APPLICATION NOTE

Simultaneous TGA-DSC

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Pharmaceutical Compounds are Analyzed in Half the Time by Simultaneous TGA-DSC

Introduction

In an aggressive business climate, PerkinElmer improves pharmaceutical laboratory productivity and increases sample analysis throughput by performing two analytical techniques simultaneously. The STA 6000 Simultaneous Thermal Analyzer performs both Thermogravimetric Analysis and Differential Scanning Calorimetry together, at the same time.

In the "Early Drug Discovery Phase" of pharmaceutical development when there is a minimum amount of synthesized drug candidate, quick thermal analysis using a small amount of sample is the norm. The sample amount could be less than 3 mg. Because of the rush to identify possible drug candidates, analytical answers must be given within the day. The STA 6000 with its sensitivity of 0.1 µg allows minimum sample material to obtain reproducible results in half the time.

This application note examines three typical drug-discovery-type pharmaceutical materials by Simultaneous Thermal Analysis, TGA-DSC.

- Sample A: free-base, small-molecule crystalline powder
- Sample B: HCl salt of Sample A, monohydrate
- Sample C: Mesylate salt of Sample A, trihydrate

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Results

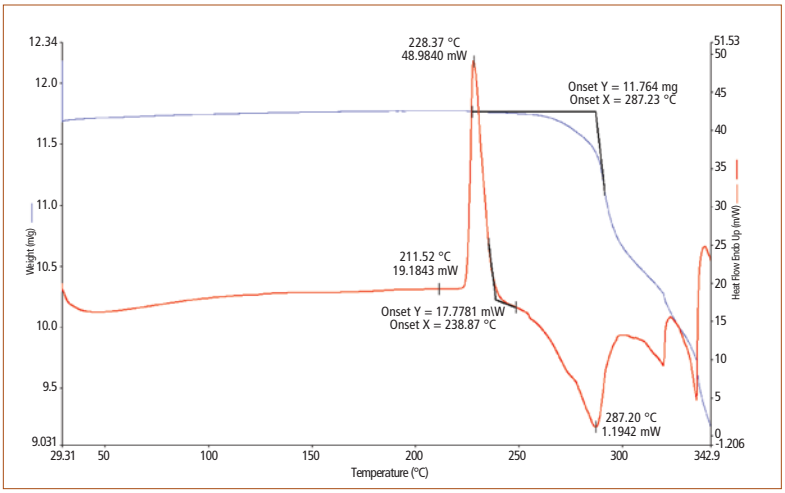


Figure 1. **Sample A:** Sample A characterized by the STA 6000 displays the Red DSC thermal curve and the Blue TGA weight loss curve. Sample A is a free base, small-molecule crystalline powder (11.679 mg). The DSC curve indicates that there is a crystalline melt defined by the peak temperature at 228.37 °C. After the melt transition, the baseline returns to a slightly lower position than the pre-melt baseline. The post-melt baseline changes slope as the sample begins decomposition. The DSC exothermic decomposition peak at 287.2 °C corresponds to the TGA extrapolated onset temperature of 287.2 °C as this sample decomposes.

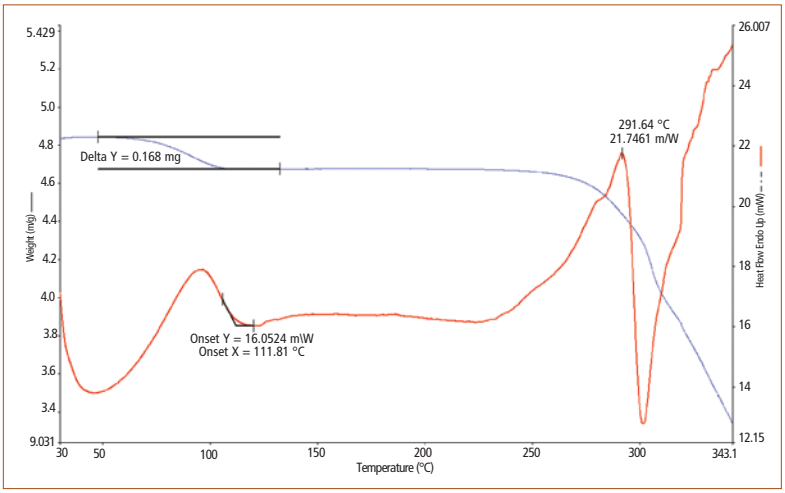


Figure 2. **Sample B:** Sample B (4.89 mg), a HCl salt of Sample A monohydrate, exhibits a weight loss of water upon heating of 0.168 mg. The amount of lost water is measured by a simple delta Y calculation on the TGA curve. It closely matches the calculated value from the stoichiometric 1:1 ratio for a monohydrate. The accompanying DSC thermal curve exhibits a corresponding endothermic reaction that begins just after the start-up transient and concludes at 111.81 °C. The sample continues to heat until it begins an endothermic event at the very beginning of decomposition. This is acknowledged by the onset of the endothermic DSC event and its correlation to the start of the weight loss curve. Then the sample experiences an abrupt decomposition exothermic event beginning at 291.64 °C as displayed by the DSC Peak temperature.

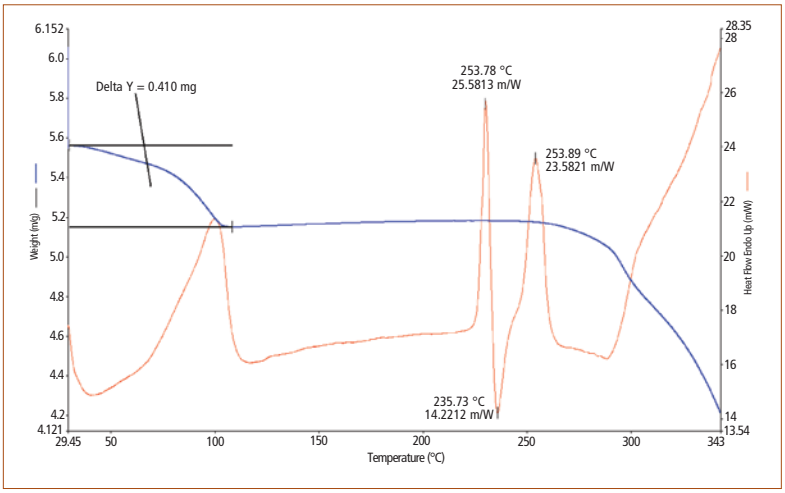
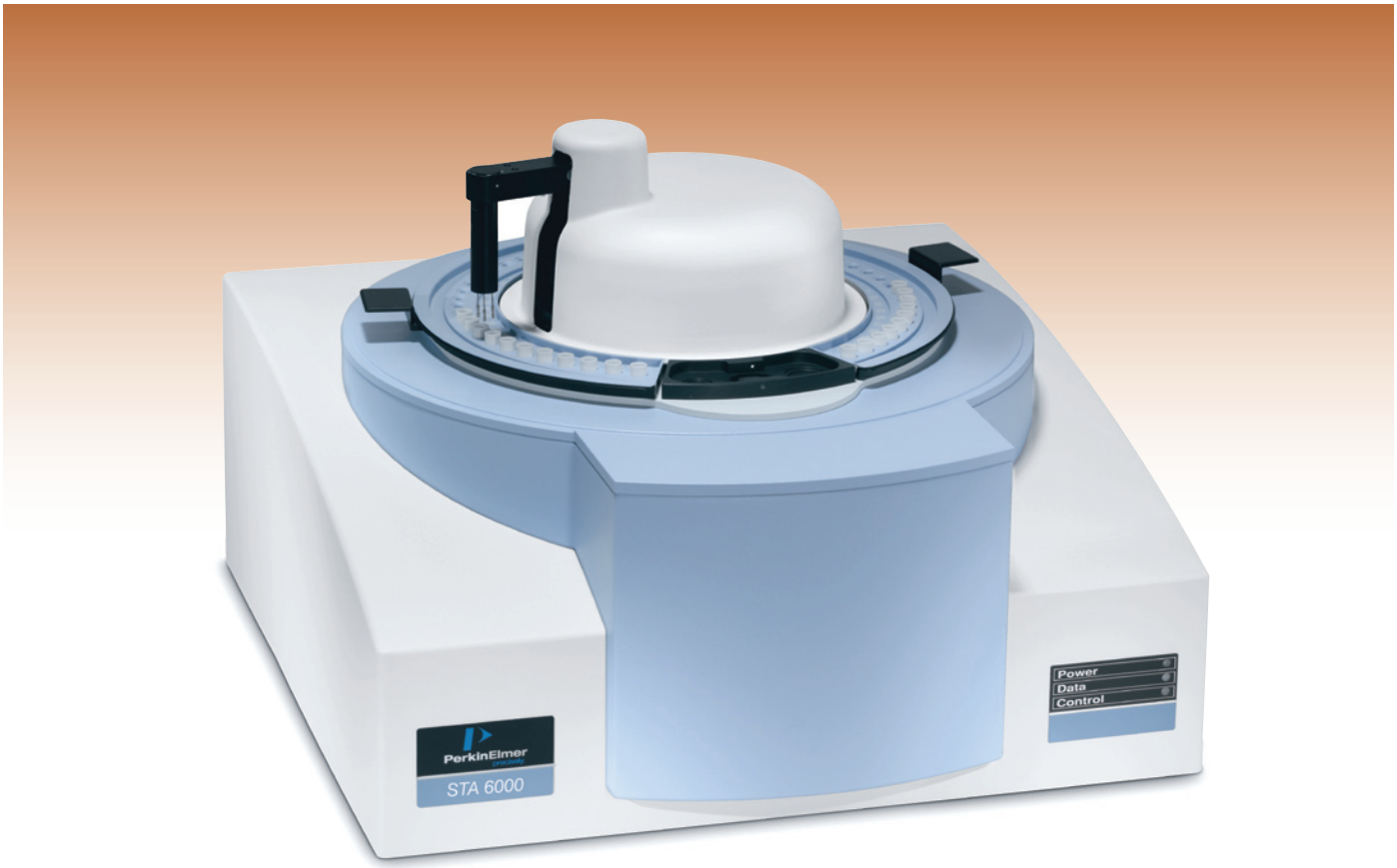


Figure 3. **Sample C:** Sample C (5.562 mg) Mesylate salt of Sample A, exists as a trihydrate. The TGA curve exhibits the surface water weight loss of 0.410 mg, and decomposes above 250 °C. As expected the DSC thermal curve exhibits three peaks. The first DSC endothermic peak is due to the release of all the hydration water from the crystalline lattice. This corresponds to surface water weight loss of 0.410 mg on the TGA curve. The series of endothermic and exothermic events between 215 °C and 270 °C represent a crystal-crystal transformation upon heating, with the initial endothermic peak representing a crystalline melt (an essentially anhydrous crystalline phase since the hydration water was previously removed); the next peak at 236.73 °C, an exothermic event, is a recrystallization of the melted material forming a new crystalline structure, immediately followed by the melt of that crystalline form. The melt-recrystallization-melt series of events are also called a polymorph conversion (phase transition) process. This is a typical characteristic of small-molecules organic crystals.[1] All this occurs just before final decomposition.



Experimental

The analysis was performed on a PerkinElmer® STA 6000 Simultaneous TGA-DSC, using alumina ceramic pans and a standard furnace. The instrument's furnace was calibrated using a metal reference material's melting temperature. In this case, a single point indium melting event was used to calibrate temperature and heat flow. The instrument's balance was calibrated using a certified weight. The sample purge was dry nitrogen with a flow rate of 30 mL/minute. The large Sample A was run just to show that the STA 6000 can easily run any sample size. The temperature program was from 30 ˚C to 350 ˚C, with a scanning of 10 ˚C/minute.

Sample Weights:

- Sample A: 11.679 mg
- Sample B: 4.829 mg
- Sample C: 5.562 mg

Conclusion

The STA 6000 provides the productivity that pharmaceutical companies and others are seeking. It combines DSC and TGA thermal techniques to give the user reproducible results in half the time. Designed with routine and research applications in mind, the STA 6000 Simultaneous Thermal Analyzer applies leading edge sensor technology to yield higher accuracy and quality results. The patent pending SaTurnA™ sensor and proven compact furnace ensure better temperature control, more consistent measurements, and the fastest cool-down time. To further productivity, the STA 6000 with its easy-to-load vertical system can be equipped with an autosampler that runs an unprecedented 45 samples unattended.

Acknowledgement

1. PerkinElmer thanks Dr. Ilie Saracovan, Material Scientist and Consultant, for his comments in regard to the content of this application note.

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