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Modeling Freezing & Thawing Temperature Profiles in Celsius® FFT 75 L Containers With the Celsius® S³ Benchtop System

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Abstract

The Celsius® S³ benchtop system is a laboratory instrument designed to simulate production-scale freezing and thawing processes at lab scale (30 mL – 100 mL). The benchtop system can accommodate up to ten 30 mL or 100 mL single-use bags and features a flexible hardware configuration capable of generating a wide variety of controlled temperature profiles.

In this study, the Celsius® S³ benchtop system was used to simulate the freezing and thawing behavior of the production-scale Celsius® FFT Freezer, with scale-down recipes developed to match typical freeze and thaw temperature profiles at production scale. These profiles offer end users an efficient tool to investigate bulk drug substance stability under different freezing and thawing conditions, thereby supporting formulation development, stability assessment, and production-scale process selection without using large quantities of drug substance.

Introduction

The Celsius® S³ (scale-up, scale-down, stability) benchtop system enables the execution of freeze and thaw process development and stability studies using low product volumes. Freezing and thawing runs are performed with as little as 30 mL of product while reproducing the thermal performance observed at production scale.

The scalability concept of the Celsius® S³ benchtop system is based on the use of identical product-contact materials of construction and equivalent freezing kinematics at both lab and production scales. Since biopharmaceutical formulations vary in robustness against freeze-thaw stresses, it is best practice to conduct lab-scale studies to confirm the impact of freezing and thawing operations on drug substances prior to confirming process and formulation conditions.

Sartorius offers the Celsius® FFT Platform as a unique, scalable, end-to-end solution for handling frozen bulk drug substances in large volumes. Using robust single-use Celsius® FFT containers in a palletized format, the platform has the capacity to process up to 300 L of drug substance. The equipment offering consists of the Celsius® FFT Freezer (blast freezer), AliquoT® Pallet (for pallet filling and draining), Celsius® FFT Lift (for pallet handling), Celsius® FFT Mixer (for pallet content homogenization), and a shipping solution for safely handling palletized frozen containers.

Single-use Celsius® FFT containers are sterile, pre-assembled, and ready to use for freezing and thawing biopharmaceutical drug substances. Celsius® FFT 75 L containers can be used with a variety of cold rooms, walk-in freezers, and other freezing systems, but are specifically designed for the Celsius® FFT Freezer. This blast freezer offers consistent freezing and thawing performance for up to four palletized Celsius® FFT 75 L containers at a time. Process consistency is achieved by design, with carefully controlled airflow distribution, state-of-the-art refrigeration technology, and an agitation system to reduce thawing time.

Figure 1: Celsius® platform components used in this study



Palletized Celsius® FFT 75 L | Celsius® S³ benchtop system | Celsius® FFT Freezer

In this study, Celsius® S³ benchtop system profiles were developed and tested to reproduce the performance obtained at production scale with Celsius® FFT 75 L containers. These profiles were designed to match temperature trends at the last point to freeze (LPTF) and last point to thaw (LPTT) at both scales. This scaling approach is well documented in the industry and supported by the following principles: (1) active pharmaceutical ingredients are exposed to ice–liquid interfacial stresses for equivalent periods of time across scales; (2) solute migration (e.g., cryoconcentration) evolves under similar dynamics across scales; (3) equivalent local thermal histories at the LPTF | LPTT ensure similar phase-change kinetics and ice formation behavior across scales.

Materials and Methods

Selecting the temperature profile for the Celsius® FFT 75 L container

Representative production runs in the Celsius® FFT 75 L container were selected from in-house data generated during development of the Celsius® FFT platform. Results from these runs were averaged to generate a golden batch for freezing and thawing performance. The outputs were temperature profiles matching LPTF and LPTT behavior for four Celsius® FFT 75 L containers processed in a Celsius® FFT Freezer operating at the maximum achievable heat transfer rate. All golden batch data were generated using a model solution of 10 mM sodium acetate, 9% (w/v) sucrose, pH 5.2, 0.01% (w/v) Polysorbate 80 (PS80).

Freezing temperature profile

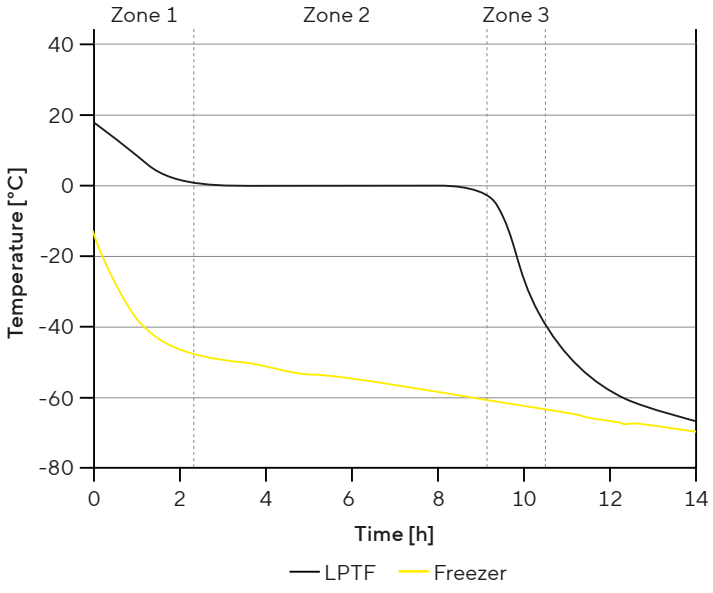
Details of the production-scale freezing process conditions to be reproduced with the Celsius® S³ benchtop system are described in Table 1.

The following three process parameters from the golden batch freezing curve (Figure 2) were considered in the development of the temperature profiles in the Celsius® S³ benchtop system:

- Time to reach the freezing point, defined as the time required for the LPTF temperature to reach 3 °C (Figure 2, zone 1)
- Time to remove the latent heat (i.e., nominal freeze time), defined as the time required for the LPTF temperature to decrease from +3 °C to -5 °C (Figure 2, zone 2)
- Time to complete freeze, defined as the time required for the LPTF temperature to reach -40 °C (Figure 2, zone 3)

The LPTF monitoring location in the Celsius® FFT 75 L container is near the center of mass of the contents.

Figure 2: Golden batch freezing temperature profile for the Celsius® FFT 75 L container



Thawing temperature profile

Details of the production-scale thawing process conditions to be reproduced with the Celsius® S³ benchtop system are described in Table 1.

The following three process parameters from a typical thawing curve were taken into account to develop the temperature profiles (Figure 3) in the Celsius® S³ benchtop system:

- Time to reach the melting point, defined as the time required for the LPTT to reach around 8 °C (Figure 3, zone 1)
- Time at the melting point, defined as the time required for the LPTT temperature to increase from 8 °C to 12 °C (Figure 3, zone 2)
- Time to complete thaw, defined as the time required for the LPTT temperature to reach 18 °C, with no ice remaining (Figure 3, zone 3)

The LPTT monitoring location in the Celsius® FFT 75 L container is in a zone on the upper bag surface where the ice block moves due to the agitation feature of the Celsius® FFT Freezer. This allows for the most consistent tracking of thaw progression. One consequence of the monitoring location is that the reported temperature is the average of the ice temperature, liquid temperature, and environment temperature, with a plateau around 10 °C.

Figure 3: Golden batch thawing temperature profile for the Celsius® FFT 75 L container

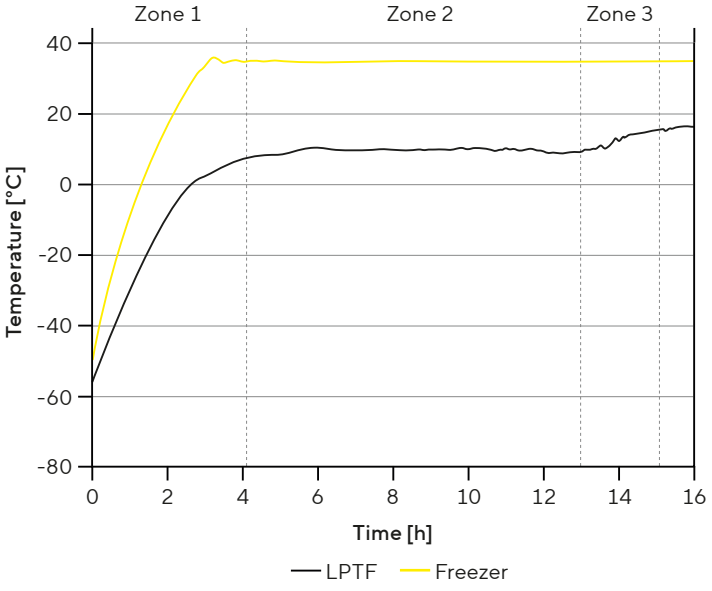


Table 1: Freezing and thawing conditions at production scale selected for scale-down operation

Operation	Celsius® FFT Freezer setpoint	Loading pattern	Freezing | thawing parameter duration
Freezing	-70 °C	Four Celsius® FFT 75 L containers, each filled at the maximum working volume of 75 L (300 L total)	▪ Time to freezing point: ~ 2 h (Zone 1) ▪ Nominal freeze time: ~ 6.5 h (Zone 2) ▪ Complete freeze time: ~ 11 h (Zone 1 – 3)
Thawing	+35 °C with 70 rpm agitation	Four Celsius® FFT 75 L containers, each filled at the maximum working volume of 75 L (300 L total)	▪ Time to melting point: ~ 4 h (Zone 1) ▪ Time at melting point: ~ 9 h (Zone 2) ▪ Complete thaw time: ~ 15 h (Zone 1 – 3)

Development of temperature profiles in the Celsius® S³ benchtop system

Loading samples for freezing and thawing

Ten 100 mL Celsius® Pak bags were filled to the nominal fill volume via a syringe. The sample solution was 10 mM sodium acetate, 9% (w/v) sucrose, pH 5.2, 0.01% (w/v) PS80, matching the model solution used in production-scale experiments. Celsius® Pak bags were placed in the heat exchange slots of the module of the Celsius® S³ benchtop system. Thermocouples were placed into the thermowells of the bags to be monitored and secured. The thermocouple tips were positioned at the LPTF | LPTT location, 1 ± 0.5 cm below the liquid surface. The module was then closed.

Creating new temperature profiles

New temperature profiles were developed so that the product temperature curves obtained using the Celsius® S³ benchtop system matched those obtained using the production-scale Celsius® FFT 75 L containers (Tables 1 and 2). Based on freezing and thawing curves from Celsius® FFT 75 L containers, a series of stepwise temperature setpoints were defined and translated into a set of numerical instructions in a text format readable by the CryoPilot software. CryoPilot software controls the chiller and the mixer by following a defined profile, which specifies changes to the chiller temperature setpoint and the mixer mode setpoint (on | off) as a function of time.

Once the freezing and thawing runs were completed, the data files were analyzed alongside data from the production-scale conditions. Data from both scales were plotted to identify areas of the setpoint profile that required modification. This procedure was repeated until the profiles from lab- and production-scale runs matched to the desired degree.

Running a freeze and thaw cycle

After creating and selecting the desired profile, the CryoPilot software was started, and the cycle was run without further modification.

Results and Discussion

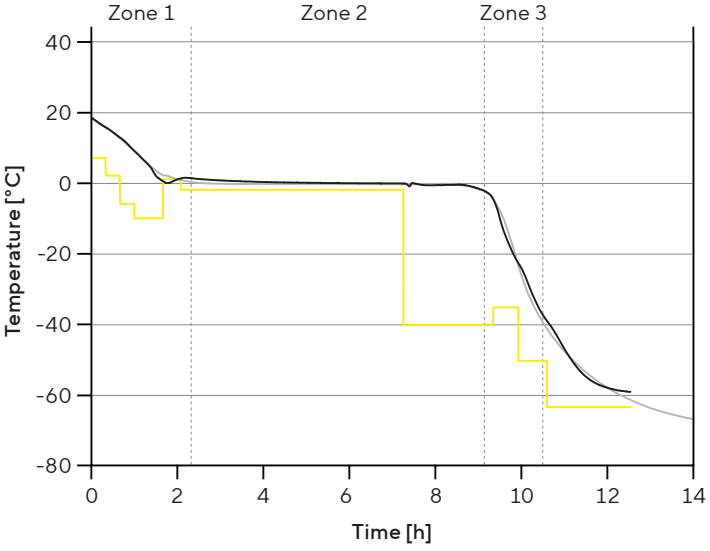
As shown in Table 2, the newly created lab-scale temperature profiles obtained with the Celsius® S³ benchtop system matched the critical freezing and thawing process parameters of the corresponding Celsius® FFT 75 L container profiles. Freezing and thawing temperature profiles for both systems are shown in Figures 4 and 5, respectively. The lab- and production-scale profiles were sufficiently aligned to meet the objective of this study.

Table 2: Comparison of reference Celsius® FFT 75 L container profiles and freeze | thaw model results obtained with the scaled-down Celsius® S³ benchtop system

Scenario	Parameter	Profile	
		Celsius® FFT 75 L container	Celsius® S³ benchtop system
Freezing	Time to freezing point (Zone 1)	~2 h	~2 h
	Nominal freeze time (Zone 2)	~6.5 h	~6.5 h
	Complete freeze time (Zone 1 – 3)	~11 h	~11 h
Thawing	Time to melting point (Zone 1)	~4 h	~4 h
	Time at melting point (Zone 2)	~9 h	~9 h
	Complete thaw time (Zone 1 – 3)	~15 h	~15 h

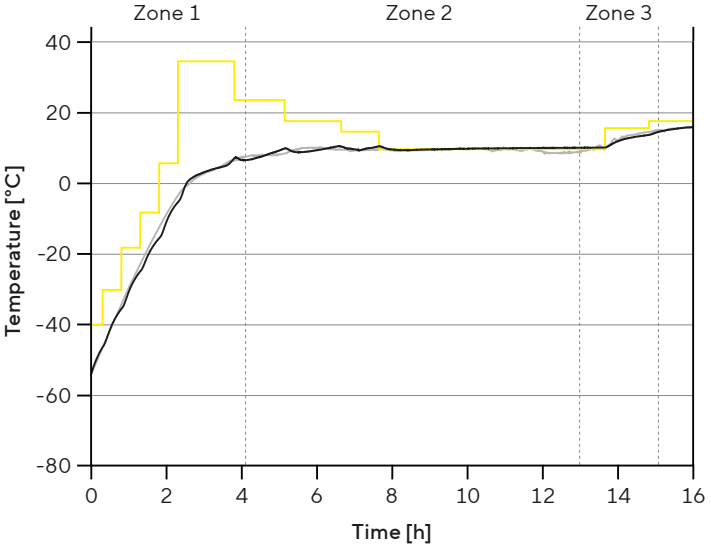
Note. The lower temperature limit of the Celsius® S³ benchtop system is -60 °C, even if the setpoint is programmed below this value.

Figure 4: Overlay of production-scale and corresponding lab-scale freezing profiles generated with the Celsius® S³ benchtop system. The lab-scale profile represents the average temperature measured across ten 100 mL Celsius® Pak bags using ten thermocouples. The target production-scale profile corresponds to the Celsius® FFT 75 L container golden batch freezing profile.



Target production-scale profile (Celsius® FFT 75 L container)
Lab-scale profile (Celsius® S³ benchtop system)
Chiller setpoint profile

Figure 5: Overlay of production-scale and corresponding lab-scale thawing profiles generated with the Celsius® S³ benchtop system. The lab-scale profile represents the average temperature measured across ten 100 mL Celsius® Pak bags using ten thermocouples. The target production-scale profile corresponds to the Celsius® FFT 75 L container golden batch thawing profile.



Target production-scale profile (Celsius® FFT 75 L container)
Lab-scale profile (Celsius® S³ benchtop system)
Chiller setpoint profile

Conclusion

This study demonstrated that the Celsius® S³ benchtop system is suitable for reproducing temperature profiles obtained with Celsius® FFT 75 L containers at production scale.

Production-scale temperature profiles from Celsius® FFT 75 L containers were screened to select conditions representative of typical manufacturing environments. The selected conditions reflect the performance expected for an equivalent 4 × 75 L container configuration. Specific end-user process conditions (freezing and thawing setpoints, fill volume, and number of containers) will influence the overall production-scale freezing and thawing profiles.

While this study focused on an equivalent 4 × 75 L container configuration with a defined model solution, the scale-down methodology can be extended to other palletized container configurations, fill volumes, and product types.

The profiles obtained from the Celsius® S³ benchtop system allow end users to explore the impact of freezing and thawing processes on their active pharmaceutical ingredient, optimize formulations, and evaluate the suitability of the Celsius® FFT 75 L container for their production-scale needs.

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