BioPharma Solutions

white paper edition

Process Development for Lyophilized Products

Baxter

Process Development for Lyophilized Products

Introduction

A common approach to process development for lyophilized products is to thermally characterize the solution formulation to determine the critical product temperature that should not be exceeded during primary drying. This is conducted using differential scanning calorimetry (DSC) and freeze-dry microscopy (FDM). The approach to development of the lyophilization cycle is often less precise. Some scientists may choose intentionally conservative conditions to avoid failure of the product during primary drying. This can lead to long processing times that are inefficient for routine production. Another approach is to choose the shelf temperature and chamber pressure for primary drying and then conduct a few experiments that utilize temperatures and pressures near those set points to propose an operating range. The challenge with both approaches is that there is no way to know if the process is operating near the failure point for the product. This can be catastrophic when transferring the process to full-scale.

Baxter approaches formulation and process development with the intention of identifying the failure points for the product. Knowing where the product fails enables the development scientist to design a formulation and process with meaningful ranges supported by data. This document describes the approach to process development for lyophilized products conducted at Baxter.

Lyophilization

Lyophilization (freeze-drying) is the process of removing water from temperature sensitive products by the sublimation of ice. The process typically involves three main steps (Table I).

Steps	Description
Thermal Treatment	The product is cooled to around -40°C to freeze. Annealing at a higher temperature may be used to encourage crystallization.
Primary Drying	Shelf temperature and chamber pressure are manipulated to control product temperature and remove ice.
Secondary Drying	Shelf temperature is increased to remove unfrozen water associated with the product.

Table I. List of the Main Steps During Freeze-Drying

The step that is least controlled during the process is thermal treatment or freezing. The shelf temperature is decreased at a controlled rate during this step but, for conventional freeze-dryers, there is no control over ice nucleation. Thermal characterization studies are conducted to determine the behavior of the product at low temperature and the data can help determine if an annealing step is needed.

The bulk of process development involves investigating the appropriate conditions for primary and secondary drying.

Thermal Characterization

Thermal characterization involves investigating the behavior of a solution formulation at low

temperature or of a dried solid at high temperature. The instruments that are typically used are DSC and FDM. DSC utilizes approximately 10 µL of solution filled into an aluminum pan and hermetically sealed. The sample is cooled to around -40°C to -50°C and the temperature is slowly increased back to above 0°C. The instrument senses changes in heat flow in the sample that may be associated with an exothermic event such as crystallization, an endothermic event such as melting, or glass transition of the maximally concentrated frozen solute (Tg'). These data provide an idea of the changes that can occur in the formulation and the temperatures at which they may occur.

FDM utilizes 3 µL of the formulation placed between a quartz slide and a glass coverslip. The sample is placed in a freeze-dry stage attached to a polarized light microscope. The experiment is conducted by cooling the sample to around -40°C, initiating a vacuum, and waiting until an acceptable dry layer is observed (Figure 1).

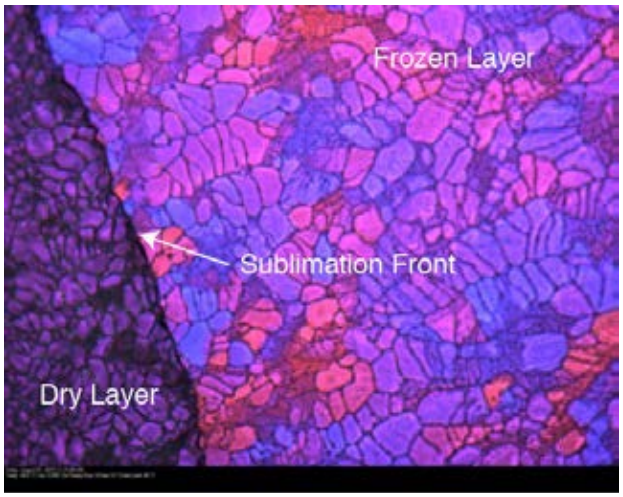

Figure 1. Photomicrograph of a Mannitol / Sucrose Formulation Showing an Acceptable Dry Layer at -40°C and 100 mTorr.

The temperature of the sample is slowly increased until changes in the appearance are observed. The temperature at which changes are first observed is recorded and the temperature at which complete failure occurs is documented. It is especially important to conduct the experiment to complete failure for formulations containing mixtures of amorphous and crystalline components (Figures 2 and 3). The failure point observed in the FDM experiment more closely matches with the failure point observed during primary drying experiments.

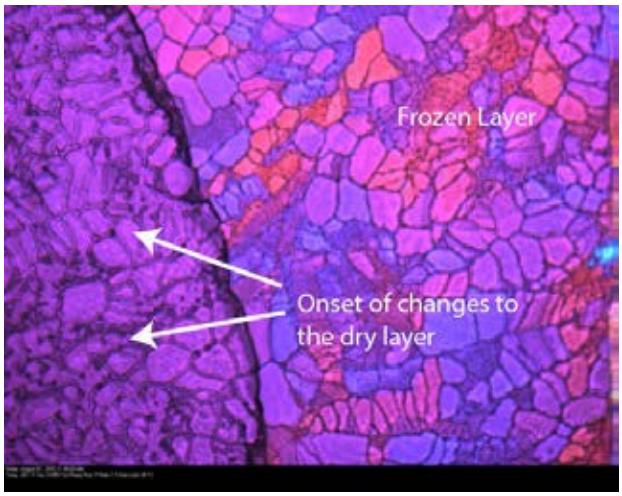

Figure 2. Photomicrograph of a Mannitol / Sucrose Formulation Showing the Onset of Physical Changes to the Appearance of the Dry Layer at -28°C and 100 mTorr.

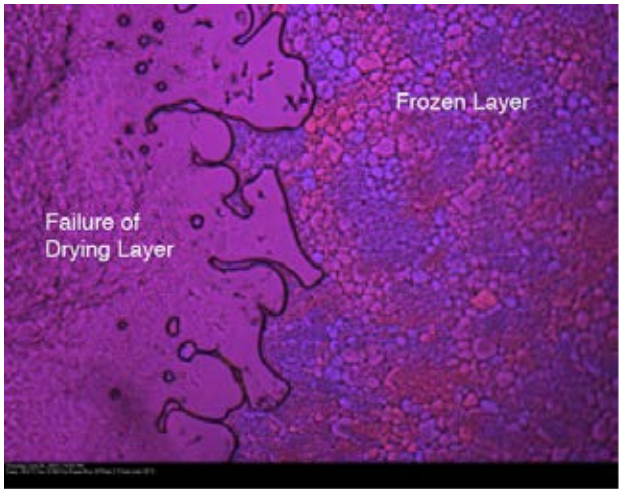

Figure 3. Photomicrograph of a Mannitol / Sucrose Formulation Showing Failure of the Dry Layer (Collapse) at -20°C and 100 mTorr.

The failure point for some formulations may remain quite low. This is particularly true for amorphous sugars such as sucrose mixed with salts or certain buffers such as tris. The dry layer can easily be obtained at -39°C and 100 mTorr for a sucrose / tris formulation (Figure 4) but failure is observed at the relatively low temperature of -37°C (Figure 5).

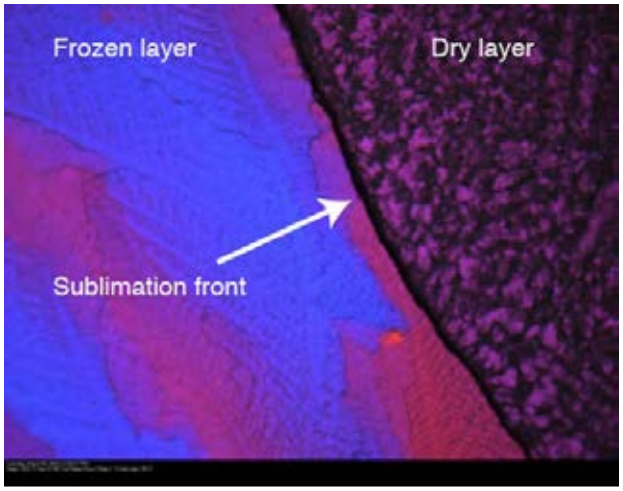

Figure 4. Photomicrograph of a Sucrose / Tris Formulation Showing an Acceptable Dry Layer at -39°C and 100 mTorr.

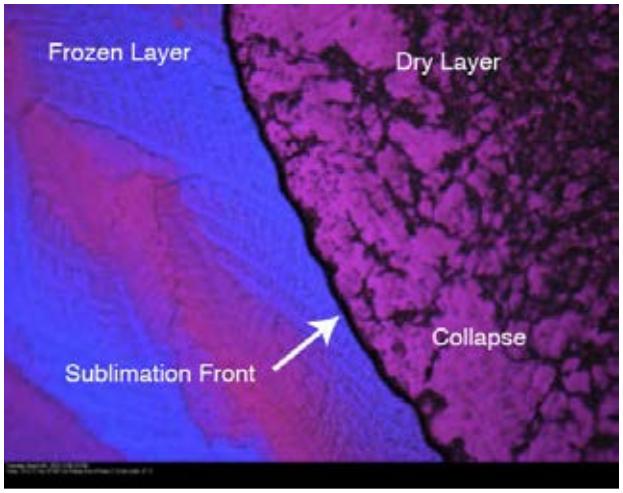

Figure 5. Photomicrograph of a Sucrose / Tris Formulation Showing Failure (Collapse) of the Dry Layer at -37°C and 100 mTorr.

The data obtained during thermal analyses are used to develop initial testing conditions for primary drying experiments.

Process Development

Primary Drying

Thermal characterization data are used to identify the maximum acceptable product temperature during primary drying. The shelf temperature and chamber pressure are manipulated during primary drying to ensure the product temperature is below the failure point for the product. The goal is to design the process to operate at the highest possible product temperature. Operating at the highest acceptable product temperature ensures the highest possible vapor pressure of ice which improves the efficiency of the process. One method of identifying these conditions and of determining the effect of the processing conditions on the appearance of the product is by conducting failure point studies during primary drying. The studies involve completing experiments using aggressive shelf temperatures during primary drying and examining the effect of the conditions on the product temperature and the appearance of the dried solid.

A formulation containing mannitol and sucrose can be dried using shelf temperatures as high as +30°C with 100 mTorr chamber pressure without observing changes to the appearance of the dried solid during primary drying (Figure 6). A slight change in the appearance was observed when using a shelf temperature of +40°C.

Figure 6. Photographs of Mannitol / Sucrose Formulations Lyophilized Using a Shelf Temperature of +30C (above) and +40C (below) with Chamber Pressure of 100 mTorr.

The product temperature remained between approximately -22°C and -23°C during primary drying using a shelf temperature of +30°C (Figure 7). The product temperature increased to approximately -16°C when using a shelf temperature of +40°C. The data match well with the FDM data that showed complete failure when the product temperature reached -20°C, but the structure of the dried solid was not completely lost when drying in the vial using aggressive conditions.

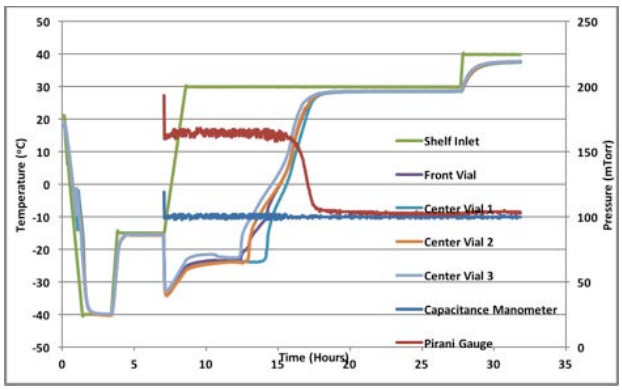

Figure 7. In-Process Lyophilization Cycle Data for the Mannitol / Sucrose Formulation When Using a Shelf Temperature of +30C and 100 mTorr Chamber Pressure During Primary Drying.

Loss of structure was apparent when the product temperature of the sucrose / tris formulation approached -37°C (Figure 8).

Figure 8. Appearance of a Sucrose / Tris Formulation When the Product Temperature Reached the Collapse Temperature of -37C During Primary Drying.

The data demonstrate that formulations containing both an amorphous sugar and a crystallizing sugar are more forgiving during primary drying and can be dried under aggressive conditions as long as the equipment is capable of supporting the high sublimation rates.

Careful consideration of formulation components is required to prevent creating a formulation with a low critical product temperature. Formulations with low critical product temperatures will require operating using low shelf temperatures and chamber pressures during primary drying. This increases the primary drying time and may result in primary drying conditions that maintain the product temperature near the failure point. This leaves little room for excursions during the process.

Secondary Drying

All of the ice has been removed at the end of primary drying and it is now safe to increase the temperature of the product to remove the unfrozen water associated with the dried solid. It is common to conduct secondary drying using shelf temperatures between +30°C and +50°C to provide sufficient energy to reduce the residual moisture. The shelf temperature is often approached conservatively by increasing the temperature using a rate of approximately 0.5°C/min. However, the effect of residual moisture on the stability of the dried solid must first be determined. The approach at Baxter is to collect samples at the end of primary drying and after incremental increases in the shelf temperature using a sample thief connected to the door of the lyophilizer (Figure 9).

Figure 9. Collection of Samples from the Lyophilizer Using a Thief Sampler.

The samples are tested for residual moisture using infrared spectroscopy, and a calibration curve is developed by testing the same samples using Karl Fischer analysis. This study also provides information on the shelf temperatures at which specific residual moisture levels can be obtained for the product (Figure 10).

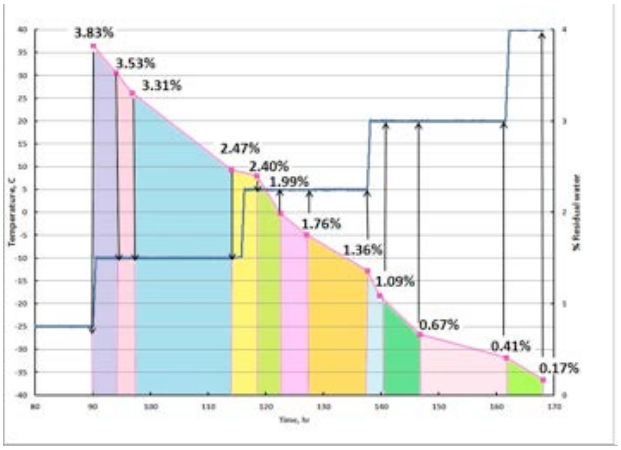

Figure 10. The Effect of Shelf Temperature on the Level of Residual Moisture.

A second experiment is then conducted to obtain samples prepared with high, medium, and low levels of residual moisture. The samples are placed on accelerated stability at 40°C / 75% RH and sometimes at 50°C. Samples are examined over 4 months using analytical methods for the specific product, thermally characterized using DSC, and examined for changes in crystallinity over time using x-ray powder diffraction. The data are used to establish the maximum acceptable level of residual moisture for the product.

Summary

Identifying where and when a product fails is a necessary part of process development. Failure point studies are incorporated in the development of lyophilization processes at Baxter. They incorporate the same studies that are typically used for development but include aggressive pursuit of the conditions that lead to failure. The product temperature at which complete failure is observed during freeze dry microscopy experiments often matches well with the failure point identified during primary drying. The data also provides the range of product temperatures that are acceptable during primary drying.

Secondary drying studies are conducted to determine the maximum acceptable level of residual moisture for the product. Samples are removed from the end of primary drying and throughout secondary drying to obtain samples with specific levels of residual moisture. The samples are placed on accelerated stability and are studied for the effect of residual moisture on data from stability indicating methods.

Baxter Healthcare Corporation
One Baxter Parkway, DF6-2E
Deerfield, Illinois, USA 60015
United States: 1-800-4-BAXTER International: 1-847-948-4770
Email: biopharmasolutions@baxter.com
www.baxterbiopharmasolutions.com