Vial Mechanical State Characterization During Lyophilization Using Wireless Strain Gauges

Collaboration with Corning

The addition of certain crystallizable bulking agents to lyophilized formulations can improve robustness and reduce drying time by significantly increasing the critical temperature. However, care must be taken when using these materials to ensure that complete crystallization occurs since a phase change during storage can lead to instabilities. Additionally, this crystallization process can place a significant amount of stress on the vial. In many cases, this stress can exceed the critical strength and lead to breakage. Vial breakage during lyophilization can be catastrophic to the process due to the potential for batch contamination and loss of process pressure control. Additionally, the cleanup costs following a breakage event can be significant, requiring thorough manual cleaning by a skilled technician. Therefore, the ability to monitor the crystallization characteristics of new formulations is critical to effect process development.

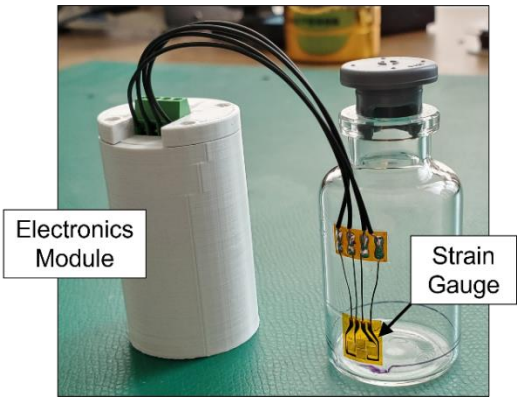

Figure 1: Image of assembled strain sensor. Strain-sensitive elements were bonded to directly to the glass vial and sampled by the electronics module.

A series of custom wireless strain sensors were developed in partnership with Corning to investigate the influence of fill volume, shelf temperature ramp rate, and excipient (mannitol) concentration on vial stress throughout the lyophilization process. Strain-sensitive elements were bonded directly to the outer surface of 20mL vials, roughly 1 cm from the heel. Gages were arranged in a "full bridge" configuration to minimize the influence of parasitic thermal stresses. Battery-powered electronics modules, having an identical footprint to the 20mL vials, sampled the strain response of the gages and broadcast the data to an external host in real time with a measurement period of 30 seconds. An image of the assembled sensor is shown in Figure 1. The sensors were placed in a full rack of 148 vials. Target vials were isolated from the electronics modules by an inert sample to reduce parasitic heating. A comparison of the strain response between 15% w/v mannitol formulations and empty borosilicate and Corning Valor® vials is shown in Figure 2. Thermocouples were placed inside the target vials to synchronize strain and temperature data. During nucleation, a clear step response in strain signal results from the simultaneous influence of ice crystal growth and increase in product temperature. Following solidification, the mannitol formulations produced a sharp decrease in strain magnitude as the mannitol crystallized. A second crystallization event occurred during warming as the cycle entered primary drying. Here, the ultimate stress in the borosilicate vial was exceeded which

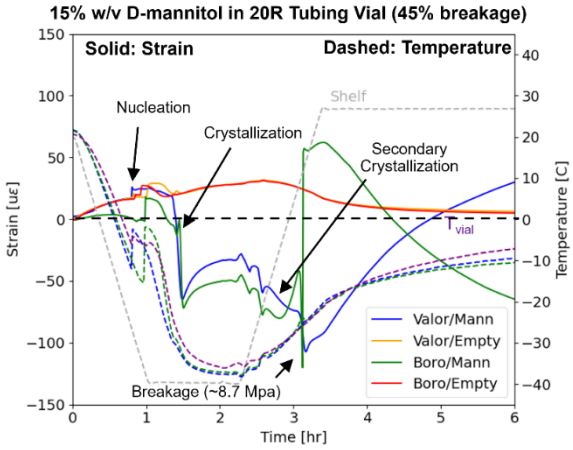

Figure 2: Strain data from 15%w/v mannitol formulation. Nucleation, crystallization, and breakage events are

ultimately led to failure. The strain sensors developed during this study demonstrated several applications as a process analytical technology. Specifically, the devices can be directly applied to process development to both verify excipient crystallization and ensure vial ultimate stress is not exceeded.