SII NanoTechnology Inc.

# DSC AS PROBLEM-SOLVING TOOL: OPTIMIZATION OF THE LYOPHILIZATION PROCESS

## Problem

A thermal analytical scientist working for a pharmaceutical R&D center needs to accurately determine the glass transition temperature (Tg) of aqueous solutions containing an active drug, cryoprotectant, and other agents in order to help optimize the lyophilization (freeze-drying) process. Lyophilization is necessary for drug formulations which exhibit a lack of liquid stability; and, during the lyophilization process, the aqueous formulation is cooled down to a sufficiently low temperature where primary drying can be applied to generate a freeze-dried 'cake'. However, the selection of the proper lyophilization formulations and conditions required to generate a satisfactory cake mandates a good deal of knowledge about the particular formulation and the effects of temperature and time on its thermal characteristics.

One key parameter that has been identified as crucial to understanding the lyophilization process is the glass transition temperature, or Tg, of the given formulation. Generally, the process temperature is set below the subambient Tg of the formulation during primary drying in order to avoid 'collapse' of the product during lyophilization. In addition to the glass transition temperature, data indicates that the magnitude of the change in heat capacity (Cp) at Tg along with the occurrence of any recrystallization events can have a major effect on the success of avoiding collapse of the product. Thus, an analytical technique is required which yields accurate, sensitive and reproducible data on Tg and recrystallization transformations in the subambient temperature regions.

## Solution

Differential scanning calorimetry (DSC) provides a means of addressing the key issues surrounding the production of a successful cake during lyophilization. In particular, the Seiko EXSTAR DSC6000 system is ideally suited for this particular application. The Seiko DSC offers the pharmaceutical scientist the following advantages:

- high sensitivity (the highest sensitivity of any commercial DSC instrument)
- excellent subambient performance
- ease of use
- highly stable baseline characteristics

With the Seiko DSC6000 system, the scientist can quantitatively examine and test the following characteristics associated with the generation of proper cake formulation:



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- bulking agents
- cryoprotectors
- buffer salts
- surfactants

The cryoprotectors are typically sugars (e.g., sucrose or mannitol) that preferentially bind to the active drug or protein and protect it against denaturation during freezing of the bulk solution. The effects of the different additives on the thermal properties of the formulations can be determined using the Seiko DSC6000 system, which is increasingly becoming the DSC of choice among pharmaceutical R&D centers.

Aqueous lyophilization formulations are best analyzed in an open aluminum pan since the properties of interest are below 0°C. Between 10 to 20 mg of solution is injected into an open pan and then analyzed with the DSC. The sample is cooled to a temperature of -75°C, held for 5 minutes, and then heated at a rate of 5 or 10°C/min back to room temperature.

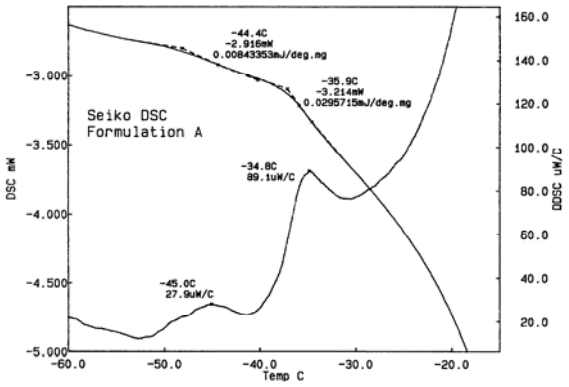


**Figure 1**

Displayed in Figure 1 are the results obtained from the Seiko DSC for aqueous formulation A. The plot shows the DSC heat flow and derivative trace as a function of temperature below the main melting of the ice. Two glass transition events are obtained for this particular formulation at -44 and -36°C. The magnitude of the derivative peak at Tg helps to determine the relative size of the Tg event and its importance to the lyophilization process and of the propensity of the formulation to collapse during processing. The Seiko DSC has the necessary high degree of sensitivity and stability required to detect the weak Tg's of the formulation, even under prolonged operating subambient conditions.



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Displayed in Figure 2 are the DSC results obtained from an aqueous solution containing 5% sucrose cryoprotector. The Tg of this

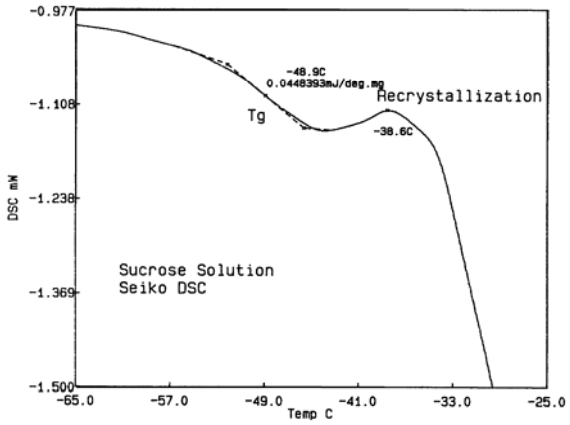


**Figure 2**

solution is observed at –49°C. With further heating, the solution undergoes recrystallization at –39°C. There is evidence that formulations which exhibit a recrystallization event during heating will lyophilize successfully regardless of the product temperature and the magnitude and temperature of Tg.

## Summary

The Seiko EXSTAR DSC6000 system provides the necessary high degree of sensitivity and stable subambient performance necessary to observe the weak glass transition and recrystallization events associated with formulations undergoing lyophilization. The Seiko DSC can provide information on the thermal properties of formulations and aid in the knowledge regarding the propensity of the solution to collapse during processing by measuring the following key parameters:

- temperature of Tg(s)
- magnitude of Tg(s)
- occurrence of recrystallization.



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