

## ***Application of Thermal Analysis in Pharmaceutical Field - Revefenacin***

### **1. Introduction**

Thermal analysis techniques are widely applied in pharmaceutical research for evaluating polymorphism, phase transitions, hydration states, decomposition behavior, purity, compatibility, and stability. Among these techniques, **Differential Scanning Calorimetry (DSC)** and **Thermogravimetric Analysis (TGA)** are most frequently used and are officially recognized in many pharmacopeias for drug quality control.

**Differential Scanning Calorimetry (DSC)** measures heat flow associated with thermal events during a controlled temperature program. This includes endothermic and exothermic transitions such as melting, glass transitions, recrystallization, and polymorphic transformations. In the pharmaceutical field, DSC is often used to determine melting points, glass transitions, drug purity, polymorphs, and compatibility between active pharmaceutical ingredients (APIs) and excipients.

**Thermogravimetric Analysis (TGA)** records changes in a sample's mass as a function of temperature under a defined atmosphere. TGA is valuable for characterizing the presence of adsorbed water, crystallization solvents, thermal stability, and decomposition behavior. For hydrates and solvates, TGA can differentiate between loosely bound and tightly bound solvent molecules by observing weight loss patterns across different temperature ranges.

**Revefenacin**, a long-acting muscarinic antagonist (LAMA), is used as a maintenance therapy for chronic obstructive pulmonary disease (COPD). It improves lung function, alleviates symptoms, and slows disease progression. Revefenacin exhibits polymorphism, with multiple crystalline forms (I–IV) reported. Only **Form III** is currently used in commercial formulations due to better processability. However, challenges such as solvate formation and solvent residue during crystallization necessitate continued development of more stable forms. For example, **Revefenacin trihydrate Form A** has demonstrated improved chemical stability, higher polymorphic purity, and enhanced solubility.

## 2. Experimental Method

Thermal analysis was conducted using the **AMI DSC 600** and **AMI TGA 1000** systems.

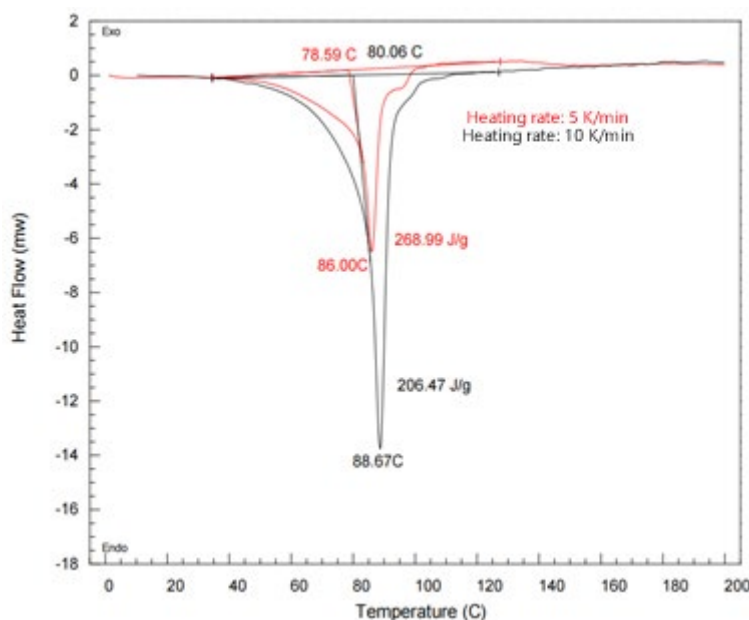
### DSC Characterization

Powdered Revefenacin samples were placed in aluminum crucibles and analyzed under a nitrogen purge (50 mL/min). Two heating rates—**5 K/min** and **10 K/min**—were evaluated over a temperature range from **5 °C to 200 °C**. The impact of crucible type (sealed vs. unsealed) and heating rate on the detection of polymorphic forms was investigated.

### TGA Characterization

Powdered samples were placed in platinum crucibles and analyzed under a nitrogen atmosphere (50 mL/min). The temperature was ramped from **room temperature to 300 °C** at a rate of **5 °C/min**.

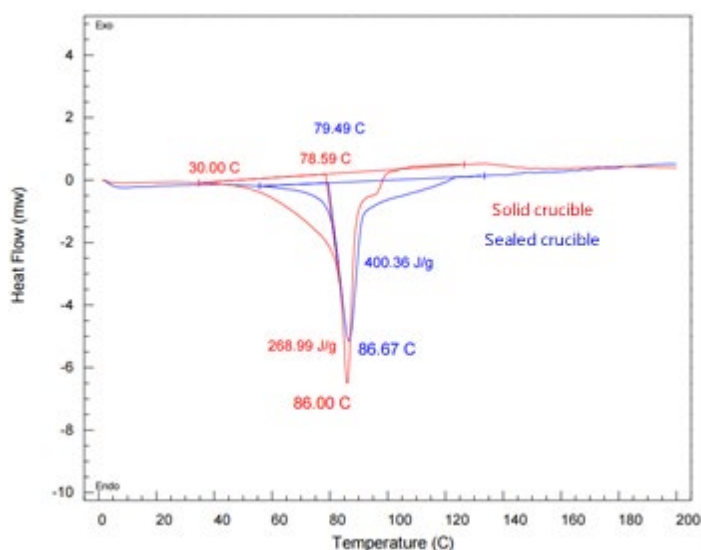
## 3. Results and Discussion



**Figure 1:** DSC curves of Revefenacin at different heating rates

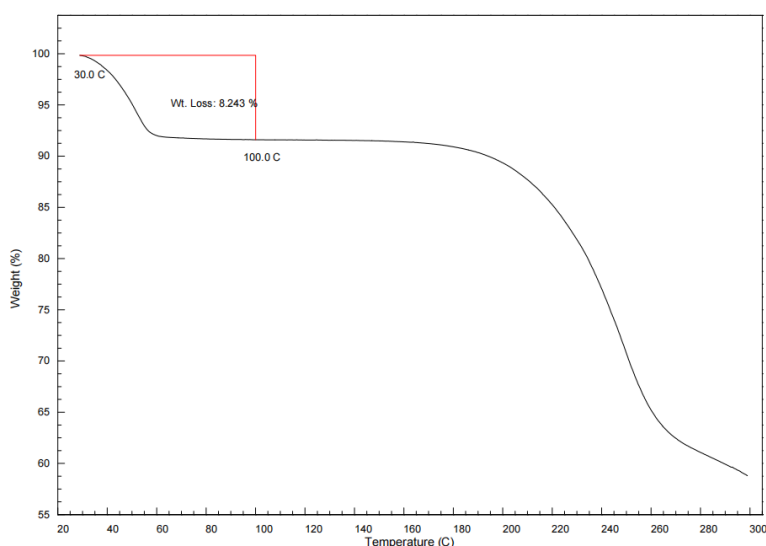
At higher heating rates (10 K/min), the melting peaks are larger and sharper due to faster energy input. At 5 K/min, a **secondary melting peak becomes visible**, indicating the presence of another polymorph. This suggests that slower heating rates may improve the resolution of closely spaced

transitions and help distinguish between multiple crystalline forms. Appropriate heating rate selection is therefore essential for accurate polymorph identification.



**Figure 2:** DSC curves of Revefenacin using sealed vs. solid crucibles

The melting behavior is influenced by the crucible type. In sealed crucibles, a clean melting peak is observed. In open (solid) crucibles, **adsorbed and crystallization water** evaporates during initial heating, leading to a broader melting profile beginning near **30 °C**. This early peak is attributed to moisture loss rather than actual melting.



**Figure 3:** TGA curve of Revefenacin

The TGA curve supports the DSC findings by showing a **stepwise mass loss**, corresponding to the removal of adsorbed and crystallization water. A total weight loss of **8.243%** was recorded. From the weight loss between plateaus, the **molar ratio of crystallization water** can be calculated, confirming the hydrate content and its thermal release characteristics.

## Conclusion

The AMI DSC 600 and AMI TGA 1000 provided complementary thermal and gravimetric data critical for evaluating Revefenacin's polymorphic forms and hydration behavior.

- **DSC** enabled clear differentiation between polymorphs and revealed the influence of heating rate and crucible type.
- **TGA** verified the presence and amount of crystallization water, supporting accurate formulation development and process control.

These methods play a vital role in the development and quality assurance of pharmaceutical compounds where polymorphic stability, solvate formation, and residual solvent content are major concerns.

