A mathematical model for the secondary drying of a freeze-drying process

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Abstract. In this manuscript a mathematical model describing the secondary drying stage of a freeze-drying process is presented. The model consists in governing equations for the transport of an air-vapour mixture in a porous medium. The production of water vapour due to the desorption of bound water is accounted for by means of a source term in the equation for the water vapour concentration. We show how, in the limit of small Peclet numbers, the model can be solved analytically. In addition, we provide with an explicit expression for the total time for the secondary drying stage of the freeze-drying process amenable for real time control applications.

1. Introduction

Freeze-drying or lyophilisation is a dehydration process widely used in the food and pharmaceutical industries, mainly for product preservation and storage purposes. The process enables materials or slurry products, which have been previously frozen, to be dried under vacuum conditions. In the case of pharmaceuticals, the substance to be dried is distributed in vials and placed on trays in a freeze dryer. Then, the freeze-drying proceeds through three successive steps:

1. Freezing: The product in the vials is frozen to a very low temperature. Depending on the particular product involved this process must be fast or slow, as nucleation rates and the size of the ice crystals can affect the quality of the final product.

2. Primary drying: The pressure in the chamber is decreased to nearly vacuum conditions, resulting in the sublimation of the ice content of the product. Once all the ice is removed, a porous dried material is obtained.

3. Secondary drying: The temperature is increased to evaporate adsorbed water (desorption) that did not freeze during the first stage of the process. At the end of the secondary drying a dried porous material with typically less than 1% of water content is obtained.

There is a reasonable amount of literature dealing with mathematical models that describe the different stages of a freeze-drying processes. In general, these models consist in systems of coupled partial differential equations describing the heat and mass transfer in a vial where phase change and chemical reactions are typically involved [1, 2, 3]. Thus, solving this models is usually computationally expensive and not feasible for real time applications [4]. Soft sensors
and other control systems require simple models that can be easily implemented in a software and provide information of a process in real time.

In the present study, we will focus on the description of the secondary drying step of the freeze-drying process. In section 2 we formulate a mathematical model describing the transport of water vapour in the porous medium inside a cylindrical vial. In section 3 we present some exact and approximate solutions and provide an explicit formula for the total time of the secondary drying. In section 4 we discuss the results and in section 5 we present the conclusions.

2. Mathematical Model
An illustration of the model is presented in figure 1. The cylindrical body on the left represents a vial containing a porous medium with adsorbed bound water at the beginning of the secondary drying stage. Note, vials are small glass containers with the upper section open. The right side of the image illustrates the interior of the porous medium. The white spots represent the non-porous dried parts of the material which are surrounded by a thin blue layer representing the adsorbed bound water. The gray area represents the porous space where the gas mixture circulates.

In a porous medium the transport of a component in a gas mixture is determined by the local conservation of mass of each component in the mixture. One form of the mass conservation equations for an air-vapour mixture is

\[
\begin{align*}
\epsilon \frac{\partial \rho_v}{\partial t} + \nabla \cdot (\mathbf{v} \rho_v) &= -\nabla \cdot \mathbf{J}_v + q_v, \\
\epsilon \frac{\partial \rho_a}{\partial t} + \nabla \cdot (\mathbf{v} \rho_a) &= -\nabla \cdot \mathbf{J}_a,
\end{align*}
\]

where \(\rho_v, \rho_a\) are mass concentrations of vapour and air, \(\epsilon\) the porosity, \(\mathbf{v}\) is a volume flux with units of velocity, \(\mathbf{J}_{v,a}\) the diffusive fluxes and \(q\) the source term accounting for desorption. In the present study, the diffusive fluxes are given by the Fick’s law, \(\mathbf{J}_{v,a} = -\epsilon D \nabla \rho_{v,a}\). For more discussion about other forms of fluxes see [5, 6]. Addition of equations (1)-(2) gives the continuity equation for the mixture

\[
\epsilon \frac{\partial \rho}{\partial t} = -\nabla \cdot (\mathbf{v} \rho) + q,
\]

where \(\rho = \rho_v + \rho_a\). The source term \(q\) contains the information of how the desorption of water takes place in the porous medium. In the present study we take the approach followed in [2]: if
\( \rho_{bw}^0 \) is the initial amount of bound water and \( \rho_v \) the vapour generated from bound water only, one approximation that models the desorption of water is

\[
\frac{\partial \rho_v}{\partial t} = k \rho_{bw}^0 e^{-kt},
\]

(4)

where \( k \) is the desorption rate.

As we are interested in the water vapour concentration we focus on equation (1). Noting that the gas circulation in the vial occurs mainly in the vertical direction, as the gas is only allowed to leave from the top of the vial, the radial and angular transport components can be dismissed. Then, equation (1) can be written as

\[
\epsilon \left( \frac{\partial \rho_v}{\partial t} + v \frac{\partial \rho_v}{\partial x} \right) = \epsilon D \frac{\partial^2 \rho_v}{\partial x^2} + k \rho_{bw}^0 e^{-kt},
\]

(5)

where \( x = 0 \) and \( x = L \) represent the top and bottom of the vial, respectively. As a first approximation we assume the following boundary conditions

\[
\rho_v(0, t) = \rho_v^0, \quad \frac{\partial \rho_v}{\partial x} \bigg|_{x=L} = 0,
\]

(6)

accounting for a constant concentration of vapour in the chamber, and so at the top of the vial, and insulation at the bottom. We close the system with the initial condition \( \rho_v(x, 0) = \rho_v^0 \).

The governing equation (5) can be nondimensionalised by introducing the following variables

\[
\hat{t} = \frac{t}{\tau}, \quad \hat{x} = \frac{x}{L}, \quad \hat{\rho} = \frac{\rho_v - \rho_v^0}{\Lambda}, \quad \hat{v} = \frac{v}{V}.
\]

(7)

By looking at equation (5) it is clear that there are three different time scales in our model: the diffusion time scale, \( \tau_{\text{dif}} = L^2 / D \), the desorption time scale, \( \tau_{\text{des}} = 1 / k \), and the time scale of the convective flux, \( \tau_{\text{con}} = L / V \). As we are interested in how long it takes for all the bound water to evaporate, we choose \( \tau = \tau_{\text{des}} = 1 / k \). The overall variation of vapour concentration in the vial will be mainly determined by the initial amount of bound water existent in the system, so we choose \( \Lambda = k(\rho_{bw}^0 L)^2 / \epsilon D \). The resulting nondimensional equation for the vapour concentration in the vial is

\[
\delta \frac{\partial \hat{\rho}_v}{\partial \hat{t}} + \text{Pe} \hat{v} \frac{\partial \hat{\rho}_v}{\partial \hat{x}} = \frac{\partial^2 \hat{\rho}_v}{\partial \hat{x}^2} + e^{-\hat{t}},
\]

(8)

where \( \text{Pe} = VL/D \) is the Peclet number and \( \delta = L^2 k / D \).

3. Solution

The secondary drying step is a long process that can take several hours where the pressure in the freeze-dryer chamber is typically kept constant. In such conditions, it is believed that convection terms, usually accounted for by means of Darcy’s law, are unimportant compared to diffusion terms, which translates in a small value of the Peclet number. Setting \( \text{Pe} = 0 \) in (8) and dropping the hat notation we obtain the boundary value problem

\[
\delta \frac{\partial \rho_v}{\partial t} = \frac{\partial^2 \rho_v}{\partial x^2} + e^{-t}, \quad \rho_v(0, t) = 0, \quad \frac{\partial \rho_v}{\partial x} \bigg|_{x=1} = 0, \quad \rho_v(x, 0) = 0.
\]

(9)

The above problem can be solved analytically by means of the eigenfunction expansion method

\[
\rho_v(x, t) = \sum_{n=1}^{\infty} \frac{2(e^{-t} - e^{-\lambda_n t / \delta})}{(\lambda_n - \delta)\sqrt{\lambda_n}} \sin \left( \sqrt{\lambda_n} x \right), \quad \lambda_n = \frac{(2n - 1)^2 \pi^2}{4},
\]

(10)
where $\lambda_n$ are the eigenvalues and $\sin(\sqrt{\lambda_n} x)$ corresponding eigenfunctions.

The nondimensional parameter $\delta$ gives information of the relative importance between the diffusion and desorption time scales, $\delta = \tau_{\text{diff}}/\tau_{\text{des}}$. If the desorption time scale is much larger than the diffusion time scale, $\tau_{\text{des}} \gg \tau_{\text{diff}}$, then $\delta \ll 1$ and the boundary value problem (9) suggests an approximate series solution of the form $\rho_v = \rho_v^0 + \delta \rho_v + \mathcal{O}(\delta^2)$. At leading order, we obtain

$$0 = \frac{\partial^2 \rho_v^0}{\partial x^2} + e^{-t} \Rightarrow \rho_v(x, t) \approx e^{-t} \left(1 - \frac{x}{2}\right)x. \quad (11)$$

Note, in (11) the initial condition $\rho(x, 0) = 0$ is not satisfied as $\rho_v \neq 0$ for $t = 0$, indicating the presence of a boundary layer. In the next section we will compare the approximate solution (11) to the exact solution (10). We will also provide a numerical solution of (9), by means of backward Euler finite differences, to test that the exact solution found is correct. Applying such numerical scheme to this problem is straightforward and the details will not be provided in this manuscript.

In a freeze-drying process, a key factor to obtain a final product with the desired final concentration of water is the right adjustment of the primary and secondary drying times. An estimation of the total time for secondary drying, $t_{2\text{dry}}$, can be obtained by inverting expression (11). Noting that the highest concentration of water vapour occurs at $x = 1$ (bottom of the vial), this gives

$$t_{2\text{dry}} = -\ln \left(2\rho_v\right). \quad (12)$$

By establishing a level of acceptance of water vapour concentration in the vial, e.g. $\rho_v = 0.01$, an explicit value for $t_{2\text{dry}}$ can be found by means of (12).

### 4. Results

In figures 2 and 3 we show the concentration of water vapour inside the vial for $\delta = 0.1$ and $\delta = 0.5$, respectively, at two different times, $t = 0.29$ and $t = 1.29$. The solid lines represent the exact solution given by (10), the dash-dotted lines the approximate solution (11)b and the dashed lines the numerical solution. We observe that the numerical and the exact solution match in all cases, confirming that our exact solution is correct. By comparing figure 2 with figure 3, it can be seen how the approximate solution is much closer to the exact solution for $\delta = 0.1$ than for $\delta = 0.5$. Indeed, the approximate solution is based in the limit of $\delta \to 0$ and the behaviour observed is consistent with this fact.

As mentioned previously, the right adjustment of the primary and secondary drying times is of crucial importance in a freeze-drying process. Typically, the drying times, which are usually found experimentally by trial and error, strongly depend upon the physical and chemical properties of the product to be dried. In freeze-drying studies a common practice to use skimmed milk for experiments and model testing. For skimmed milk the value of the desorption rate is $k = 7.8 \times 10^{-5}\text{s}^{-1}$ [2]. Then, using the diffusion coefficient for an air-vapour mixture $D = 0.28 \times 10^{-4}\text{m}^2\text{s}^{-1}$ and assuming a length scale of $L = 0.01\text{m}$ we obtain $\delta = 2.79 \times 10^{-4}$. In this case, where the desorption time scale strongly dominates the process, expressions (11) and (12) are very accurate. By substituting $\rho_v = 0.01$ in (12) we obtain $t_{2\text{dry}} = 3.91$. Multiplying the resulting time by $\tau_{\text{des}} = 1/k = 1.28 \times 10^4\text{s}$ leads to a total time for secondary drying of 13.93 h. This value shows good agreement with the values found in [2].

### 5. Conclusions

In this paper we have presented a mathematical model describing the secondary drying stage of a freeze-drying process. The model is based in the standard equations for mass transport of gas mixtures in porous medium with an additional term accounting for the production of vapour due to the desorption of bound water. After nondimensionalizing and making some consistent
assumptions, we have reduced the model to a partial differential equation for the evolution of the water vapour concentration which has exact solution. In addition, we have provided with an explicit formula, valid in the limit of small ratio of diffusion to desorption time scales, for the total time of the secondary drying stage. The simplicity of the expression suggests an easy implementation for real time control applications.

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