Use of DSC for Lyophilization Optimization

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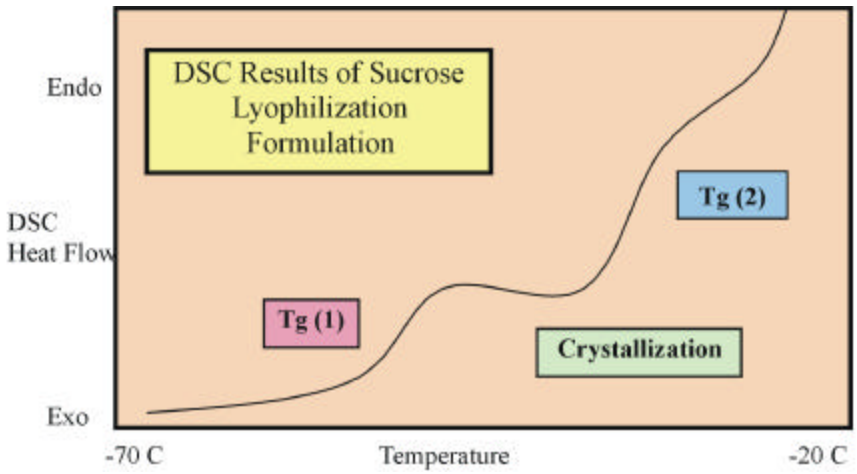
Problem

A thermal analytical scientist working for a pharmaceutical R&D center has a need to optimize the freeze-drying or lyophilzation process associated with their particular products. Lyophilization is necessary when attempting to produce a drug, which will be easily ingested or dissolved in water. The lyophilzation process involves cooling an aqueous formulation to subambient temperatures and then pulling a vacuum to drive off the free water. Due to energy utilization considerations, this can be expensive and it is desirable to know the maximum acceptable temperature to which the solution can be cooled before a vacuum is applied. It is also essential to ensure that the temperature is sufficiently low enough to avoid the 'collapse' of the freeze-dried cake, which renders a useless product.

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 the 'collapse' of the product during lyophilization. In addition to the glass transition temperature, the magnitude of the change in heat capacity (ΔCp) at Tg along with the occurrence of any



recrystallization events may have a major effect on the successful avoidance of the collapse of the product during processing. Thus, an analytical technique is required which yields accurate, sensitive and reproducible data on Tg(s) and recrystallization transformations in the subambient temperature regions. This information is valuable in the generation of a 'pharmaceutically elegant' freeze-dried product.

Solultion

Differential scanning calorimetry (DSC) provides a means of addressing the key issues surrounding the production of a successful lyophilized material.

In particular, the state of the art PerkinElmer Pyris 1 DSC system is ideally suited for this particular application. The Pyris 1 DSC offers the pharmaceutical scientist the following advantages:

- Very high sensitivity
- Outstanding resolution
- Excellent subambient performance
- Use of platinum resistance thermometers (PRT) for the highest possible accuracy and precision
- Ease of use with Pyris Software for Windows

With the PerkinElmer Pyris 1 DSC system, the scientist can quantitatively examine and test the following characteristics associated with the generation of proper cake formulation:

- cyroprotectors
- bulking agents
- buffer salts

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- surfactants

The cryoprotectors are typically simple sugars (generally 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 Pyris 1 DSC.

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 quickly 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.

Displayed in the figure above are the DSC results representing those obtained from a solution containing 5% sucrose cryoprotector. The results are presented in high sensitivity scaling emphasizing the small transitions below the main melting transition of the ice phase.

The Tg of this solution is observed at -45 C. Upon further heating, the solution may undergo 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.

At approximately –27 C, a second, higher temperature Tg is believed to occur. The exact nature and interpretation of the DSC results obtained in the subambient regions on sucrose solutions or formulations is a matter that is still being researched and discussed. However, it is certain the proper understanding of this transition is critical for obtaining a better handle on the overall freeze-drying process.

Summary

Detection of glass transition events in frozen formulations can be challenging and difficult due to the inherently weak nature of these transitions. The state of the art PerkinElmer Pyris 1 DSC system provides the necessary high degree of sensitivity, resolution and stable subambient performance necessary to observe the weak glass transition(s) and recrystallization events associated with formulations undergoing lyophilization. The Pyris 1 DSC can provide information on the thermal properties of formulations and aid in the knowledge regarding the propensity of the solution to avoid collapse during processing by measuring the following key parameters:

- temperature of Tg(s)
- magnitude of Tg(s) or ΔCp
- occurrence of recrystallization

This DSC data is valuable in the efficient generation of a ‘pharmaceutically elegant’ end product.

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