Preserving Proteins and Peptides during Spray Drying of Inhalable Pharmaceutical Powders

Willard R. Foss and Reinhard Vehring
Nektar Therapeutics, San Carlos, California

NEKTAR

ABSTRACT

The thermal history of micron-sized solution droplets containing pharmaceutical proteins and peptides is modeled during evaporation, with the goal of examining the temperature stress on these molecules in a spray drying process. Particular attention is paid to the late stage of drying, where the solids content is high and the droplet temperature approaches that of the surrounding gas.

A numerical model is presented that accounts for the effects of solutes on the evaporation history of individual, spherical droplets. The concentration profiles of the solutes inside the droplet are predicted and the surface concentration is then used to estimate the vapor pressure of the solvent. The evaporation rate and droplet temperature are calculated through solidification of the droplet into a dry particle.

The results show that during spray drying of respirable particles, the active pharmaceutical ingredients are protected by evaporative cooling. At typical dryer conditions, the particles remain near room temperature until the evaporation is nearly complete, at which time the active ingredients are at a sufficiently high concentration to be immobilized and protected in a glassy matrix.

OBJECTIVES

- To assess the temperature stress on active pharmaceutical ingredients during spray-drying.
- To provide numerical analysis of the droplet drying process.
- To compare the numerical model with droplet evaporation rate data as a means of validating the temperature predictions.

INTRODUCTION

Spray drying is an effective means of producing chemically stable protein and peptide powder formulations with particle sizes in the respirable size range for pulmonary delivery. The proteins and peptides in these dry powder formulations are immobilized in an amorphous glassy state, extending their resistance to degradation from typically a few hours in solution to several years in the dry form.

Droplet evaporation and spray drying literature have suggested that the presence of a solute in an evaporating droplet reduces the evaporation rate and increases the droplet temperature, with a possible detrimental effect on the pharmaceutically active ingredient [1]. Studies on the evaporation behavior of solution droplets have mostly been restricted to conditions that are atypical of the spray-drying of powders intended for pulmonary delivery. Initial droplet sizes were large and so the resultant dry particle sizes were orders of magnitude larger than respirable particles. Temperatures were typically measured by suspending droplets on a thermocouple junction, significantly altering the heat transfer characteristics.

This paper studies the evaporation behavior of spray-dried, micron-sized droplets, with particular attention to the later stages of drying, where the solids content is high and the droplet temperature approaches that of the surrounding hot gas. A numerical model is developed to predict droplet temperatures in solution droplets, accounting for the significant changes in properties as it dries into a solid particle. The numerical results of the evaporation rate is compared to data to confirm the thermal analysis.

METHODOLGY

The steady-state temperature of evaporating pure water droplets is considered first, as an approximation of droplet evaporation temperature at the early stage of drying. The steady-state droplet temperature is found from [2]

$$\frac{1-w_{water,\infty}}{1-w_{water,surface}\left(T_{droplet}\right)}=\left[\frac{\overline{C}_{p,surface}}{\Delta\overline{H}_{vap}}\left(T_{\infty}-T_{droplet}\right)+1\right]^{\mathbf{Le}}$$

where the Lewis number, **Le**, is

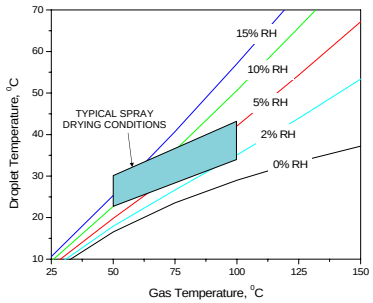
$$\mathbf{Le}=\frac{k}{\rho_{gas}D_{water,gas}\overline{C}_{p,surface}}$$

and the weight fraction of water vapor at the droplet surface is found from the vapor pressure

$$w_{water,surface}=\left\{\frac{M_{air}}{M_{water}}\left[\frac{P}{P_{water}^{sat}\left(T_{droplet}\right)}-1\right]+1\right\}^{-1}$$

The steady-state temperatures of evaporating pure water droplets are plotted as a function of the gas temperature at various humidites in Figure 1. The results show that for conditions typical of pharmaceutical spray drying, steady-state droplet temperatures remain below about 40 °C.

Figure 1. Steady-state Temperatures of Evaporating Water Droplets are Below 40 °C in Typical Pharmaceutical Spray Drying Processes



The presence of a solute is expected to change the evaporation behavior. This is of special concern for droplets containing protein and peptides, where these solutes tend to accumulate near the droplet surface due to their low diffusivity. This lowers the droplet vapor pressure and evaporation rate, thus raising the droplet temperature.

To investigate the thermal conditions inside evaporating droplets containing solutes, additional equations governing the diffusion of the solute inside the droplet are required. They must be solved simultaneously with the thermal energy balances to predict the transient thermal behavior.

NUMERICAL MODEL

A numerical model was developed that predicts the radial distribution of all substances and the temperature in a multicomponent droplet as it evaporates through time. Both the liquid and the gas phases are modeled. Spherical symmetry is assumed, since convective transport is negligible for micron-sized droplets. The model allows for variable material properties and a moving gas-droplet interface. The governing equations are given below:

Weight fraction of species i (w_i) in droplet and gas:

$$\rho\frac{\partial w_i}{\partial t}+\rho v\frac{\partial w_i}{\partial r}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\rho D_i\frac{\partial w_i}{\partial r}\right)\quad\text{and}\quad\sum_{i=1}^{n}w_i=1$$

Weight fractions at gas/droplet interface:

$$\left[\rho D_i\frac{\partial w_i}{\partial r}+\rho w_i\left(\frac{\partial R}{\partial t}-v\right)\right]_R^{(droplet)}=\left[\rho D_i\frac{\partial w_i}{\partial r}+\rho w_i\left(\frac{\partial R}{\partial t}-v\right)\right]_R^{(gas)}$$

and $a_i(w_i)\big|_R^{(droplet)}=\dfrac{p_i}{p_i^{sat}}\Big|_R^{(gas)}$ where $a_i(w_i)$ is the activity of species i

Droplet size (R):

$$\frac{\partial R}{\partial t}=\left[\frac{\left(\rho D_i\frac{\partial w_i}{\partial r}-\rho R w_i v\right)^{(gas)}-\left(\rho D_i\frac{\partial w_i}{\partial r}-\rho R w_i v\right)^{(droplet)}}{\left(\rho R w_i\right)^{(gas)}-\left(\rho R w_i\right)^{(droplet)}}\right]_R$$

Radial velocity (v) in droplet and gas

$$v=-\frac{1}{r^2\rho}\int_0^{\xi}\xi^2\frac{\partial\rho}{\partial t}d\xi$$

Gas temperature (T):

$$\rho\overline{C}_p\frac{\partial T}{\partial t}+\rho\overline{C}_p v\frac{\partial T}{\partial r}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2k\frac{\partial T}{\partial r}\right)+\sum_{i=1}^{n}\left(\overline{H}_i\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\rho D_i\frac{\partial w_i}{\partial r}\right)\right)$$

Droplet temperature ($T_{droplet}$):

$$\frac{R\rho\overline{C}_p}{3}\frac{\partial T_{droplet}}{\partial t}=\left[k\frac{\partial T}{\partial r}+\rho\sum_{i=1}^{n}\overline{H}_i D_i\frac{\partial w_i}{\partial r}+\rho\overline{H}\left(\frac{\partial R}{\partial t}-v\right)\right]_R^{(gas)}+\rho^{(droplet)}\Delta\overline{H}_{vap}\frac{\partial R}{\partial t}$$

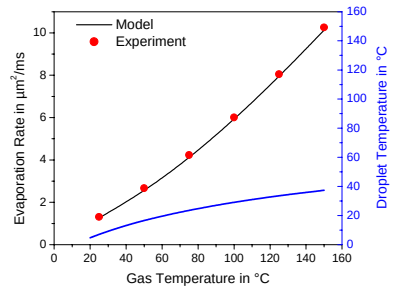
The balances are integrated through time using the implicit backwards-Euler technique. Since the evaporation rate, the gas velocity, the droplet temperature and the solute composition at the droplet surface are highly coupled, these values are iterated until convergence at each time step. In this way, the solution remains accurate through the end of the drying process, as verified by a mass balance on the solutes inside the droplet.

RESULTS

The model was validated by comparison of the calculated evaporation rates of pure water droplets with experimental data, as demonstrated in Figure 2. Excellent agreement between the model and data is obtained for air temperatures ranging from 25 to 150 °C. Details of the experiments are described in poster 3PA2.

In the same Figure, the steady state droplet temperatures predicted by the numerical model are plotted, demonstrating good agreement with the temperatures predicted using analytical solution to the steady-state model.

Figure 2. Numerical Model Agrees Well with Experimental Results. Droplet Temperatures Can be Derived from the Model.

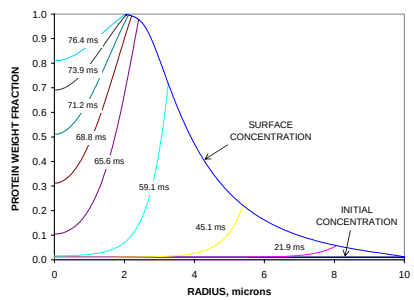


Applying the numerical model with a protein solute, the concentration profiles of the protein are calculated at various times throughout the evaporation process. Typical radial profiles are shown in Figure 3. The profiles are steep due to the low diffusivity of the large protein molecules as compared to the recession rate of the droplet interface.

For much of the evaporation, the protein concentration at the droplet surface remains relatively low, resulting in a negligible change in the evaporation rate. The droplet temperature also remains low - near the steady-state temperature – for much of the evaporation, as demonstrated in Figure 4.

Towards the end of the evaporation, as the droplet begins to solidify into a particle, the presence of the protein at the surface draws down the vapor pressure and the evaporation slows (see Figure 4 of poster 3PA2). The droplet temperature rises to the gas temperature in the last few milliseconds of drying, as shown in Figure 4.

Figure 3. Concentration Profiles of a Protein Solute at Several Time Points during the Evaporation of an Aqueous Solution Droplet

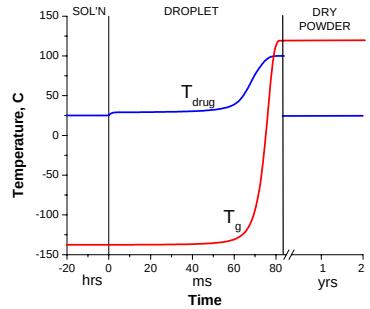


The thermal stress on protein can be estimated from the glass transition temperature (T_g) of the mixture. Proteins are stabilized from chemical degradation when their glass transition temperature is well above the ambient temperature. The T_g of the protein-water mixture is predicted using the Gordon-Taylor equation [3]

$$T_{g,mixture}=\frac{w_{solute}T_{g,solute}+k_{GT}w_{water}T_{g,water}}{w_{solute}+k_{GT}w_{water}}$$

The T_g of the protein-water mixture is plotted in Figure 4, as calculated from the droplet temperatures and protein concentrations returned by the numerical model. The results demonstrate that the protein is in an environment no less stressful than the feedstock solution during the initial stage of drying. In the late stage, as the particle temperature increases, the protein is actually stabilized by the loss of water. By the time the particle is dry, the T_g of the particle is higher than the gas temperature, and remains stable for long storage periods.

Figure 4. Temperature Stress on the Active during Production and Storage



CONCLUSIONS

- During the spray drying, the active pharmaceutical ingredients are protected from high temperature by evaporative cooling.
- When almost dry, the particle temperature will reach the drying gas temperature for a few milliseconds but the proteins or peptides are by then immobilized and protected in an amorphous phase.

Spray-drying subjects proteins or peptides to only minor temperature stress, which generally does not cause significant degradation. It is a well suited manufacturing process for temperature sensitive active pharmaceutical ingredients.

REFERENCES

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