APPLICATION NOTE

Thermal Analysis

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HyperDSC for High Throughput Formulation Development

Development of a working formulation for a drug-excipient mixture can be a time consuming and costly process. The concept of High-Throughput Design has gained more and more interest as a way to increase profitability and to decrease research costs. One technique that can increase the ability of a laboratory to evaluate formulations is HyperDSC™ or High Ramping Rate DSC. HyperDSC is the ability to quantitatively measure small samples at extreme heating and cooling rates, typically 100-500 ˚C/min. Because of the advantages of the power compensated design (PCD), accurate data can now be obtained in a fraction of the time traditionally needed. This allows much higher throughput, shorter turn-around times, and substantially lowers costs, especially when used with an autosampler (Figure 1). Using HyperDSC techniques, a typical run on a protein-excipient formulation can be completed in less than 2 minutes for a simple heating run and in less than 6 minutes for a heat-cool-heat run, making it is possible to run 264 to 720 samples a day.

Figure 1. DSC 8500

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Figure 2 shows the progression of heating rates on a sample of lyophilized trehalose-Bovine Serum Albumin. Heating at a normal rate would give the classical Tg and often shows an overshoot that obscures it. As we increase the heating rate, we notice that the Tg transition increases in size. Table 1 shows the results for these series with the run time.

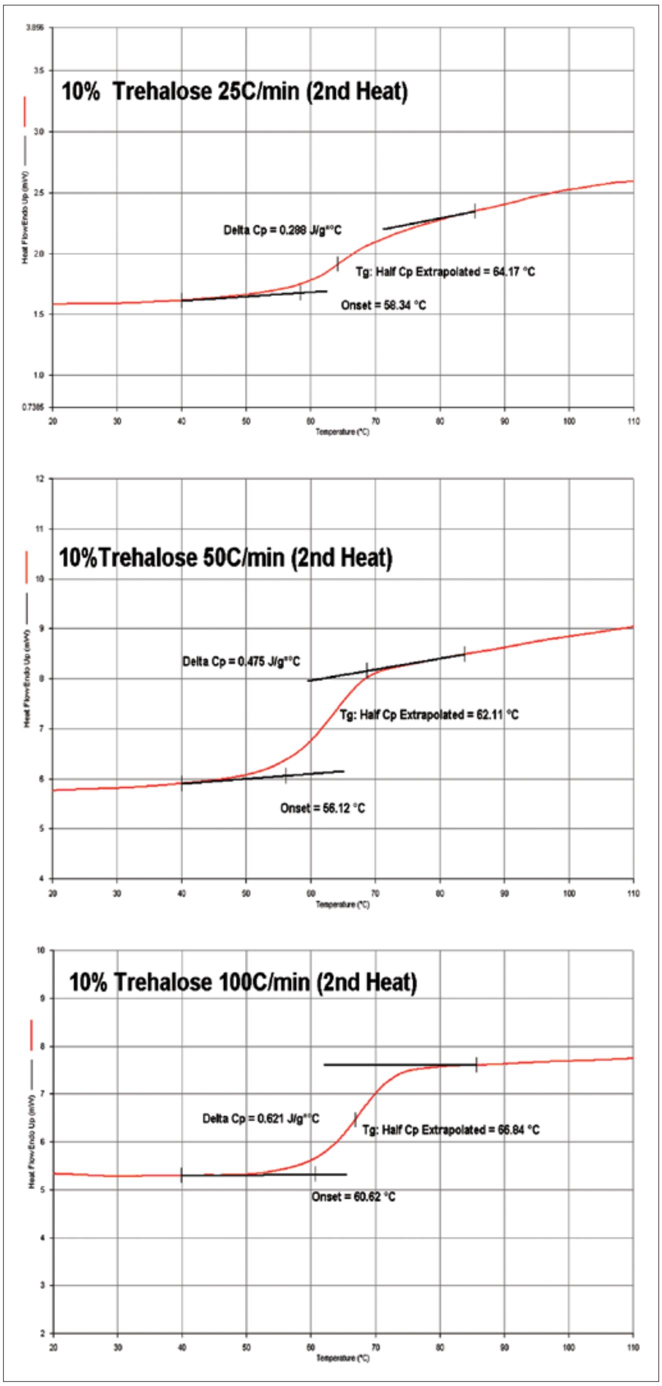

Figure 2. Samples of a 10% Trehalose formulation were run at 25, 50 and 100 ˚C/minute using Nitrogen purge, Intercooler 2 for cooling, and aluminum pans. Sample sizes were approximately 1.5 to 2.2 mg.

***Table 1.* Results for the Tg Study shown in Figure 2.**

Scan Rate in ˚C/min	Run Time in minutes	Tg Onset in ˚C Tg	Mid-point
10	60	60	65
25	28	58	64
50	14	56	62
100	6	61	66

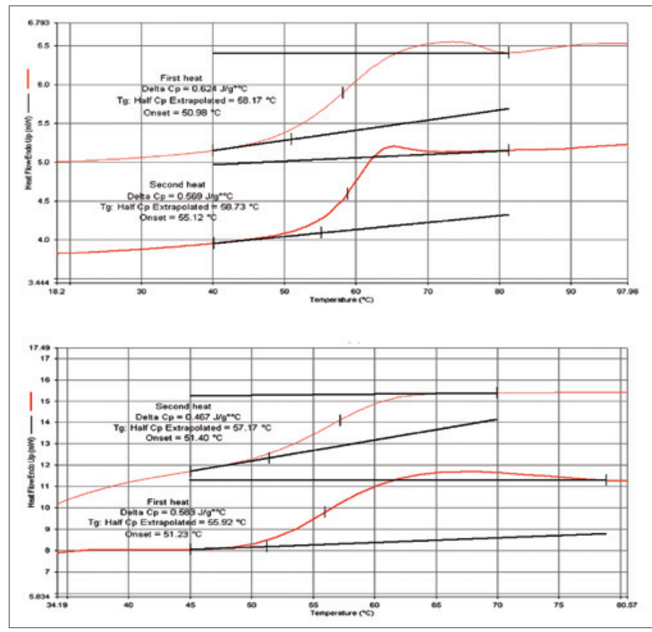

Figure 3. Comparison of initial heating for the Sucrose Bovine Serum Albumin (BSA) formulation after lyophilization. Sample size was 1.8 mg and instrumental conditions were the same as in Figure 2. (a) shows heating at 5 ˚C/min (b) shows heating at 100 ˚C/min. Note the Hyper DSC run shows almost no shift in the Tg on the second heat.

Often, because HyperDSC scans the material at heating rates that do not permit kinetic changes to have time to occur, the heat-cool-heat cycle often used in study formulations is unnecessary. Figure 3 shows a sucrose-BSA formulation scanned at 5 ˚C/minute and also at 100 ˚C/minute. Note the enthalpic overshoot in the 5 ˚C/minute run is greatly reduced in the HyperDSC run. As the Tg is easily measurable on the first heating, the cooling and reheating cycle can be dropped.

HyperDSC also can be used to accurately measure the initial percentages of thermally reactive materials, like polymorphs, and to analyze very small quantities of material. Increasing the heating rate increases the apparent peak size in power compensation DSCs as we can see in Figure 3. This allows for the detection of very small peaks or for the measurement of very small samples, such as a piece of artificial knee or hip removed from a patient. High heating rates have another observed affect on materials: the material can actually be heated faster than kinetic events can occur. For example, if a polymorphic material is heated fast enough, you can trap the reactive form as shown in Figure 4. Initial heating at standard rates like 5 ˚C/minute show two peaks. As the rate is increased to 250 ˚C/minute, the area of the first peak increases as the heating rate exceeds the time needed by the materials to change forms.

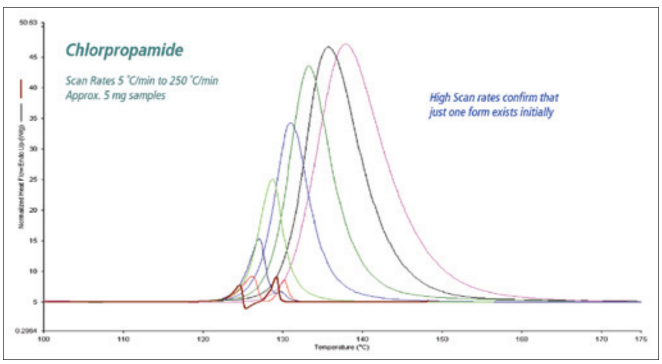

Figure 4. Hyper DSC permits scanning quickly enough that a kinetic event does not have time to happen as shown for this polymorph samples.

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