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Modeling the Secondary Drying Stage of Freeze Drying: Development and Validation of an Excel-based Model

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ABSTRACT

Although several mathematical models of primary drying have been developed over the years, with significant impact on the efficiency of process design, models of secondary drying have been confined to highly complex models. The simple-to-use Excel-based model developed here is, in essence, a series of steady state calculations of heat and mass transfer in the 2 halves of the dry layer where drying time is divided into a large number of time steps, where in each time step steady state conditions prevail. Water desorption isotherm and mass transfer coefficient data are required. We use the Excel "Solver" to estimate the parameters that define the mass transfer coefficient by minimizing the deviations in water content between calculation and a calibration drying experiment. This tool allows the user to input the parameters specific to the product, process, container, and equipment. Temporal variations in average moisture contents and product temperatures are outputs and are compared with experiment. We observe good agreement between experiments and calculations, generally well within experimental error, for sucrose at various concentrations, temperatures, and ice nucleation temperatures. We conclude that this model can serve as an important process development tool for process design and manufacturing problem-solving.

Introduction

Freeze drying is increasingly being employed to manufacture the final dosage form for a variety of injectable products, including therapeutic proteins and vaccines. Although the freeze-drying process is complex, with many interacting variables, the basic physics is relatively well understood, which means that modeling the process can be a very useful endeavor, particularly for the drying stages. Modeling freeze drying has a long history[1-7] with some of the approaches being very rigorous approaches based on solving coupled differential equations governing heat and mass transfer, both in primary drying and in secondary drying.[4-6] However, very simple pseudo steady state models for primary drying have also proved very useful.[8] Primary drying, or the ice sublimation stage, is normally the longest phase of the process, and it is during primary drying that improper heat input can either result in exceeding the collapse temperature and suffering loss of product elegance or lead to unnecessarily long processes. Thus, primary drying is usually the target for process optimization, and simple steady state models can be very useful in such exercises. Examples of applications include development of a design space for primary drying[9,10] as well as estimation of the impact of variability in the process on product temperature history and product quality.[8] These applications use an Excel-based version of the original algorithm that is often termed the "LyoCalculator."[8] Here, the software (Excel) is generally available, the input is quick, and the product temperature history and drying times are evaluated essentially instantly with high accuracy based on comparisons with experimental data[8] or the more rigorous non−steady state differential equation−based models.[5] Experimental or estimated values of the vial heat transfer coefficient, specific to the vials used, and values of the mass transfer coefficient for vapor flow through the dry layer, specific to the product, are needed input parameters.

Secondary drying is the stage of the process that begins in a local region of the product once ice sublimes from that region, meaning some secondary drying occurs during the ice sublimation or primary drying stage. For example, with sucrose, the water content at the top of the cake is only about half the water content at the bottom where the ice was last present. In spite of this partial secondary drying during primary drying, the usual terminology defines the start of the secondary drying stage for a given vial as the

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time when all ice has been sublimed from that vial. However, for a batch, this definition is somewhat ambiguous because not all vials finish primary drying at the same time, and therefore enter the "secondary drying stage" at the same time. In most discussions, and in the context of this research, we define the start of secondary drying as the average start of secondary drying for the vials in the batch as a whole, meaning the end of primary drying for the average vial in the batch. The non−steady state differential equation−based models consider both primary drying and secondary drying, including the secondary drying that occurs while ice is still in the vial.[5] This rigor is compromised, however, by the fact that not all vials finish primary drying at the same time, so comparison with experiment is not entirely straightforward. In this research, we seek to develop a highly simplified model for secondary drying, which runs on Excel as does the LyoCalculator that is much easier to use than the rigorous models but still gives useful prediction for the impact of freezing variations and shelf temperature variations on the time course of residual water.

The Excel-based model that we develop makes a number of simplifying approximations that are described later in this document. Two approximations are most critical. First, we consider the dry layer to be a composite of 2 homogenous regions, top and bottom. This is a crude approximation to the actual situation of variable water content from top to bottom at the end of primary drying. Secondly, the model is not based on solving coupled heat and mass transfer differential equations, but is in essence a series of steady state calculations of heat and mass transfer in the 2 halves of the dry layer where the time of drying is divided into a large number of time steps, Δt, where in each time step steady state conditions prevail. The assumptions are justified by the good agreement between calculations and experiment as well as the essentially exact agreement between the Excel-based model and the more rigorous differential equation−based model (Passage II).[5]

Applications would include optimizing the secondary drying process, as well as investigating the impact of formulation and freezing process on secondary drying. Such calculations would be particularly useful in cases where the optimal residual water content was "intermediate" between "dry" and "wet." However, as with the more rigorous approach (Passage II),[5] several key input parameters need to be estimated or evaluated experimentally. The 2 most important are the secondary drying mass transfer coefficient and the water desorption isotherm. The water desorption isotherm may be evaluated as a function of temperature and water activity by employing a "moisture balance," and the mass transfer coefficient for secondary drying needs a detailed study of residual moisture during secondary drying, usually using a "sample thief" and traditional residual moisture assay.

Materials and Methods

Crystalline sucrose was obtained from Sigma-Aldrich Company (St. Louis, MO). Vials used for freeze drying were 20-mL tubing vials from West Pharmaceutical Company (Lionville, NJ) with 20-mm finish Daikyo Flurotec® stoppers (West Pharmaceutical Company) designed for freeze drying.

Freeze Drying

Freeze-drying experiments were performed in a laboratory-scale freeze dryer (Lyostar II, SP Scientific, Stone Ridge, NY), using sucrose at different concentrations (5% w/w, 10% w/w, and 15% w/w) at several controlled ice nucleation temperatures (−5°C, −7°C, and −10°C) and secondary drying temperatures (25°C, 40°C, and 50°C) with conditions as shown in Table 1. A chamber door with a sampling thief was used to periodically remove samples at different times during secondary drying for residual water assay by Karl Fischer analysis. Aqueous solution of the solute was prepared and filtered through a 0.22-μm membrane filter. A total of 160 vials were filled with appropriate fill volume (5 mL for 5% w/w sucrose; 3 mL for 10% w/w and 15% w/w sucrose) and loaded onto the lowermost temperature-controlled shelf of the freeze dryer. The height of the shelf was adjusted to facilitate easy removal of vials during primary and secondary drying stages using the sample thief. Product temperature was measured using 30-gauge copper-constantan (type T) thermocouples (Omega Engineering, Inc., Stamford, CT) with a resolution of ±0.1°C. The thermocouples were calibrated using ice-water slush and those within ±0.5°C were used in the experiments. Thermocouples were placed in the bottom center of vials in the center of the vial array. The arrangement of thermocouple vials is shown in Figure 1. A Pirani/capacitance manometer comparative pressure measurement was employed to determine the end of primary drying for essentially all vials. Freeze drying was performed without collapse.

Table 1
Solute Concentration, and Ice Nucleation and Secondary Drying Temperatures for Freeze-drying Experiments

Sucrose Concentration (w/v)	Controlled Ice Nucleation Temperatures (°C)	Secondary Drying Temperatures (°C)
5%	−5°C	25°C
5%	−5°C	40°C
5%	−5°C	50°C
5%	−7°C	40°C
5%	−10°C	40°C
10%	−5°C	40°C
15%	−5°C	40°C

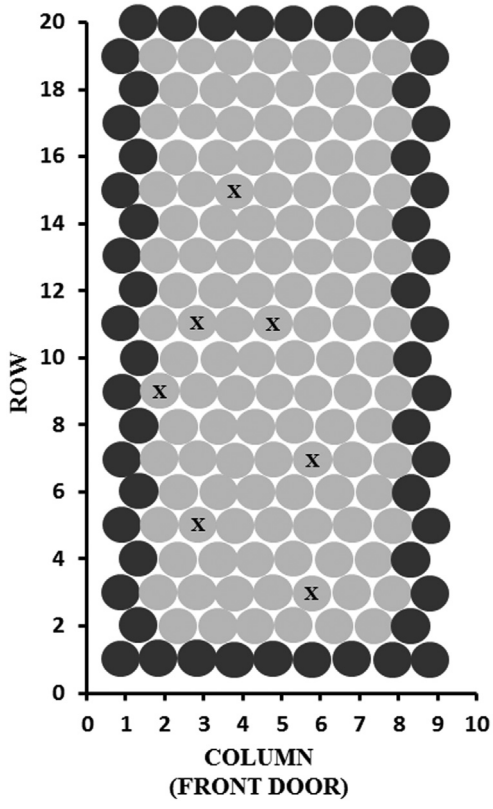

Figure 1. Representation of the vial map for the freeze-drying experiments. The outermost rows of vials (dark circles) represent edge vials and "X" represents thermocouple vials.