Thermogravimetric Analysis and Crystalline Hydrates

1. Background

Crystalline hydrates are widely encountered in pharmaceutical, chemical, and materials applications, where the presence and stability of water within the crystal lattice can strongly influence physicochemical properties such as stability, solubility, mechanical behavior, and processability.(1,2) Understanding the nature of water incorporation, whether as loosely bound surface moisture or as stoichiometric water of crystallization, is critical for controlling material performance and ensuring product quality. Hemihydrates often exhibit complex thermal behavior due to partial occupancy of hydration sites, anisotropic diffusion pathways, or structural rearrangements accompanying water loss. As a result, dehydration of hemihydrates can proceed through multiple steps, sometimes involving intermediate phases prior to formation of the anhydrous crystal. Among the available analytical techniques, thermogravimetric analysis (TGA) is particularly well suited for the study of hydrated solids due to its sensitivity, quantitative accuracy, and ability to probe thermal stability and mass-loss processes as a function of temperature and time.(3-5)

TGA provides valuable insight into dehydration mechanisms and kinetics. The temperature dependence of mass loss can reveal whether water is released in a single concerted step or through multiple, sequential events corresponding to distinct binding environments within the crystal structure. When combined with controlled heating programs or isothermal measurements, TGA data can be analyzed using kinetic models to extract activation energies and rate parameters, thereby offering mechanistic information that supports interpretation of solid-state transformations.(6,7) Deviations from simple first-order behavior may indicate the influence of diffusion, nucleation and growth, or structural reorganization during dehydration.

In this *AMI Note*, the thermal behavior of a representative hemihydrate compound is examined using a combination of dynamic (scanning) and isothermal TGA experiments. Dynamic measurements are employed to characterize the overall dehydration profile and identify discrete mass-loss steps, while isothermal experiments enable detailed kinetic evaluation under well-defined thermal conditions. Model-based analysis is applied to the mass-loss data to assess the governing dehydration mechanisms, with particular emphasis on diffusion-controlled behavior. Together, these results demonstrate how TGA can be used to gain insight into dehydration pathways and rate-limiting processes in crystalline hemihydrate systems.

2. Experiment

A crystalline organic hemi-hydrate was analyzed via isothermal TGA at multiple temperatures: 50 °C, 55 °C, 60 °C, and 77 °C. TGA was performed using the **TGA 1000** from **AMI**. Each sample was held under constant temperature while weight loss was recorded over time. The total dehydration corresponds to the release of 0.5 mol of water per mole of compound, or approximately 2.7% of the sample's initial mass.

3. Results

Across all isothermal conditions, water release occurred in distinct stages. At lower temperatures, the dehydration began abruptly, then slowed, accelerated again, and gradually tapered off as full dehydration approached. This behavior indicates a complex sequence of water loss rather than a single kinetic step.

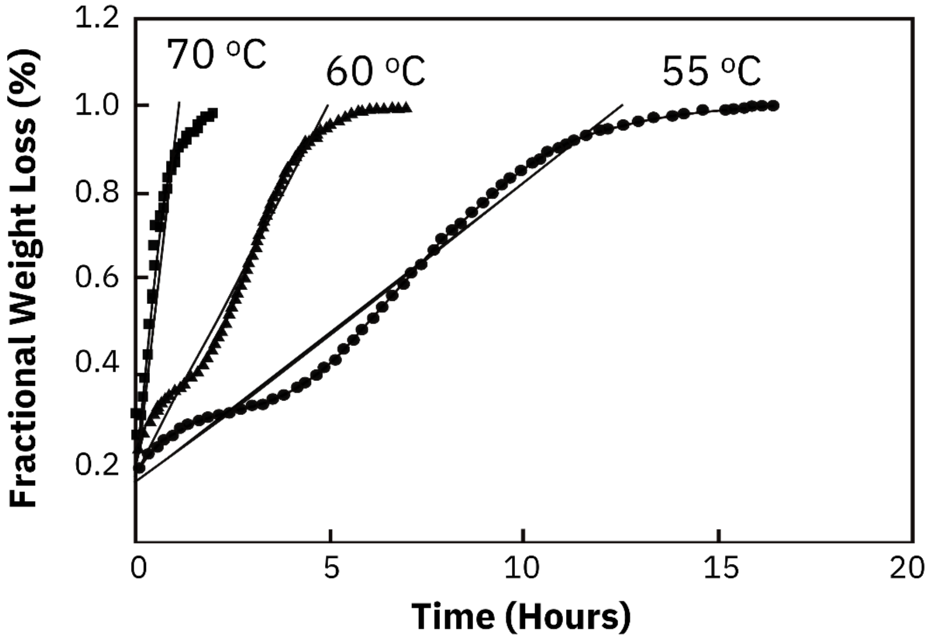

Figure 1: Fractional weight loss profiles (α vs. time) at 55 °C, 60 °C, and 70 °C

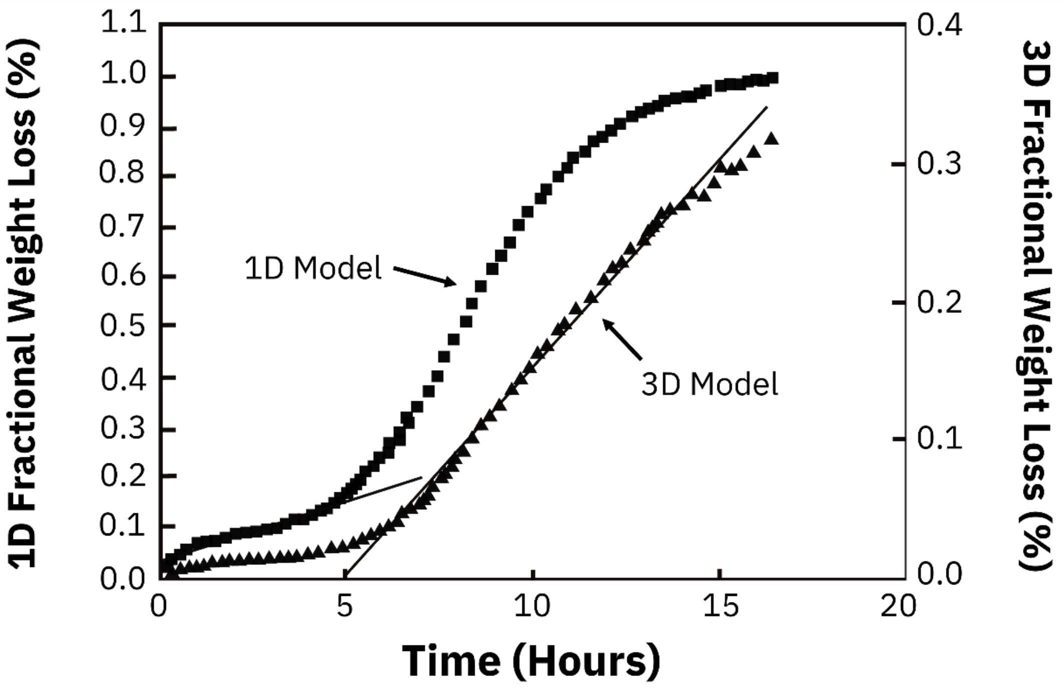

Figure 2: Comparison of model fits to experimental data at 55 °C

Weight loss data were processed to generate fractional decomposition profiles (α), shown in Figure 1. Despite the sequential nature of dehydration, a global linear regression approach was used to estimate apparent rate constants for each temperature. These values were then used in an Arrhenius plot to estimate the activation energy (E_a), yielding a value of approximately 29 kcal/mol.

To better understand the stepwise kinetics, a detailed kinetic model analysis was applied to the 55 °C isotherm. Two common diffusion-controlled models were considered, as described in Byrn's work on solid-state chemistry:(8)

- ✓ One-dimensional diffusion: $\alpha^2 \propto kt$
- ✓ Three-dimensional diffusion (Jander equation): $1 - (2/3)\alpha - (1 - \alpha)^{0.666} = kt$

These observations, shown in Figure 2, suggest that water at the crystal surface escapes rapidly once liberated, while deeper hydration layers require diffusion through dehydrated material, a classic feature of diffusion-limited kinetics.

4. Conclusions

Thermogravimetric analysis offers more than just quantitative mass loss data. It provides real-time visibility into dehydration mechanisms and supports kinetic modeling. In this study:

- ✓ Sequential water loss was observed in a hemi-hydrate compound.
- ✓ Activation energy for overall dehydration was determined to be ~29 kcal/mol.
- ✓ A shift from one- to three-dimensional diffusion mechanisms was detected across time.

These findings demonstrate how TGA can be used not only to monitor weight loss, but to understand complex solid-state transformations relevant to pharmaceuticals, materials science, and process engineering.

*Figure 3: Highlighted features of **TGA 1000** from **AMI***

The results demonstrate that the **TGA 1000** is exceptionally well suited for the investigation of crystalline hemihydrate dehydration. Its high-sensitivity microbalance enables accurate resolution of small, sequential mass-loss events characteristic of partial hydration states, while precise temperature control supports both dynamic and isothermal experiments essential for kinetic differentiation. Flexible heating programs and stable baseline performance allow clear separation of overlapping dehydration steps, facilitating reliable interpretation of complex thermal pathways. In addition, controlled gas-atmosphere capabilities minimize external influences on dehydration behavior, ensuring reproducible and mechanism-relevant measurements. Combined with integrated software tools for model-based kinetic analysis, the **TGA 1000** provides a comprehensive platform for quantifying water of hydration and elucidating diffusion-controlled dehydration mechanisms in crystalline hemihydrate systems.

5. References

(1) Vippagunta, S. R.; Brittain, H. G.; Grant, D. J. W. Crystalline solids. *Adv. Drug Delivery Rev.* **2001**, *48*, 3-26.

(2) Jurczak, E.; Mazurek, A. H.; Szeleszczuk, Ł.; Pisklak, D. M.; Zielińska-Pisklak, M. Pharmaceutical hydrates analysis – Overview of methods and recent advances. *Pharmaceutics*, **2020**, *12*, 959.

(3) Giron, D.; Goldbronn, C.; Mutz, M.; Pfeffer, S.; Piechon, P.; Schwab, P. Solid state characterizations of pharmaceutical hydrates. *J. Therm. Anal. Calorim.* **2002**, *68*, 453-465.

(4) Joseph, A.; Bernardes, C. E. S.; Viana, A. S.; Piedade, M. F. M.; de Piedade, M. E. M. Kinetics and mechanism of the thermal dehydration of a robust and yet metastable hemihydrate of 4-hydroxynicotinic acid. *Cryst. Growth Des.* **2015**, *15*, 3511-3524.

(5) Ren, H.; Chen, Z.; Wu, Y.; Yang, M.; Chen, J.; Hu, H.; Liu, J. Thermal characterization and kinetic analysis of nesquehonite, hydromagnesite, and brucite, using TG-DTG and DSC technicues. *J. Therm. Anal. Calorim.* **2013**, *115*, 1949-1960.

(6) Svoboda, R.; Zmrhalová, Z. O.; Galusek, D.; Brandová, D.; Chovanec, J. Thermak decomposition of mixed calcium oxalate hydrates – Kinetics deconvolution of complex heterogeneous processes. *Phys. Chem. Chem. Phys.* **2020**, *22*, 8889-8901.

(7) Lan, S.; Zondag, H.; van Steenhoven, A.; Rindtm C, Kinetic study of the dehydration reaction of lithium sulfate monohydrate crystals using microscopy and modeling. *Thermochim. Acta*, **2015**, *621*, 44-55.

(8) Stephen R. Byrn, *Solid State Chemistry of Drugs*, Academic Press: New York, 1982.