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Frequency domain image analysis for the characterization of porous products

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ABSTRACT

Many pharmaceutical products are obtained via freeze-drying of liquid solutions to obtain stable long lasting preparations. The freeze-dry process produces porous cakes whose structure strongly depends on the freezing phase, so that monitoring and optimizing this phase can help both reducing the product cost and insuring its constant quality. Nowadays the optimization is usually performed by determining the cake mass transfer coefficient via a costly process in pilot plants, while the quality is assured only by controlling the process conditions. This paper describes an alternative way of approximately estimating the mass transfer coefficient, which is based on the observation of the product structure by a simple electron microscope followed by a frequency domain imaging process. While the process has been designed and characterized specifically for pharmaceutical products, the proposed approach can be used in several other fields where the characteristics of porous material have to be monitored.

1. Introduction

The development of the industrial processes to produce drugs and pharmaceutical products is traditionally based on trial and error, both regarding the product formulation and the conditions which are used during their manufacturing. However, understanding the products characteristics and its manufacturing process is the basis for any best practice pharmaceutical development as remarked by the ICH-Q8 "Guideline on pharmaceutical development". The trial and error approach when applied to freeze-drying processes is time-consuming and often it is difficult to obtain the best quality and the most convenient freeze-drying cycle [1]. To tackle with this last aspect, several model-based approaches have been proposed to help selecting the optimal processing conditions [2,3], but unfortunately the complete freeze-drying system has to be characterized in terms of heat and mass transfer coefficients [4] to use these tools. Such determination is reasonably simple for the heat transfer coefficient, which, for a given pressure, depends only on the container and on its coupling with the shelf, and can be obtained by means of a gravimetric test [5]. The determination of the mass transfer coefficient is much more complex because it is not only product-specific, but also connected with the conditions used during freezing. Its estimation is a labor-intensive process [6] so that only few experts can manage it independently. Automatic procedures using a special scale inside the chamber have been proposed, but are generally suited only for lab scale freeze-driers and can be employed with difficulties in industrial apparatus, even though the determination would be important since their freezing conditions may be different from those of the lab scale [7].

Some approaches have been proposed that are able to determine the resistance to mass transport and which are normally based on the measurements of sublimation rate and product temperature, but these solutions can hardly be used in industrial applications as they require an a priori knowledge of the heat transfer coefficient between equipment and container [8–11] and they are bad-conditioned [12] so the required measurement uncertainty of the input quantities is not compatible with an industrial process.

This paper describes an alternative measuring approach for an approximate estimation of the mass transfer coefficient, which can be used off-line and does not require the placement of any sensor inside the freeze-dryer. The proposed solution employs an indirect estimation of the cake porosity, which is related to the mass transfer coefficient, by means of a frequency domain processing of freeze-dried cake images collected by means of a scanning electron microscope. In particular, two approaches are proposed which are based on 2D-FFT transform [13] and on Wavelets compression

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[14] showing how both solutions are suitable for the proposed estimation.

2. Direct gravimetric mass transfer coefficient estimation

As anticipated in previous section the estimation of the mass transfer coefficient, k_m, is a labor intensive procedure which is widely discussed in the literature. In this work the three-step procedure described below is used:

1. A preliminary estimation of the actual heat transfer coefficient (k_v) between the container and the shelf, is carried out for product and position on the shelf of interest. This is based on measuring temperatures on the shelf and inside the product and the product mass changes at different time steps.
2. A freeze-drying process is started and, during primary drying phase both the temperatures of the product (T_p) and of the shelf (T_f) are measured by means of miniaturized thermocouples, while the vapor flow rate released by ice sublimation (J_w) is estimated thanks to the heat transfer coefficient k_v:

$$J_w = \frac{k_v(T_f - T_p)}{\Delta H_s} \tag{1}$$

where ΔH_s is the enthalpy of ice sublimation.
3. The instantaneous vapor flow rate is directly correlated with the mass transfer coefficient according to Eq. (2):

$$J_w = \frac{k_m M_w}{RT_p L_d}[P(T_p) - P_c] \tag{2}$$

where M_w is the water molecular weight, $P(T_p)$ is the ice vapor pressure, which is a function of the temperature as described in [15], L_d is the thickness of the freeze-dried layer, which can be computed by integrating the vapor flow rate and R is the ideal gas constant.

Once k_v is determined, this method allows one to evaluate k_m by simple measurements of product and heat transfer fluid temperatures and thus can be applied with relative easiness, even though the presence of the TC sensors can alter the drying process thus impairing the quality of the estimations. One should note that, even though this method is effective in determining the mass transfer coefficient, its use is limited to lab pilot plants, since the use of thermocouples is not compatible with the Good Manufacturing Practice procedures, which are used by pharmaceutical industry and the work connected to the measurements prevents it to be used during regular industrial production.

3. Image-based mass transfer coefficient estimation

The mass transfer coefficient is related to the pore dimension as well to the pore interconnection, so that the k_m estimation by visual observation would require at least observing the dried cake both in-section and in cross-section. Unfortunately this would turn out in a complex sample preparation since multiple cake sections are extremely difficult to obtain due to the inherent fragility of the dried product. Therefore in this work only cross-sections at cake center have been used. While the information obtained in this way is obviously incomplete, the common observation that cakes with low values of the mass transfer coefficient are characterized by large pores is immediate. Fig. 1A shows two pictures collected by means of a Field Emission Scanning Electron Microscope (FESEM) of two different formulations each tagged with the mass transfer coefficient estimated by the gravimetric approach.

Even though a visual correlation between the actual mass transfer coefficient and the surface morphology appears, the derivation from the picture of a single parameter representative of the mass transfer coefficient is quite difficult. As mentioned above, the mass transfer coefficient is related to the resistance of the material to the vapor flow, and, therefore, to the dimensions of the cake pores and to their interconnection non only on the cross section, but also in-section. Specifically, there is a possibility that a cake which appears to have large cross-section pores has a low mass transfer coefficient if the vapor flow is impaired by a poor interconnection and vice versa.

In any case the image based analysis has to try to extract from the surface aspect, i.e. from the pixel brightness, same data regarding the distribution of the pore diameters i.e. some data about the spatial distribution of the image brightness. Several different approaches can be used to get information about the surface aspect and roughness by means of image processing, which are based on speckle processing [16] and on brightness frequency distribution, such as the conventional and multi-resolution bi-dimensional Fourier transform [17], different types of wavelet and small kernel transformations [18].

Among these possibilities, the authors decided to explore two solutions:

- A processing based on a 2D-FFT. This approach allows one to obtain an estimation of the brightness spatial frequency distribution i.e. an estimation of the distribution of the pore sizes. This way, if one is able to relate the pore size to k_m, it is possible to try to derive an equation to link the spatial frequency distribution to the mass transfer coefficient.
- A 'blind' processing based on a wavelet compression followed by an Artificial Neural Network (ANN) trained to estimate the mass transfer coefficient. This solution is potentially quite effective, though more critical with respect to the analysis of images of types never seen by the ANN and which were not included in the network training.

3.1. 2D-FFT processing

An equation, which links the pore size to the mass transfer coefficient, can be easily obtained if the pores are considered linear, tubular with low radius compared to their length and with limited flow to ensure a laminar flow. In this case the relationship between pressure difference and flow (J_p), through a single pore can be obtained by solving the Navier-Stokes equation to obtain the Hagen-Poiseuille equation [19]:

$$J_p = \Delta P \frac{\pi r_p^4}{8\eta l_p} \tag{3}$$

where ΔP is the pressure difference at tube ends, l_p and r_p are respectively pore length and radius and η is the dynamic viscosity.

In this simplification based on straight tubular pores, the total flow (J_w) through the cake is simply the sum of the flows through all pores:

$$J_w = \sum J_{p-i} = \Delta P \frac{\pi}{8\eta l_p} \sum n_{p-i} r_{p-i}^4 \tag{4}$$

where n_{p-i} is the number of pores having radius r_{p-i} which are present in the cake.

Eq. (4) can be rewritten making reference to the part of area A_{p-i} occupied by pores of radius r_{p-i}.

$$A_{p-i} = n_{p-i} k_c \pi r_{p-i}^2 = A \cdot p_{p-i} \tag{5}$$

where p_{p-i} is the fraction of the total area A, which is occupied by pores having radius r_{p-i} and k_c is a coefficient which takes into account the coverage factor of pores with respect to the total area.