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Fast freeze-drying cycle design and optimization using a PAT based on the measurement of product temperature

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Abstract

This paper is focused on the use of an innovative Process Analytical Technology for the fast design and optimization of freeze-drying cycles for pharmaceuticals.

The tool is based on a soft-sensor, a device that uses the experimental measure of product temperature during freeze-drying, a mathematical model of the process, and the Extended Kalman Filter algorithm to estimate the sublimation flux, the residual amount of ice in the vial, and some model parameters (heat and mass transfer coefficients).

The accuracy of the estimations provided by the soft-sensor has been shown using as test case aqueous solutions containing different excipients (sucrose, polyvinylpyrrolidone), processed at various operating conditions, pointing out that the soft-sensor allows a fast estimation of model parameters and product dynamics without involving expensive hardware or time consuming analysis.

The possibility of using the soft-sensor to calculate in-line (or off-line) the design space of the primary drying phase is here presented and discussed. Results evidences that by this way it is possible to identify the values of the heating fluid temperature that maintain product temperature below the limit value, as well as the operating conditions that maximize the sublimation flux. Various experiments have been carried out to test the effectiveness of the proposed approach for a fast design of the cycle, evidencing that drying time can be significantly reduced, without impairing product quality.

Keywords

Freeze-drying, process design, monitoring, design space, mathematical modeling.

Introduction

One of the challenges in freeze-drying of pharmaceuticals and biologicals is the fast design and optimization of the freeze-drying cycles, with the goal to preserve product quality. In fact, the market of products like biologicals and biopharmaceuticals is rapidly growing [1] and freeze-drying is required to allow their stabilization, ensuring their long term preservation, as these molecules can be highly heat sensitive, and can be damaged by higher temperature drying processes [2].

Even if the operating conditions in a freeze-drying cycle can be very gentle towards the product, there are some constraints that have to be respected in order to get a product with acceptable quality. Product temperature has to remain below a limit value, that is a characteristic of the formulation being processed, in order to avoid product degradation. Besides, for an amorphous (or a partially amorphous) formulation it is necessary to maintain the temperature of the product below a limit value in order to avoid the loss of freeze-dried cake structure (collapse). Notwithstanding the fact that not always collapse is associated with degradation, cake elegance is often a required attribute. This allows preserving product elegance, decreasing both the residual water content and the reconstitution time of the product at the end of the drying process, and avoiding possible product degradation (which is, in any case, dependent on specific degradation pathways for each formulation) [3]. Besides, it is necessary to identify the ending point of primary drying in order to modify the operating conditions to favor water desorption from the cake (secondary drying) only when all the ice has been removed from the product, avoiding unnecessary prolongation of primary drying. Finally, the solvent flux from the product to the condenser has to remain below a limit value that causes choking flow in the duct and, thus, the loss of pressure control in the chamber [4] - [6].

Usually, the operating conditions of a freeze-drying cycle (i.e. the values of heating shelf - or fluid - temperature, chamber pressure, and drying duration) for a given drug are set after experimental investigation, using a trial-and-error approach: various tests are carried out modifying the operating conditions in order to identify suitable operating conditions and, in some cases, also to optimize the process. The Guidance for Industry PAT [7] issued by US FDA in 2004 suggests to modify this approach, and to develop suitable tools, called Process Analytical Technologies (PATs), to get product quality during pharmaceuticals manufacturing processes, instead of testing it at the end. In this framework various methods have been proposed in recent years to monitor the process (see, among the others, [8]-[10]) and to design freeze-drying cycles either in-line or off-line.

When designing in-line the cycle it is necessary to use some monitoring tools, with the goal to estimate the state of the product (temperature and residual amount of ice) and some parameters used to characterize the heat flux from the fluid to the product in the vial, and the mass flux from the sublimation interface to the chamber. Generally, these two fluxes are written as a function of their respective driving force according to the following equations (see, among the others, [11] -[13]):

$$J_w = \frac{1}{R_p}\left(p_{w,i} - p_{w,c}\right) \tag{1}$$

$$J_q = K_v\left(T_{fluid} - T_B\right) \tag{2}$$

Therefore, the monitoring system has to estimate the parameters K_v and R_p. The SMART^{TM} Freeze-Dryer [14], [15] uses the technique of the pressure rise test: the valve in the duct between the chamber and the condenser is closed for a short time interval, thus causing pressure increase in the chamber due to vapor accumulation. An algorithm, the Manometric Temperature Measurement [16] in this case, is used to estimate the desired variables looking for the best fit between calculated and measured values of the pressure rise curve. On the

basis of the estimated variables and of some rules of thumb, the SMART^{TM} Freeze-Dryer calculates the values of fluid temperature and chamber pressure to be implemented in the cycle. The working principle of LyoDriver^{TM} [17], [18] is someway similar: it uses the pressure rise test to estimate the state of the system (with the Dynamic Parameters Estimation algorithm [19]), and a control algorithm to drive product temperature as close as possible to the limit value, thus minimizing the drying time and performing a true optimization. Recently, the possibility of using a Model Predictive Control algorithm to optimize in-line the process has also been investigated [20]-[22]: also in this case the pressure rise test is used as measurement system.

In case the cycle is designed in-line the values of the operating conditions suitable for the process are unknown at the beginning of primary drying (generally low values of temperature of the heating fluid and of pressure in the drying chamber are set at the beginning) and, then, according to the information about the state of the product obtained from the monitoring system, the operating conditions are modified during primary drying in order to achieve a pre-specified goal (the minimization of the duration of the primary drying stage, without violating the constraint about product temperature). A different approach consists of getting a suitable (or the optimal) freeze-drying cycle off-line: in this case preliminary experiments are required to get information about the system and to identify the operating conditions; then, a test is carried out with the selected values of fluid temperature and chamber pressure in order to validate the cycle, and during this test the values of the operating conditions are no longer modified. A freeze-drying cycle can be designed off-line using the design space of the process. According to "ICH Q8 Pharmaceutical Development Guideline" [23] the design space is the multidimensional combination of input variables and process parameters that have been demonstrated to provide assurance of quality. Extended experimental campaigns, mainly based on a trial-and-error approach, are required to

determine the design space for a given formulation [24]. The experimental effort, and thus the cost (in terms of money and time), can be reduced in case a mathematical model is used to calculate the design space [25]-[30]: in this case process modeling allows simulation of product dynamics *in silico*, thus identifying the values of the operating conditions that allow fulfilling the goals of the process. Few experiments are required to estimate the values of model parameters (K_v and R_p) using methods that are well known in the scientific literature. The heat transfer coefficient, at a given pressure, can be estimated by carrying out the gravimetric test [31], or using one of the algorithms proposed to interpret the pressure rise curve, e.g. the Manometric Temperature Measurement [16], the Pressure Rise Analysis [32], or the Dynamic Parameters Estimation [19]. Recently, the Tunable Diode Laser Absorption Spectroscopy (TDLAS) has been proposed to rapidly estimate K_v [33], [34]. The heat transfer coefficient can differ from vial to vial due to different heat transfer mechanisms to the product [35]-[36] and with both the pressure rise test and TDLAS it is possible to get only a "mean" value of K_v over the batch. The cake resistance R_p can be determined using the pressure rise test, the measurement of product temperature [37], the TDLAS sensor [38], and, as it has been recently proposed, a weighing device placed in the drying chamber that allows measuring both the weight loss and product temperature in a group of vials [39].

It has to be highlighted that both SMART™ Freeze-Dryer and LyoDriver™ could be used to design the cycle off-line. In fact, at the end of a test run they provide values of K_v and R_p that can be used to calculate off-line the design space of the process.

It should be clear from the previous literature survey that when a freeze-drying cycle is designed both in-line and off-line a suitable monitoring system is required, and time is needed to carry out the experimental investigation. A challenging issue is to use cheap hardware sensors, ordinarily available in a freeze-dryer, to get all the desired parameters in just one production run (or in few runs), thus avoiding the purchase of expensive sensors and saving

time. In this framework Velardi et al. [40], [41] proposed using a soft-sensor (observer) based on the measurement of product temperature (obtained with a thermocouple) and on a mathematical model of the process to estimate in-line both the residual amount of ice and model parameters K_v and R_p. The original algorithm was modified by Bosca and Fissore [42] to account for a non-linear dependence of cake resistance on its thickness, and, finally, by Bosca et al. [43] to improve its robustness.

The use of the temperature measure to get the value of dried cake resistance was proposed by Kuu et al. [37]. Such method required to solve a multivariable non-linear optimization problem, and a robust method, although computationally demanding, was proposed to get a fairly accurate initial estimation of the parameters that had to be estimated, otherwise it would have been impossible to solve the minimization problem. Besides, in order to use that method, the value of K_v had to be known, and preliminary investigations were required to this purposes. Finally, dried cake resistance could be estimated only at the end of the manufacturing process, thus allowing the design of the cycle only at the end of the test run. Differently from this approach, the Smart Soft-Sensor does not solve any complex optimization problem, it does not require any preliminary investigation about model parameters, and it allows estimating K_v and R_p during manufacturing, thus allowing in-line cycle design. The use of a mathematical model and of temperature measurement to optimize a freeze-drying cycle was proposed by Kuu et al. [44]. Unfortunately, also in this case preliminary investigations are required to get values of K_v and R_p, and cycle design is performed using a simplified method and not by means of the design space of the primary drying stage.

The goal of this paper is, at first, to give experimental evidence of the accuracy of the estimations obtained when using the soft-sensor proposed by Bosca et al. [43] and, then, to show how this soft-sensor, that we have called Smart Soft-Sensor (S^3), can be used to

calculate the design space and, finally, to get the freeze-drying cycle either in-line or off-line, without requiring preliminary investigations or solving non-linear multivariable optimization problems. Various experiments are presented in the following, pointing out how this simple (and cheap) PAT can be used to monitor the process, as well as to optimize it.

Materials and Methods

The Smart Soft-Sensor S^3

Figure 1 illustrates the working principle of the Smart Soft-Sensor S^3. It is composed by two distinct elements: an observer, based on the Extended Kalman Filter algorithm, used in the first part of the primary drying phase, and a mathematical model of the process, used in the second part of primary drying.

A soft-sensor is a device whose goal is the estimation of any system variable or product quality by using mathematical models, substituting some physical sensors and using data acquired from other available ones (see, among the others, ref. [45]). The key element of the Smart Soft-Sensor is thus the mathematical model of the process that estimates the dynamics of the product in the vial given the values of the operating conditions (T_{fluid}, P_c):

$$\dot{\mathbf{x}} = \mathbf{f}\left(\mathbf{x}, u\right) \tag{3}$$

$$y = \mathrm{h}\left(\mathbf{x}, u\right) \tag{4}$$

where u is the manipulated variable (T_{fluid}), $\mathbf{x}$ is the state of the product (T_i), and y is the measured variable (T_B). The functions $\mathbf{f}$ and h are model equations: in this case the simplified one-dimensional model of Velardi and Barresi is used to describe the dynamics of the process [13]: it is based on the heat balance equation for the frozen product and the mass balance equation for the water vapor in the dried layer (taken in pseudo-stationary conditions due to

the slow process dynamics), and the energy balance at the moving interface. If we are able to measure the temperature of the product at the bottom of the vial (y) we can compare this value with that calculated using the model, and this difference, that is not equal to zero for various reasons (the simplifications at the basis of the model, the uncertainty of model parameters, the experimental error) can be used to "correct" model calculations as shown in the following:

$$\dot{\hat{\mathbf{x}}} = \mathbf{f}\left(\hat{\mathbf{x}}, u\right) + \mathbf{K}\left(t\right)\left(\hat{y} - y\right) \tag{5}$$

$$\hat{y} = \mathrm{h}\left(\hat{\mathbf{x}}, u\right) \tag{6}$$

where $\hat{\mathbf{x}}$ is the variable estimated by the observer, $\hat{y}$ is its estimate of the measured variable obtained with the observer, and $\mathbf{K}(t)$ is a parameter, calculated using the algorithm of the Extended Kalman Filter [43], that guarantees the convergence of the observer, i.e. that after a transient the difference between the calculated and the measured variable goes to zero. Equations (5) and (6) constitutes an observer for the system. It has to be highlighted that in case of the freeze-drying process the variables estimated by the observer are T_i and K_v and, thus, the equations of the observer become the followings:

$$\begin{pmatrix} \dot{\hat{T}}_i \\ \dot{\hat{K}}_v \end{pmatrix} = \begin{pmatrix} f_1\left(\hat{T}_i, \hat{K}_v, T_{fluid}\right) \\ 0 \end{pmatrix} + \mathbf{K}\left(t\right)\left(\hat{T}_B - T_{B,meas}\right) \tag{7}$$

$$\hat{T}_B = \mathrm{h}\left(\hat{T}_i, \hat{K}_v, T_{fluid}\right) \tag{8}$$

In order to run the algorithm (i.e. to solve eqs. (7) and (8)) it is necessary an initial estimate of T_i and K_v: for the first variable it is possible to use the value of the temperature of the product after freezing, while for the second variable it is possible to use a guess based on the fact that common values of K_v may range in a limited interval of values (e.g. from 5 to 30 W $m^{-2}K^{-1}$). If an estimate obtained from the same (or from a slightly different) vial-freeze-dryer system is available, it can be used, but this is not mandatory. Then, using the measurement of T_B the observer estimates T_i and K_v and, from their values, the sublimation flux J_w (and, thus, the

residual amount of ice in the vials, and the thickness of the dried cake L_d) and R_p (using the heat balance at the sublimation interface). Obviously, the estimated values of T_i and K_v can be inaccurate at the onset of primary drying, as the convergence velocity of the observer is a function, among the others, of the accuracy of the initial estimations, but, after, the transient fairly accurate estimates are obtained.

The temperature measurement

The observer uses, in the first part of primary drying, the measurement of product temperature obtained with a thermocouple. Drying rate of the product in the monitored vial is generally assumed to be higher than that in the non-monitored vials due to the effect of the presence of the thermocouple on the nucleation temperature. In fact, the presence of the thermocouple is expected to increase the nucleation temperature, thus decreasing sub-cooling and resulting in larger ice crystals with respect to the product in the other vials. As a consequence cake structure of the product in the monitored vials should have larger pores, thus resulting in a higher drying rate and, finally, in a different product temperature. In any case, if we carry out a freeze-drying cycle at lab-scale, in non GMP conditions, as it is in most cases, the difference in the nucleation temperature between monitored and non-monitored vials is expected to be small, and, thus, sublimation rate and product temperature in monitored vials should be almost equal to those obtained in non-monitored vials. This is confirmed by the comparison between product temperature measured with thermocouple and estimated using one of the pressure rise test based algorithms (see, among the others, [19], [46]). Nakagawa et al. [47] reported values of cake permeability for mannitol (and BSA) solutions as a function of nucleation temperature, and simple calculations, based on these data, can be used to support previous conclusions. In fact, if we consider two different nucleation temperatures, e.g. -4°C and -10°C, permeability changes from $0.65 \cdot 10^{-3}$ $m^2 s^{-1}$ to $0.5 \cdot 10^{-3}$ $m^2 s^{-1}$. In case of a freeze-

drying cycle carried out with T_{fluid} = -20°C and P_c = 10 Pa, assuming K_v = 15 W $m^{-2}K^{-1}$, then product temperature can be calculated by equating the heat transferred to the product and that used for ice sublimation, thus obtaining a difference in product temperature of 0.003°C (as a consequence of a difference of 6°C in the nucleation temperature!). In case nucleation temperature changes from -4°C to -14°C then the calculated variation of product temperature in the same conditions is 0.1°C. Obviously slightly different results can be obtained with different product, exhibiting a different dependence of cake permeability on nucleation temperature, but this confirms that in case the difference in nucleation temperature is not so high, than product temperature during primary drying remains almost unaffected (or, at least, the variation is in the uncertainty range of the thermocouple measurement). Obviously, in case controlled nucleation at a well defined value is used during the freezing stage, there will be no differences between monitored and non-monitored vials.

Unfortunately, while the thermocouple is able to correctly measure the temperature of the product in the first part of primary drying, at a certain moment the measured temperature increases and reaches the value of the shelf temperature well before the ending of primary drying in the other vials of the batch, even if the operating conditions are not modified at all. Various explanations were proposed in the past to give reason of this behavior, e.g. the loss of thermal contact between the thermocouple and the ice, and the fact that the sublimation front advances past the thermocouple tip. In any case, when this temperature rise occurs, the measurement of product temperature is no longer reliable, and, thus, it cannot be used by the observer. Therefore, the same mathematical model of the process used to design the observer can be used to estimate the dynamics of product temperature, sublimation flux and residual amount of ice, with the model parameters estimated by the soft-sensor in the first part of primary drying. Details about the algorithm are omitted as they can be found in Ref. [43] and the goal of this paper is to show the application of the soft-sensor to cycle design.

Experimental validation

In order to verify the accuracy of the soft-sensor estimations it is necessary to compare the estimated variables with their experimental measure.

An experimental campaign has been carried out considering the freeze-drying of some excipients in glass tubing vials ISO 8362-1 8R. Each vial was filled with 2.0 mL of solution prepared with sucrose as is (Riedel de Haën), or with polyvinylpyrrolidone (Fluka), and ultra-pure water obtained by a Millipore water system (Milli-Q RG, Millipore, Billerica, MA), corresponding to a product thickness of 6.7 mm (after freezing).

All the experimental runs were carried out in a prototype freeze-dryer (LyoBeta 25, Telstar, Spain) with a chamber volume of 0.2 m^3, four shelves (with a total area of 0.5 m^2), and an external condenser (with a maximum ice capacity of 40 kg). The pressure in the chamber is regulated by controlled leakage of inert gas. The freeze-dryer is equipped with thermocouples (T type, Tersid, Milano, Italy), capacitance (Baratron type 626A, MKS Instruments, Andover, MA, USA) and thermal conductivity (Pirani type PSG-101-S, Inficon, Bad Ragaz, Switzerland) gauges.

Vials (162 vials for each batch) are directly placed on the heating shelf (without the interposition of any tray) and arranged according to a hexagonal array. The same freezing protocol has been used in all the runs: after vial load, the product was frozen at -50°C (the temperature of the technical fluid was decreased at 1°C/min). In this study, all the tests were carried out with non-GMP conditions. Nucleation temperature ranges from -12.5°C to -7.5°C in case of sucrose solutions, and from -11.5°C to -6.5°C in case of polyvinylpyrrolidone solutions. The pressure rise curves are interpreted by means of a computer-based system using DPE+ algorithm [48].

As we can see from Figure 1, the first estimated variable is the product temperature at

the sublimation interface. This variable can be compared with the temperature measured by the thermocouple: in fact, although the two values are not equal (the thermocouple measures the temperature at the bottom, while the observer estimates the temperature at the interface, which is lower), the trend of both the profiles should be the same, so we can immediately verify if the observer estimates are converging to the correct values.

Concerning the value of the overall heat transfer coefficient K_v, the estimated values can be compared with the measured values obtained with the gravimetric test carried out at the same chamber pressure. To this purpose, a batch of 162 ISO 8362-1 8R vials is filled with water, and each vial is weighed before being loaded in the drying chamber; 5 thermocouples are placed in vials in the central part of the batch. Then, the temperature of the heating fluid is decreased to -50°C (the cooling rate is about 1°C/min) in order to freeze all the water in the vials, and pressure is decreased (to the value of interest) to provoke ice sublimation. After a time interval Δt the process is stopped, and weight loss in each vial (Δm) is measured and used to calculate K_v with the following equation:

$$K_v = \frac{\Delta m \Delta H_s}{\int_0^{\Delta t} \left(T_{fluid} - T_B \right) dt} \tag{9}$$

In order to use eq. (9) it is required to know the value of T_B *vs.* time. This temperature is measured with the thermocouples placed in contact with the bottom of the vial: the mean value of the temperature measured by thermocouples in vials in the central part of the batch is used to calculate K_v for those vials. Once the value of K_v is known for each vial it is possible to calculate both the mean value and the standard deviation.

By using the previous estimations the soft sensor is able to calculate the value of the sublimation flux, that can be compared with the experimental value obtained from the pressure rise test.

Finally, the Smart Soft-Sensor is also able to calculate mass transfer resistance as a

function of dried layer thickness using the estimations on sublimation flux and product temperature: it is straightforward to understand that if both the sublimation flux estimations and the product temperature values (needed to calculate the partial pressure of water at the interface) are correct, then also the value of the mass transfer resistance obtained should be correct.

Finally, the soft-sensor is able to predict the evolution of the sublimation front and to give an estimation of the duration of the primary drying phase. This value can be validated using the ratio between the pressure values measured by two pressure gauges, namely a capacitance (Baratron) and a thermal conductivity gauge (Pirani). The value of the pressure ratio remain almost constant during primary drying, and decreases when the gas composition in the chamber changes from mostly water to nitrogen, i.e. when ice sublimation is "essentially" completed. In the pressure ratio curve it is possible to identify three points, namely the onset, the midpoint and the offset: the onset is determined from the intersection between the higher asymptote of the curve and the tangent to the curve in the inflection point,, while the offset is determined from the intersection between the lower asymptote of the curve and the tangent to the curve in the inflection point, and the midpoint is in the half of the time interval identified by onset and offset. A very detailed investigation of the use of this curve to detect the ending point of primary drying has been carried out by Patel et al. [49] considering 5% sucrose and 5% mannitol solutions. Their analysis investigated that in case of an amorphous product, like sucrose, the time difference between the Pirani onset and offset can be quite large with respect to that obtained with a crystalline product. Moreover, when considering the residual water content in the product, it appears that primary drying is completed at the onset in case of mannitol solutions, and at the offset in case of sucrose solutions. In any case, as water concentration in the chamber can be affected by the characteristics of the freeze-dryer (e.g. chamber volume) and by the operating conditions (e.g.

sublimation rate and nitrogen flux), it is not obvious at all to state that primary drying is completed at the onset or at the offset of the curve. For this reason we compared the drying time estimated by the soft-sensor with the value obtained at the midpoint of the curve, using the onset and the offset to identify the uncertainty range.

In order to evaluate the accuracy of the estimations provided by the soft-sensor we used 5 different measurements of product temperature obtained in 5 different vials in the central part of the batch, thus identifying minimum, maximum and mean value of K_v and drying time.

Design Space calculation and cycle design

Cycle design is based on the calculation of the design space of the primary drying phase, i.e. the values of the temperature of the heating fluid and of the pressure in the chamber that maintain product temperature below the selected limit value. Differential Scanning Calorimetry (DSC) can be used to identify the glass transition temperature of the product, that is usually considered the limit temperature, being the collapse temperature generally 2-3°C higher than this value. For the sucrose solutions a glass transition temperature of -32°C was determined using a differential scanning calorimeter (DSC type Q200, TA Instruments, New Castle, DE, USA), where samples were frozen -60°C and, then, heated at 10°C min^{-1} up to room temperature (the entire analysis was carried out in inert atmosphere). For the polyvinylpyrrolidone solution the glass transition temperature results to be equal to -22°C.

Once the limit temperature has been determined, it is necessary to identify, for each admissible value of chamber pressure, the maximum allowable temperature of the heating fluid ($T_{fluid,max}$). According to what discussed by Fissore et al. [29], the value of $T_{fluid,max}$ for a given formulation and vial-freeze dryer system is a function of cake thickness. This is due to the fact that the temperature of the product can change during drying even if the values of the operating conditions are not modified. In fact, as drying goes on the thickness of the frozen

layer decreases, and cake resistance increases. As a consequence, values of the temperature of the heating fluid (T_{fluid}) and of the pressure in the drying chamber (P_c) belonging to the design space at the beginning of primary drying may lay outside the design space after a certain time interval from the onset of ice sublimation.

The design space can be calculated using the following equation, i.e. the energy balance at the sublimation interface:

$$K_v\left(T_{fluid}-T_B\right)=\Delta H_s\frac{1}{R_p}\left(p_{w,i}-p_{w,c}\right) \tag{10}$$

If the heat flux to the product is written as a function of T_i, then eq. (10) becomes:

$$\left(\frac{1}{K_v}+\frac{L_f}{k_f}\right)^{-1}\left(T_{fluid}-T_i\right)=\Delta H_s\frac{1}{R_p}\left(p_{w,i}-p_{w,c}\right) \tag{11}$$

Product temperature T_i can then be calculated once the values of T_{fluid}, P_c and L_d are known (as $p_{w,i}$ is a function of T_i, R_p is a function of L_d and $L_f = L_0 - L_d$). Therefore, for a given value of P_c and, thus, of K_v, the limit value $T_{fluid,max}$ is the one that brings T_i to the limit value (T_{max}):

$$T_{fluid,max}=T_{max}+\left(\frac{1}{K_v}+\frac{L_f}{k_f}\right)\Delta H_s\frac{1}{R_p}\left[p_{w,i}\left(T_{max}\right)-p_{w,c}\right] \tag{12}$$

For a given value of P_c it is thus possible to calculate $T_{fluid,max}$ as a function of L_d.

In order to use eq. (12) it is necessary to know the values of the model parameters K_v and R_p. The Smart Soft-Sensor can be used to this purpose in two different ways:

i. If we are optimizing in-line the cycle, then we need to set a time interval (e.g. 30 minutes) and to maintain T_{fluid} constant at a value lower than (or equal to) $T_{fluid,max}$, where this limit value is calculated using eq. (12) with the available estimates of K_v and R_p. After this time interval, the new estimates of K_v and R_p are used to calculate the new value of $T_{fluid,max}$. Evidently, at the beginning of primary drying the accuracy of the estimates of K_v and R_p can be poor, and a certain safety margin could be required, but when the convergence of the observer is reached, than the estimate of $T_{fluid,max}$ as a

function of L_d is very accurate.

ii. If we are optimizing off-line the cycle, then we may just monitor the freeze-drying cycle with the Smart Soft-Sensor and, then, we can use the final estimates of K_v and R_p to calculate the design space and, finally, the optimal cycle at a given value of P_c [43]. In case the entire design space is required, at least three tests at different values of P_c have to be carried out, using the Smart Soft-Sensor to determine the pressure dependence of K_v. However, when using the Smart Soft-Sensor it is possible to save time with respect to the gravimetric test, and the heat transfer coefficient can be determined in normal production runs.

It has to be highlighted that with the proposed approach model parameters can be obtained in a manufacturing run just using ordinary thermocouples, without using expensive sensors or carrying out the pressure rise test. Moreover, as wireless temperature sensors were proposed in the past [50], [51], the Smart Soft-Sensor can be used even in large-scale freeze-dryers, provided that the instrumented vial is compatible with automatic loading-unloading systems. In this case it is required to use a controlled nucleation system, as in GMP environment the difference between nucleation temperature in monitored and non monitored vials could be relevant, thus impairing the accuracy of temperature measurement unless nucleation occurs in the whole batch at (about) the same temperature.

Cycle design in case of non-uniform batch

As it is possible to measure product temperature in vials placed in different positions over the shelf, whose temperature can be different as a consequence of the different heating mechanisms, the proposed soft-sensor allows monitoring the whole batch accounting for its non-uniformity, i.e. it is able to estimate the value of K_v for vials in different positions over the shelf using the temperature measurement in these vials. By this way it becomes possible to

calculate the design space for vials in central position and for vials at the edge of the shelf. Evidently, for a given value of chamber pressure the maximum allowed temperature of the heating fluid is lower in case of vials at the edge of the shelf as they are heated also by radiation. Therefore, in case T_{fluid} is set according to the limit value calculated for vials at the edge of the shelf, then the constraint on product temperature will be fulfilled in the whole batch. When the temperature of the heating fluid is set according to the limit value calculated for vials in central position, then drying time can be significantly reduced (as higher T_{fluid} are used), but the product in the edge vials can be overheated. These issues are deeply investigated in Refs. [30] and [39] as they prescind from the method used to determine model parameters.

Results and discussion

The first purpose of this study is to evaluate experimentally the accuracy of the estimations of product state and model parameters provided by the Smart Soft-Sensor. To this purpose various freeze-drying cycles have been carried out processing sucrose solutions at different operating conditions, namely the concentration of the aqueous solution, the temperature of the heating fluid and the pressure in the chamber. Then, the accuracy of the estimations has been tested in case polyvinylpyrrolidone solutions are freeze-dried.

In a first group of tests the operating conditions were not modified (T_{fluid} = -20°C, P_c = 10 Pa), and three different formulations containing, respectively, 5%, 10% and 20% by weight sucrose were freeze-dried. The coefficient K_v is the same in the three runs (as neither the vial-freeze dryer system nor the pressure in the chamber are modified), while R_p is expected to increase as the sucrose concentration increases, thus prolonging the duration of

primary drying. In a second group of tests the sucrose concentration has not been modified (5% by weight), as well as the chamber pressure (P_c = 10 Pa), while the heating fluid temperature was set at -20°C and -10°C respectively. In this case it is expected that K_v is the same in the tests (due to the poor influence of T_{fluid} on K_v), while drying time decreases, due to the higher product temperature, when T_{fluid} is increased. Finally, in the last group of tests the sucrose concentration and the heating fluid temperature are kept at the same value (5% by weight and -20°C respectively), while chamber pressure was set to 5 and 10 Pa respectively. In this case K_v is expected to increase with P_c and, in case heat transfer to the product has a strong influence on the process, drying time has to decrease when chamber pressure is increased.

Among the variables of interest, the first we consider is the overall heat transfer coefficient K_v, whose values can be experimentally determined by means of the gravimetric test as previously described. The soft-sensor requires an initial estimation of this coefficient (even if it is not necessary to be very accurate) and then, according to the equations of the algorithm, this guess value is modified and an accurate estimation of the value of K_v is obtained. In Figure 2 (a-c) the estimated values of K_v are compared with those determined using the gravimetric test. In each run five different values of K_v have been estimated, using five different thermocouple measurements: this allows identifying the mean value estimated by the soft-sensor, as well as the uncertainty range, identified by the minimum and maximum estimated values. The investigation shows that fairly accurate estimations of K_v are obtained whichever thermocouple is considered, taking into account the uncertainty of the values measured with the gravimetric test. Among the operating conditions considered in this work, the only one that influences the value of the heat transfer coefficient is the chamber pressure. Therefore, as expected, the heat transfer coefficient does not depend both on the concentration value and on the heating fluid temperature: as we can see in Figure 2 (graph a) the soft-sensor

predicts the same value of K_v for all the three cycles carried out with different concentrations of sucrose, and in Figure 2 (graph b) the same estimate of K_v is obtained in the two cycles with different fluid temperature. Figure 2 (graph c) shows that when chamber pressure is different, then the Smart Soft-Sensor estimates different values of K_v, close to the values estimated using the gravimetric test.

The second variable studied is the duration of the primary drying phase. Also in this case five values are obtained when using five different thermocouple measurements, thus allowing identifying a mean value and the uncertainty range. In Figure 2 (graphs d-f) the estimated values are compared with the experimental ones obtained from the pressure ratio: a fairly good agreement is obtained as in all cases the value estimated by the soft-sensor is close to the experimental one, taking into account the uncertainty of the experimental values. In particular, the soft-sensor is able to predict a higher duration when the solution is more concentrated (graph a): in fact, when the concentration of the solution increases, then cake porosity decreases, thus increasing the resistance of the cake to the sublimation flux and the primary drying phase lasts more time. Similarly, in case shelf temperature is increased, the soft-sensor estimates accurately the decrease of drying time (graph b) due to higher heat flux, and in case chamber pressure is increased, the soft-sensor estimates accurately the decrease of drying time (graph c) due to higher heat transfer coefficient to the product. With respect to the drying time estimated using the pressure ratio, it has to be highlighted that the difference between the onset and the offset of the curve can be quite large in some cases, as reported by Patel et al. [49] for sucrose solutions. In any case the values estimated by the soft-sensor are close to the onset and/or midpoint of the pressure ratio curve in almost all cases (only for the drying of the 20% sucrose solution the estimated value is close to the offset of the pressure ratio curve, but, in any case, it is inside the uncertainty range of the experimental data).

By using the estimations of product temperature and of the heat transfer coefficient the

Smart Soft-Sensor is able to estimate the heat flux to the product (see eq. (2)), and assuming that all the heat transferred to the product is used for ice sublimation:

$$J_q = \Delta H_s J_w \tag{13}$$

it is possible to estimate the sublimation flux during the primary drying phase. Figure 3 (graphs a-c) shows the estimated fluxes obtained in three different cycles where sucrose solutions characterized by different values of solute concentration are processed. The experimental data used to carry out a comparison with the estimated values are obtained from the pressure rise test. It can be highlighted that the higher is sucrose concentration the lower is the sublimation flux, due to the higher product resistance (shown in graph c), but product temperature can increase and, thus, the variation of the drying time can be small. For the three sucrose solutions investigated, product temperature changes from about 238 K in case of 5% sucrose solution, to 240 K for 10% sucrose solution, and to 241 K for 20% sucrose solution, and, thus, drying time for the 20% sucrose solution appears to be close to that obtained with the 10% sucrose solution. In all cases the agreement between estimated and measured values is fairly good, in particular in the second part of primary drying. In fact, at the beginning of primary drying the estimated values of K_v (and of T_i) can be far from the correct values, and time is needed to get accurate estimates of K_v and T_i (and, then, of J_w).

From the values of sublimation flux it is possible to calculate the mass transfer resistance R_p using eq. (1). The value of this parameter can be hardly obtained experimentally, in particular if we consider industrial-scale apparatus. In fact, the most used method to obtain dried cake resistance is the pressure rise test, but this test generally cannot be carried out in industrial-scale apparatus. In any case, as reliable estimates of the sublimation flux and of product temperature at the sublimation interface are obtained using the Smart Soft-Sensor, then the curve of R_p *vs.* dried layer thickness can be considered reliable. In Figure 3 (graph d) an example of the estimated values of R_p is shown: depending on the value of the

concentration of the solution the sensor provides different values of R_p and, in particular, an increase of the concentration of the solution corresponds to a higher value of R_p, as a consequence of the lower porosity of the dried cake.

Figure 4 shows results obtained when using the soft-sensor to monitor the drying of a 5% by weight polyvinylpyrrolidone solution using the same value of heating fluid temperature (-20°C) and two different values of chamber pressure (5 and 15 Pa). Also in this case fairly accurate estimations of K_v and t_d are obtained (it has to be pointed out that the drying has been carried out in the same type of vials used to process sucrose solutions, and that the soft-sensor provides accurate estimations of K_v whichever excipient is used). The sublimation flux is shown in graph c, evidencing that it is higher when the process is carried out at higher chamber pressure, thus motivating the lower drying time (graph b); in fact, when chamber pressure increases also the heat transfer coefficient to the product increases.

As the Smart Soft-Sensor appears to be a reliable tool to estimate not only the state of the system (product temperature and residual amount of ice) but also model parameters (K_v and R_p), it can be used to calculate the design space of the primary drying and to optimize the process, by minimizing the duration of the freeze-drying cycle. As it has been discussed in the Materials and Methods section, the design space can be determined by means of process simulation, provided that model parameters are known. In case the Smart Soft-Sensor is not used, we need to carry out various (time consuming) gravimetric tests to determine K_v as a function of P_c, and at least one experiment to determine R_p as a function of L_d (using the pressure rise test), and the design space can be determined using the algorithm of Fissore et al. [29]. In Figure 5, the complete three-dimensional design space for the lyophilization of a 5% by weight aqueous solution of sucrose is shown (surface A). This diagram can be used to determine, as a function of time, i.e. of dried cake thickness, the maximum value of heating shelf temperature at a given value of chamber pressure: this design space is given by the

intersection of surface A with a vertical plane passing through the point corresponding to the selected value of chamber pressure (10 Pa, in the case shown in Figure 5).

When using the Smart Soft-Sensor to monitor the process it becomes possible to calculate in-line the design space for a given value of chamber pressure: evidently, at the beginning of primary drying there will be a difference between the design space calculated using the parameters estimated by the Smart Soft-Sensor and that calculated using the parameters determined from *ad hoc* experiments. As far as primary drying goes on, and the accuracy of the estimations provided by the Smart Soft-Sensor increases, the estimated design space approaches the correct one. Figure 6 (graphs a-d) shows an example of these calculations: at the beginning of the drying, when the percentage of dried layer (L_d/L_0) is less than 30% (graphs a and b), the maximum value of heating fluid temperature given by the Smart Soft-Sensor is significantly lower than the correct value, but then the accuracy of the estimated design space improves. It is thus possible to calculate $\Delta T_{fluid,max}$, i.e. the difference between the correct value of maximum allowed heating fluid temperature and that given by the Smart Soft-Sensor. Figure 6 (graphs e-g) shows the values of $\Delta T_{fluid,max}$ obtained when using the Smart Soft-Sensor to calculate in-line the optimal cycle in various operating conditions: it appears that apart from the first part of primary drying, when $\Delta T_{fluid,max}$ can be large due to the fact that the observer estimates have not yet reached the convergence to the correct values, then this error is very small, about 1-2°C. In this framework it could be unexpected the low value of $\Delta T_{fluid,max}$ at the beginning of primary drying, as in that moment the estimated values of model parameters can be quite far from the correct ones. This can be explained by considering that a limit value has been assumed for T_{fluid} (10°C in the case study considered): thus, as at the beginning of primary drying $T_{fluid,max}$ is equal to 10°C, as it is shown in Figure 6 (graphs a-d), then, in case the value of $T_{fluid,max}$ calculated by the soft-sensor is higher than (or equal to) 10°C, then it is set equal to 10°C (due to the constraint on

maximum fluid temperature) and $\Delta T_{fluid,max}$ becomes equal to zero.

As an alternative, it is possible to calculate off-line the design space at the end of the experimental test: in this case the final values of model parameters are used to determine the design space according to the procedure proposed by Fissore et al. [29]. As after the initial transient fairly accurate estimations of model parameters are obtained using the Smart Soft-Sensor, then the accurate design space is obtained (in most cases $\Delta T_{fluid,max}$ is not higher than -1°C). It has to be remarked that when using the Smart Soft-Sensor to monitor the process carried out at a given value of P_c then it allows calculating the design space at that value of P_c. If the entire design space is required, than it is necessary to carry out various tests at different values of chamber pressure in order to determine the pressure dependence of K_v. In any case the use of the Smart Soft-Sensor allows saving time with respect to the gravimetric test.

Using the design space it is possible to get the optimal cycle either in-line or off-line according to the procedure described in the Materials and Methods section. Figure 7 (graph a) shows the profile of heating fluid temperature calculated using the soft-sensor during freeze-drying of a 5% sucrose solution and calculating in-line the design space. The limit temperature of the product (-32°C) is never trespassed during the cycle (graph b) and drying is completed in about 13 h (graph d). Product dynamics is compared with that obtained in a cycle where shelf temperature is maintained constant throughout primary drying and equal to about -20°C in order to maintain the product inside the design space during primary drying (as shown in graph c). In this case primary drying duration is about 16 h (graph d), i.e. about 20% higher than that obtained using the Smart Soft-Sensor to optimize in-line the cycle, as a consequence of the lower sublimation flux (graph e). In graphs b and c it is possible to see the comparison between product temperature measured by thermocouples in the two runs, and the values estimated by the Smart Soft-Sensor, even in the second part of primary drying, when

temperature measurement are no longer used by the sensor.

Conclusion

The fast design of a freeze-drying cycle, without using expensive hardware sensors and spending too much time to carry out experiments, is a challenging goal that can be achieved using the Process Analytical Technology described in this paper. It requires measuring product temperature and using a soft-sensor based on a model of the process and on the Extended Kalman Filter, a monitoring algorithm well known in chemical engineering domain. Product temperature can be measured using sensors that are ordinary available in a freeze-dryer, e.g. thermocouples and Resistance Thermal Detector (provided that accurate measurements can be obtained).

From the temperature measurement in a production run it becomes possible to estimate the residual amount of ice (thus identifying the ending point of primary drying), as well as some model parameters. This allows calculating in-line the design space of the process, even if in the initial transient the estimations of model parameters and, thus, of the design space, are not so accurate. As an alternative it is possible to calculate off-line the design space, at the end of the test run, using the final estimations of model parameters. Once the design space is known, than the cycle can be optimized: this can be done either in-line or off-line, thus obtaining the optimal cycle in just one run.

Notation

c_S	solute concentration, $kg_{solute}\ kg^{-1}_{solution}$
$\mathbf{f}$	vectorial function giving the derivates of the state
h	state-space equation of the measured variable
ΔH_s	sublimation enthalpy, J kg^{-1}
J_q	heat flux to the product, W $m^{-2}K^{-1}$
J_w	sublimation flux, kg $m^{-2}s^{-1}$
$\mathbf{K}$	observer gain (function of time)
K_v	heat transfer coefficient between the shelf and the product in the vial, W $m^{-2}K^{-1}$
k_f	thermal conductivity of the frozen product, W $m^{-1}K^{-1}$
L_0	thickness of the product after freezing, m
L_d	thickness of the dried cake, m
L_f	thickness of the frozen product, m
Δm	ice loss during the gravimetric test to determine K_v, kg
P_c	chamber pressure, Pa
$p_{w,c}$	water vapor partial pressure in the drying chamber, Pa
$p_{w,i}$	water vapor partial pressure at the interface of sublimation, Pa
R_p	dried product resistance to vapor flow, m s^{-1}
T_B	product temperature at vial bottom, K
$T_{B,meas}$	product temperature measured at vial bottom, K
T_{fluid}	heating fluid temperature, K
$T_{fluid,max}$	maximum allowed heating fluid temperature, K
$\Delta T_{fluid,max}$	difference between the maximum allowed heating fluid temperature given by the Smart Soft Sensor and the correct value, K

T_i	product temperature at the sublimation interface, K
T_{max}	limit product temperature, K
T_p	product temperature, K
t	time, s
Δt	duration of the gravimetric test to determine K_v, s
t_d	duration of primary drying, h
u	system input
$\mathbf{x}$	state variables array
y	system output

Superscripts

^	observer estimate
.	derivative

Abbreviations

PAT	Process Analytical Technology

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List of Figures

Figure 1. Sketch of the working principle of the soft-sensor.

Figure 2. Comparison between the values of the heat transfer coefficient between the shelf and the product (graphs a-c) and of the primary drying duration (graphs d-f) estimated with the soft-sensor (▨) for the core vial temperature measurement, and measured experimentally (▭) for some freeze-drying cycles of sucrose aqueous solutions carried out varying the operating conditions (graphs a and d: solute concentration; graphs b and e: heating fluid temperature; graph c and f: chamber pressure). Graphs a and d: T_{fluid} = -20°C, P_c = 10 Pa; graphs b and e: P_c = 10 Pa, c_S = 5% by weight; graphs c and f: T_{fluid} = -20°C, c_S = 5% by weight.

Figure 3. Graphs (a)-(c): Comparison between the sublimation flux estimated with the soft-sensor (filled symbols) and measured experimentally with the pressure rise test (empty symbols) during freeze-drying of sucrose solutions (T_{fluid} = -20°C, P_c = 10 Pa) with different solute concentration (graph a: 5%; graph b: 10%; graph c: 20%). Graph (d): Values of mass transfer resistance as a function of cake thickness estimated by the soft sensor during freeze-drying of sucrose solution (T_{fluid} = -20°C, P_c = 10 Pa) with different solute concentration (▲ = 5%; ● = 10%; ■ = 20%).

Figure 4. Comparison between the values of the heat transfer coefficient between the shelf and the product (graph a) and of the primary drying duration (graph b) estimated with the soft-sensor (▨) and measured experimentally (▭) during freeze-drying of 5% by weight polyvinylpyrrolidone aqueous solution at different values of chamber pressure (T_{fluid} = -20°C).

Sublimation flux is shown in graph c (○ = 5 Pa, ▲ = 15 Pa).

Figure 5. Design space for the lyophilization of a 5% by weight aqueous sucrose solution processed in a glass tubing vial ISO 8362-1 8R filled with 2.0 mL of solution (T_{max} = -32°C).

Figure 6. Graphs (a)-(d): Comparison between the design space of the primary drying of a 5% by weight aqueous sucrose solution (solid line) and the design space estimated by the soft-sensor (symbols) at different times during primary drying (a: L_d/L_0 = 0.17; b: L_d/L_0 = 0.31; c: L_d/L_0 = 0.40; d: L_d/L_0 = 0.49). Graphs (e)-(g): Values of $\Delta T_{fluid,max}$ *vs.* cake thickness for various operating conditions (graph e: c_S = 5%, T_{fluid} = -20°C, P_c = 10 Pa; graph f: c_S = 20%, T_{fluid} = -20°C, P_c = 10 Pa; graph g: c_S = 5%, T_{fluid} = -20°C, P_c = 5 Pa).

Figure 7. Comparison between the results obtained in a freeze-drying cycle (for a 5% by weight sucrose aqueous solution, P_c = 10 Pa) carried out with a constant value of the shelf temperature (●, T_{fluid} = -20°C) and with a shelf temperature optimized using the soft-sensor (□). Graph a: values of shelf temperature vs. time; graphs b and c: product temperature detected with a thermocouple in close contact with vial bottom and values estimated using the soft-sensor (dotted lines); graph d: ratio between pressure signals from Pirani and Baratron gauges; graph e: sublimation flux measured with the pressure rise test.

Figure 1

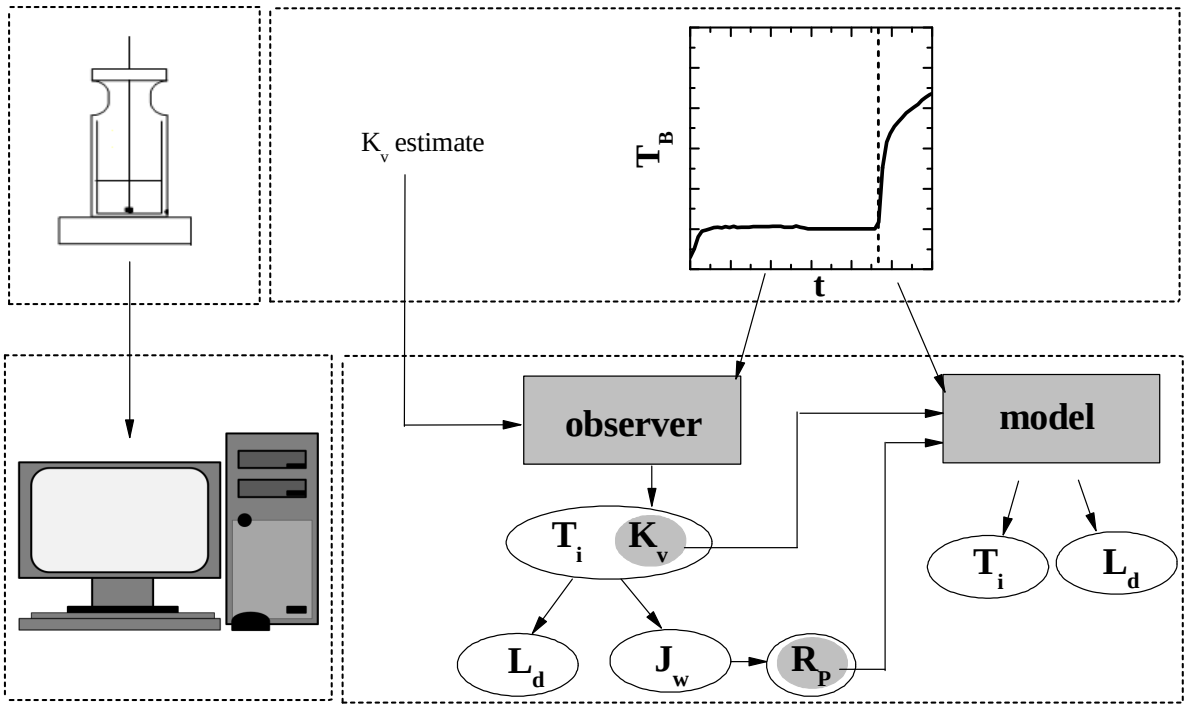


Figure 2

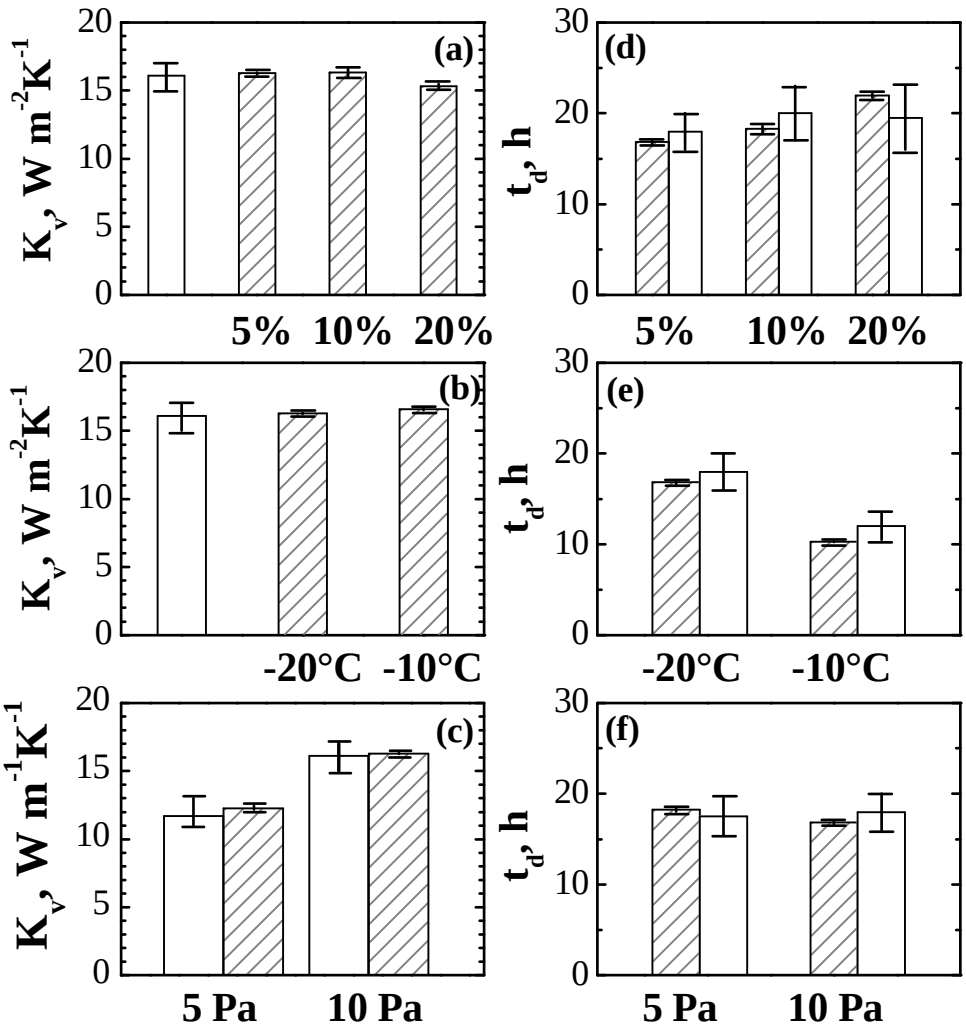


Figure 3

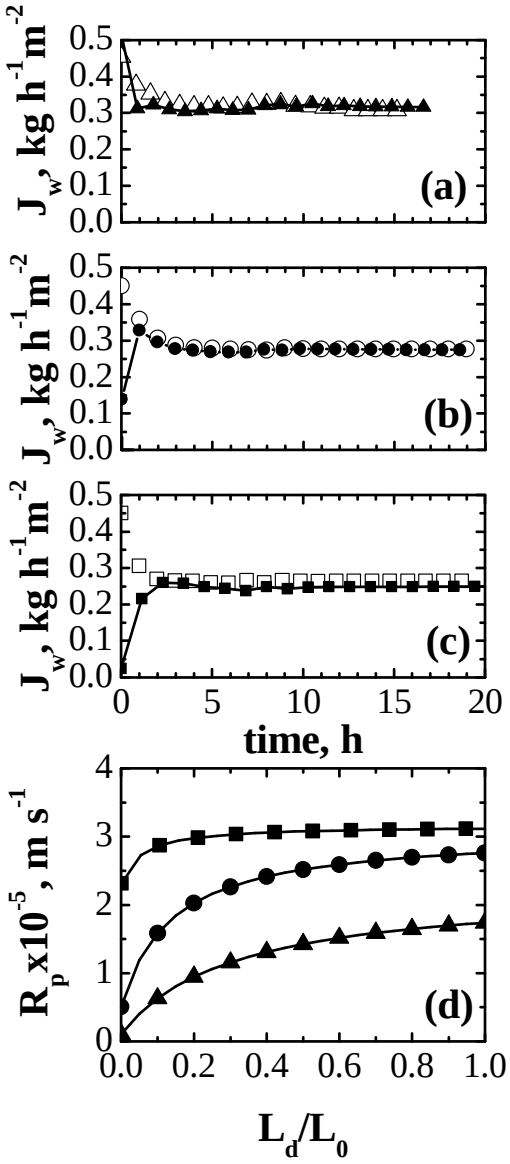


Figure 4

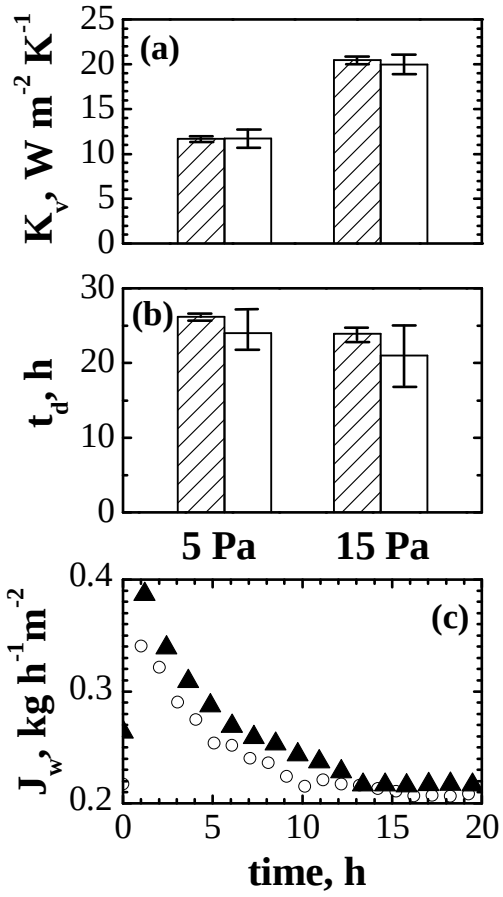

(a)
K_v, W m^{-2} K^{-1}
25
20
15
10
5
0
(b)
t_d, h
30
20
10
0
5 Pa
15 Pa
(c)
J_w, kg h^{-1}m^{-2}
0.4
0.3
0.2
0
5
10
15
20
time, h

Figure 5

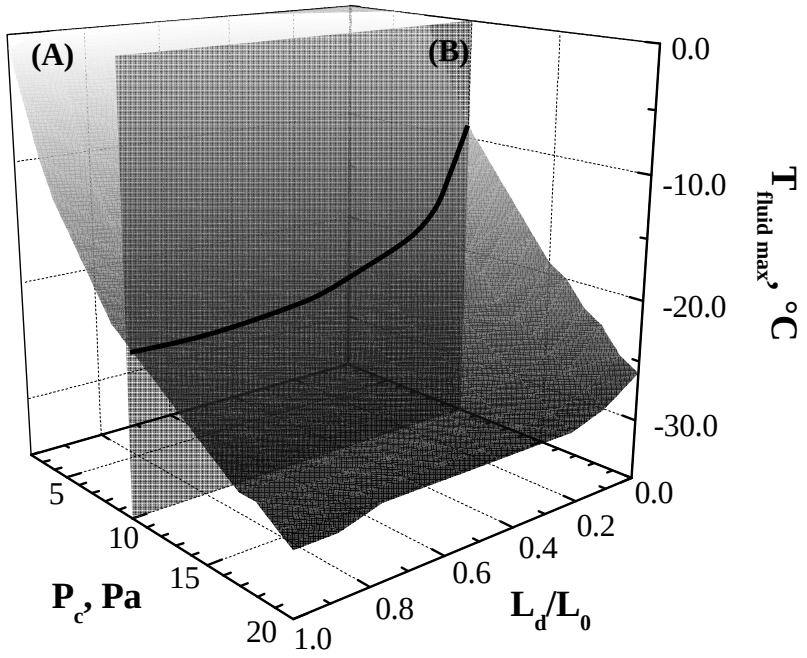

(A)
(B)
0.0
-10.0
-20.0
-30.0
$T_{fluid\ max}$, °C
5
10
15
20
P_c, Pa
0.0
0.2
0.4
0.6
0.8
1.0
L_d/L_0

Figure 6

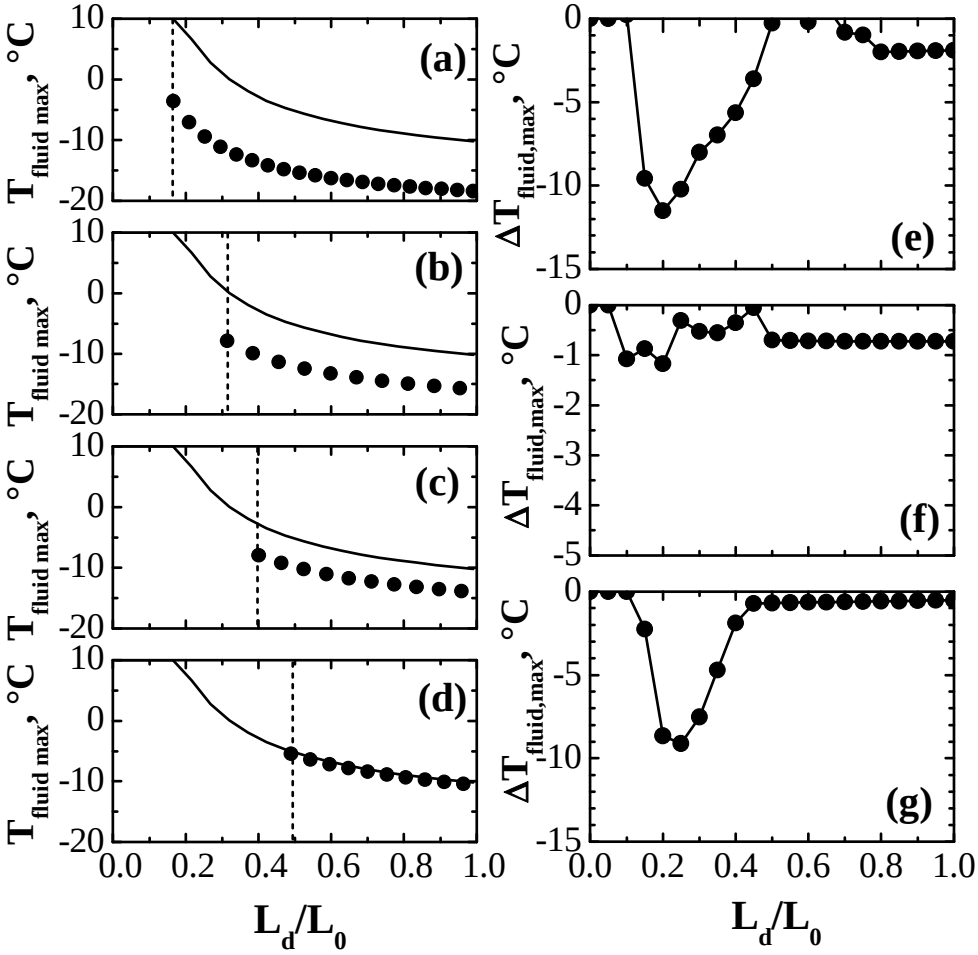
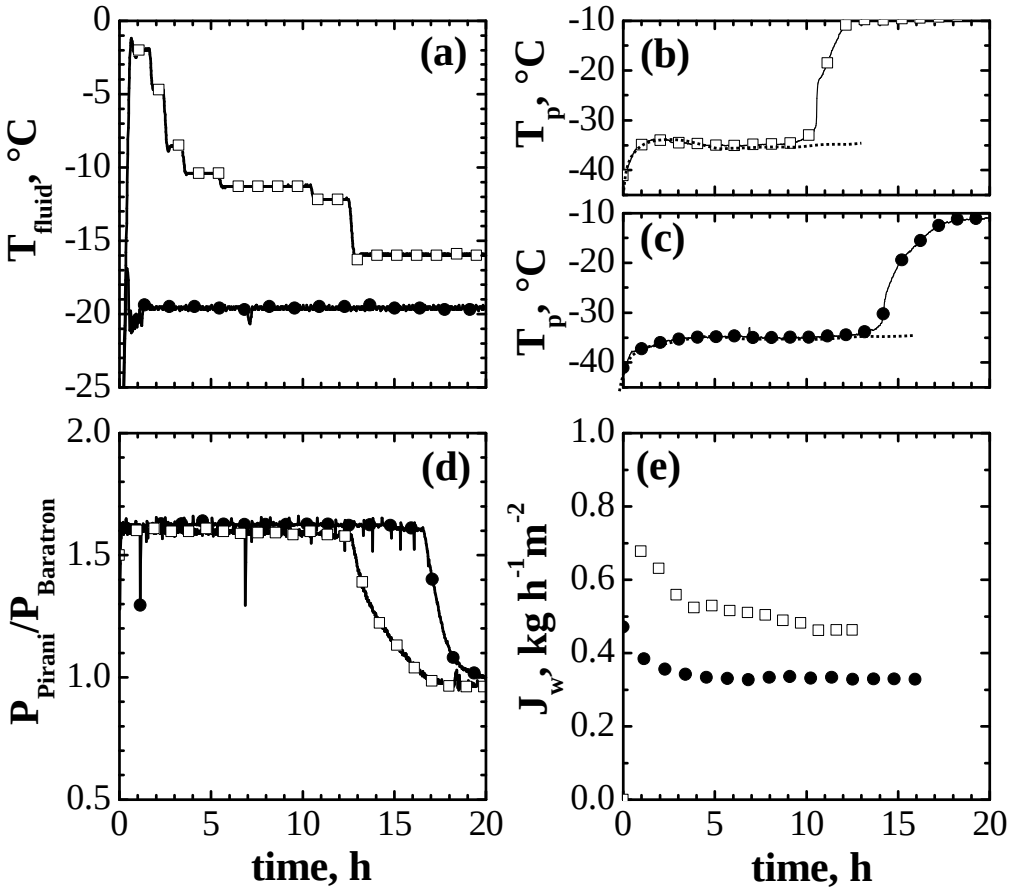

(a)
(b)
(c)
(d)
(e)
(f)
(g)
$T_{fluid\ max}$, °C
$\Delta T_{fluid,max}$, °C
L_d/L_0
10
0
-10
-20
-5
-15
-1
-2
-3
-4
0.0
0.2
0.4
0.6
0.8
1.0

Figure 7


(a)
(b)
(c)
(d)
(e)
T_{fluid}, °C
T_p, °C
T_p, °C
$P_{Pirani}/P_{Baratron}$
J_w, kg h^{-1}m^{-2}
time, h
time, h