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MONITORING OF A VIAL FREEZE-DRYING PROCESS WITH IR THERMOGRAPHY

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Abstract

This work presents a new device constituted by an IR camera placed inside the drying chamber to monitor the temperature of the vials without interferences. It is possible to estimate the ending point of the primary drying, the heat transfer coefficient to the product and the resistance of the dried product to vapor flux. Experiments were performed in a freeze-dryer using thermocouples and the IR camera. The measurements validate the IR camera as an effective technology for the process.

***Keywords**: freeze-drying monitoring, IR camera, temperature, process analytical technology*

1. Introduction

Freeze-drying process is used to remove a solvent, in most case water, from a product. The product is firstly frozen and, then, the water is removed by sublimation, at low pressure and low temperatures (primary drying). The target value of residual moisture can be finally reached by increasing product temperature, thus promoting the desorption of the water molecules bounded to the product. Freeze-drying is not a cheap process, so it is mainly used for food and pharmaceutical products (Mellor 1978, Jennings 1999, Oetjen 2004, Fissore 2013).
In freeze-drying process is necessary to monitor the product temperature: in fact, product temperature must remain below a threshold value, aiming to avoid drug denaturation, or collapse of the dried product in case of amorphous products, or even the melting in case of crystalline products (Bellows and King 1972, Adams and Iron 1993, Pikal 1994). Furthermore, the temperature monitoring can be used to identify the end of the primary drying step by monitoring the residual amount of ice in the product. Moreover, the sublimation flux must be monitored because it has to be compliant with duct and condenser capacity (Searles 2004, Patel *et al.* 2010). Another way to monitor in-line the process is by using mathematical modeling in order to estimate that mathematical parameters that describe the process (Pisano *et al.* 2010, Daraoui *et al.* 2010, Pisano *et al.* 2011). In particular, these parameters are resistance of the dried product to the vapor flow, R_p, and the overall heat transfer coefficient, K_v. These two coefficients describe the dynamics of the heat flux to the product (J_q) and the sublimation flux (J_w).

$$J_q = K_v(T_{fluid} - T_B) \quad (1)$$

$$J_w = \frac{1}{R_p}(p_{w,i} - p_{w,c}) \quad (2)$$

Where T_{fluid} is the temperature of the fluid in the heating shelf, T_B is that of the product at the bottom of the vial, $p_{w,i}$ is the solvent partial pressure at the solid interface and $p_{w,c}$ is the pressure in the drying chamber.

Because of the reasons mentioned above, there is interest in a monitoring system that can monitor the whole batch. This because the behaviour of the product is different depending on the position of the vial on the shelf. It is also important that the detector does not interact with the product (e.g. thermocouples) because it could affect the dynamic of the process (Barresi *et al.* 2010).

Emteborg et al. proposed an IR system where the infrared camera was placed on the top of the drying chamber, monitoring the shelves from the above. Unfortunately, with this arrangement, the temperature monitored were that of the sufrace of the product.

This work will present a monitoring system constituting of an infrared camera placed inside of the chamber of the freeze-dryer that can monitor the temperature of the vials that stand in front of the sensor, without interfering with the product.

2. Material and method

IR Camera

The equipment used to monitor the product temperature is a thermographic recording system TICEM characterized by a 320x256 pixels resolution. It operates in the LW spectrum of the IR electromagnetic waves. It also has a visible recording system, with a lower resolution. This equipment is placed into a case in order to protect it against the conditions of low temperatures and pressures that can be reached during a freeze-drying cycle (*Figure 1*). The data acquisition system is wireless and the software architecture allows to operate in absence of external terminals.
Several parameters must be known in order to correct the measurements from the parasitic radiations. The key parameters are:

- Emissivity of the subject;
- Distance from the subject;
- Reflected apparent temperature.

The emissivity of the object and its distance from the camera are fixed for the whole duration of the test. Instead, the reflected apparent temperature is very important, it represent the parasitic heat that influences the object, coming from sources that reflect on the thermal imager and, for these reasons it changes during the test. Unfortunately, the reflected apparent temperature influences a lot the measurements. The system here presented, is supported by a software that measure and update this variable in-line automatically.

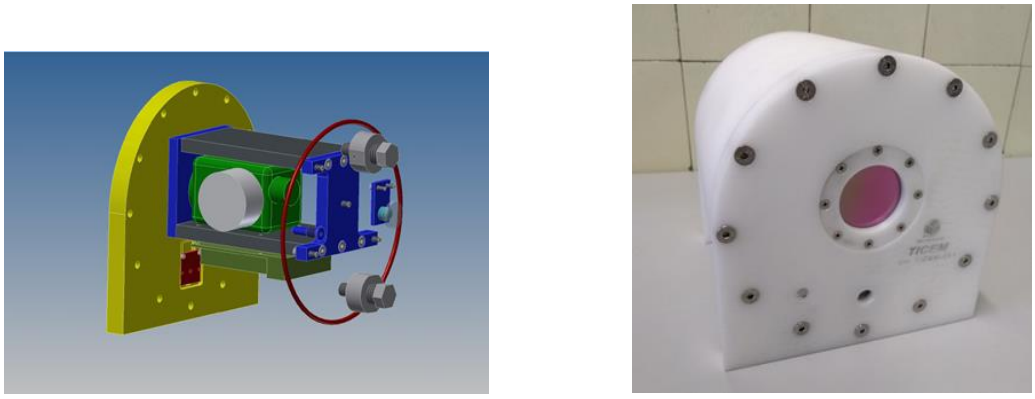


Figure 1: the scheme of the inside of the sensor on the left, and the sensor from the front side, on the right.

Case Study

Freeze-drying tests were carried out using a LyoBeta 25™ (Telstar, Madrid, Spain) freeze-dryer (drying chamber: 0.2 m^3, total area: 0.5m^2). Tests were performed with a 10% by weight sucrose solution and a 5% by weight sucrose solution. Reactants were purchased from Sigma-Aldrich and used as received; ultra-pure water obtained with a Millipore water system (Milli-Q RG; Millipore, Billerica, MA) was used to prepare the solutions processed in the various tests. The vials used in the tests were ISO 8362-110R and they were filled with 5mL of solution. The distance of the thermal imager from the vials was about 30 cm and the sample time was 300 seconds. T-type thermocouples (Tersid, Milano, Italy) were placed in some vials for validation motivation. Chamber pressure was monitored using both a capacitance (Baratron type 626A; MKS Instruments) and a thermal conductivity (Pirani type PSG-101-S; Inficon, Bad Ragaz, Switzerland) gauge. Product freezing was achieved by decreasing the temperature of the technical fluid until a temperature of about -40°C was observed from the thermocouples.

3. Results and discussion

Study of the effect of the presence of the IR camera on the batch evolution

First of all, the influence of the presence of the equipment in the freeze-dryer chamber on product dynamics was investigated. Gravimetric tests were used to this purpose, considering a 10% by weight sucrose solution and comparing the sublimation rate in case the camera is placed in the dryer with that obtained in case the camera is not used. Some tests were performed with a row of ten vials in front of the IR camera, some other with a batch of 45 vials in 3 rows (*Figure 2*).
The comparison showed that the infrared camera does not affect product dynamics: it does not heat the product in the vial but, on the contrary, it shields it from the chamber wall irradiation. In particular, we can compare the shielding effect given by the presence of the IR camera whit that is obtained, in a batch of vials, from the external files. This is extremely important as, obviously, the camera may track the dynamics of the vial of the first raw of a batch, where

radiation effects from chamber walls may be more relevant and whose dynamics is not representative of the dynamics of the vials in the central part of the batch that constitute most of the batch. The result of the investigation evidenced that the dynamics of the vials in front of the camera is similar to that of the central vials.

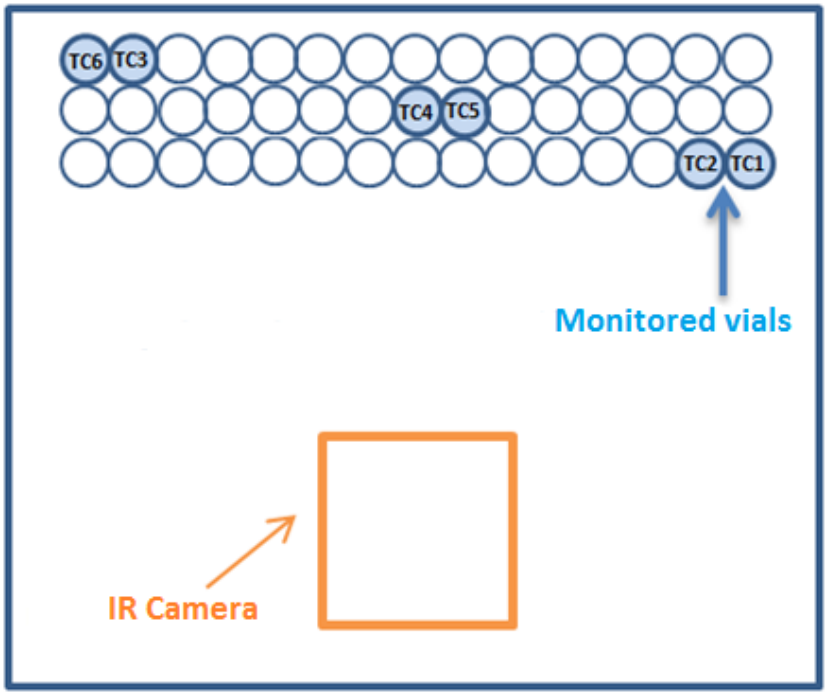


Figure 2: configuration of the vials and the IR camera on the shelf in the chamber of the freeze-dryier during some gravimetric tests.

Validation of the monitoring system based on the IR camera

In order to validate the monitoring system based on the use of the IR camera in the freeze-dryer, the temperature profiles obtained from some thermocouples, placed into some vials, were compared with the temperature profiles obtained with the thermal imager (*Figure 4*). The IR camera provides a temperature map of the vials (*Figure 3*), the temperature profile is detected in 5 points on the bottom of the vial, because it is not possible from the thermography to determine the point measured by the thermocouple. Similar tests were performed, for validation motivation, with different operating conditions and with different products. In particular 10% and 5% by weight sucrose and mannitol solutions were used, in order to analyze both crystalline and amorphous behavior.

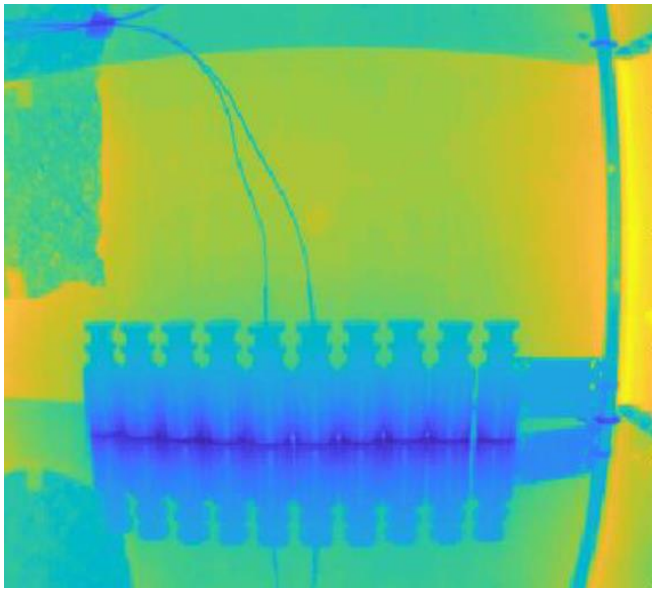


Figure 3: thermography of a test performed for the validation of the monitoring system

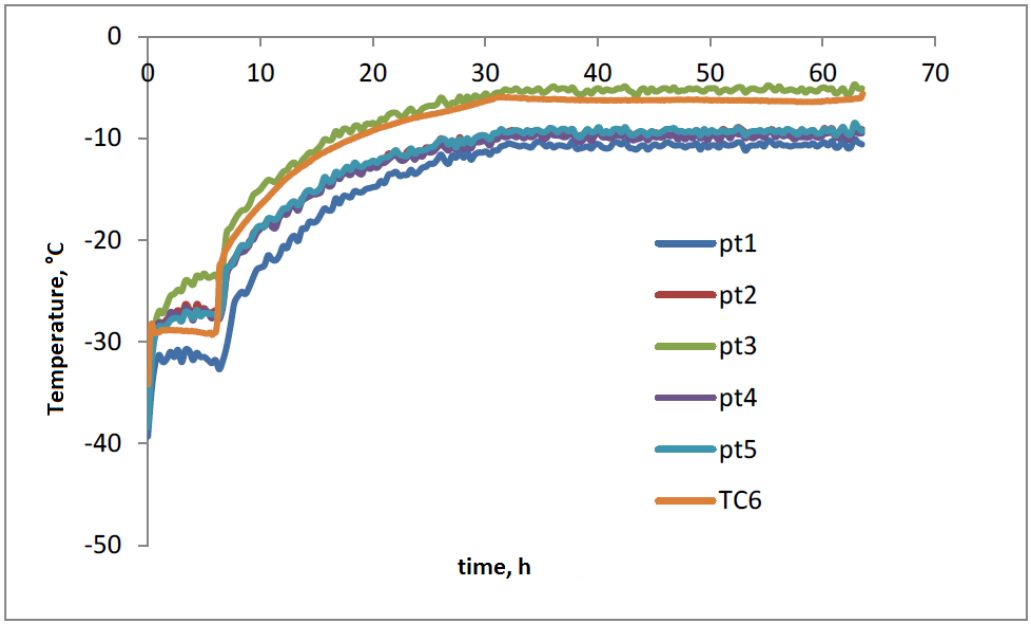
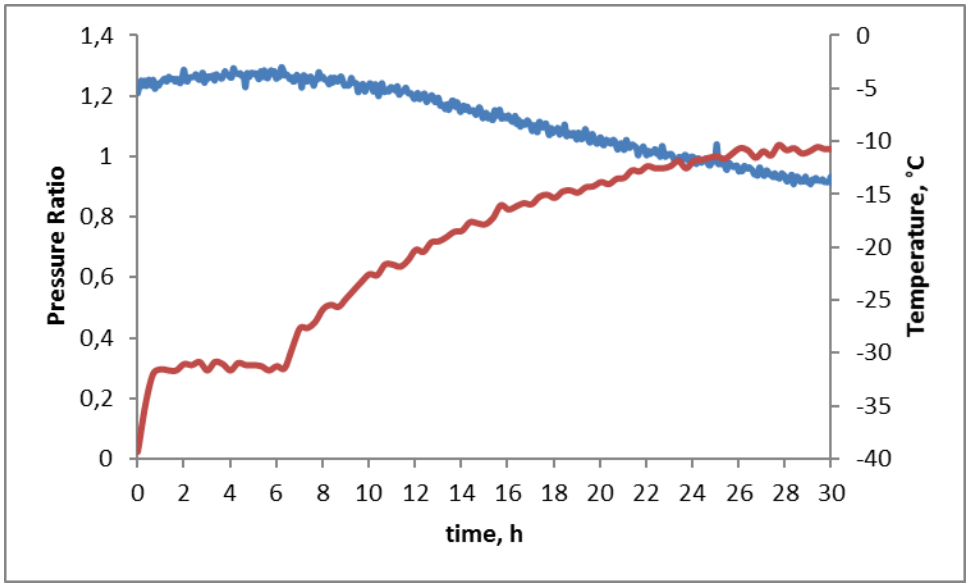


Figure 4: Comparison between the temperature detected in the 5 points at the bottom of the vial, and the measurement of a thermocouple TC6 placed in the same vial. Case study: freeze-drying of a 10% w/w sucrose solution, processed at 20 Pa and -20°C.

End of primary drying estimation

The temperature profiles obtained from the IR camera can be used to identify the end of the primary drying and, for validation purposes, this value is compared with tat obtained from the

Pressure Ratio profile. For this purpose, the minimum temperature profile was considered, in order to consider the point of the bottom in which there is ice for a longer time interval. A good agreement between the results obtained from the temperature profile and from the Pressure Ratio profile was obtained as both systems identify the same ending point: in fact, when the temperature drastically increases, the Pressure Ratio start decreasing (*Figure 5*).



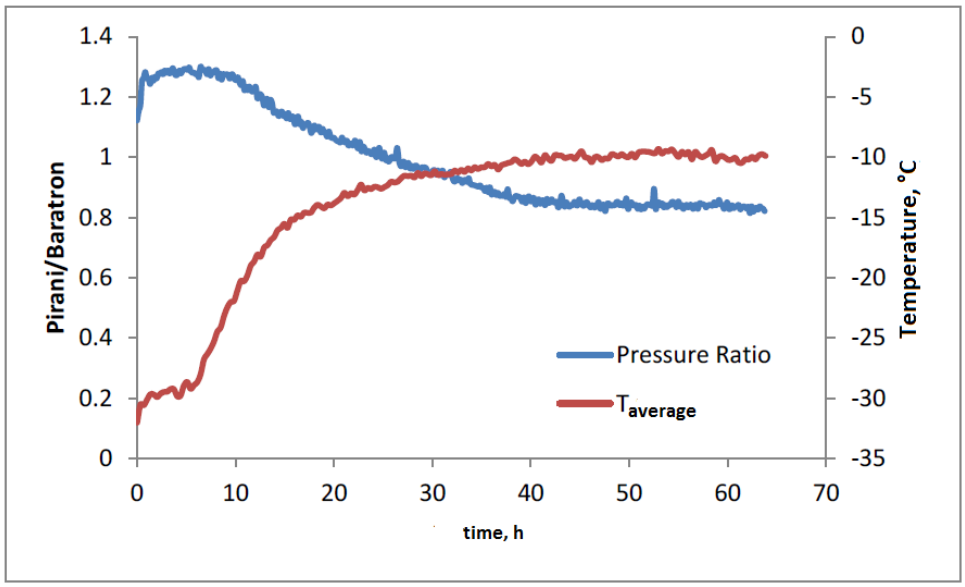


Figure 5: Comparison between the mean value of product temperature (dashed line) detected through the IR thermal camera in the 5 points at the bottom of the vial and the ratio between the Pirani and Baratron signals (solid line) when processing a 10% (upper graph) or a 5% (lower graph) w/w sucrose solution at 20 Pa and -20°C.

Parameter estimation

Finally, the temperature detected by the IR camera were used to estimate the values of the heat and mass transfer coefficients K_v and R_p, defined in Equations 1 and 2, it was done using the temperature measurement obtained with the thermocouple (calculations on Overcashier *et al.*). The test was performed using the 10% sucrose solution and measuring product temperature with both thermocouple and IR camera in the freeze-dryer. The test was repeated 5 times. Considering the temperature profiles obtained with the thermocouples, the global mean value of K_v obtained was 156.5 $Wm^{-2}K^{-1}$ (with a variance of 8.65%). Using the global mean bottom temperature obtained by the IR camera, the global mean value of K_v obtained was 153.0 $Wm^{-2}K^{-1}$ (with a variance of 12.33%),that is a perfect agreement with the precedent value. With respect to the coefficient R_p, it was calculated using the temperature profile (detected through the thermocouple or the IR camera) and the K_v value. With the value of K_v, the temperature evolution of the heating shelf and the temperature profiles of the product at the bottom of the vial, the heat flux to the product was calculated, using Equation 1. Then, considering the heat balance to the product:

$$J_q = \Delta H_s J_w \tag{3}$$

assuming that all the heat transferred to the product is used for sublimation, the water vapor flow can be calculated and the value of R_p using Equation 2. This was don considering $p_{w,c}$ as equal to chamber pressure (because the composition of the atmosphere in the chamber is about 100% water vapor), and $p_{w,i}$ is a function of product temperature (calculations Overcashier *et al.*). The values are interpolated using the following equation:

$$R_p = R_{p,0} + \frac{AL_{dried}}{1 + BL_{dried}} \tag{4}$$

Also in this case, it is possible to observe that there is an acceptable agreement between the values of R_p versus L_{dried} obtained using the thermocouple measurement and the thermal camera profiles.

4. Conclusions

The monitoring system based on the IR camera here presented is an innovative monitoring system that allows the in-line monitoring of the freeze-drying process without interfering with the product. The IR camera doesn't give information only on temperature profiles, but it also provides information about the end of the primary drying step. Moreover, values obtained from this sensor can be used to estimate the mathematical parameters describing the process as well as those values obtained from thermocouples. Finally, the accuracy is similar to that obtained with traditional monitoring systems (e.g. thermocouples), but it is important to observe that in this case the sensor is not in contact with the product and the measurements are not limited to a single vial.

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