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Original
Use of a soft-sensor for the fast estimation of dried cake resistance during a freeze-drying cycle / Bosca, Serena; Barresi, Antonello; Fissore, Davide. - In: INTERNATIONAL JOURNAL OF PHARMACEUTICS. - ISSN 0378-5173. - STAMPA. - 451:(2013), pp. 23-33. [10.1016/j.ijpharm.2013.04.046]

Publisher:
Elsevier

Published
DOI:10.1016/j.ijpharm.2013.04.046

A definitive version was subsequently published in *International Journal of Pharmaceutics*, Vol. 451, Issue 1-2, 23-33 (25/04/2013).

DOI: 10.1016/j.ijpharm.2013.04.046

Use of a soft sensor for the fast estimation of dried cake resistance during a freeze-drying cycle

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Abstract

This paper deals with the determination of dried cake resistance in a freeze-drying process using the Smart Soft Sensor, a Process Analytical Technology recently proposed by the authors to monitor the primary drying stage of a freeze-drying process.

This sensor uses the measurement of product temperature, a mathematical model of the process, and the Kalman filter algorithm to estimate the residual amount of ice in the vial as a function of time, as well as the coefficient of heat transfer between the shelf and the product and the resistance of the dried cake to vapor flow. It does not require expensive (additional) hardware in a freeze-dryer, provided that thermocouples are available.

At first, the effect of the insertion of the thermocouple in a vial on the structure of the product is investigated by means of experimental investigations, comparing both sublimation rate and cake structure in vials with and without thermocouple. This is required to assess that the temperature measured by the thermocouple is the same of the product in the non-monitored vials, at least in a non-GMP environment, or when controlled nucleation methods are used. Then, results about cake resistance obtained in an extended experimental campaign with aqueous solutions containing different excipients (sucrose, mannitol and polyvinylpyrrolidone), processed in various operating conditions, are presented, with the goal to point out the accuracy of the proposed methodology.

Keywords

Freeze-drying/lyophilization, PAT, soft sensor, dried cake resistance, process monitoring.

Introduction

The Guidance of Industry PAT (Process Analytical Technology), issued by U.S. Food and Drug Administration in September 2004, promotes the design and implementation of effective monitoring and control systems with the goal to avoid testing product quality at the end of the manufacturing process, and to get the desired quality by design or during the process.

Unfortunately, even if this guideline has been generally accepted by the industry (DePalma, 2011), the response to this initiative appears to be quite weak (Shanley 2009, 2010; Kristan and Horvat, 2012). On the basis of a survey involving 102 pharmaceuticals companies Shanley (2010) evidenced that about 35% of them were not implementing PAT into their manufacturing processes, mainly due to time and cost reasons. In most cases, in fact, PAT require using expensive devices, as well as to modify existing equipment, and this can prevent its implementation, even if the use of suitable Process Analytical Technologies allows obtaining a thorough understanding of the process and of product evolution during manufacturing, and this can be exploited to get Quality by Design, i.e. to identify (off line) the operating conditions that allow meeting specific product critical quality attributes.

Freeze-drying is quite often one of the most important operations in pharmaceuticals manufacturing. It allows removing water from a product at low operating temperatures and, thus, it is suitable for those products that can be damaged by drying processes at higher temperatures. Furthermore, the freeze-dried products can be stored for long time, they can be easily reconstituted, and the process can be easily carried out under sterile conditions (Liapis, 1987; Snowman, 1991; Nail and Gatlin, 1992; Oetjen and Haseley, 2004; Franks, 2007).

During the process it is necessary to carefully select the operating conditions, namely the temperature of the heating shelf (or that of the heating fluid) and the pressure in the drying chamber, with the goal to preserve product quality. In fact, it is mandatory to maintain product temperature below a limit value, that is a characteristic of the product, to preserve both the stability and the activity of the drug, and also the cake appearance, that can affect the velocity of the reconstitution of the product. If the product to freeze-dry is amorphous, this temperature is related to the glass transition temperature (to avoid the collapse of the dried cake), while for a crystalline product the limit value is represented by the eutectic temperature (to avoid the formation of a liquid phase). In this framework, the primary drying stage, when ice sublimation takes place, is crucial in order to obtain a product with the desired quality as the limit temperature can be particularly low, and it is the longest stage.

The operating conditions of a freeze-drying cycle are generally selected by means of a trial and error approach: the product is inserted into vials placed on the shelves in a drying chamber, and the temperature is measured placing a thermocouple into one or more vials, in central position and in contact with the product at the bottom, in order to check if the constraint on product temperature is fulfilled for the selected operating conditions. The use of the thermocouple is common in lab-scale equipment, while in industrial-scale freeze-driers the use of a resistance thermal detector is preferred, even if this sensor is larger than a thermocouple and the accuracy of measurement can be affected by the geometry of the detector (Willemer, 1991; Oetjen, 1999; Presser, 2003). The effects of the thermocouple (or of the resistance thermal detector) on the product contained in the monitored vial are numerous. In the literature it is often reported that the drying rate of the product in the vial containing the thermocouple is higher than that obtained in the rest of the batch. The influence of the thermocouple on the nucleation temperature is used to explain this phenomenon. In fact, the product in the monitored vials shows, generally, a nucleation temperature higher than that occurring in the others vials. The smaller under-cooling determines the formation of larger ice crystals and, consequently, of a dried cake with higher porosity. This may result in a lower resistance of the cake to vapor flow and, thus, the sublimation flux can be higher, and the drying process faster. Increased heat transfer rate, that can be a consequence of the insertion of the probe, has been also supposed.

As an alternative, a suitable cycle can be obtained either in-line, using a control system (Pisano et al., 2010; Pisano et al., 2011a), or off-line, determining the design space of the process (Sundaram et al., 2010; Koganti et al., 2011; Giordano et al., 2011; Fissore et al., 2011a). In both cases the mathematical model of the primary drying stage is used and, thus, it is required to know accurately the values of the parameters of the model in order to get reliable results (Fissore et al., 2012a, 2013a).

Generally, the mathematical model of the primary drying is based on the mass and energy balances and, thus, it is necessary to know the values of the mass flux from the interface of sublimation to the drying chamber, and of the heat flux to the product. The mass flux depends on the resistance of the dried cake to vapor flow (R_p) and on the driving force given by the difference between the partial pressure of the water at the sublimation interface ($p_{w,i}$) and in the drying chamber ($p_{w,c}$), that is generally coincident with total chamber pressure:

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

The heat flux depends on the overall heat transfer coefficient (K_v), that takes into account all the heat transfer mechanisms, and on the driving force given by the difference between the temperature of the heating fluid (T_{fluid}) and the temperature of the product at the bottom of the vial (T_B):

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

The coefficient K_v is a characteristic of the vial-freeze dryer system and is, evidently, not affected by the product processed. It can be easily determined by means of various methods, e.g. the gravimetric test (Pikal, 1985; Hottot et al., 2005) and the pressure rise test (Milton et al., 1997; Chouvenc et al., 2004; Velardi et al., 2008). In all cases the test has to be repeated at (at least) three different values of chamber pressure in order to get information about the pressure dependence of K_v (Pisano et al., 2011b). Tunable Diode Laser Absorption Spectroscopy (TDLAS) has also been proposed to estimate K_v: in this case it is possible to determine the dependence of K_v on chamber pressure within one experiment (Gieseler et al., 2007; Kuu et al., 2009; Schneid and Gieseler, 2009; Schneid et al., 2009).

Also with respect to cake resistance R_p estimation, there are various methods available in the literature, e.g. the microbalance proposed by Pikal et al. (1983), the pressure rise test, the measure of product temperature, in case K_v is known (Kuu et al., 2006), and a device placed in the drying chamber that allows measuring both the weight loss and product temperature in a group of vials (Fissore et al., 2012b). TDLAS sensor has also been proposed to estimate R_p: in case a preliminary estimation of K_v has been done, then TDLAS allows estimating product resistance data non-invasively (even in a GMP environment); in case the value of the K_v is not available, then TDLAS requires the measurement of product temperature to estimate R_p (Kuu et al., 2011).

While the heat transfer coefficient is a characteristic of the vial-freeze-dryer system, as said before, that can eventually be determined using inexpensive sensors (using the gravimetric test), even in industrial-scale freeze-dryers, the dried cake resistance is a characteristic of the formulation being freeze-dried, and for certain products, like sucrose solutions, also of the process conditions. Furthermore, every method that can be employed exhibits a drawback:

1. When using the microbalance of Pikal et al. (1983) an additional hardware is required, and freezing conditions are different from those of the other vials of the batch and, thus, R_p estimations are inaccurate.
2. When using the pressure rise test it is generally necessary to acquire pressure data at a

sufficiently high frequency (and, thus, a modification of the software for data acquisition could be necessary) and, then, pressure rise data have to be interpreted by means of a suitable software, and difficulties may arise in industrial-scale freeze-dryers. Moreover, as pointed out by Tang et al. (2005) there are various limitations if this method is used to determine product resistance to vapor flow, e.g. a minimum number of vials is required to give a useful pressure rise curve, in particular in case of low dried layer resistance product, and in case shelf temperature is low.

3. The use of the product temperature, as proposed by Kuu et al. (2006) requires solving a complex multidimensional non-linear optimization problem. As pointed out by the authors, a critical issue is the determination of the initial estimate of the parameters: they propose to indicate the range of variability of the parameters that have to be estimated, to identify within these ranges the potential values of these parameters, and, finally, to repeat the calculations using each possible set of values as initial estimate. Moreover, the calculation procedure proposed by the authors require a preliminary determination of the heat transfer parameter K_v, and the calculation of the dried cake resistance is possible only at the end of the drying stage. Finally, from a certain time instant during primary drying the temperature measurement is no more accurate (when it sharply increases).
4. The use of TDLAS requires an additional (expensive) hardware, beside the temperature measurement.
5. The use of a weighing device in the drying chamber poses, again, the problem (and the cost) of an additional hardware.

The challenge is thus to estimate cake resistance without using expensive devices, possibly using the instrumentation that is generally available in a freeze-dryer, and with a technique usable also in industrial-scale freeze-dryers. A useful device is the observer developed by Barresi et al. (2009a, 2009b): it is a tool based on a mathematical model of the process, on the experimental measures of product temperature provided by a thermocouple, and either on the Kalman filter (Velardi et al., 2009) or the High Gain technique (Velardi et al., 2010). The observer is able to provide estimations of the temperature profile, of the residual amount of ice, and of the values of both model parameters K_v and R_p. Bosca and Fissore (2011) developed a different observer, based on the Kalman Filter algorithm, in order to account for a nonlinear dependence of the cake resistance on the dried layer thickness. Afterwards, this tool has been improved by reducing the number of variables that are estimated, thus obtaining a very robust sensor, called Smart Soft Sensor, able to provide accurate estimations of the variables of interest for the primary drying stage (Bosca et al., 2013a). When using this approach it is no longer required to carry out any optimization process, and thus the computational effort can be significantly reduced; moreover, it is not required to preliminary evaluate K_v.

When using the Smart Soft Sensor the temperature measurements could be obtained using wireless sensors, that are particularly useful in industrial-scale apparatus, with active or passive transponders. The formers use batteries to get energy for sensor operation and data transmission. Corbellini et al. (2010) proposed wireless thermocouples, suitable for both lab-scale and industrial freeze-driers, with the only limitation on the operating time, that depends on the battery capacity. The passive transponders, instead, get the energy required for data transmission from an electromagnetic field (Hammerer, 2007). Vallan et al. (2005a) proposed a measuring system composed of several modules that use thermocouples as measuring devices, and get energy from a 125 kHz Radio Frequency link. Schneid and Gieseler (2008) developed the Temperature Remote Interrogation System (TEMPRIS) that allows, if correctly placed into the vial, to obtain a real-time temperature measurement. However, the TEMPRIS probe is larger than thermocouples and, consequently, its interference with product dynamics is much higher. Recently, a new kind of thermocouple has been developed with the aim to minimize the effect of the sensor on the product dynamics. It is a plasma sputtered thermocouple, based on thin film sub-micrometric wires embedded into the vials wall and coated with a glass (SiO_2) like thin film. By this way both the vial surface and its thermal conductivity are not altered, and the sensor does not interact with the product (Parvis et al., 2012; Grassini et al., 2013).

When using the Smart Soft Sensor it is very important to assess if the temperature measurement is accurate and representative of the temperature of the product in the non-instrumented vials, and if the insertion of the thermocouple affects the structure of the monitored vial and, thus, the resistance of the dried cake. The goal of the first part of the paper is to address these questions, therefore assessing the reliability of the temperature measurement using a thermocouple, and the possibility of using the Smart Soft Sensor to estimate R_p in-line, even in a production run. Examples of application of this methods in presence of various formulations are presented and discussed in the second part of the paper.

Materials and Methods

The Smart Soft Sensor and dried cake resistance estimation

The Smart Soft Sensor is the tool used in this work to estimate the resistance of the dried product to vapor flow (as a function of the thickness of the dried cake). This soft sensor uses the measurement of product temperature at the bottom of the vial and a mathematical model of the process describing the evolution of the temperature and of the residual amount of ice during time as a function of the operating conditions (chamber pressure, P_c, and temperature of the heating fluid, T_{fluid}).

The model used by the soft sensor is the simplified mono-dimensional model of Velardi and Barresi (2008): this model is constituted by three equations, namely the heat balance for the frozen product, the mass balance for the vapor in the dried layer, and the energy balance at the interface of sublimation. By comparing the calculated and the measured values of product temperature at the bottom of the vial (T_B) it is possible to evaluate the error of the model (due to the fact that a model of a process cannot account exactly for all the heat and mass transfer processes occurring in the system, and the knowledge of model parameters cannot be perfect). The algorithm of the soft sensor uses information about this error to "correct" model equations, and to estimate product temperature and K_v using the following equations (Bosca et al., 2013a):

$$\begin{pmatrix} \dfrac{d\hat{T}_i}{dt} \\ \dfrac{d\hat{K}_v}{dt} \end{pmatrix} = \begin{pmatrix} \mathrm{f}\left(\hat{T}_i, \hat{K}_v, T_{fluid}\right) \\ 0 \end{pmatrix} + \mathbf{K}\left(\hat{T}_B - T_B\right) \tag{3}$$

$$\hat{T}_B = \mathrm{h}\left(\hat{T}_i, \hat{K}_v,, T_{fluid}\right) \tag{4}$$

In order to solve eqs. (3)-(4) we need an initial estimate of T_i and K_v. Then, using the mathematical model of the process and the error between the calculated ($\hat{T}_B$) and the measured (T_B) values of product temperature at the bottom of the container (multiplied by the parameter **K**), it is possible to calculate the values of T_i and K_v. Obviously, when working at constant chamber pressure, as it is generally the case, K_v does not change during the primary drying, but the algorithm of the observer changes its value according to the error ($\hat{T}_B$ - T_B) until the convergence of the observer (i.e. an error equal to zero) is achieved.

Dried cake resistance is calculated from the energy balance at the interface of sublimation:

$$\hat{K}_v\left(T_{fluid} - \hat{T}_B\right) = \Delta H_s \frac{1}{R_p}\left(p_{w,i}\left(\hat{T}_i\right) - p_{w,c}\right) \tag{5}$$

that gives:

$$R_p = \Delta H_s \frac{p_{w,i}\left(\hat{T}_i\right) - p_{w,c}}{\hat{K}_v\left(T_{fluid} - \hat{T}_B\right)} \tag{6}$$

Once, at a given time, R_p is known, it is possible to calculate the sublimation flux (using eq. (1)) and, by numerical integration of the flux, the thickness of the dried cake. The gain **K** of the soft sensor is calculated using the Kalman filter algorithm, as shown by Bosca et al. (2013a). To this purpose it is required to account for the dependence of R_p on dried cake thickness (L_{dried}). The following equation, often proposed in the literature (see, among the others, Kuu et al., 2006, 2011), is used:

$$R_p = R_{p,0} + \frac{A_{R_p} L_{dried}}{1 + B_{R_p} L_{dried}} \tag{7}$$

Therefore, the soft sensor requires an estimation of $R_{p,0}$ and B_{R_p} and, using eq. (6) the value of A_{R_p} is calculated. In any case, the user is interested in knowing the value of R_p, that can be calculated using eq. (7) for every values of L_{dried}.

In order to use the soft sensor the following steps are then required:

1. Estimate product temperature at the beginning of primary drying: this value can be assumed to be equal to the temperature of the product at the end of the freezing stage.
2. Estimate K_v: it is possible to carry out a preliminary investigation for the given vial-freeze-dryer system (but this is not indispensabile), or to use values taken from the literature for similar vials, or, considering that values of K_v generally range in a narrow interval, e.g. 5-30 W $m^{-2}K^{-1}$, a value in this interval can be selected. In any case, it is not necessary to have a very accurate initial estimation of K_v, as this parameter is then estimated by the soft sensor.
3. Solve equations (3)-(4), using the measurement of product temperature to correct the calculated values of T_i and K_v and to estimate A_{R_p} (and, thus, R_p) using eq. (5)-(7). It is

possible to see that the estimated values of K_v (and A_{R_p}) moves from the initial guess to a steady-state value once convergence of the observer is reached.

4. Using the value of A_{R_p} given by the soft sensor and the estimates of $R_{p,0}$ and B_{R_p} the whole curve of R_p *vs*. L_{dried} can be calculated.

The values of primary drying duration and product temperature measured experimentally and those calculated using the simplified model of Velardi and Barresi (2008) with the values of R_p *vs*. L_{dried} given by the soft sensor can be compared with the goal to validate the estimated values of R_p.

The problem of temperature measurement

As it is well known to every freeze-drying practitioner the dynamics of product temperature detected by a thermocouple in the first part of the primary drying stage of a freeze-drying cycle carried out at a constant value of T_{fluid} can be basically of two types:

1. in case of products (e.g. mannitol and polyvinylpyrrolidone solutions) whose dried cake resistance vary (almost) linearly with L_{dried}, product temperature increases from the freezing temperature at first more rapidly, and then more slowly;
2. in case of products (e.g. sucrose solutions) whose dried cake resistance exhibits an asymptotic curve, with a significant variation at the onset of sublimation and then a value almost constant, product temperature increases from the freezing temperature and reaches an asymptotic value.

In both cases at a certain moment the temperature of the product detected by the thermocouple increases up to the value of the temperature of the heating fluid, and this occurs well before the conclusion of primary drying in the other vials of the batch. This could be caused by the loss of thermal contact between the ice and the thermocouple, or by the fact that the sublimation front advances past the thermocouple tip, or by the ending of the sublimation stage in the monitored vial. As it will be shown in the following, drying is not completed in the instrumented vial when the sudden temperature increase occurs: therefore it is necessary to assess, at first, the effect of the insertion of the thermocouple in the vial on dried cake structure, and, then, the accuracy of the temperature measurement as it is used by the soft sensor to estimate R_p. Obviously, it is necessary to get convergence of the observer before the occurrence of sharp temperature rise because after this moment the temperature measure is either inaccurate, or useless (in case drying is completed): in all the tests carried out in this study the observer convergence was achieved well before the sudden increase of product temperature.

The accuracy of the estimations of dried cake resistance relies on the accuracy of temperature measurement: it is therefore necessary to use accurate probes to measure product temperature. When using T-type thermocouples it is possible have an accuracy of the measure as low as ±0.5 °C. It can be very difficult to assess the effect of the measurement uncertainty on the accuracy of R_p. In fact, the soft-sensor estimates both K_v and R_p, and all the variables are related through the heat balance at the interface of sublimation. Therefore, the measurement error can affect both model parameters. If we assume, in the worst case with respect to dried cake resistance, that K_v is correctly estimated, the error on the heat flux to the product (and on the sublimation flux) is small even with a ±0.5 °C error on temperature measurement, while the error on R_p can be larger, about 10%, due the exponential dependence of ice vapor pressure on the interface temperature. In any case, the uncertainty on the estimations of R_p is similar to that obtained when using methods based on the pressure rise test to estimate R_p, as reported by Pisano et al. (2013).

Experimental set-up and case study

All the freeze-drying cycles of this study have been carried out in a LyoBeta 25 freeze-dryer

(Telstar, Terrassa, Spain): it is a pilot-scale unit with a vacuum-tight chamber of 0.2 m^3, equipped with four shelves that provide a total area of 0.5 m^2. The vacuum system is composed by an external condenser and a vacuum pump for the removal of the incondensable gases. Controlled leakage, based on the manipulation of the flow rate of nitrogen introduced in the chamber, has been used to regulate the pressure in the drying chamber. A capacitance (Baratron 626A, MKS Instruments, Andover, USA) and a thermal conductivity gauge (Pirani Bad Ragaz, Switzerland) have been used to measure the pressure in the drying chamber. T-type miniature thermocouples (Tersid, Milano, Italy) have been used to measure the product temperature: they have been placed in the centre of the vial and in close contact with the bottom. The pressure data obtained during the pressure rise tests have been interpreted using the DPE+ algorithm (Velardi et al., 2008; Fissore et al., 2011b) to estimate product temperature and sublimation flux. The ending point of primary drying has been estimated from the ratio between the pressure values provided by the Pirani and the Baratron gauges: in fact, when the primary drying is going to be concluded, the value of this ratio starts decreasing until it reaches an asymptotic value as the Baratron sensor is a capacitance gauge, while the Pirani sensor is a thermo-conductivity gauge, whose measurement is affected by the composition of the gas in the drying chamber. It is not clear when the primary drying can be considered concluded, but it is sure that this occurs in a time interval between the beginning of the decrease of the curve and the lower asymptote (Armstrong, 1980). Recently, Patel et al. (2010) have identified three points in the pressure ratio curve, i.e. the onset, determined from the intersection between the higher asymptote of the curve and the tangent to the curve in the inflection point, the midpoint and the offset, identified by the intersection between the lower asymptote of the curve and the tangent to the curve in the inflection point. An extended experimental investigation has evidenced that, considering the residual amount of water in the product, primary drying can be considered completed at the onset in case of mannitol solutions, and at the offset in case of sucrose solutions. In any case, the dynamic of the pressure ratio curve is affected by water concentration in the chamber and this depends on the characteristics of the freeze-dryer (e.g. chamber volume) and on the operating conditions (e.g. sublimation rate and nitrogen flux), it is not obvious to state that primary drying is completed at the onset or at the offset of the curve.

The LyoBalance, a weighing device placed in the drying chamber, has been used to investigate the effects of the thermocouple on drying kinetics (Vallan et al., 2005b; Vallan 2007; Carullo and Vallan, 2012; Fissore et al., 2012b). With this device it is possible to measure at the same time the temperature and the weight loss in a group of vials (up to 15 in the prototype used), with a resolution of about 10 mg. The weight of the vials is measured by lifting them periodically, and the temperature, measured with a thermocouple inserted into one or more vials of the group, is transmitted to the balance with a miniaturized radio-controller. It has to be remarked that when using LyoBalance the weighed vials are frozen with all the other vials of the batch, thus avoiding the problems related to the weighing systems of Pikal et al. (1983) and Bruttini et al. (1991). Moreover, the same vials of the batch can be used, thus avoiding using specific vials as with the devices of Roth et al. (2001), Gieseler (2004), and Gieseler and Lee (2008a, 2008b).

Tubular glass vials ISO 8362-1 8R (external diameter = 22±0.2 mm, wall thickness = 1±0.04 mm) and screw neck vials DIN 58378-AR10 (external diameter = 18±0.25 mm, wall thickness = 1.2±0.06 mm) have been used in the tests: they have been placed directly on the chamber shelves (without the interposition of a tray), arranged according to a hexagonal mesh, and maintained in place using a metal frame.

The freeze-drying cycles have been carried out processing aqueous solution containing ultra-pure water, obtained by a Millipore water system (Milli-Q RG, Millipore, Billerica, MA), and one excipient as is, namely sucrose (Riedel de Haën), mannitol (Riedel de Haën) or polyvinylpyrrolidone (Fluka), in different concentrations (between 5% and 20% by weight).

The same freezing protocol has been used in all the tests: after vial load, the temperature of the technical fluid has been decreased at 1°C/min until the temperature of -50°C has been reached. All the runs have been carried out in non-GMP conditions. Different operating conditions (heating shelf temperature and chamber pressure) have been set for the primary drying stage of each freeze-drying cycle, as shown in the results section, and the have been maintained constant throughout the primary drying stage.

Cake structure analysis

The morphology of freeze-dried samples has been investigated using a Scanning Electron Microscope (FEI, Quanta Inspect 200, Eindhoven, The Netherlands) at 15 kV and under high vacuum. Freeze-dried samples have been fixed on aluminum circular stubs and sputtered with chrome. The pore size distribution of the dried cake of each sample have been determined analyzing the SEM images with the software ImageJ.

Results and discussion

As the measure of product temperature is used by the soft sensor to estimate dried cake resistance to vapor flow, the first part of this study is focused on the investigation of the effect of the insertion of the thermocouple on product temperature, drying kinetics and dried cake structure in the instrumented vial.

In Figure 1 (graph a) the evolution of the residual amount of ice in a vial during the primary drying phase is shown. The vial is weighed by LyoBalance in order to detect the time instant when the primary drying can be considered completed (i.e. the value of the residual ice mass is close to zero) and to measure product temperature during drying (graph b). At the beginning of the primary drying the product temperature rises from the value reached during the freezing step until it reaches a constant value, corresponding to a pseudo steady-state where all the heat provided by the shelf is used for the ice sublimation. After some hours from the beginning of primary drying, and well before the ending point (as detected from the weight loss measurement), product temperature suddenly increases, notwithstanding no modifications in the operating conditions occur. Patel et al. (2010) argued that when the temperature reaches the final asymptotic value the primary drying is completed for the entire batch of vials. Such a conclusion can be supported by the comparison of the temperature measurement with the curve of residual amount of ice: when the asymptotic temperature is reached, also the amount of ice in the sample is negligible. It has to be remarked that in case a perfectly shielded batch is monitored, the temperature measured by the thermocouple should reach the value of the shelf temperature at the end of primary drying. In case the product receives heat also by radiation, as it can occur in small-scale freeze-dryers, the final value of product temperature detected by the thermocouple can be higher than the temperature of the heating shelf (as in graph b).

The sudden temperature rise can be explained assuming that the first portion of product that dries is that close to the thermocouple: when the drying of that portion is concluded, sublimation does not occur any more, and the temperature rises. However, around the dried portion there is still some frozen product and, then, the temperature measured by the thermocouple can be a sort of average value for the product. Furthermore, it is also possible that the dried cake collapses on the thermocouple wire, closing a possible channel for the water vapor flow. The vapor that is forming has now to spread also radially into the product volume and to overcome a higher resistance to diffusion; so, the temperature rapidly increases. This last hypothesis has an experimental evidence: in fact, at the end of a lyophilization cycle the extraction of the thermocouple from the dried cake requires a soft mechanical action, as the dried product is stuck on the thermocouple wire.

The unexpected temperature increase detected by the thermocouple occurs when there is still a relevant amount of ice in the monitored vial (about 25%). As we would like to use the temperature measurement to estimate R_p, it appears clear that this measure cannot be used after the sudden temperature increase as it is expected that the product temperature remain almost constant until the end of primary drying, unless the operating conditions are modified or some collapse or micro-collapse occurs. Therefore, till experimental measurements of product temperature are available, they are used by the soft sensor and then the model of the process is used to calculate the evolution of the product using the parameters estimated by the observer. Figure 1 (graph c) shows an example of these calculations for the frozen layer thickness: filled circles identify values calculated by the observer, and empty circles identify values calculated by the model. With this respect it has to be highlighted that the remaining ice layer thickness should be comparable to the remaining mass of ice and therefore decrease faster at the start of drying and slower later in the process, as shown in graph a. Actually, when using the soft sensor to estimate dried cake thickness at the beginning of the primary drying stage the estimated values of model parameters are not accurate, as some time is required to get the convergence of the observer (depending on various issues, e.g. the accuracy of the initial estimations of model parameters). Moreover, when the ending point of the primary drying stage is approaching, the curvature of the moving interface, which is neglected when using a one-dimensional model, can play a significant role, in particular when the vial receives a significant amount of heat by radiation, as in case the balance is used. Nevertheless, the estimated value of drying time, i.e. when frozen layer thickness goes to zero, is in fairly good agreement with the value obtained from the weight measurement.

The effect of the insertion of the thermocouple on the sublimation rate has been investigated by carrying out a freeze-drying cycle where the core vials have been weighed at the beginning of the test, and then, just after the occurrence of the sudden temperature increase (to this purpose the cycle was stopped at that moment). Figure 2 shows the values of sublimated ice measured in the 179 vials not monitored (graph a) and in the 9 vials with a thermocouple (graph b). The comparison evidences that the mean value of the sublimated mass (identified by the triangle marker) is almost the same in both groups of vials. The distribution of the values of sublimated mass in the vials with the sensor appears to be narrower than that obtained in the vials without the sensor, but it has to be highlighted that a thermocouple was inserted only in few vials (in this case).

Sublimation flux, product temperature and cake resistance (that is affected by the pore size distribution) are related through eq. (1). Thus, in case also the pore structure in the cake obtained in a vial with a thermocouple is similar to that obtained in case no sensor is inserted, then we can conclude that the product temperature detected by the thermocouple is (almost) the same of the product in the other vials of the batch. To this purpose we have analyzed the distribution of the pore sizes in the dried cakes obtained in vials with and without the sensor. Figure 3 shows the pore size distribution of the dried cake obtained after freeze-drying of a 5% by weight aqueous sucrose solution both in a monitored and in a non-monitored vial. It can be evidenced that the pore size distribution obtained for the sample with the thermocouple inside (graph c) is slightly narrower, but the value of the mean pore size is close in both cakes. This is due to the influence of the nucleation temperature. In fact, the nucleation temperature of the monitored vials are not significantly different, and, therefore, in agreement with the results by Nakagawa et al. (2007), the ice crystal dimension is close. The structure of the previous samples is shown in graphs b and d. It is necessary to point out that this analysis has been carried out using samples freeze-dried in a laboratory-scale equipment, and that in an industrial-scale equipment the effect of the thermocouple into the vial could be different, and likely more marked. In fact, when working under GMP conditions, as in an industrial environment, there are no impurities that can contaminate the freeze-drying environment (and, thus, the drying chamber) and promote the nucleation of the ice crystals, thus reducing under-cooling and the differences between the product in a vial with the sensor and in a vial without the sensor. In order to estimate dried cake resistance in a GMP environment (i.e. in an industrial scale environment) it is thus necessary to use either a non-invasive technique (e.g. the pressure rise test, or the TDLAS, with the advantages and the drawbacks discussed in the Introduction section), or the soft sensor proposed in this paper in case a controlled nucleation method is used (Rambhatla et al., 2004; Morris et al., 2004; Nakagawa et al., 2006; Patel et al., 2009; Konstantinidis et al., 2011): in fact, in this case, there will be no difference between the dynamics of the product in monitored and in non-monitored vials. Moreover, in a industrial scale freeze-dryer it is necessary to use wireless sensors to measure product temperature (Vallan et al., 2005a; Schneid and Gieseler, 2009; Corbellini et al., 2009 and 2010; Bosca et al., 2013b).

On the basis of the results previously shown we can claim that the presence of the thermocouple does not affect significantly the dynamics of the product in the monitored vial: both the sublimation rate and the cake structure are similar to those obtained in vials close to the monitored one. This means that the temperature measured by the thermocouple is representative not only of the monitored vial, but also of the other vials around it, and it can be effectively used by the soft sensor to track the dynamics of the product in the whole batch (or, at least, in the portion of the batch where the heating conditions are the same of the monitored vial). Figure 4 compares the measurement of product temperature obtained using thermocouples placed in vials in the central part of the batch with the estimations obtained from the pressure rise test and DPE+ algorithm. As it is well known, the pressure rise test-based algorithms estimate accurately product temperature in the first part of primary drying, and, then, the estimated values of temperature decreases, while product temperature is expected to remain (almost) constant (or to slightly increase). Moreover, using the pressure rise test a “mean” value of product temperature is obtained for the batch: in fact, a batch of vials is non-uniform, mainly due to the different heat transfer mechanisms to the vials, and product temperature can be different in central vials and in vials at the edge of the shelf (due to radiation effect), while DPE+ and other pressure rise test-based algorithms estimate product temperature assuming the batch uniform. As the percentage of edge vials is generally small with respect to the other vials, then the temperature estimated by DPE+ is expected to be very close to that of vials in central position. As shown in Figure 4, product temperature estimated by DPE+ coincides with the thermocouple measurements until realistic values are measured using the thermocouples.

In order to test the possibility of using the soft sensor to determine R_p a first drying cycle has been carried out processing a 5% by weight aqueous solution of sucrose at constant values of the shelf temperature (-20°C) and chamber pressure (10 Pa). Figure 5 (graph a) shows the estimations of the values of the cake resistance R_p as a function of its thickness for two different core vials, and in a vial placed at the edge of the shelf. The temperature measurement obtained in each vial is used by the sensor. It has to be highlighted that in this figure (and in the followings) the units of measurement of R_p are m s^{-1}, as the sublimation flux is measured in kg $s^{-1}m^{-2}$ and the pressure is measured in Pa. Actually, quite often in the literature R_p is given in cm^2Torr $h^{-1}g^{-1}$: it is straightforward to pass from the values of R_p shown in this paper to those expressed in cm^2Torr $h^{-1}g^{-1}$ multiplying the value of R_p by $2.0835 \cdot 10^{-5}$. If the temperature dynamics during the freezing phase is considered (graph b), it is possible to see that the nucleation temperature difference is about 2.3°C, and the freezing rate is almost the same, in the monitored vials. As a consequence, only a slight difference between the values of cake resistance is expected (Nakagawa et al., 2007), as detected by the soft sensor (in Figure 5, graph a, two curves, i.e. those corresponding to nucleation temperature equal to 261.5 and 262.4 K, are perfectly overlapping). Beside cake resistance, the soft sensor estimates also the value of the overall heat transfer coefficient K_v: as shown in Figure 5 (graph c) using the (quite) different temperature profiles obtained in core and edge vials the soft sensor is able to estimate in a fairly accurate way the value of K_v (the estimated value is compared with the measure obtained using the gravimetric test). Moreover, for core vials, where two (slightly) different values of product temperature are used by the soft sensor, the value of K_v appears to be almost the same.

In case of sucrose-based solutions cake resistance can vary with product temperature due to the occurrence of micro-collapse (Kuu et al., 2009): in particular, the higher is the temperature of the product, the lower is the resistance of the cake to vapor flow. A test has thus been carried out processing two 5% sucrose solutions with different values of the temperature of the heating fluid, namely -10 and -20°C. As it is possible to see in Figure 6 (graph a), product temperature is higher, as it can be expected, when the temperature of the heating fluid is higher, and this causes a significant reduction of the drying time, as detected from the ratio between the signals of the Pirani and Baratron pressure gauges (graph b). Cake resistance estimated by the soft sensor decreases when product temperature increases (graph c), in agreement with the occurrence of the micro-collapse phenomenon. It can be highlighted that in this case the value of the overall coefficient of heat transfer K_v determined with the gravimetric test is 16.11±1.0 W $m^{-2}K^{-1}$ and the values estimated by the soft sensor in the two tests are 16.31 W $m^{-2}K^{-1}$ (when T_{fluid} = -20°C) and 16.54 W $m^{-2}K^{-1}$ (when T_{fluid} = -10°C). This can be regarded as a further validation of the estimations of the soft sensor: in fact, it uses different measures of product temperature (that is evidently affected by T_{fluid}) and it estimates almost the same value of K_v (and, in fact, this parameter is almost not affected by the temperature of the heating shelf), and different values of R_p.

In Figure 7 (graph a) the values of R_p obtained for two sucrose solutions processed at different values of chamber pressure are compared. It appears that when chamber pressure is higher (10 Pa) slightly lower values of R_p are obtained: this is due to the fact that the higher is the pressure in the chamber, the higher is the temperature of the product (due to the increase of the heat transfer coefficient from the shelf to the product) and this can cause micro-collapse, and thus a lower cake resistance. This is confirmed by the analysis of the sublimation flux, estimated from the pressure rise test, that appears to be higher in case of the test carried out at 10 Pa.

Figure 8 shows the values of R_p obtained for mannitol and polyvinylpyrrolidone solutions processed at different values of chamber pressure. In this case micro-collapse is not expected to occur, and, in fact, the same values of R_p are obtained when the solution is processed at different values of chamber pressure, despite the variation of product temperature.

The experimental determination of R_p is required in order to use a mathematical model to optimize off-line the freeze-drying cycle, as it has been pointed out in the Introduction section. Therefore, in order to assess the usefulness of the estimation of R_p with the Smart Soft Sensor we have used the estimated values to simulate the drying process of sucrose, mannitol and polyvinylpyrrolidone solutions, and compared the calculated values of product temperature and drying time with the experimentally obtained values. The model of Velardi and Barresi (2008) has been used to carry out the simulations; product temperature has been measured using thermocouples, and drying duration has been determined using the ratio between Pirani and Baratron sensors. Figure 9 shows the comparison between measured and calculated values of drying time. Drying duration has been identified using the midpoint of the pressure ratio, and the onset and the offset of the curve are used to identify the uncertainty range. For all the experimental tests (whose details are given in the caption of the Figure) fairly good agreement between calculated and measured values of drying time are obtained. With this respect it can 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. With respect to product temperature, in all cases the maximum difference between calculated and measured values has been lower than 0.5°C (data not shown), well below the measure uncertainty of a thermocouple.

Conclusion

The determination of dried cake resistance using inexpensive (or additional) devices, both in lab-scale and in industrial-scale units, is a challenging issue as it would allow using mathematical modeling to get quality by design. This paper shows that the measurement of product temperature using a thermocouple, that is widespread in freeze-drying processes, could be exploited to get this result. In fact, product temperature in the monitored vials appears to be roughly the same of the product in the other vials of the batch, and also cake structure, that affect the resistance to vapor flow, is almost unaffected by the insertion of the thermocouple in the vial. Preliminary tests aiming to estimate the heat transfer parameter are not required, and no highly computational demanding non-linear estimations are involved.

Unfortunately, a reliable temperature measurement is available only up to the moment when the temperature suddenly increases, and reaches the shelf temperature value. This does not pose any problem to the sensor as the parameters required to model the dependence of dried cake resistance to vapor flow are generally obtained with sufficient accuracy in the first part of primary drying, when temperature measurement is accurate.

Once dried cake resistance is determined with the Smart Soft Sensor, it can be used to calculate off-line drying time as well as product temperature for a given set of operating the conditions, thus allowing off-line process optimization and getting quality by design. The method can be used also in a GMP environment (e.g. in industrial-scale freeze-dryers) provided that a controlled nucleation method is used (in such a way that the dynamics of the product is the same in monitored and non-monitored vials), and wireless sensors are available.

Notation

A_{R_p}	parameter used to calculate R_p, s^{-1}
B_{R_p}	parameter used to calculate R_p, m^{-1}
d	diameter of a pore of the dried product cake, mm
f	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}
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}
L_0	thickness of the product after freezing, m
L_{dried}	thickness of the dried product, m
L_{frozen}	thickness of the frozen product, m
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}
$R_{p,0}$	parameter used to calculate R_p, m s^{-1}
T_B	product temperature at vial bottom, K
T_{fluid}	heating fluid temperature, K
T_i	product temperature at the sublimation interface, K
t	time, s

Superscripts

^	observer estimate

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Figure 1: Freeze-drying of a 5% by weight sucrose solution, processed in one glass tubing vial (DIN 58378-AR10), monitored with the LyoBalance (T_{fluid} = -10°C, P_c = 5 Pa). Graph a: Evolution of the residual ice weighed by the LyoBalance. Graph b: Product temperature measured by the thermocouple of the LyoBalance. Graph c: Estimated values of frozen layer thickness (●: observer; ○: mathematical model).

Figure 2: Distribution of the sublimated mass in the vials of the core of the batch, excluding those where a thermocouple was inserted (graph a) and in the vials (of the core of the batch) where a thermocouple was inserted (graph b). Data refer to the freeze-drying of a 5% by weight sucrose solution, processed in glass tubing vials (DIN 58378-AR10); T_{fluid} = -20°C, P_c = 10 Pa.

Figure 3: Comparison between the pore size distribution in the dried cake (at 1 mm from the bottom) in a vial in the core of the batch (graph a), and in a vial, close to the previous one, where a thermocouple was inserted to monitor the product temperature (graph c). Data refer to the freeze-drying of a 5% by weight sucrose solution, processed in glass tubing vials (ISO 8362-1 8R); T_{fluid} = -20°C, P_c = 10 Pa. Cake structures as a function of the axial position (at 1 mm from the bottom) obtained by Scanning Electron Microscope in a vial without thermocouple (b) and in a vial with thermocouple (d).

Figure 4: Comparison between product temperature measured by thermocouples inserted in core vials of the batch (dashed lines) and estimated using the DPE+ algorithm (symbols) during freeze-drying of a 5% by weight sucrose solution, processed in glass tubing vials (DIN

58378-AR10); T_{fluid} = -10°C, P_c = 5 Pa.

Figure 5: Values of the cake resistance estimated by the S^3 sensor (graph a) and product temperature during the freezing stage (graph b; time is set equal to zero at the beginning of the freezing step) in two different core vials (solid and dotted lines) and in a vial placed at the edge of the shelf (dashed line). Graph c: Comparison between the values of the heat transfer coefficient K_v measured using the gravimetric test (▨) and estimated by the S^3 sensor (☐) in the monitored vials. Data refer to the freeze-drying of a 5% by weight sucrose solution, processed in glass tubing vials (ISO 8362-1 8R0); T_{fluid} = -20°C, P_c = 10 Pa.

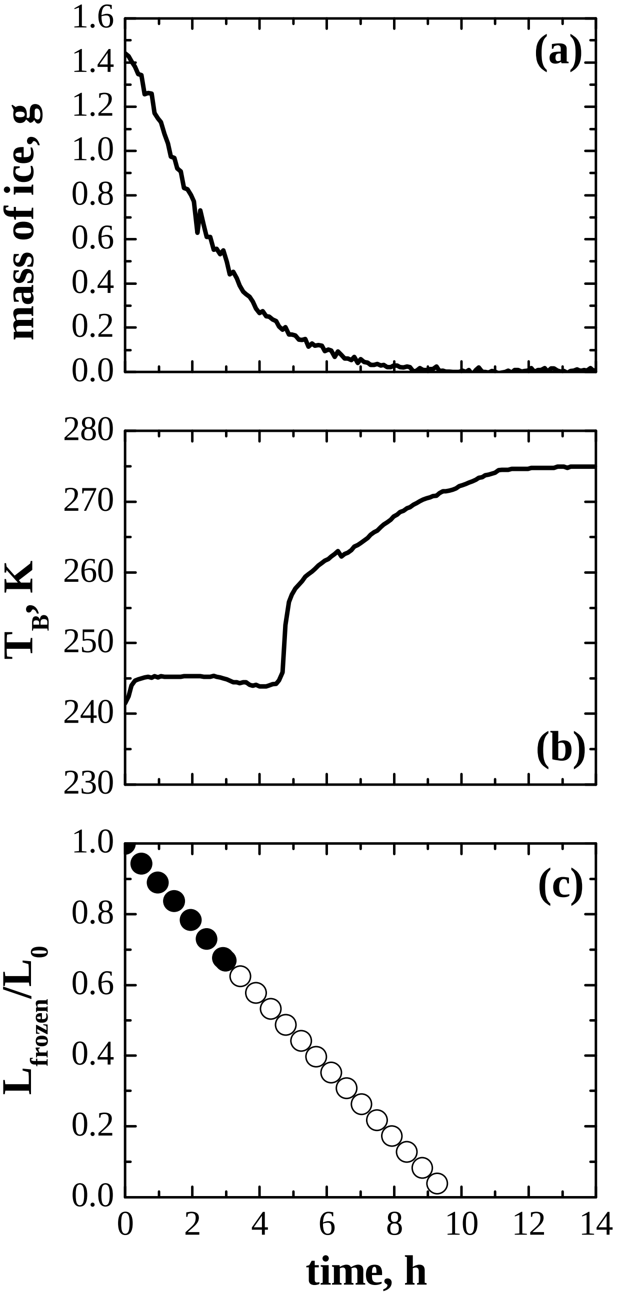
Figure 6: Comparison between the values of product temperature (graph a), ratio between Pirani and Baratron pressure gauges (graph b), and dried cake resistance (graph c), in case of the freeze-drying of a 5% by weight sucrose solution processed in glass tubing vials (ISO 8362-1 8R), at two different values of heating fluid temperature: T_{fluid} = -20°C (solid line), and: T_{fluid} = -10°C (dashed line), (P_c = 10 Pa.).

Figure 7: Graph a: Comparison between the values of the dried cake resistance (a) and sublimation flux (b) obtained in case of the freeze-drying of a 5% by weight sucrose solution processed in glass tubing vials (ISO 8362-1 8R), at two different values of chamber pressures P_c = 10 Pa (□), and: P_c = 5 Pa (▲) (T_{fluid} = -20°C).

Figure 8: Comparison between the values of dried cake resistance in case of the freeze-drying of a 5% by weight mannitol solution (graph a; ○: P_c = 10 Pa, ●: P_c = 5 Pa) and of 5% by weight polyvinylpyrrolidone solution (graph b; □: P_c = 5 Pa, ■: P_c = 15 Pa) processed in glass tubing vials (ISO 8362-1 8R), T_{fluid} = -20°C.

Figure 9: Comparison between the experimental (white bars) and the calculated (grey bars) values of drying time for various case studies (T_{fluid} = -20°C, glass tubing vials ISO 8362-1 8R): a: 5% by weight sucrose solution, P_c = 10 Pa; b: 5% by weight sucrose solution, P_c = 15 Pa; c: 5% by weight mannitol solution, P_c = 10 Pa; d: 5% by weight mannitol solution, P_c = 5 Pa; e: 5% by weight polyvinylpyrrolidone solution, P_c = 15 Pa; f: 5% by weight polyvinylpyrrolidone solution, P_c = 5 Pa.

Figure 1



(a)
mass of ice, g
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
(b)
T_B, K
280
270
260
250
240
230
(c)
L_{frozen}/L_0
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
time, h

Figure 2

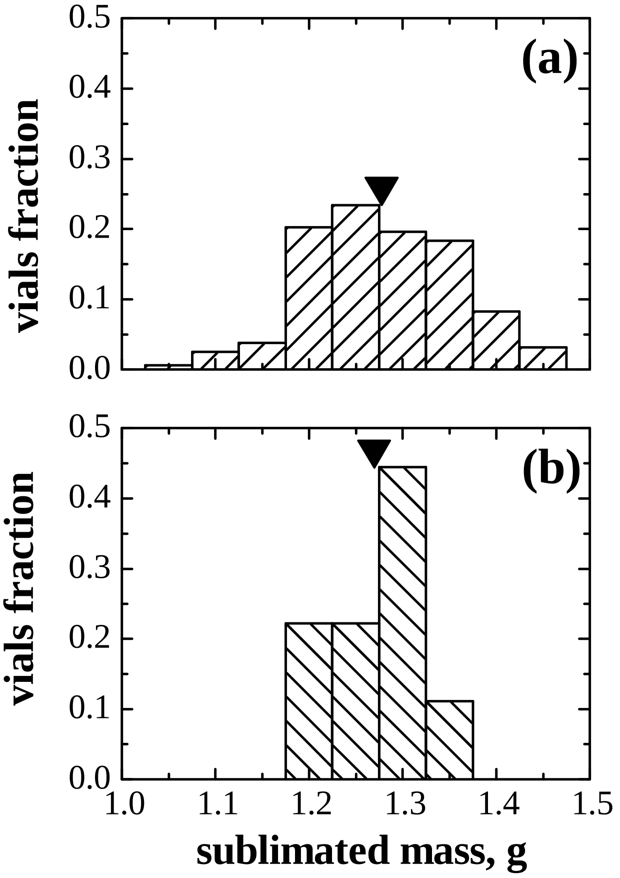

(a)
(b)
vials fraction
vials fraction
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1.1
1.2
1.3
1.4
1.5
sublimated mass, g

Figure 3

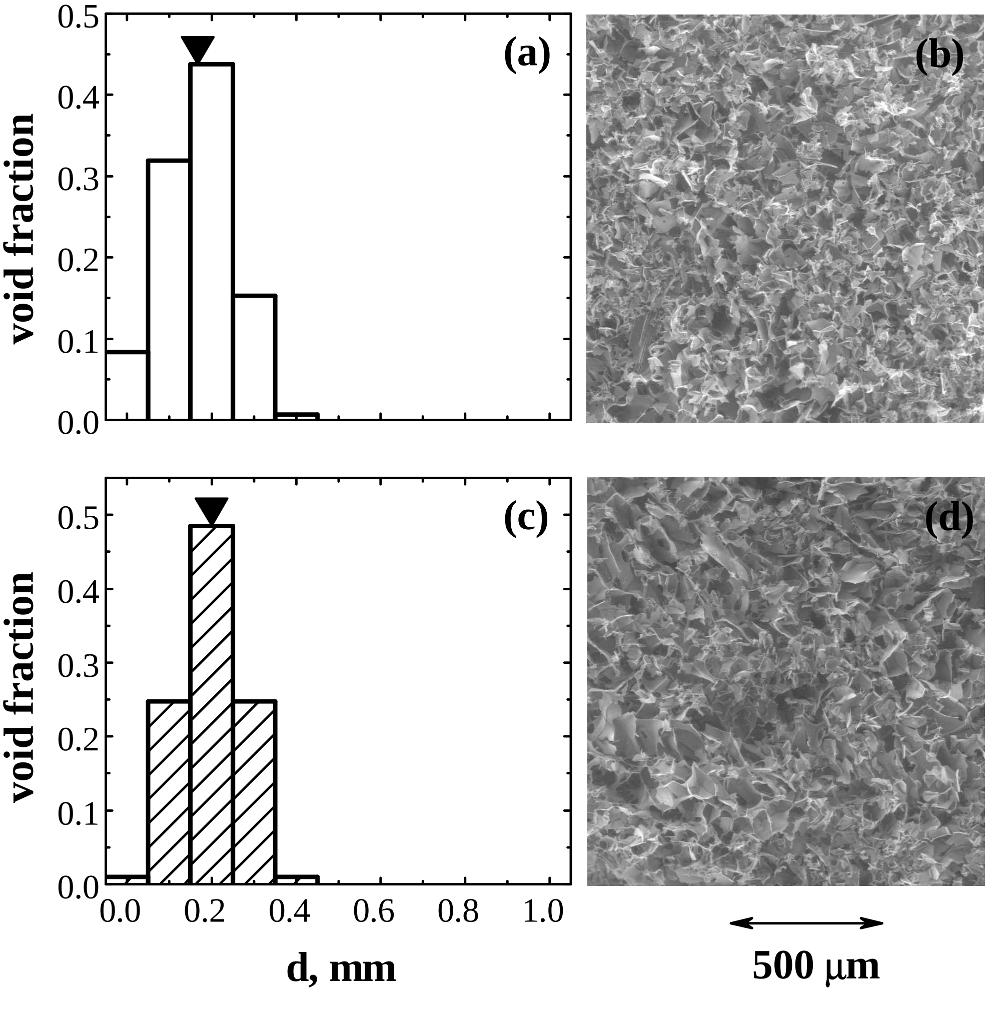


Figure 4

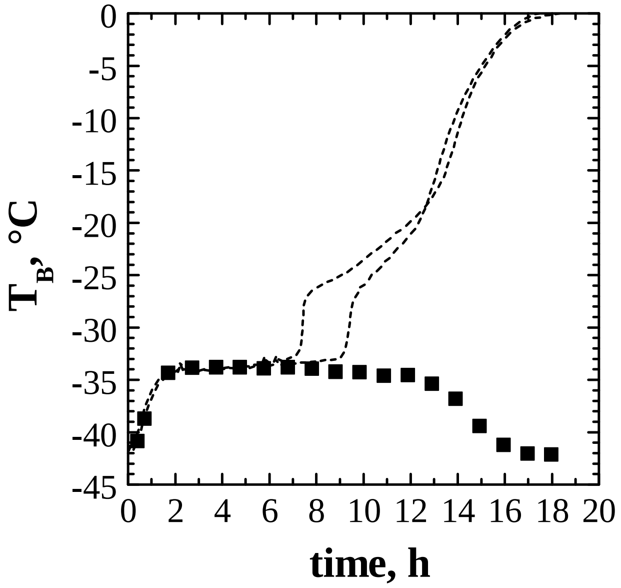
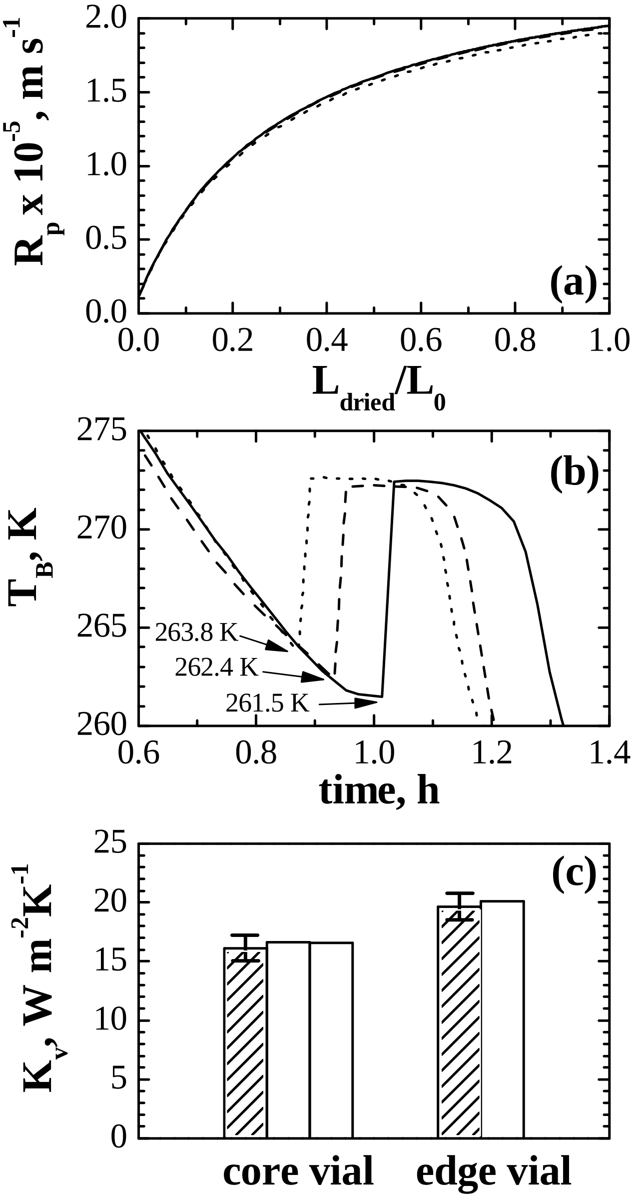


Figure 5



(a)
R_p x 10^{-5}, m s^{-1}
2.0
1.5
1.0
0.5
0.0
0.0
0.2
0.4
0.6
0.8
1.0
L_{dried}/L_0
(b)
T_B, K
275
270
265
260
263.8 K
262.4 K
261.5 K
0.6
0.8
1.0
1.2
1.4
time, h
(c)
K_v, W $m^{-2}K^{-1}$
25
20
15
10
5
0
core vial
edge vial

Figure 6

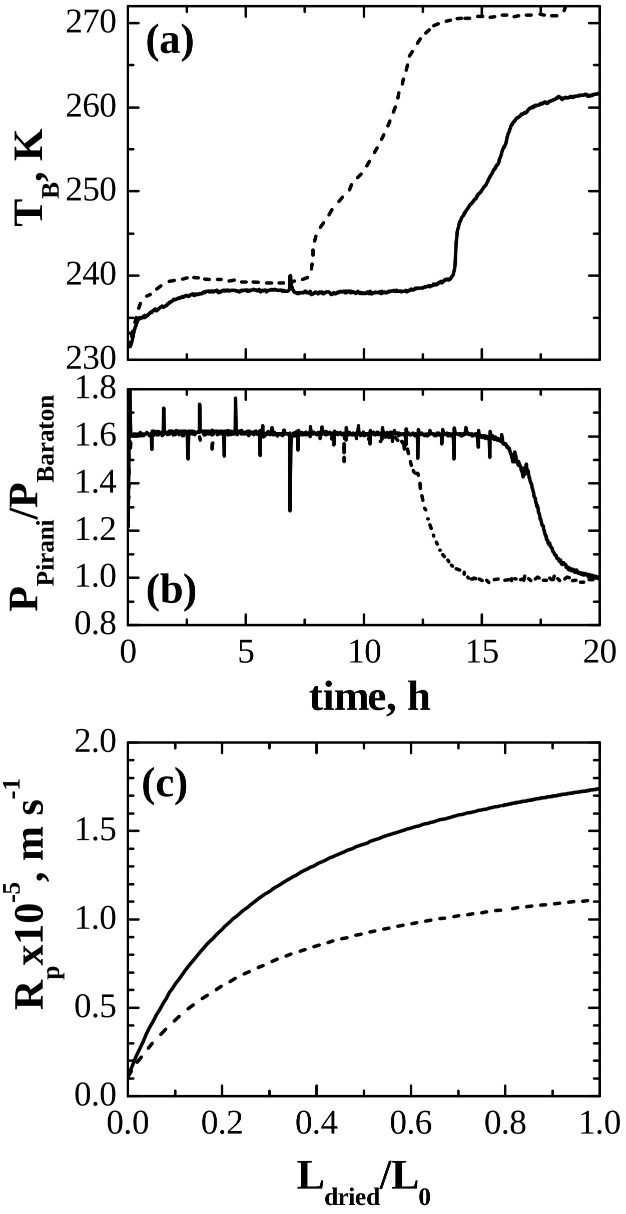

(a)
T_B, K
230
240
250
260
270
(b)
P_Pirani/P_Baraton
0.8
1.0
1.2
1.4
1.6
1.8
0
5
10
15
20
time, h
(c)
R_p x10^-5, m s^-1
0.0
0.5
1.0
1.5
2.0
0.0
0.2
0.4
0.6
0.8
1.0
L_dried/L_0

Figure 7

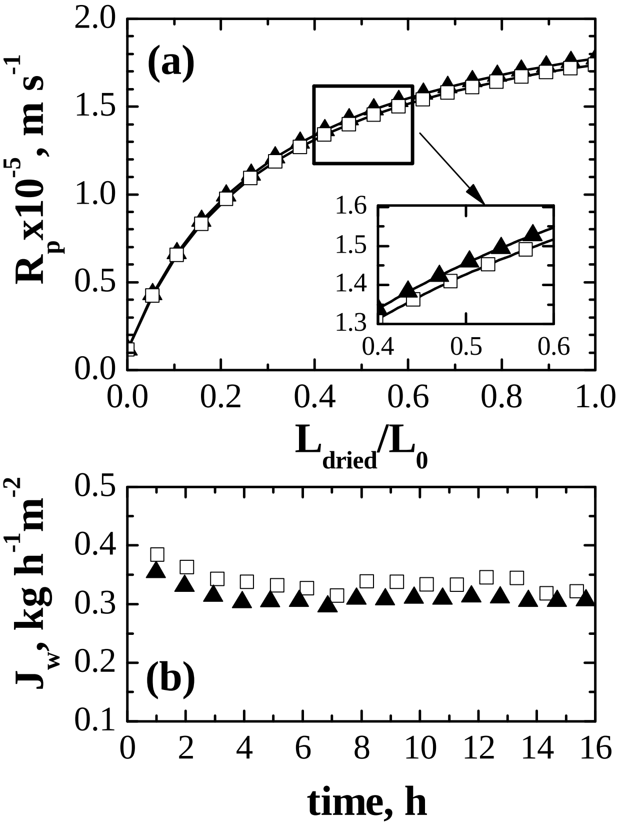

(a)
R_p x10^{-5}, m s^{-1}
2.0
1.5
1.0
0.5
0.0
0.0
0.2
0.4
0.6
0.8
1.0
L_{dried}/L_0
1.6
1.5
1.4
1.3
0.4
0.5
0.6
(b)
J_w, kg h^{-1} m^{-2}
0.5
0.4
0.3
0.2
0.1
0
2
4
6
8
10
12
14
16
time, h

Figure 8

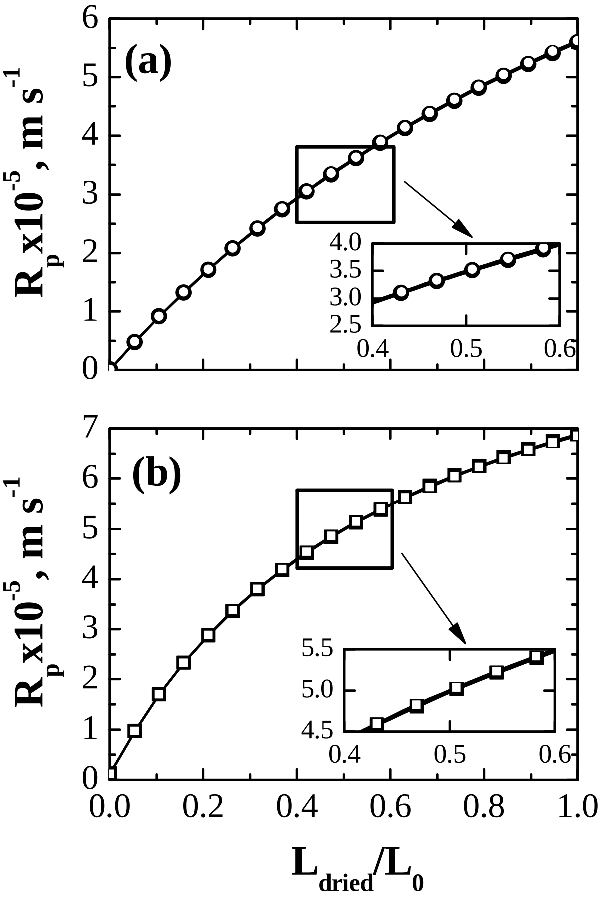

(a)
(b)
$R_p x10^{-5}$, m s^{-1}
$R_p x10^{-5}$, m s^{-1}
0
1
2
3
4
5
6
7
4.0
3.5
3.0
2.5
5.5
5.0
4.5
0.4
0.5
0.6
0.0
0.2
0.4
0.6
0.8
1.0
L_{dried}/L_0

Figure 9