adjusts the controller signal in direct proportion to the error, according to the parameter K_P . The additional integral mode is required to eliminate the offset between the set-point and the process, according to the parameter K_I .

Figure 7 shows the results obtained simulating this feedback controller with a Kalman filter observer (Barresi et al., 2006; Galan et al., 2007) that uses the measurement of the external temperature at the bottom of the vial. The values of the tuning parameters of the PI controller have been selected in order to minimise the predicted integral of the square error (ISE), given by:

$$\min_{K_P, K_I} (ISE) = \min_{K_P, K_I} \int_{t_0}^t \left(T_{p, \max, \text{predicted}}(\tau) - T_{p, \max}^* \right)^2 d\tau \quad (9)$$

where $T_{p, \max, \text{predicted}}$ is the maximum product temperature predicted by the detailed model of the process, which is integrated in time, starting from the knowledge of the process parameters provided by the observer at time t_0 . By this way, the tuning of the compensator is performed with an adaptive strategy in which the controller parameters are iterated until a minimum of the ISE is reached, and the obtained values of K_P and K_I are finally implemented in the control law (7)-(8). In the example it has been assumed to control the true product temperature to a target value $T_{p, \max}^* = 245$ K. The shelf temperature is initially ramped up to $T_{shelf} = 273.15$ K. After about 4 hours from the beginning of the operation, the observer predicts that the limit temperature has been approached and the control action is taken, regulating the value of T_{shelf} according to the law (7).

The proposed feedback control strategy has been also tested assuming to use the temperature of the frozen product at the bottom of the sample as the measured variable. Figure 8 shows the results of a simulation in which the heating shelf temperature is initially ramped from 228.15 to 268.15 K at constant velocity. The target is to maintain the maximum product temperature at a value $T_{p, \max}^* = 240$ K. Also in this case, simulations show that the sublimation temperature settles to the set-point very rapidly, thus allowing to carry on all the primary drying phase at the

maximum possible rate without impairing the quality of the product. The value of the interface temperature estimated by the observer is also shown in Figure 8, evidencing that this value is lower than the temperature at the bottom of the vial. After about 5 hours from the beginning of the operation the maximum allowable temperature is obtained and the controller starts decreasing the temperature of the shelf.

As a final remark, it must be pointed out that the proposed control strategy can be successfully implemented if the response of T_{shelf} to changes in the set-point of the heating/cooling fluid temperature is almost instantaneous. This can be a reasonable assumption when the process is carried on in a small-scale freeze-dryer. If it is not the case, large overshoots in the dynamics of $T_{p,max}$ could arise, which can damage the product. In order to minimise this effect, the equation describing the dynamic response of T_{shelf} should be added to the model of the process. This would allow to anticipate the time at which the control action is taken, thus minimising the deviation of $T_{p,max}$ from the set-point value.

Conclusions and final remarks

The effect of the main operating conditions, namely chamber pressure and heating shelf temperature, has been investigated in this paper. An ideal model-based control strategy has been firstly proposed: it continuously changes the shelf temperature in order to maintain the product temperature at a safe level. The possibility of manipulating the pressure in the chamber to control rapidly the maximum product temperature in case of malfunctioning of the control system has also been studied: the method is effective, but after an initial decrease, the temperature increases again, even if to a lower value.

This strategy, based on the perfect knowledge of the process, allows to minimise the drying time. However, under real conditions, the state of the system is

not perfectly known. Thus, a feedback controller has been proposed in which the estimate of the controlled variable, i.e. the maximum product temperature, is provided by an observer inserted in the control loop. Simulations showed that the proposed controller, based on a proportional-integral action, is able to control the product temperature at a pre-determined value, obtaining a stable and fast response.

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Notation

c	constant vector
c_p	specific heat at constant pressure, $\text{J kg}^{-1}\text{K}^{-1}$
e	error in the predictions of the observer
e_{PI}	deviation from the observer estimate of the controller variable and the PI controller set-point
f	non-linear function
H	moving front position, m
K	gain of the observer
K_P	tuning parameter for the proportional mode of the PI compensator
K_I	tuning parameter for the integral mode of the PI compensator, s^{-1}
K_v	overall heat transfer coefficient, $\text{W m}^{-2}\text{K}^{-1}$
k	thermal conductivity, $\text{W m}^{-1}\text{K}^{-1}$
L	initial frozen layer thickness, m
P_c	chamber pressure, Pa
p_v	vapour pressure, Pa
r	internal radius of the vial, m
s	vial wall thickness, m
t	time, s
T	temperature, K
$T_{p,\max}^*$	maximum temperature allowed by the product, K
$T_{p,\max}$	maximum temperature of the product, K
u	input of the system
x	state of the system
y	output of the system

Greeks

ΔH_s	enthalpy of sublimation, J kg ⁻¹
ΔH_v	enthalpy of vaporisation, J kg ⁻¹
ρ	density, kg m ⁻³
τ	integration variable, s

Subscripts and superscripts

\wedge	estimated value
0	initial time of the control action
I	dried layer
II	frozen layer
B	bottom of the vial
gl	vial glass
i	interface value
<i>measured</i>	measured value
<i>observer</i>	observer estimate
<i>opt</i>	optimal value
<i>shelf</i>	heating shelf
<i>predicted</i>	value calculated by mean of a mathematical model

Abbreviations

BSA	Bovine Serum Albumin
FDA	Food and Drug Administration
ISE	Integral of the Square Error
MTM	Manometric Temperature Measurement

PAT Process Analytical Technology

PI Proportional Integral

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List of Tables

<i>Table 1</i>	Main parameters of the solutions considered as case studies.
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Figure 1 Effect of the chamber pressure and of the heating shelf temperature on the primary drying time in case of constant shelf temperature (upper graph) and adopting the model-based control strategy that maintains the maximum product temperature at a value lower than 240 K (lower graph). The locus corresponding to the minimum of the primary drying time for the various shelf temperatures is also shown (dotted line). In the upper graph the dashed line corresponds to the values of chamber pressure and of shelf temperature that allow to satisfy the constraint on the maximum product temperature. Case study: BSA solution.

Figure 2 Comparison between the model-based control strategy (solid line) and the constant T_{shelf} (dashed line). L.h.s.: time evolution of the temperature of the heating shelf and of the maximum temperature of the product. R.h.s.: moving front position. (Chamber pressure = 15 Pa). Case study: BSA solution.

Figure 3 Comparison between the maximum product temperature in the vial obtained in the optimum condition at constant $T_{shelf} = 280$ K (dashed line, chamber pressure = 3.30 Pa) and in the optimum condition at variable T_{shelf} with initial set-point 280 K (solid line, chamber pressure = 6.75 Pa). Case study: BSA solution.

Figure 4 Effect of the chamber pressure on the primary drying time

using the model-based control strategy that maintains the maximum product temperature at a value lower than 240 K (initial shelf temperature = 320 K) for various values of the overall heat transfer coefficient (upper graph) and of the initial frozen layer thickness (lower graph). The locus corresponding to the minimum of the primary drying time is also shown (dashed lines).

Figure 5 Effect of the maximum temperature allowed by the product on the optimal chamber pressure using the model-based control system that optimise the shelf temperature; the values calculated using the correlation of Tang et al. (2005) are also shown (dotted curve). The primary drying time is also shown (dashed curve, right hand axis). In the base case $L = 8 \cdot 10^{-2}$ m and $K_v = 0.789 \cdot (P_c - 5.11) + 10.0$ kJ h⁻¹m⁻²°C⁻¹ (value taken from Brülls and Rasmuson, 2002).

Figure 6 Time evolution of the heating shelf temperature (dashed line) and of the maximum product temperature in case of constant chamber pressure (6.75 Pa, dotted line) and in case of variation of chamber pressure (solid lines) occurring at 4.7 h. Case study: BSA solution.

Figure 7 Feedback control strategy: time evolution of the shelf temperature (dash-dotted line), of the maximum product temperature estimated by the observer (solid line), of the true maximum product temperature (dotted line) and of the vial

bottom temperature (dashed line) during the primary drying phase. Case study: skim milk; total chamber pressure = 5 Pa.

Figure 8 Feedback control strategy: time evolution of the shelf temperature (dash-dotted line), of the product temperature at the bottom (dotted line) and of the interface temperature (solid line) during the primary drying. Case study: BSA solution; total chamber pressure = 5 Pa.

Table 1

Parameter	BSA solution	Skim milk
$c_{p,I}$, J kg ⁻¹ K ⁻¹	2590	2595
$c_{p,II}$, J kg ⁻¹ K ⁻¹	1930	1967
k_I , W m ⁻¹ K ⁻¹	$2.596 \cdot 10^{-4} \cdot p + 3.9806 \cdot 10^{-2}$	$8.826 \cdot 10^{-5} \cdot p + 2.707 \cdot 10^{-2}$
k_{II} , W m ⁻¹ K ⁻¹	2.56	2.1
p_v , Pa	$e^{-\frac{6140.4}{T} + 28.916}$	$133.32e^{23.9936 - \frac{2.19\Delta H_c}{T}}$
ρ , kg m ⁻³	215	145
ρ_{II} , kg m ⁻³	1030	1058
ΔH_s , J kg ⁻¹	$2687.4 \cdot 10^{-3}$	$2791.2 \cdot 10^{-3}$
ΔH_v , J kg ⁻¹	$2840.3 \cdot 10^{-3}$	$2791.2 \cdot 10^{-3}$
L , m	$8 \cdot 10^{-3}$	$8 \cdot 10^{-3}$
r , m	$7.125 \cdot 10^{-3}$	$7.125 \cdot 10^{-3}$
s , m	$1 \cdot 10^{-3}$	$1 \cdot 10^{-3}$

Figure 1

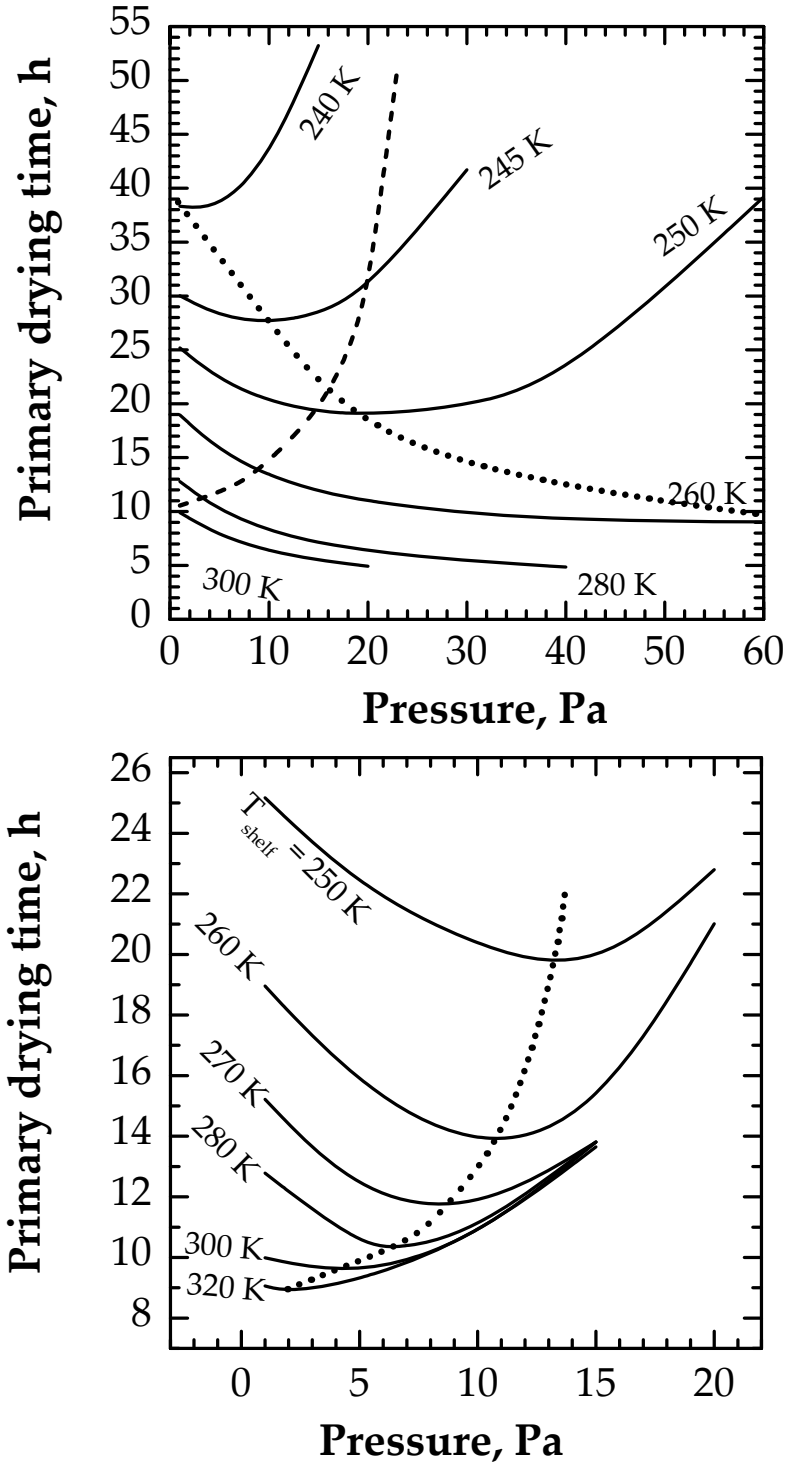


Figure 2

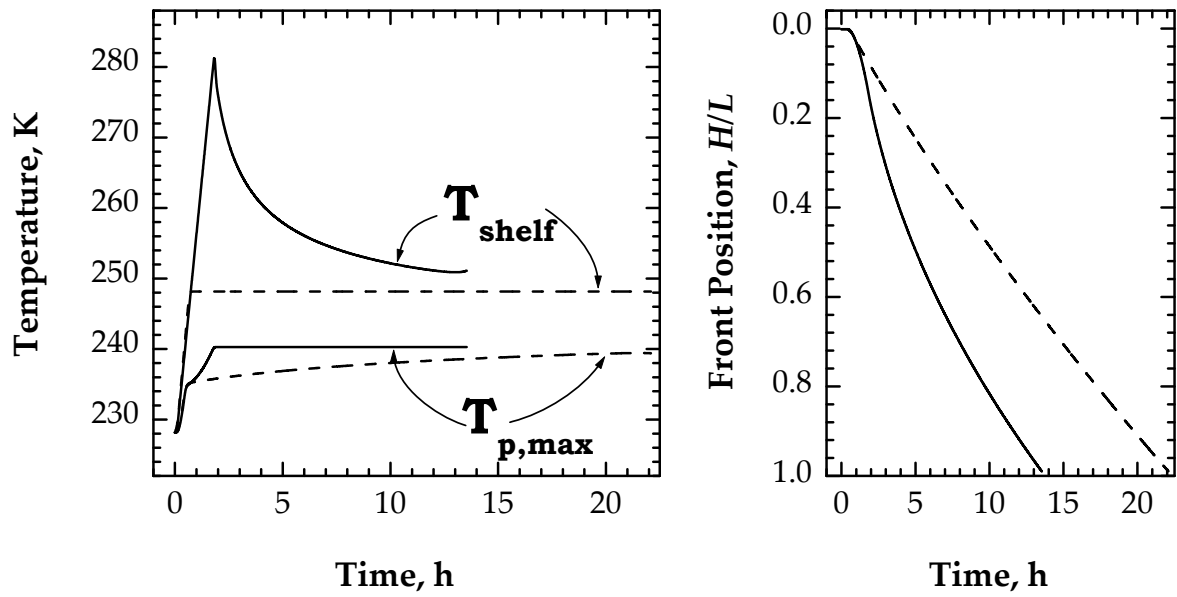


Figure 3

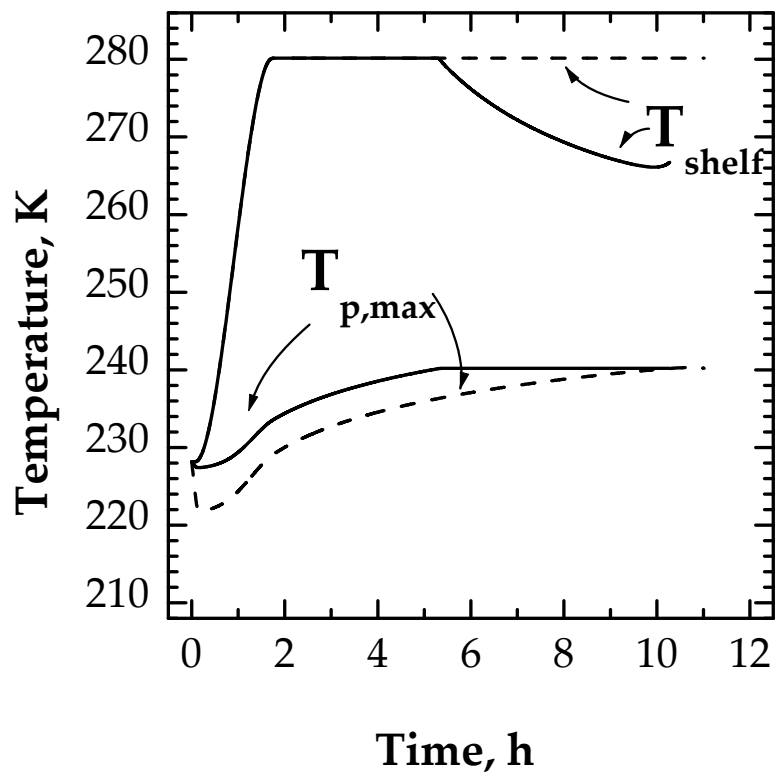


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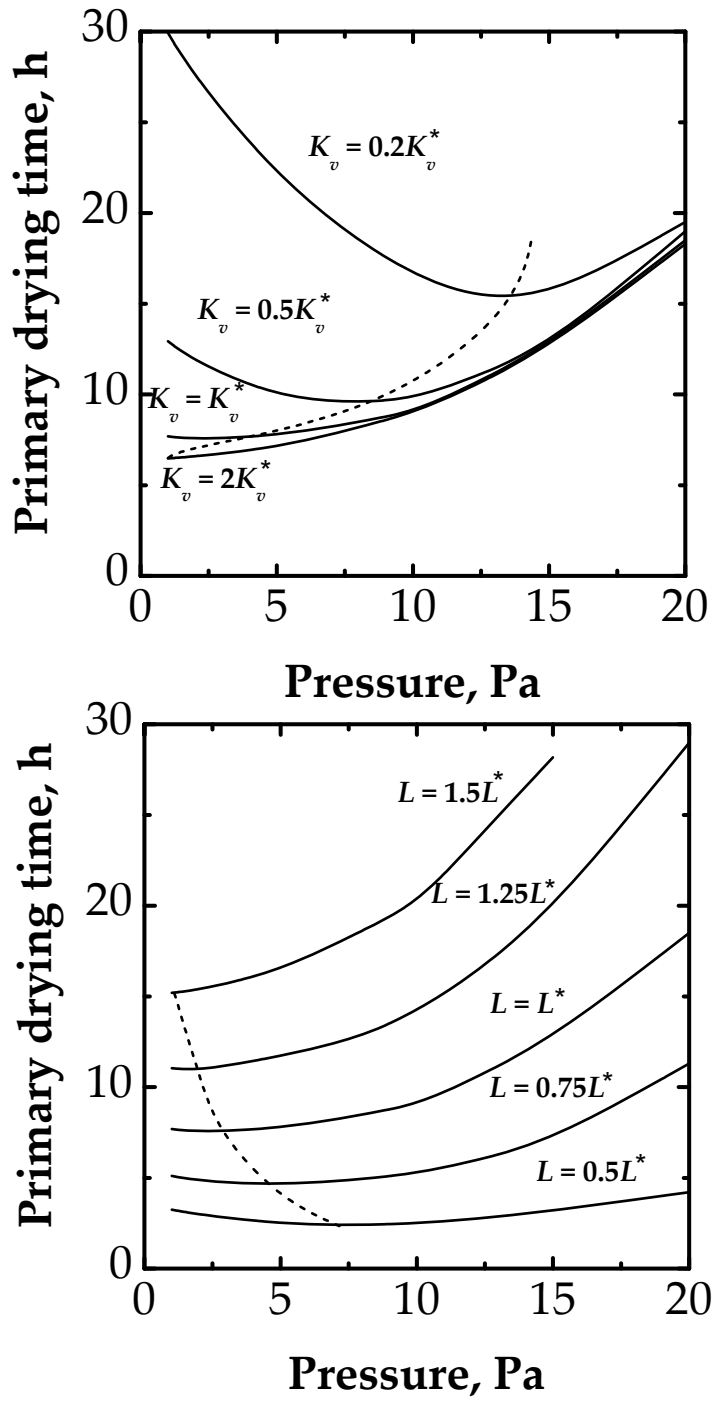


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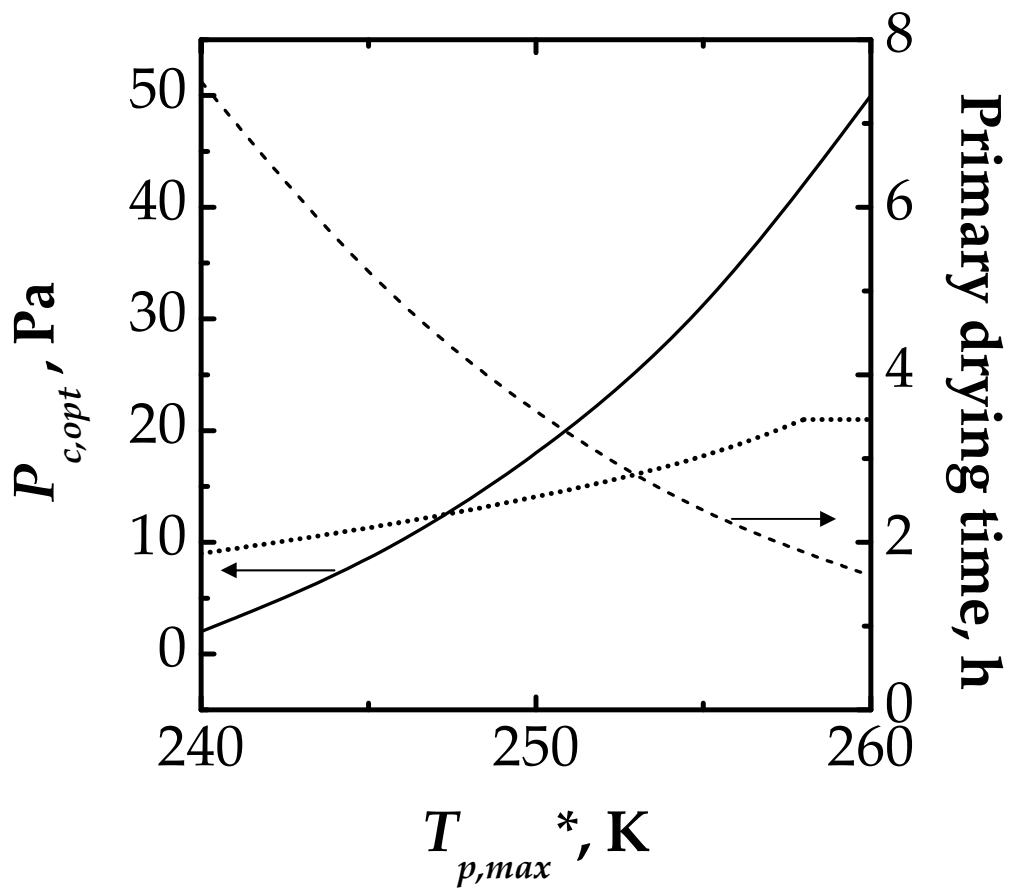


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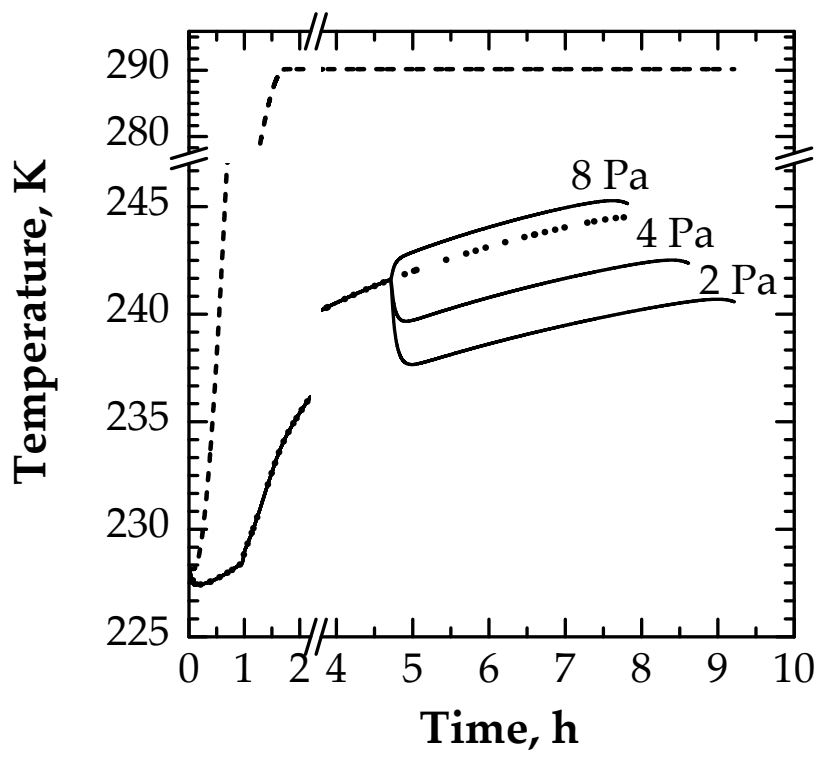


Figure 7

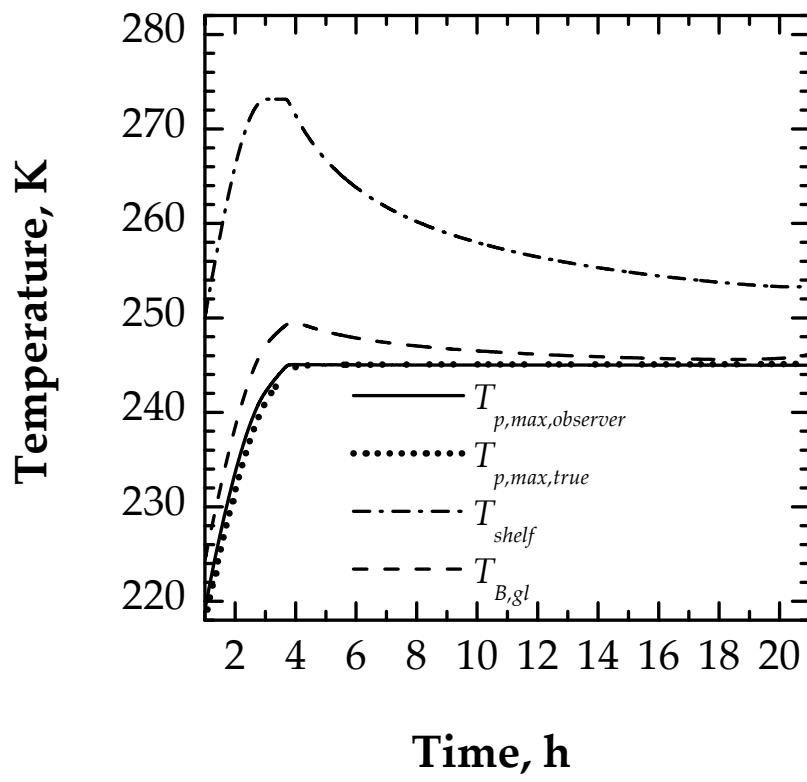


Figure 8

