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In-line and off-line optimization of freeze-drying cycles for pharmaceutical products

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ABSTRACT

The problem of process design for the freeze-drying of pharmaceutical products is here addressed. A comparative analysis between the various optimization tools so far proposed is given. The above analysis aims to give some guidelines to lyophilization professionals in the choice of the best design strategy compatible with their objectives and the technology available. In particular, this study examines the strengths and weaknesses of design space and of the different model-based control techniques so far proposed with a view to a better understanding of factors which still limits the use of these techniques at the manufacturing scale. With this regard, the above methods are compared in terms of robustness and scalability of the recipe, number and type of input parameters, management of product and equipment constraints, as well as batch unevenness. The first part of the study is carried out by means of mathematical simulations, as this approach makes it possible to better investigate the controller performance eliminating the uncertainty due to the experiment reproducibility. This study shows that although design space can provide a detailed view of the impact of processing conditions on product quality, its use for recipe development cannot lead to a real process optimization. By contrast, this objective can be achieved if model-based control is used. Experiments obtained for mannitol and sucrose-based formulations confirmed this result.

KEYWORDS

Freeze-drying, mathematical modeling, process optimization, control, scale-up

INTRODUCTION

Freeze-drying is often used as preservation method for those pharmaceutical products that are sensitive to the presence of water and, therefore, cannot be commercialized as ready-to-use liquid products. Furthermore, this process is particularly suitable for heat sensitive products because of the low processing temperatures.

Freeze-drying encompasses three different steps: freezing, primary and secondary drying. In this paper, however, we will focus only on the design of the primary drying phase as it is the most risky phase of the entire process and, thus, care must be paid in the selection of the processing conditions. In particular, to get a manufacturing procedure that is efficient and safe, the product temperature has to be maintained below a critic value to avoid irreversible damage. This value corresponds to the eutectic point in case of products that crystallize during freezing, or to the glass transition temperature in case of products that remain amorphous. Furthermore, the vapor flow rate has to be lower than a limit value, beyond which choked flow conditions can occur in the spool connecting the drying chamber to the condenser (1). Because of product and equipment constraints, processing conditions have to be carefully designed. The final objective is to build in quality by design as recommended in the Guidance for Industry PAT (Process Analytical Technology) issued by US-FDA in 2004 (2).

The design of the primary drying phase entails the definition of some process variables: fluid temperature, chamber pressure and drying time. With this regard, both off-line and in-line strategies can be used to assist lyophilization professionals: off-line methods are based on mathematical simulations to determine the optimal processing conditions, while in-line methods rely on a closed-loop controller that modifies the in-line processing conditions to meet the desired product characteristics. Various control strategies have been proposed in literature (3), but in this paper we focus on model-based control approaches. All these methods aim to fulfill the same requests: preserve product quality, maximize the sublimation rate, and minimize the drying time.

The objective of this study is to give a general view of the above methods, which can support lyophilization professionals in the choice of the most appropriate method to be used during process development. For this purpose, this paper offers a comparison between the various process optimization techniques that are commonly used in freeze-drying. The first part of the investigation is carried out by means of mathematical simulation. This approach

makes it possible to investigate the performance of the controllers as a function of the system parameters and of the product characteristics, covering a wide range of values and eliminating the uncertainty due to the experiment reproducibility or batch unevenness. In the second part, experimental results concerning the performance of the closed loop control system, as well as off-line process optimization, are presented with a view to discussing the strengths and the weaknesses of the various strategies. All the tests were carried out in a lab-scale freeze dryer and using two different formulations.

STATE OF THE ART

A freeze-drying cycle is usually the result of an extended experimental campaign, wherein the design of experiments method can be used to support lyophilization professionals to define the experimentation strategy. In the past, various authors showed that mathematical modeling makes it possible to minimize the experimental effort, as well as human resources, time and cost required by traditional approaches. In the following sections, a short review of the various model-based tools proposed to address the problem of recipe design is given, distinguishing between off-line and in-line strategies.

Off-line optimization methods

In the last decade, freeze-drying practitioners showed an increasing interest in the application of the design space concept as a tool for process design. The design space is a two-dimensional map that identifies all those combinations of fluid temperature and chamber pressure that result in a final product with the desired level of quality. In early works, this diagram was obtained by an extended experimental campaign (4), or by a combination of statistical design of experiments and mathematical simulation (5). This approach, however, requires a significant investment in terms of cost, human resources and time. In order to minimize this effort, various authors showed how mathematical modeling can be used to support the process development phase. With this regard, a lot of mathematical models for the freeze-drying process are available in literature, but only a limited number of them are useful for process development (6). For example, bi-dimensional models are useful to better understand the phenomenon of freeze-drying (7), but less valuable in the process development phase, as they require a large number of parameters that can be hardly gathered from literature or measured experimentally (8). As a general guideline, the level of detail is dictated by the final use of the model. Concerning the problem of process design, the model has to support

professionals in understanding the relationship between processing conditions and product dynamics. Therefore, this model should describe accurately the phenomenon of freeze-drying and involve few parameters that can be easily estimated by a limited number of experiments. The reduced mathematical model proposed by Velardi and Barresi (6), and in particular the simplified model I, wherein both the heat transfer through the dried layer and along the glass vial are neglected, is particularly suitable for this purpose, and for this reason is used in this work.

Over the last five years, various authors (9, 10) showed that mathematical modeling can be used to obtain the design space map with minimum effort, keeping also into account equipment constraints (11-13). As widely discussed by Fissore et al. (14), all these methods lead to a single-step cycle for the primary drying wherein processing conditions are maintained constant throughout the primary drying step. In this study, we refer to these methods as static design space. However, this recipe is usually very conservative and far from the optimized one. In fact, they showed that the design space can change with time, because the dried layer thickness, and hence the product resistance to vapor flow, increases with time. They also showed that the design space is very large at the beginning of the drying when the product resistance is low, then it progressively shrinks as the drying goes ahead and moves toward the curve calculated by traditional methods. It follows that a more aggressive heating strategy can be used, especially in the first part of the drying, with respect to the recipe developed by using static design space algorithms. Another important aspect that deserves attention from lyophilization scientists is the batch heterogeneity. With this regard, Pisano et al. (15) showed how the design space can be used for recipe design of uneven batches, and also showed how the model parameter uncertainty can be effectively taken into account during design space calculations. Table 1 compares general and technical information for a number of widely used and currently available design space algorithms (5, 9, 14).

Regardless of the calculation method used, the design space gives a complete and detailed picture of the relationship between operating conditions, product temperature, and vapor flow rate. This feature is very convenient for process design, as it allows lyophilization practitioners to design a cycle that is robust enough to preserve the product quality even in presence of limited process disturbances, inter-vial variability, and accounts for parameter uncertainty. In order to obtain a robust design, freeze-drying practitioners can use different strategies:

- Add a margin of safety on the fluid temperature and/or on chamber pressure;

- Overestimate model parameter uncertainty, e.g. multiplying by 2 the value of the heat transfer coefficient (K_v) and/or of product resistance (R_p) used for the calculations, in such a way that both inter-vial variability and parameter uncertainty can be taken into account;
- Use of an intelligent design, where the critical product and process design parameters are identified, and their distribution are described by an appropriate mathematical relationship, such as a Gaussian distribution. This information can then be included in the calculation of the design space as it has been widely discussed by Fissore et al. (14) and Pisano et al. (15).

The procedure proposed by Fissore et al. (14) is used here to build the design space. In the following section, an example is given of how the design space can be used to define a cycle. It is also shown how a robust cycle can be designed in order to preserve the product quality even in presence of temperature and pressure oscillations.

In-line optimization methods

The freeze-drying process is usually carried out using a predefined cycle that, as widely discussed in the above section, is the result of an extensive study. This approach, even if very simple, does not guarantee to obtain always the optimal cycle or to meet the desired product quality attributes. In fact, undesired changes of the product structure and of processing conditions are quite common in manufacturing practice. As it has been shown above, a margin of safety can be introduced to reduce the impact of these changes on the quality of the drug, but this approach reduces the yield and the process performance. According to the Good Manufacturing Practice concept, a manufacturing process has to be controlled, and any changes to the process have to be evaluated, especially in terms of impact on the quality of the drug. This request motivates the increasing number of industrial-academic collaborations, which aim at developing new control systems that, on the one side, can effectively evaluate process changes and, on the other side, manipulate the in-line processing conditions with the scope of ensuring the desired product quality and maximize the vapor flow rate to obtain the most cost effective cycle.

In the past, various techniques have been proposed to control the sublimation step in lab-scale productions, as summarized by various authors (3, 16). The above tools mainly differ in the type and number of manipulated variables, as well as equipment/product constraints. Another important characteristic is the type of information required from the

process, as it dictates which monitoring technique has to be used in order to close the control loop. In this paper a general review is given for the systems so far proposed in literature for the control of the primary drying phase. Nevertheless, specific details are given only for model-based techniques as they will be object of the subsequent discussion. With this regard, Table 2 shows the main features of the control systems discussed in this study.

A first attempt to control the primary drying phase was made by Tang et al. (17). They proposed the use of an expert system that manipulates both the chamber pressure and the fluid temperature on the basis of process information given by the pressure rise test technique, and of some empirical and common practice rules. This approach, however, has not any predictive capacity (i.e. the controller cannot determine the optimal control policy taking also into account the future process reaction to such a policy) and cannot lead toward a real process optimization (18). A significant improvement was given by Fissore et al. (19), who coupled a software sensor to monitor the process and a classical feedback controller to calculate the optimal heating strategy. This approach is very promising as it allows an almost continuous adjustment of the heating strategy and, thus, can compensate potential process disturbances as soon as their effect on the product temperature is shown. However, this control system has some limitations. For example, it can manipulate only the fluid temperature, while the value of chamber pressure has to be fixed by the user. Furthermore, the application of software sensors, at least in their current form, is not yet completely compatible with the automatic loading and unloading system of manufacturing plants.

Other feedback control systems have been recently proposed in literature. These systems use the pressure rise test technique as sensing device. The combination of feedback control and pressure rise test technique provides an easy and reliable control of the product temperature without the necessity of using temperature probes in a production line. Unlike the controller developed by Fissore et al. (19), the above control systems do not modify continuously the heating strategy, but a new control action is calculated and implemented only after a new system state estimation is available, that is, only after a new PRT has been done. However, the use of predictive controllers can in part compensate this drawback.

Oetjen (20) proposed the use of Thermodynamic Lyophilization Control (TLC). This process automation tool uses a simple feedback controller to manipulate the fluid temperature in such a way that the product temperature (estimated by the PRT technique coupled with the Barometric Temperature Measurement, BTM) is maintained at a desired value. Concerning the monitoring system, it must be said that various algorithms have been proposed to interpret the pressure rise curve. The BTM algorithm (21) is the simplest one, but its estimation of the

product temperature is less accurate than that supplied by other algorithms, like the Manometric Temperature Measurement (MTM) (22), the Pressure Rise Analysis (PRA) (23), and the Dynamic Parameters Estimation (DPE) (24). Fissore et al. (25) compared these approaches and showed that all these algorithms can estimate reliably the product temperature at least in the first part of the drying, while their estimation worsen as the drying goes ahead. A further improvement is given by the modified DPE algorithm described in Ref. (25). As general guidelines, PRA and DPE algorithms give a more robust and accurate estimation of process/product parameters, therefore their use is advisable when model-based controllers are used.

Pisano et al. (26) proposed the LyoDriver^{TM} controller (LD), which includes two different model-based control strategies. Regardless of the control algorithm used, LD can calculate the optimal heating policy (still at constant chamber pressure) by means of a mathematical model that describes the process dynamics. As shown by Ref. (26), all the model parameters required by the control algorithm can be supplied by the PRT technique coupled with the Dynamic Parameters Estimation algorithm (24, 25, 27, 28) and, thus, no additional experiments are needed. Compared with the previous control methods, LD controller has a predictive capacity that can prevent potential product temperature overshoots. Furthermore, LD can include the product temperature rise due to PRT in the calculation of control actions. With this regard, it is true that the above temperature increase can be reduced by an appropriate setting of the PRT duration (25), but in order to optimize the cycle we need to work very close to the maximum allowable product temperature. Therefore, even small and short deviations in product temperature can produce a final product that does not meet the desired quality attributes. In order to prevent this situation, a margin of safety can be introduced on the maximum allowable product temperature, which is used by the control system to calculate the heating strategy.

The use of mathematical modeling has another important advantage. As already stated above, both TLC and LD methods can modify the fluid temperature only when a new system state estimation is available. Both TLC and LD use the PRT technique as sensing device, therefore the system state is typically updated every 30 minutes. TLC modifies the fluid temperature as a typical feedback controller; therefore the control action depends on the basis of the error between the current product temperature and the desired value. Consequently, the future behavior of the system (e.g. the effect of control actions on the product dynamics) is not taken into account. Instead, LyoDriver^{TM} controller can define an appropriate sequence of control actions taking also into account the future product dynamics. Furthermore, the

calculations of LD recognize the dynamics of the heating/cooling systems of the freeze-dryer. All these aspects make the LyoDriver^{TM} controller an ideal tool to support lyophilization professionals during the process development phase. Finally, it must be noted that the robustness of the controller depends on the monitoring system used. The PRT technique coupled with the modified DPE algorithm (25) or with a more sophisticated algorithm, which includes also the heat transfer through the dried layer (28), gives the most robust and complete system state estimation with respect to the other monitoring tools proposed in literature.

Over the last two years, various authors proposed the use of advanced methods of process control (based on the Model Predictive Control technique) for the sublimation step optimization. With respect to the model-based controllers designed by Pisano et al. (26), these new control algorithms provide an implicit nonlinear feedback, wherein model predictions errors can be directly embedded in the control strategy calculation. This approach can compensate both parameter uncertainty and errors due to approximation in the model formulation. Todorov and Tsvetkov (29), and Todorov and Petrov (30) proposed the use of a nonlinear predictive controller based on black-box models to optimize the drying time, but neither product nor equipment constraints are taken into account. Concerning this last aspect, a further improvement was given by Daraoui et al. (31), who also discussed the problem of transforming a constrained optimization problem into an unconstrained one, and investigated the controller robustness with respect to model parameters uncertainty.

All the control systems described above can manipulate only the fluid temperature, while the value of chamber pressure is fixed. As widely discussed in Pisano et al. (32), the manipulation of both P_c and T_{fluid} is advisable when the drying is rate limited by the mass transfer resistance. This situation occurs when only a part of the heat received by the product is used for ice sublimation, while the rest is accumulated in the frozen layer. The accumulated heat is responsible of product temperature increase (33). An effectively solution to manage the above problem is the control system proposed by Pisano et al. (32), which can control the vapor flow rate, and hence the drying time, modifying both the fluid temperature and chamber pressure.

To better investigate the advantages of using the Model Predictive Control technique, with respect to the previous control approaches, the authors designed a second controller that manipulates only the fluid temperature. This control system, even if very similar to the LyoDriver^{TM} controller, has an important advantage, that is, it can manage both product and equipment constraints. Therefore, the optimal heating strategy is limited not only by the

maximum allowable product temperature, but also by the equipment capacity. For example, the above controller can also recognize the upper bound on the maximum vapor flow rate, which is imposed by choked flow conditions. This control system can also take advantage of the internal model control structure (34). This feature can recognize errors in model predictions, which are evaluated at the end of each control action when a new system state estimation is available. Specific details on the various control algorithms can be found in Ref. (32).

Regardless of the type of control policy used, all the above controllers have some advantages:

- Fixed the desired product quality attribute (e.g. the product temperature has to be maintained below a limit value during the entire drying step), the optimal cycle can be calculated in only one experimental test;
- Cycle optimization can be carried out in lab-scale freeze-dryers, but theoretically also in the manufacturing unit. This approach makes it possible to avoid the necessity of scaling up the recipe.

and disadvantages:

- The freeze-dryer has to be equipped by an appropriate monitoring device, which gives a regular estimation of the product temperature, residual ice content and, if a model is used for control actions calculation, an estimation of model parameters such as the heat and mass transfer coefficients.
- If feedback control systems are not used to control in-line the process, but to design the optimal cycle, the robustness of the resulting recipe is not guaranteed in case of process transfer. However, as already shown for the off-line optimization, a margin of safety can be introduced for the maximum product temperature.

MATERIAL AND METHODS

Experimental set-up

The case study investigated here is the freeze-drying of a placebo, constituted by 5% (w/w) sucrose or by 5% (w/w) mannitol solutions, processed in a pilot-scale freeze-dryer (LyoBeta 25 by Telstar, Spain) using ISO 8362-1 2R tubing vials filled with 1.5 ml of solution. The total product thickness is 10.6 mm. The product temperature at the bottom of the vial is measured by using T-type miniature thermocouples (by Tersid S.p.A., Milano, Italy), while

the product temperature at the interface of sublimation and the residual ice content are estimated by PRT technique coupled with DPE$^+$ algorithm (25). The end of primary drying is estimated using the ratio of Pirani and Baratron sensors (27).

Off-line optimization via design space

The design space was calculated by using the method proposed by Fissore et al. (14). The main steps of this approach can be so summarized:

1) Identification of the range of interest for the fluid temperature and chamber pressure. The third parameter of the diagram, that is, the ratio between the dried layer thickness and the total product thickness ranges from 0 to 1.
2) Definition of a sampling interval for each of the above variables;
3) Selection of the first value of L_{dried} to be considered for the calculations;
4) Selection of a couple T_{fluid} and P_c;
5) Calculation of product dynamics, that is the evolution of product temperature and vapor flow rate by using the mathematical model proposed by Velardi and Barresi (6).
6) Check if the desired product quality attribute (e.g. product temperature and vapor flow rate are lower than a limit value) is respected. If this check is positive, the combination of processing conditions selected at point 4 belongs to the design space.
7) Repeat points 4-6 for all the processing conditions of interest. The result of this calculations is the design space for the value of L_{dried} selected at point 3. The effect of parameter uncertainty on the design space can be taken into account by using the approach proposed by Refs. (9, 14, 15).
8) Repeat points 3-7 for all the values of L_{dried} of interest. The result of this calculation is a design space curve for each value of L_{dried} considered.

The dynamics of the product has been simulated by using the simplified model of Velardi and Barresi (6). The heat flux from the shelf to the product is described by the following equation:

$$J_q = K_v \left(T_{\text{fluid}} - T_B \right) \qquad (1)$$

where T_B is the temperature of the product at the vial bottom, and K_v is an overall heat transfer coefficient, which accounts for the various heat transfer mechanisms from the shelf to the

product. The drying behavior of a batch of vials is heterogeneous, as the heat transfer coefficient varies with the vial position on the shelf. Therefore vials were grouped into families as shown by Pisano et al. (35). The solvent flux from the interface of sublimation to the drying chamber is calculated by using the following equation:

$$J_w = \frac{1}{R_p}\left(P_{\mathrm{w,i}} - P_{w,c}\right) \qquad (2)$$

Details about the methods used to determine K_v and R_p can be found in Pisano et al. (15). The above approach makes it possible to build a design space for each group of vials and thus to identify the optimal operating conditions for the whole batch. In order to select the optimal combination of T_{fluid} and P_c that maximizes J_w, a contour plot for J_w is used. This diagram displays isolines of J_w vs. processing conditions as calculated close to the end of the primary drying.

In-line optimization via model-based control

In this study, the in-line optimization was carried out by using three types of model-base control strategies. First, we used the LyoDriver^{TM} controller (26); then we used a more sophisticated control strategy, that is, the MPC algorithms proposed by Pisano et al. (32). With regard to MPC, we considered two configurations:

- MPC A: only T_{fluid} is manipulated, with the goal of minimizing the difference between product temperature and $T_{\max}$. In this study, the results obtained by off-line optimization were used to select the value of chamber pressure.
- MPC B: both T_{fluid} and P_c are manipulated with the goal of minimizing the duration of primary drying (i.e. maximizing the sublimation flux). Various constraints (e.g. $T_{\max}$ and heating and cooling rates) were handled by using penalty functions. The Internal Model Control strategy was used to take into account modeling errors. The pressure rise test coupled with DPE^{+} algorithm was used as sensing device and, thus, the average batch behavior is monitored. Consequently, batch heterogeneity was not considered.

To carry out laboratory and simulation experiments, the range of processing conditions were set according to the equipment characteristics ($P_c \in [2.5, \quad 30]$ Pa, $T_{\mathrm{fluid}} \in [193, \quad 313]$ K). The guidelines given by Ref. (32) were used to set the controller parameters. In particular, in this

study the prediction horizon was 210 min, the control horizon was 120 min, the control time was 30 min, and the move suppression factors (that penalizes variations in T_{fluid} and P_c) were set equal to 0.1. The reference trajectory for J_w was calculated by a local steady-state optimization, which recognized equipment and product constraints. At the completion of each control action, the state of the system (in terms of J_w and T_B) was updated by using the estimations obtained by the pressure rise test technique coupled with DPE$^+$ algorithm for laboratory experiments, and by the detailed mathematical model proposed by Velardi et al. (6) for simulation experiments. Then, starting from the new system state, a new control action was calculated. The above action can also take into account the error of the model predictions.

All simulation experiments (both for in-line and off-line methods) were carried out considering as case study the freeze-drying of a 10% (w/w) sucrose solution, T_{max} = 240 K and L = 5 mm.

RESULTS

Analysis of off-line optimization methods

As widely discussed above, two different approaches can be used for the cycle development via design space. The former method leads to a static cycle, where chamber pressure and fluid temperature are kept constant throughout the primary drying phase. The second one, instead, can calculate the evolution of the design space as the drying goes on (i.e. dynamic design space), and therefore leads to a dynamic recipe where the fluid temperature and/or chamber pressure are progressively adjusted as the sublimation phase proceeds. Figure 1 shows how the design space of sucrose 10% (w/w) varies with the thickness of the dried layer. Calculations were performed by using the algorithm proposed by Fissore et al. (14). Figure 2 and Figure 3 show the static recipe and the dynamic recipe, respectively. The evolution of product temperature calculated by mathematical simulation is also shown. Both recipes were able to maintain the product temperature below the limit value, that is, below 240 K. As expected the second recipe involved a more aggressive heating step in the first part of the drying, which reduced the drying length. In fact, the duration of the static recipe was about 10% longer than the duration of the dynamic recipe. The drying time for the two cycles was identified in Figure 3 as the time at which L_{dried}/L was equal to 100%. Furthermore, in the dynamic recipe both the fluid temperature and the chamber pressure were modified to obtain the highest sublimation rate compatible with product constraints (see the isoflux curves in Figure 1).

The above recipes were designed considering an average value for the heat transfer coefficient. However, as widely emphasized in literature, the heat transfer coefficient varies with the position of the vial in the array (35, 36). Therefore, the application of the two cycles shown above can compromise the product quality for all those vials that have a heat transfer coefficient that is higher than the mean value. Various solutions are currently available to overcome this problem:

1) Vials are grouped in a limited number of families on the basis of their position within the batch (35). The heat transfer coefficient is experimentally measured and the design space is calculated for each group of vials. Then, the most restrictive design space is used for the recipe design. Typically this design space is that of edge-vials, as these vials have the highest value of K_v. The resulting recipe makes it possible to meet product quality attribute for all the vials of the batch, even if it might be very conservative for the other groups of vials.
2) The mean heat transfer coefficient of only central vials is experimentally measured. This approach reduces the effort required to carry out experiments because the heat transfer coefficient does not have to be measured for the entire batch of vials. The value of K_v for central vials can be used to obtain a rough estimation of the heat transfer coefficient of edge-vials. In fact, we can assume that the value of K_v for edge-vials is 2-3 times higher than that of central ones. This information can be used to calculate the design space, and hence an appropriate recipe, for edge vials. This approach, even if very simple, can give misleading results. In fact, if the value of K_v for edge vials is overestimated, the resulting recipe is too conservative. By contrast, if K_v is underestimated the recipe can be not robust enough. In order to obtain a reliable estimation of the safety factor that allows the estimation of the heat transfer coefficient for edge-vials from the value of central vials, side-wall radiation can be characterized experimentally as shown in Pisano et al. (28).
3) A margin of safety is introduced on the maximum product temperature used for the design space calculation. A mathematical model can be used to choose a proper margin of safety that account for parameter uncertainty or inter-vial variability.

Once a proper combination of the chamber pressure and fluid temperature is chosen, the duration of the drying can be determined by means of the same mathematical model at the basis of the design space calculation. For this purpose, the model has to be used for predicting the product evolution of central vials, as the total drying length is dictated by vials with the

lowest value of heat transfer coefficient.

The resulting recipe has to be robust enough to guarantee the product quality even in presence of limited variations in processing conditions with respect to the desired values. With this regard, an important advantage of the design space approach is that a margin of safety on the chamber pressure and fluid temperature can be introduced directly during the recipe design. Figure 4 and Figure 2 compares two recipes obtained via design space when a margin of safety on the fluid temperature was used or not. Both recipes maintained the product temperature below the limit value. However, if the recipe of Figure 4 was used, a longer time was required to complete the ice sublimation with respect to the recipe of Figure 2. Nevertheless, if a pulse disturbance was introduced on the fluid temperature after 5 hours of drying (amplitude = 5 °C, duration = 60 min), only the recipe of Figure 4 was able to maintain the product temperature below the limit value, see Figure 5. It must also be said that the robustness of the above recipe is not guaranteed when it is transferred to new equipment, even if the two pieces of equipment have the same scale. Even more risky is the case of scale up. In this case, a new recipe has to be defined according to the design space of the new equipment.

A further comment concerns the value of R_p vs. L_{dried}, which is used to calculate the design space. This relationship is dictated by the composition of the formulation and by the freezing protocol used, while it is usually independent of processing conditions at which is carried out the drying step. This statement however is not always true. For example, amorphous products can modify their structure, without collapsing, when they are processed at temperatures between the glass transition and the collapse value (37-40). Because of this modification, the value of R_p vs. L_{dried} can be described by different curves depending on the temperature at which the product is processed and, hence, on the processing conditions used. Let us now consider an example, that is, the freeze-drying of a 5% (w/w) sucrose solution when it is processed at a product temperature higher than the glass transition value, but always below the collapse temperature. Following on from what stated above, the R_p vs L_{dried} varies as the product overcomes the glass transition temperature, because of micro-collapse phenomenon. For the formulation investigated, an example of this dependence was shown by Fissore et al. (14) (see product C). Figure 6 compares the design spaces calculated for the 5% (w/w) sucrose solution when $T_{\max}$ is higher than the glass transition value and lower than the collapse temperature. In the first design space, the value of R_p vs L_{dried} is described by a unique relationship, which has been determined at product temperatures lower than the glass transition value. By contrast, in the second design space the value of R_p vs L_{dried} is modified

when the product temperature is higher than the glass transition value.

In this analysis calculations were carried out considering a 5% (w/w), rather than 10% (w/w), sucrose solution as structure modifications, and hence R_p vs. L_{dried} changes, are more marked for low solid content. As expected, the design space was larger in the second case, as the micro-collapse of the solid matrix reduced the product resistance to vapor flow. It follows that if I neglect this dependence, the resulting recipe might be not optimal, but is still good in terms of product quality preservations.

Analysis of in-line optimization methods

The objective of the below analysis is to discuss the impact of different control structures on the optimized recipe. The results of this analysis can support lyophilization professionals in the choice of the best control algorithm compatible with the control objectives.

The analysis of in-line optimization methods is here confined to predictive controllers as they supply the best process performance. Therefore, we will limit our discussion to the LyoDriver^{TM} controllers and MPC systems proposed by Pisano et al. (32).

First, let us consider the LyoDriver^{TM} controller. This control method can manipulate only the fluid temperature, while the chamber pressure is fixed by the user. This choice can significantly affect the controller performance. For example, Figure 7 shows that there is a value of chamber pressure that minimizes the drying length. For the freeze-drying of 10% (w/w) sucrose solution, the optimal chamber pressure was the minimum value that can be set compatibly with equipment characteristics. Probably, this result is due to the fact that the drying was under mass transfer control conditions. For the same case study, Figure 8 compares LyoDriver^{TM} performance when chamber pressure was set by the user according to three different criteria:

1) The lyophilization professional had no indications on the optimal chamber pressure for the specific case study investigated. Since this variable typically varies from 5 to 30 Pa, P_c was set to an intermediate value, that is, 20 Pa;
2) The value of chamber pressure was set according to the rule of thumb proposed by Tang et al. (17). Therefore, P_c was set to one third of the ice vapor pressure value calculated at the maximum allowed product temperature. The optimal chamber pressure value was thus 9 Pa;
3) The value of chamber pressure was optimized off-line as proposed by Fissore et al. (41), and according to the results shown in Figure 7, therefore P_c was set to 5 Pa.

The above results show that even when an in-line controller was used to manage the process, if the chamber pressure was not properly set, the length of the drying was longer than the value observed when P_c was optimized off-line (see Figure 8, graph c). However, it must be said that the optimal value for chamber pressure can vary as the drying goes on, as the characteristic curve shown in Figure 7 depends on product characteristics (41) that, in turn, can vary during drying. Therefore, a further improvement can be obtained by optimizing in-line both the fluid temperature and the chamber pressure. This result can be achieved, for example, by using the MPC B control algorithm described in this paper, which solves a multi-variable optimization problem. Figure 9 compares the heating policy obtained when the freeze-drying cycle for a 10% (w/w) sucrose solution was carried out under the supervision of LyoDriver™ (graph a), MPC A (graph b) and MPC B (graph c). As expected, the heating strategies calculated by LyoDriver™ and MPC A were very similar, and the resulting drying time was not significantly modified. On the contrary, the concurrent manipulation of the fluid temperature and chamber pressure significantly speeded up the ice sublimation, which was about 15% higher.

Regardless of the control approach used, all the heating policies above reported were characterized by an aggressive heating at the beginning of the drying. This step makes it possible to bring the product close to its limit temperature (but obviously always below it) and, thus, to maximize the vapor flow rate. Then, the heating is reduced to compensate the increasing value of the product resistance. Pisano et al. (26) showed that this initial step has a significant impact on the length of the drying. It must be said that this control policy is typical of model-based controllers. By contrast, expert systems like the Smart Freeze-Dryer™ and the TLC usually involve a more precautionary heating policy, mainly in the first part of the drying. This strategy makes longer the drying phase. These expert systems, in fact, proceed step by step evaluating the results of the previous control action, and without the possibility of optimizing the next step.

A final comment concerns the number and type of parameters required by the various control logics. All the three control algorithms considered here require the specifications of some parameters: maximum allowable product temperature, product constraints (e.g. T_{max}) and characteristics (e.g. product resistance to vapor flow), thermal characterization of the container (i.e. the value of the heat transfer coefficient), equipment characteristics (e.g. cooling and heating rate) and constraints (e.g. minimum and maximum value for P_c and T_{fluid}), control parameters (e.g. prediction and control horizon, control interval). All these parameters have an impact on the controller performance, therefore care must be paid by the user in their

selection.

The use of a MPC system has remarkable advantages with respect to LyoDriver™ when the mathematical model does not describe accurately the real process dynamics. However, MPC setting is more troublesome, as it requires much more information. For example, beside the control parameters above mentioned, the MPC systems also require the specification of the move suppression factors. These parameters penalize changes in the processing conditions and therefore can have a significant impact on the controller performance. For example, high values of these parameters can lead to precautionary cycles. By contrast, low values of the move suppression factors can introduce drastic variations of processing conditions, which are usually undesired in a production unit. However, simple but effective guidelines on their choice are given by Pisano et al. (32).

In the previous discussion, it has been remarked that chamber pressure manipulation improves the process performance. However, to achieve this result, the control system needs additional information like the pressure dependence of the heat transfer coefficient. The pressure rise test technique, which is used in this study to update regularly the system state, can supply only the value of the heat transfer coefficient at the operating pressure. Therefore, prior to cycle optimization, few experiments have to be carried out for the thermal characterization of the container. By contrast, the information given by the pressure rise test technique is more than enough for the other algorithms, as they require the value of the heat transfer coefficient only at the operating pressure. The use of the MPC algorithms proposed by Pisano et al. (32) has another important advantage with respect to LyoDriver™ (but also to the other control algorithms proposed in Literature), that is, it can better manage constraints on the maximum vapor flow rate to avoid choked flow conditions. In fact, the MPC system controls directly the vapor flow rate rather than the product temperature.

Unlike the off-line optimization methods, margins of safety on processing conditions cannot be introduced directly in the calculation of the heating strategy. In fact, the in-line control systems investigated here determine the optimal value of fluid temperature, and eventually of chamber pressure, that maintains the product temperature at its limit value. Therefore, if a margin of safety is introduced on the calculated processing conditions, the control system fails to meet its objective, that is, to maintain the product temperature at its maximum value. However, a robust recipe can still be designed by translating the margins of safety on processing conditions into a margin of safety for the maximum product temperature. This calculation can be done, for example, by using a mathematical model of the process (42). For this purpose, the model is used to estimate the product temperature rise under a specific

variation in the fluid temperature and/or chamber pressure. In a similar way, this margin of safety can be enlarged to take into account also the uncertainty on model parameters. This last correction is not however necessary for the MPC systems, as they used the Internal Model Control strategy to take into account modeling errors.

A last but not least issue to be considered during the process development phase is the management of the batch unevenness. As widely discussed in literature, vials located in different positions on the shelf can show a different product dynamics. It follows that if a recipe is developed using as reference the average batch properties supplied by the pressure rise test technique, this recipe does not guarantee the product quality for all the vials of the batch. As confirmation of this statement, Figure 10 displays the evolution of the product temperature when the drying was carried out by using LyoDriver^{TM} controller and the PRT technique was used to monitor the average system state. As expected, only the product temperature of central vials was maintained below the limit value, while edge-vials overcame this limit after 0.5 h of drying, as no margin of safety was introduced on T_{max}. The heat transfer coefficient of edge vials was higher (about double) than that of central vials.

The problem of process design for uneven batches has been already discussed in the previous section for the off-line methods. In particular, it has been shown that the problem of finding the optimal recipe for an uneven batch corresponds to find the optimal recipe for edge-vials. In fact, the above recipe can preserve the product quality for the entire batch of vials. The same basic idea can still be used by the in-line methods. With this regard, in-line controllers choose the best heating policy on the basis of the system state of edge-vials, rather than the average state of the batch. To apply this idea, however, we need to overcome a still open issue in freeze-drying, that is the monitoring in case of heterogeneous drying behavior. A possible solution implies the use of observers, but as said above a lot of work has to be still done to apply this technique in a manufacturing environment. Another possibility is the application of a modified DPE algorithm to interpret the pressure rise curve (43). This algorithm introduces a third parameter to be optimized (beside the product temperature and resistance to vapor flow), which can be correlated (by a nonlinear function) to the variance and covariance of the frozen layer thickness, interface temperature and effective diffusivity of the vapor through the dried layer. In this way, the average batch properties estimated by the PRT technique can be used to retrieve the system state of edge-vials. This information can then be used to close the loop of control and lead to a robust recipe, which guarantees the product quality for all the vials of the batch. A trivial, but not always effective, solution might be to introduce a further margin of safety on the limit temperature to account for the

heterogeneous drying behavior.

Comparison between in/off-line optimization methods

Let us consider the problem of recipe design for the freeze-drying of a 5% (w/w) sucrose solution processed in tubing vials. The recipe has to be designed to maintain the product temperature of central vials below a limit value, that is, below 240 K. First, we use the design space technique to select a proper combination of processing conditions for the primary drying step. Let us imagine that few experiments have been already carried out to determine the value of R_p vs. L_{dried} for the above formulation, as well as the pressure dependence of K_v for the container used. An example of results is given in Figure 11 (top graphs). Once the design space was built for the selected product (see Figure 11, bottom graph), operating conditions could be easily identified. In particular, in order to determine the optimal combination of T_{fluid} and P_c that maximizes the sublimation flux, we used the contour plot of J_w calculated close to the end of the drying. It must be noted that in this example no margin of safety was introduced on T_{max}. According to Figure 11 a good combination of T_{fluid} and P_c that preserves product quality and maximizes J_w, is T_{fluid} = 266 K and P_c = 5 Pa. The design space considered here is significantly different from that displayed in Figure 1, as we are now considering the freeze-drying of a 5% (w/w) sucrose solution and L = 10.6 mm, while Figure 1 refers to the case of a 10% (w/w) sucrose solution and L = 5 mm. It must also be pointed out that, although the total solid content per vial was the same for the two configurations, the resulting drying length was significantly modified.

A freeze-drying cycle was carried out in a lab-scale freeze-dryer using the processing conditions determined in Figure 11 (data not shown). The drying time resulted to be about 21 h. A similar cycle was carried out by using the MPC A and MPC B algorithms to optimize in-line the recipe. In both cases the constraint imposed on product temperature was respected, but a remarkable reduction of the drying length (MPC A: t_d = 21 h; MPC B: t_d = 16 h) was obtained only when optimizing both T_{fluid} and P_c. This comparison confirms that both in-line and off-line optimization can maintain the product temperature below a desired upper limit. Shrinkage was observed only for edge-vials, while central vials retained the original volume. However, it must be said that macro-collapse phenomenon was not observed for both vial groups. Furthermore, the off-line optimization via design space and the use of a MPC controller (that manipulates only the fluid temperature) gave almost the same process performance, while a significant reduction of the drying time could be obtained only with the

in-line optimization of the chamber pressure. Similar results were also observed for a 5% (w/w) mannitol solution. A comparison in terms of drying time between the various optimization techniques and for the two formulations is shown in Figure 13.

CONCLUSIONS

The strengths and the weaknesses of both in-line and off-line strategies were discussed. This comparative analysis aims to guide lyophilization professionals in the choice of the best design strategy compatible with their objectives and the technology available.

This study shows that both the design space and model-based control strategies can operate the freeze-drying process safely and efficiently. Both approaches can be used both in small-scale and in large-scale freeze-dryers, thus avoiding the problem of scaling up the recipe. The effectiveness of various model-based strategies to optimize a freeze-drying process has been demonstrated by means of mathematical simulations and experimental investigations. Both simulations and experiments showed that the design-space provides much more information about the effect of the operating conditions on the product, but the recipe optimization can be less effective than that achieved by using model-based control. In fact, during plant operations the optimum conditions can change frequently because of process disturbances. Consequently, in order to maximize the profits from the process while satisfying the operating constraints, the optimum operating conditions have to be recalculated on a regular basis, as feedback control does.

The use of in-line strategies makes it possible to obtain the optimal recipe in only one run. Nevertheless, an effective monitoring system is required. With this regard, the availability of a robust monitoring system, which is compatible with both laboratory equipment and manufacturing plant, is still a limitation of freeze-drying technology. This study also shows that the best optimization tool is MPC B, as it can manipulate in-line both the fluid temperature and the chamber pressure. Furthermore, the combination of MPC and Internal Model Control strategy allows an effective rejection of potential disturbances affecting the dynamics of the process. With this regard, the issue of founding a robust recipe is also addressed. In particular, this work shows that margins of safety can easily be introduced during recipe design for both in-line and off-line optimization.

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LIST OF SYMBOLS

J_q	heat flux, W m^{-2}
J_w	vapor flux, kg m^{-2} s^{-1}
K_v	overall heat transfer coefficient, W m^{-2} K^{-1}
L	total product thickness, m
L_{dried}	dried layer thickness, m
P_c	chamber pressure, Pa
$P_{w,c}$	partial pressure of water into the drying chamber, Pa
$P_{w,i}$	partial pressure of water at the interface, Pa
R_p	mass transfer resistance, m s^{-1}
t_d	drying time, h
T_B	product temperature at the vial bottom, K
T_{fluid}	fluid temperature, K
T_{max}	maximum allowable product temperature, K

Greek letters

$\chi_{T_{fluid}}$	margin of safety on the fluid temperature, K

Abbreviations

BTM	Barometric Temperature Measurement
DPE	Dynamic Parameters Estimation
LD	LyoDriver
MPC	Model Predictive Control
MTM	Manometric Temperature Measurement
PRT	Pressure Rise Test
TLC	Thermodynamic Lyophilization Control

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Table 1. Comparison of technical features for off-line methods currently used for the freeze-drying cycle design.

Table 2. Comparison of technical features for in-line methods currently used for the freeze-drying cycle design.

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Figure 1. Design space for sucrose 10% (w/w) as calculated at (light-grey area) L_{dried}/L = 99%, (grey area) L_{dried}/L = 23%, and (dark-grey area) L_{dried}/L = 1%. Isoflux curves in kg m^{-2} h^{-1} (dashed lines) as calculated at L_{dried}/L=99% are also displayed. The points refer to the following processing conditions: (1) T_{fluid} = 280 K and P_c = 8 Pa and (2) T_{fluid} = 270 K and P_c = 5 Pa.

Figure 2. Example of cycle determined via static design space for sucrose 10% (w/w). Top graph: evolution of fluid temperature (solid line) and chamber pressure (dashed line). Bottom graph: evolution of the product temperature. The limit temperature (dashed horizontal line) and the drying end-point (vertical line) are also given in graph c.

Figure 3. Example of recipe determined via dynamic design space for sucrose 10% (w/w). Top graph: evolution of fluid temperature (solid line) and chamber pressure (dashed line). Bottom graph: evolution of the product temperature. The limit temperature (dashed horizontal line) and the drying end-point (vertical line) are also given.

Figure 4. Example of recipe developed via design space for a 10% (w/w) sucrose solution when a margin of safety on the fluid temperature ($\chi_{T_{fluid}}$ = 5 °C) is used. (a) Design space (grey area) and isoflux curves (dashed lines) as calculated at L_{dried}/L=99%. (b) Evolution of (solid line) T_{fluid}, (dashed line) P_c, and (c) product temperature. The maximum allowable product temperature (horizontal line) and the drying end-point (vertical line) are also given.

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Figure 7. Influence of chamber pressure on the drying length of a 10% (w/w) sucrose solution when LyoDriver™ is used. The maximum allowable product temperature is 240 K.

Figure 8. Example of freeze-drying cycles controlled by LyoDriver™ when chamber pressure is set to (solid line) $P_c = 20$ Pa, (dashed line) $P_c = \frac{1}{3} \cdot P_{\text{ice}}\left(T_{\max}\right)$ and (dotted line) optimized off-line. Evolution of (a) fluid temperature, (b) product temperature and (c) interface position. All the results have been obtained by means of mathematical simulation for the freeze-drying of a 10% (w/w) sucrose solution.

Figure 9. Comparison between freeze-drying cycles controlled by (left-side graphs) LyoDriver™, (central graphs) MPC A, and (right-side graphs) MPC B. Evolution of (a) processing conditions (solid line: T_{fluid}, dashed line: P_c) and (b) product temperature. The horizontal dashed line in graph b indicates the maximum allowable product temperature, while the dashed vertical line indicates the drying end-point. Both LyoDriver™ and MPC A uses a constant value of P_c (= 5 Pa). All the results have been obtained by means of mathematical simulation.

Figure 10. Evolution of product temperature for vials located at the edge of the shelf and in the central part. The freeze-drying cycle has been carried out according to the recipe shown in Figure 9 (graph a), wherein no margins of safety are considered. The horizontal dashed line indicates the maximum allowable product temperature.

Figure 11. (Upper graphs): mass transfer resistance vs. L_{dried} (left-side graph) and pressure dependence of K_v (right-side graph). (Lower graph): Design space for a sucrose solution (5% (w/w)). The solid line identifies the limit operating conditions nearby the endpoint of the drying, while the symbol (□) corresponds to T_{fluid} = 266 K and P_c = 5 Pa. Isoflux curves (in kg h^{-1} m^{-2}) are shown as dashed lines.

Figure 12. Cycles designed by (left-side graphs) MPC A and (right-side graphs) MPC B algorithms for the freeze-drying of a 5% (w/w) sucrose solution. Evolution of (graph a) chamber pressure, (graph b) fluid temperature, and (graph c) product temperature at the vial bottom as measured by thermocouples (solid line) and estimated by PRT technique (○). The horizontal dashed line in graph c indicates the maximum allowable product temperature, while the vertical line indicates the primary drying endpoint.

Figure 13. Comparison between drying time for the 5% (w/w) sucrose and 5% (w/w) mannitol solutions when the design space (▨), and in-line control systems (■: MPC A, □: MPC B) are used for the recipe design.

Table 1

	Trial & error	DS via DOE	Static DS via modeling	Dynamic DS via modeling
Equipment scale wherein the process design is done	Lab	Lab	Lab/industrial	Lab/industrial
Need of recipe scale-up to a manufacturing unit	yes	yes	no	no
Experimental effort & human resources	high	high	low	low
Ease of introducing some margins of safety on processing conditions	no	yes	yes	yes
Accounting for batch unevenness	no	no	yes	yes
Freeze-drying cycle optimization	no	no	no	yes
Availability of comprehensive data for better process understanding	no	yes	yes	yes

Table 2

	Smart Freeze-Dryer™	TLC	Feedback controller/ software sensor	LyoDriver™	MPC
Applicability for both lab and industrial freeze-dryer	yes	yes	yes	yes	yes
Experimental effort & human resources	low	low	low	low	low
Handling of product constraints	yes	yes	yes	yes	yes
Handling of equipment constraints (e.g. choked flow conditions)	no	no	no	no	yes
Equipment characteristics (cooling/heating rate)	no	no	no	yes	yes
Freeze-drying cycle optimization	no	no	yes	yes	yes
Predictive capacity (e.g. prediction product temperature overshoot)	no	no	no	yes	yes
Correction of model predictions errors by feedback action	n.a.	n.a.	yes	yes	yes
Compensation of model errors via internal model control	no	no	no	no	yes
Compatible with automatic loading and unloading systems	yes	yes	yes (*)	yes	yes
Sensing device	PRT via MTM	PRT via BTM	Software sensors	PRT via DPE, observers (**)	PRT via DPE, observers (**)
Availability of comprehensive data for better process understanding	no	no	no	yes	yes

(*) If the software sensor used is compatible with the loading/unloading system..

(**) Whichever monitoring tool that supplies an accurate estimation of product temperature, heat and mass transfer coefficient.

Figure 1

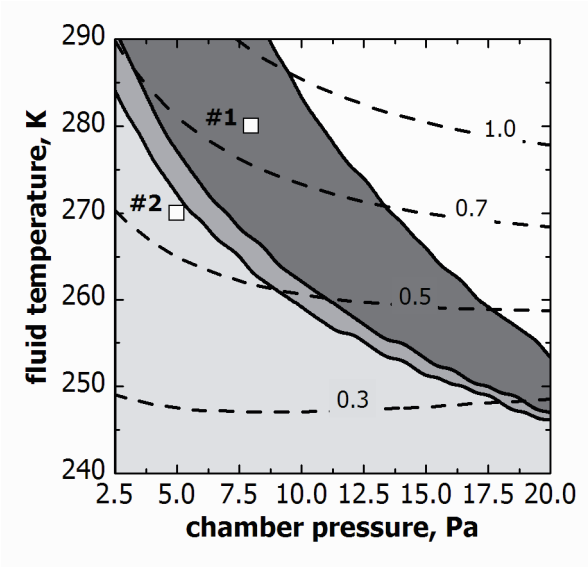
290
280
270
260
250
240
fluid temperature, K
#1
#2
1.0
0.7
0.5
0.3
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
chamber pressure, Pa

Figure 2

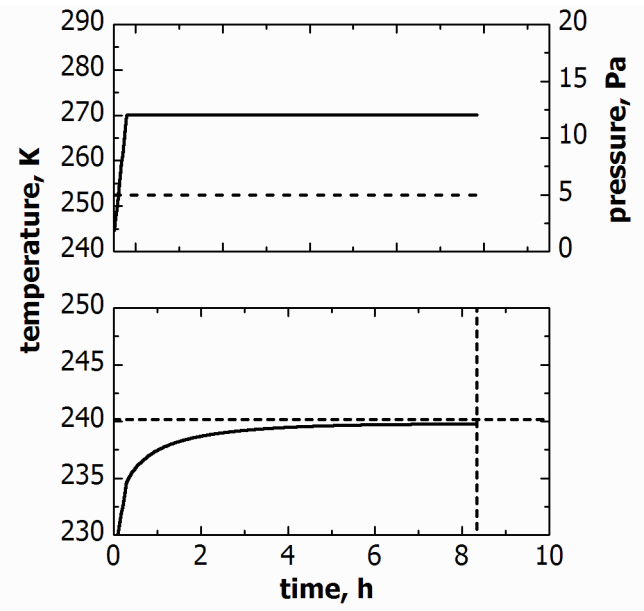
290
280
270
260
250
240
20
15
10
5
0
temperature, K
pressure, Pa
250
245
240
235
230
0
2
4
6
8
10
time, h

Figure 3

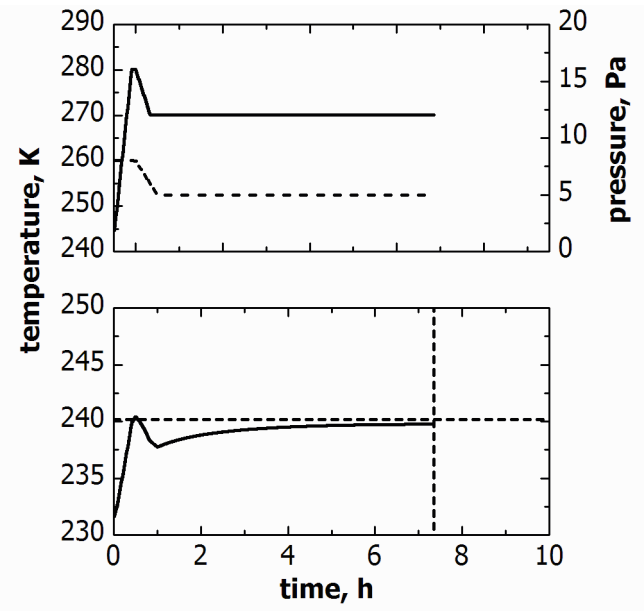
290
280
270
260
250
240
20
15
10
5
0
temperature, K
pressure, Pa
250
245
240
235
230
0
2
4
6
8
10
time, h

Figure 4

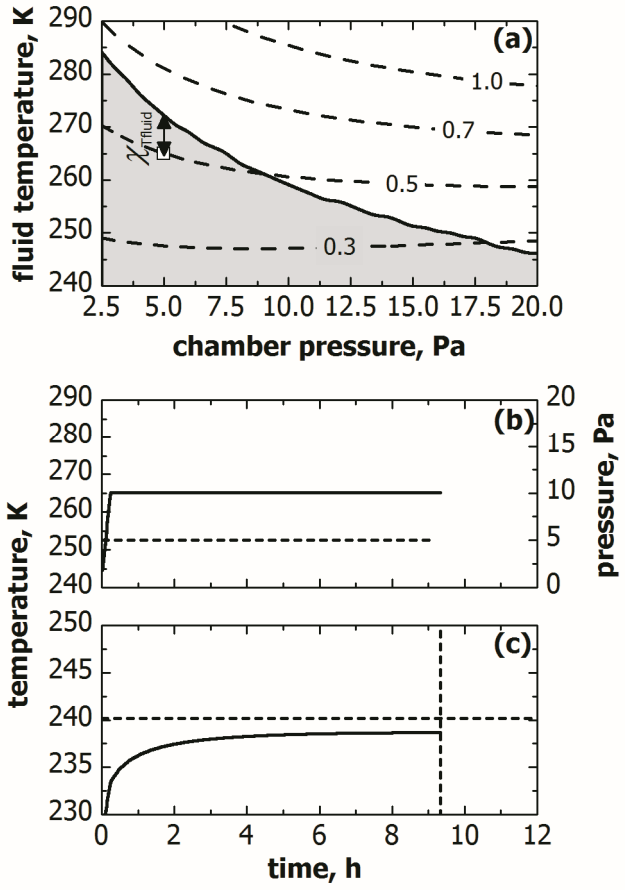
(a)
fluid temperature, K
chamber pressure, Pa
1.0
0.7
0.5
0.3
ΔTfluid
(b)
(c)
temperature, K
pressure, Pa
time, h

Figure 5

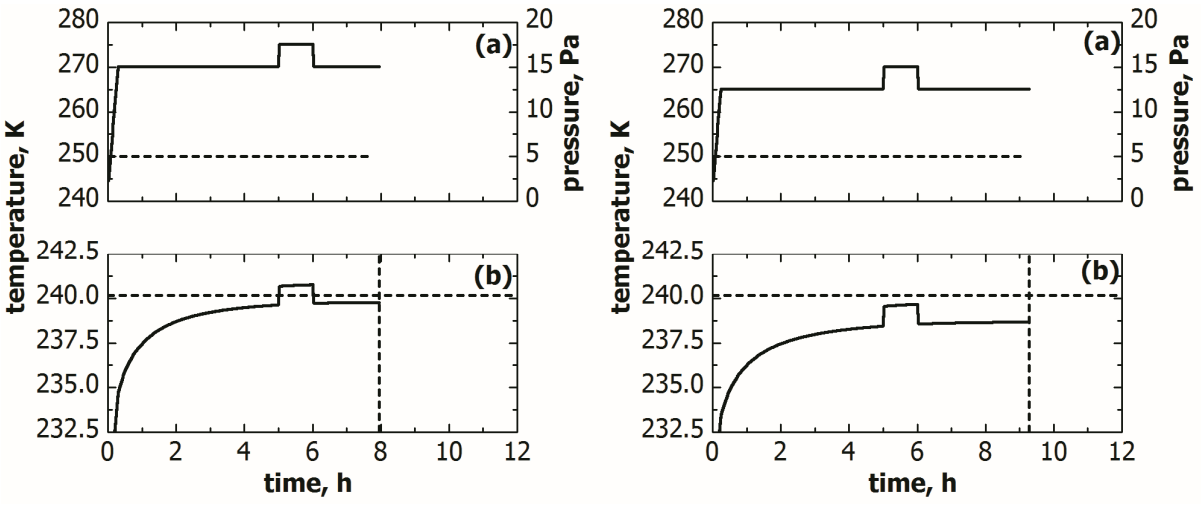
temperature, K
pressure, Pa
(a)
(b)
time, h
280
270
260
250
240
20
15
10
5
0
242.5
240.0
237.5
235.0
232.5
0
2
4
6
8
10
12

Figure 6

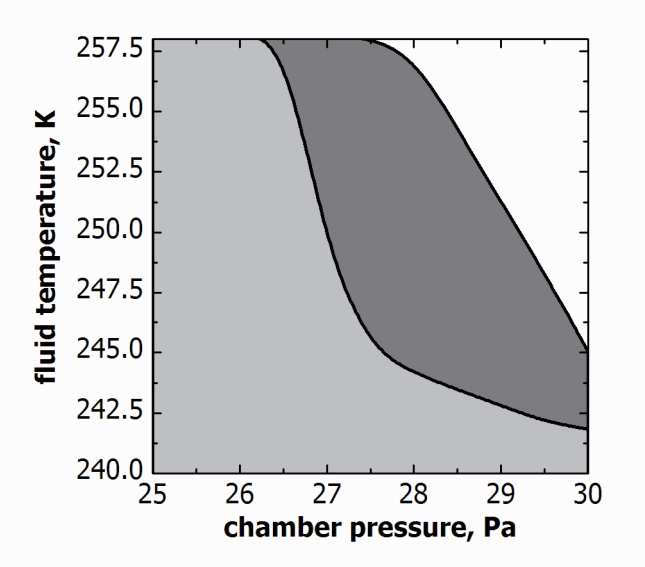
257.5
255.0
252.5
250.0
247.5
245.0
242.5
240.0
fluid temperature, K
25
26
27
28
29
30
chamber pressure, Pa

Figure 7

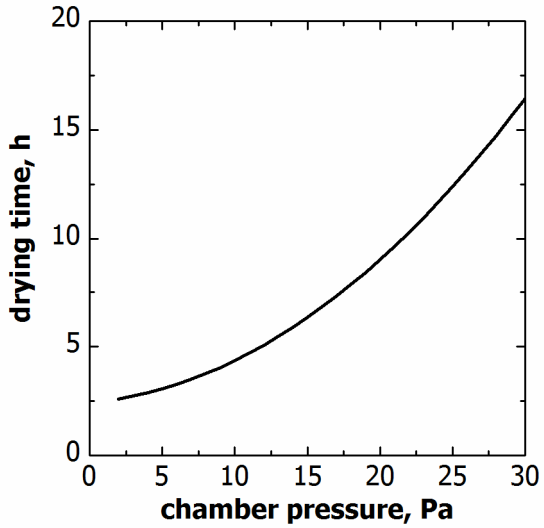

Figure 8

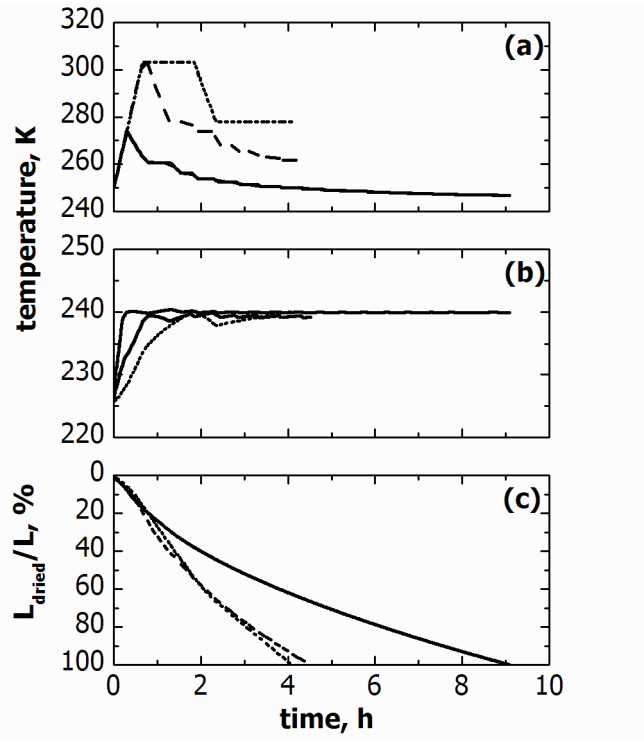
(a)
(b)
(c)
temperature, K
L_{dried}/L, %
time, h
320
300
280
260
240
250
240
230
220
0
20
40
60
80
100
0
2
4
6
8
10

Figure 9

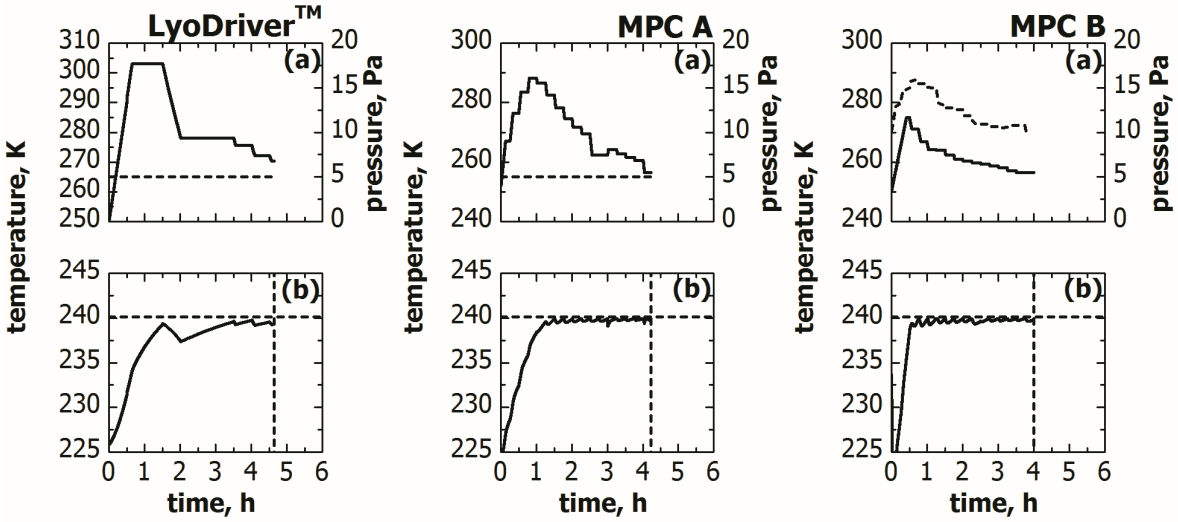

Figure 10

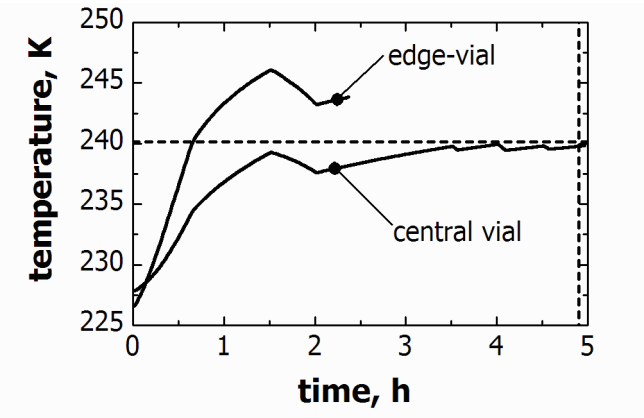
temperature, K
250
245
240
235
230
225
0
1
2
3
4
5
time, h
edge-vial
central vial

Figure 11

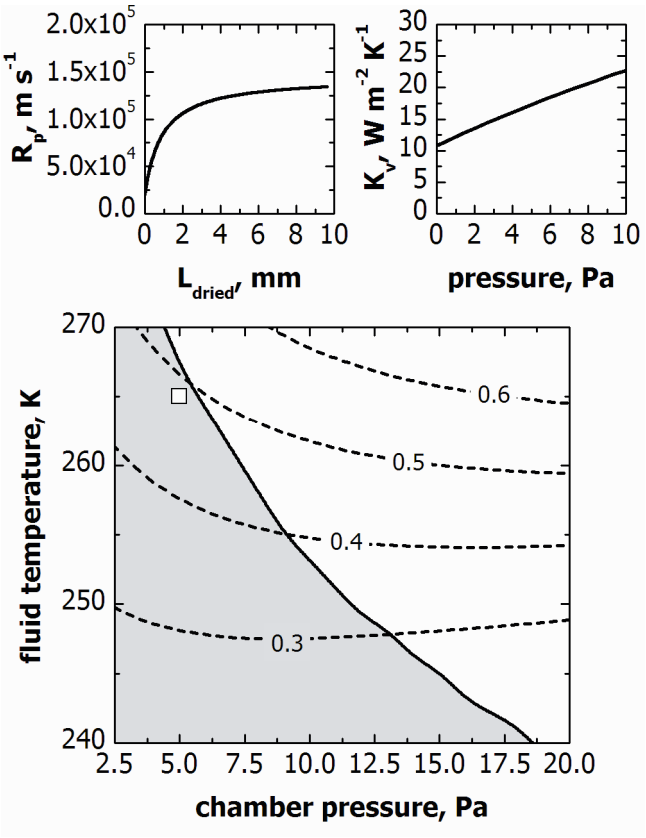
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
R_p, m s^-1
0 2 4 6 8 10
L_dried, mm
30
25
20
15
10
5
0
K_v, W m^-2 K^-1
0 2 4 6 8 10
pressure, Pa
270
260
250
240
fluid temperature, K
0.6
0.5
0.4
0.3
2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
chamber pressure, Pa

Figure 12

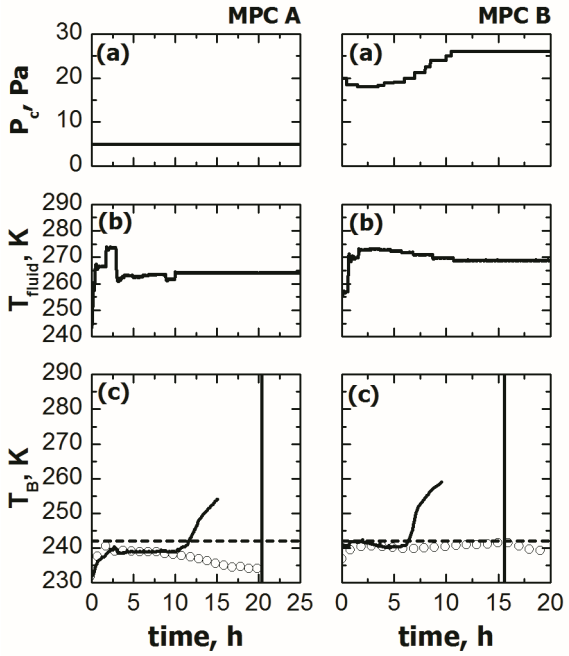
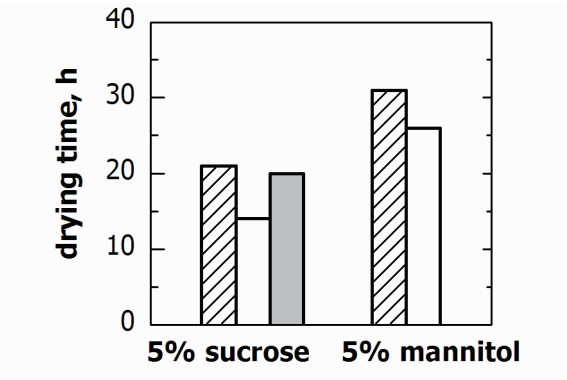
Figure 13