NUMERICAL AND EXPERIMENTAL MODELING OF LYOPHILIZATION OF LACTOSE AND MANNITOL WATER SOLITIONS IN VIALS

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ABSTRACT

The paper reports on the development of a numerical model for the simulation of a liofilization process in a vial. The lactose and mannitol-water mixtures are used as the working medium in the vial. Experimental analysis of lyofilization dynamics inside a single vial and multiple vials in a laboratory scale lyofilizer is reported, with the main focus on the primary drying phase. The key parameter measured is the temperature distribution inside the main axis of the vial filling. In the numerical model, a 1D vial approximation is used, and governing equations of heat and water vapor transport with moving front between the frozen and the porous part of the filling are solved by a dedicated finited difference method in a time stepping nonlinear iteration procedure. The comparison of numerical and experimental results show, that the developed numerical model is able to accurately capture the transition points from primary to secondary drying, accompanied by accurate capturing of the temperature levels inside the drying material. The main difference in drying of lactose and mannitol solutions lies in the fact, that the lactose shows undercooling effects during the primary drying phase, which is not the case for the mannitol solution. This effect is a consequence of shrinking behavior of lacose porous matrix, loosing contact with vial side and hence decreasing the overall heat input to the vial. The derived numerical model is able to accurately reproduce drying kinetics of mannitol, whereas for drying of lactose an upgrade of the model to axysimmetric geometry would be needed.

NOMENCLATURE

T	$[K]$	temperature
p	$[Pa]$	system, partial pressure
t	$[s]$	time
N	$[kg/m^2s]$	mass flux rate
λ	$[W/mK]$	Thermal conductivity
D	$[m^2/s]$	mass diffusivity

Subscripts

1	porous region
2	frozen region
i	inert gas
v	vapour

INTRODUCTION

Lyophilization is one of the most time and energy consuming separation processes, used in pharmaceutical industry. It is based on drying in form of a direct phase change of a frozen solvent into gaseous state, therefore it is characterised by low temperature levels and extremely low system pressures in order of 10Pa. In order to better understand the scale up process in lyophilization, extensive research have been invested into derivation of advanced theoretical [1] and computational models [2], [3], to name just a few. In the present work, a numerical model, based on the Finite Difference solution of the conjugate heat and mass transfer problem in a one-dimensional approximation of a vial filling, is presented, together with comparison to experimental results. The influence of different physical behaviour of drying solutions, lactose and mannitol water solutions in our case, on drying characteristics is discussed, especially in connection with the numerical solution of the governing equations.

COMPUTATIONAL MODEL

Lyophilization is a heat and mass transfer problem with a moving interface, separating the frozen part from the porous part with no ice. In the porous domain, we have a conjugate heat and mass transfer problem, and in the frozen part the process is driven by heat transfer only. In the frozen part of the solution, heat transfer is governed by conduction process only, so conservation of energy for the frozen part reads as

$$\underbrace{\rho_2 c_{p,2}\frac{\partial T}{\partial t}}_{accumulation} = \underbrace{\lambda_2 \nabla^2 T}_{diffusion} \tag{1}$$

In the porous region heat is governed by convection and conduction, and due to the desorption process there is an additional heat source present,

$$\underbrace{\rho_1 c_{p,1}\frac{\partial T}{\partial t}}_{accumulation} + \underbrace{\vec{\nabla}\cdot\left((\vec{N}_v+\vec{N}_i)c_{p,g}T\right)}_{convection} = \underbrace{\lambda_1\nabla^2 T}_{diffusion} + \underbrace{\Delta H_v \rho_{1,p}\frac{\partial C}{\partial t}}_{desortion} \tag{2}$$

At the sublimation front, separating the frozen from the porous part of the domain, the following comatibility condition must be satisfied:

$$\lambda_2 \frac{\partial T}{\partial n}\bigg|_2 + \underbrace{v_n \rho_2 c_{p,2} T}_{interface\ term} = \lambda_1 \frac{\partial T}{\partial n}\bigg|_1 + \underbrace{v_n \rho_1 c_{p,1} T}_{interface\ term} - \underbrace{\Delta H_s N_{v,n}}_{sublimation} - \underbrace{N_{v,n} c_{p,g} T|_1}_{convection} \tag{3}$$

with v_n the normal velocity of the interface,

$$v_n = -\frac{N_{v,n}}{\rho_2 - \rho_1} \tag{4}$$

Mass conservation is computed only for the porous part, where the inert gas and water vapour are present. For water vapour the conservation of mass reads as

$$\underbrace{\varepsilon \frac{M_v}{R} \frac{\partial}{\partial t}\left(\frac{p_v}{T}\right)}_{accumulation} + \underbrace{\vec{\nabla} \cdot \vec{N}_v}_{convection} = -\underbrace{\rho_{1,p} \frac{\partial C}{\partial t}}_{desorption} \tag{5}$$

and for the inert gas

$$\underbrace{\varepsilon \frac{M_i}{R} \frac{\partial}{\partial t}\left(\frac{p_i}{T}\right)}_{accumulation} + \underbrace{\vec{\nabla} \cdot \vec{N}_i}_{convection} = 0 \tag{6}$$

Mass fluxes of the water vapour and the inert gas are computed as follows:

$$\vec{N}_v = -\frac{M_v}{RT}(k_1 \vec{\nabla} p_v + k_2 p_v (\vec{\nabla} p_v + \vec{\nabla} p_i)) \tag{7}$$

$$\vec{N}_i = -\frac{M_i}{RT}(k_3 \vec{\nabla} p_i + k_4 p_i (\vec{\nabla} p_v + \vec{\nabla} p_i)) \tag{8}$$

where k_1, k_2, k_3 in k_4 represent diffusivities,

$$k_1 = \frac{C_2 D^0_{v,i} K_v}{C_2 D^0_{v,i} + K_{mx}(p_v + p_i)} \tag{9}$$

$$k_3 = \frac{C_2 D^0_{v,i} K_i}{C_2 D^0_{v,i} + K_{mx}(p_v + p_i)} \tag{10}$$

$$k_2 = k_4 = \frac{K_v K_i}{C_2 D^0_{v,i} + K_{mx}(p_v + p_i)} + \frac{C_{01}}{\mu_{mx}} \tag{11}$$

$$K_v = C_1 \sqrt{\frac{RT}{M_v}} \tag{12}$$

$$K_i = C_1 \sqrt{\frac{RT}{M_i}} \tag{13}$$

$$K_{mx} = \frac{p_v}{p_v + p_i} K_v + \frac{p_i}{p_v + p_i} K_i \tag{14}$$

$$D^0_{v,i} = D_{v,i}(p_v + p_i) \tag{15}$$

The presented equations (1) - (6) are discretised by applying the Finite difference method with central differencing scheme, and solved for a simplified, one-dimensional geometrical representation of the vial filling. To obtain the solution, appropriate boundary conditions have to be specified. On top of the computational domain, the following boundary condition is set for the water vapour pressure:

$$p_v^{(n)} = p_v^0 \tag{16}$$

i.e. it is equal to the water partial pressure in the drying chamber. At the sublimation front, the water vapour pressure is equal to the saturation pressure at the temperature of the interface:

$$p_i^{(1)} = p_v^\star. \tag{17}$$

with

$$p_v^\star = 133.32 Pa \cdot \exp(23.9936 - \frac{2.19 \Delta H_v}{T}) \tag{18}$$

When the primary drying stage is terminated, only the porous domain exist, and at the vial bottom the following condition, derived from the fact, that the water vapour flux through the vial bottom has to be zero, is valid:

$$p_v^{(1)} = \frac{p_v^{(2)}}{1 - \frac{k_2 \Delta z}{k_1}(\vec{\nabla} p_v + \vec{\nabla} p_i)}. \tag{19}$$

The desorption process takes place in the already dried region during the drying process on the surface of the porous solid structure. For the mass conservation equation (5) the rate of desorption has to be determined. In our case the first order kinetics model was used,

$$\frac{\partial C}{\partial t} = k_g \left(C^\star - C\right), \tag{20}$$

where k_g represents the mass transfer coefficient and $C^\star$ is the equilibrium water concentration. The equilibrium water concentration can be written in the following form:

$$C^\star = 0.01 \exp(2.3(1.36 - 0.036(T - T_0))) \tag{21}$$

where T_0 is the initial temperature of the frozen material.

Finally, material data has to be specified, collected in Table 1.

Table 1. Comparison of material data

parameter	lactose	mannitol
ε	0.95	0.95
$c_{p,1}\ [J/kgK]$	1650	1715
$c_{p,2}\ [J/kgK]$	1893	2054
$\lambda_{solid}\ [W/mK]$	0.118	0.1
$\lambda_1\ [W/mK]$	0.02686	0.02448
$\lambda_2\ [W/mK]$	2.806	2.661
$\rho_{solid}\ [kg/m^3]$	1589.6	1500
$\rho_{1,p}\ [kg/m^3]$	79.48	75.0
$\rho_2\ [kg/m^3]$	957.3	952.8
$\rho_1\ [kg/m^3]$	263	260

EXPERIMENTAL STUDY

All the experimental runs were made in a laboratory size lyophilizer with three trays. The results, presented in Figure 1, are valid for the edge vials, representing the critical vials on each of the trays, placed on the middle tray of the lyophilizer. Along with lines of drying kinetics a line, showing the temperature of the shelf and the line, showing the temperature of the gaseous mixture inside the chamber, are presented.

The essential difference between the kinetics of drying for lactose and mannitol can be explained from the experimental results of temperaure histories at different positions in the frozen material for the primary drying stage, Figure 1. In the case of lactose solution we have a significant decrease in the temperature of the frozen material, which is especially significant in the final phase of the primary drying, when the sublimation of the remaining ice

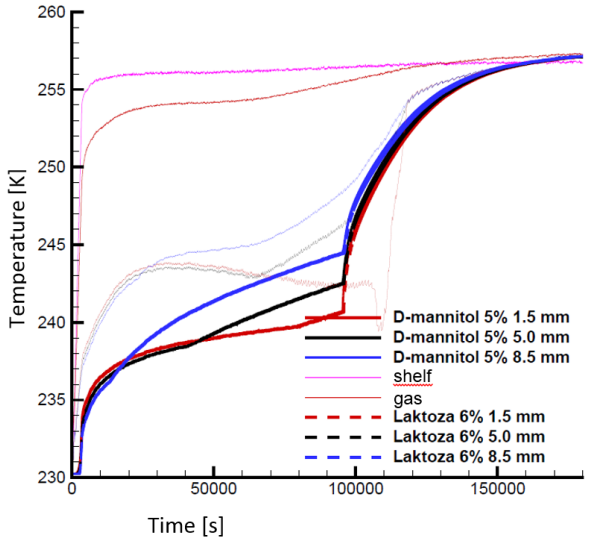

Figure 1. Experimentally determined drying kinetics for the lactose solution (weak solid lines) and mannitol solution (bold solid lines) at different positions in the vial.

at the bottom of the vial is taking place. There is no such decrease in the case of drying of the mannitol solution, where the temperature of the frozen filling gradually increases throughout the duration of the primary stage. The reason for this behavior is most likely a different behavior of the lyophilizate during drying. In the case of lactose, a loss of direct contact of lyophilisate with the sidewall occurs, which reduces the heat input to the frozen material, and consequently the energy supplied for the sublimation process. The sublimation energy is therefore withdrawn from the frozen part itself, leading to decrease in temperature, although at the bottom of the vial there is still a contact with the vial. On the other side, the mannitol solution is characterized by a good adhesion to the walls of the vial, as well in the frozen as in the dried, porous state.

COMPUTATIONAL SETUP

As the lyophilization is a time and space dependent problem, first, grid density and time step sensitivity study was performed. Several grid densities were applied, from 50 to 150 equidistantly placed grid points, with a lower limit of 10 per porous or frozen part. Similarly, the time step value was varied between 1s and 10.000s. After initial runs, a strong sensitivity of the computational results to the time step value for the first 1000s of drying was established, where a value of $\Delta t = 1.0s$ had to be used to obtain numerically stable solutions. For the remaining part of the primary stage and consequently also for the secondary stage, a much greater time step value could be used ($\Delta t = 1000.0s$ was finally selected), also with moderately dense computational grid (50 grid points), as can be seen from comparison of the results of simulation for the interface position movement within the primary stage, Figure **??**. This computational strategy greatly reduced the needed time for obtaining numerical results.

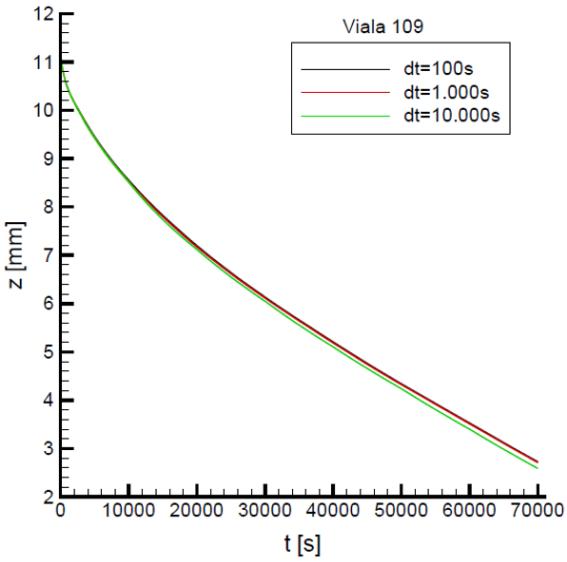

Figure 2. Numerical results for the interface position movement within the primary drying stage.

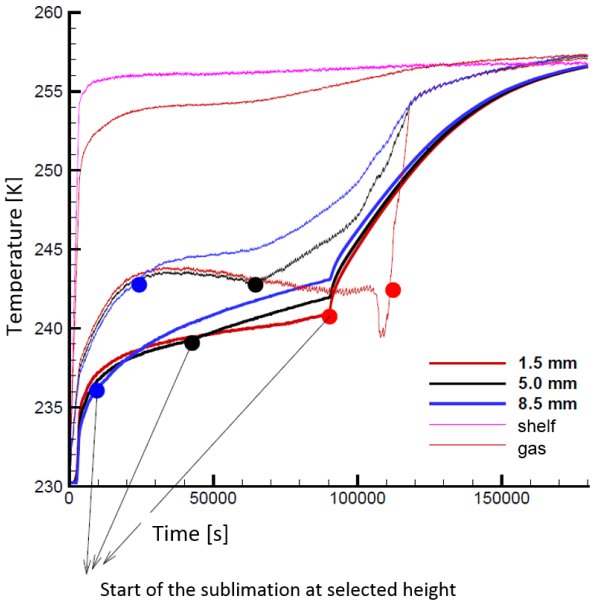

Figure 3. Comparison of temperatures at various positions bewteen the experimental results (thin lines) and computational results (thick lines), for the primary drying stage of lactose solution.

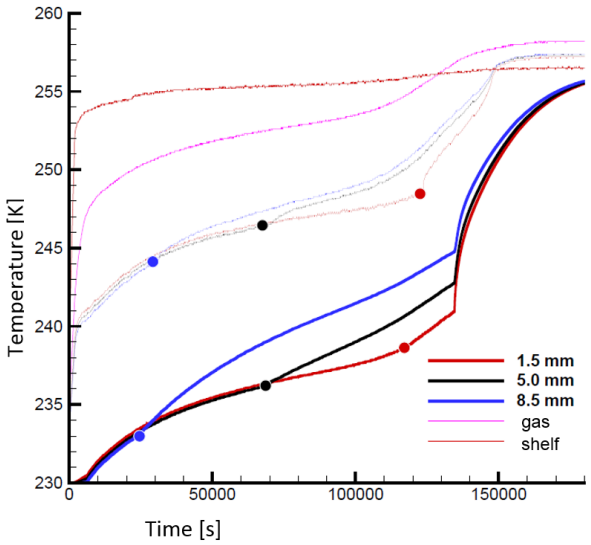

Figure 4. Comparison of temperatures at various positions bewteen the experimental results (thin lines) and computational results (thick lines), for the primary drying stage of mannitol solution.

COMPARISON OF EXPERIMENTAL AND NUMERICAL RESULTS

In Figure 3, a comparison of drying kinetics of lactose solution for the primary drying stage is shown. The temperature levels, obtained by the numerical simulation, are in the range of $5-10K$ lower than the experimental values. With dot points the transition between the primary and secondary drying stage is marked. The transition points in time at various positions in the vial filling differ significantly bewteen the experimental and numerical results. Essentially, the transition in the numerical model occurs earlier then in the experiment. In the case of the mannitol solution, a comparison of drying kinetics for the primary drying stage is shown in Figure 4. Again, the temperature levels, obtained by the numerical simulation, are approximately $10K$ lower than the experimental values. On the other hand, the transition between the primary and secondary drying stage shows a very good agreement, and numerical results give a very good estimate of the transition points.

From a direct comparison of both lyophilization kinetics of the first drying stage one could not draw a sound conclusion on the aplicability of the numerical model. However, there are two phenomena, that help explain the differences in results.

First, the lactose solution exhibits shrinking of its structure, when ice is sublimated, leaving only porous structure behind. The shrinking of the porous structure leads to loosing of a direct contact of the porous structure, but probably also a part of the upper part of the still freezed layer of solution. This has a direct consequence of a decrease of heat input from the vial side walls, so the remaining heat input from the top and the bottom of the vial can not balance the consumed sublimation enthalpy anymore, leading to a decrease in temperature during the primary stage. For the case of mannitol solution, the main difference to the lactose solution is the fact, that it adheres to the walls of the vial, regardless of its state, i.e. in the frozen as well as in the porous state. This leads to a steady increase in the temperature during drying, as is evident from the experimental data. On the side of the numerical simulation, the setup of the simulation remains constant during drying, therefore the descreas in temperature can not, under normal drying conditions, occur numerically.

Second, the lower temperature levels in both cases, in general of $10K$, are a consequence of the construction characteristics of the used laboratory dryer. In theory, lyophilization kinetics should be controlloed by varying the tray temperatures in time. However, in a small scale, laboratory type dryer, with inspection window and a large ratio of side walls area to the area of the plates, the much higher temperature levels in the surroundings of the dryer (i.e. laboratory room) contribute significantly to the increase of the temperature of the drying chamber walls. This can be proved through the analysis of temperature levels for the shelf and gas, shown in Figure 1, as in the secondary stage, the temperature of the gas exceeds the temperature of the shelf. The heat, supplied to the vials, becomes significantly affected by its position, with the critical vials, exposed to additional heat input, placed at the edge and corners of the plates. As in the numerical model the heat supplied to the top and bottom of the 1D model is dependent only on the temperature difference between the plate and vial filling, the result is a lower numerically obtained temperature level inside a vial.

CONCLUSION

In the present work, a comparison of experimental and numerical results of lyophilization of two different pharmaceutical solutions, the lactose and mannitol water solutions, was presented. The derived numerical model for the solution of the coupled heat nad mass transfer problem in the frozen and partially dried porous part was implemented by the specification of the boundary conditions, resulting from the desired specification of the shelf temperature as the main influencing process parameter. The obtained results showed, that in the case of a relatively small size of the used laboratory liophilizer, the presence of an inspection window and the vicinity of relatively warm chamber walls, the temperature conditions inside the dryer are no longer solely dependent on the setting of the shelf temperature, as the experimental results show a relatively constant positive shift in temperature levels of 5-10K. This shift should be taken into account when specifying a device specific boundary conditions for the numerical solution of lyophilization in vials. Additionally, the mechanical behaviour of the partially dry cake should also be taken into consideration, as the shrinking phenomenon directly influences the heat input from the side and bottom walls of the vial, however, this would also mean that the one dimensional approximation of the vial should be upgraded to at least axysymmetrical one.

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