THERMAL ANALYSIS AS INTEGRAL PART OF SOLID-FORM SCREENING IN API DEVELOPMENT

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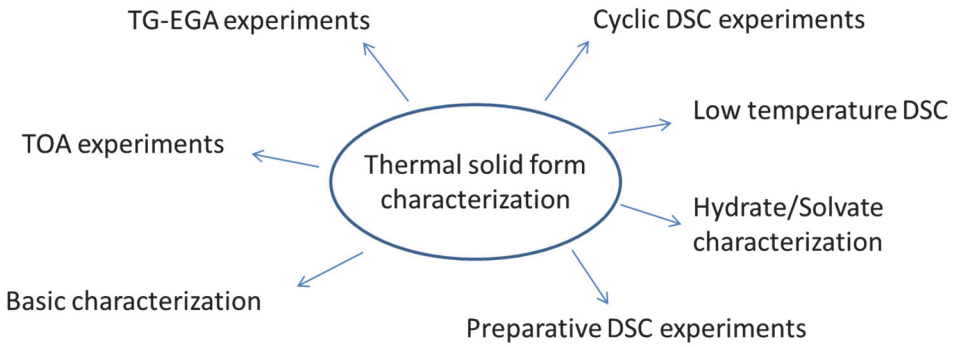
Thermal analysis is an integral part of the solid form screening activities during active pharmaceutical ingredient (API) development of small molecules. According to regulatory requirements[1] a thorough understanding of the solid form landscape must be established prior to filing of a new drug application (NDA). A control strategy for all relevant solid forms needs to be in place to ensure robust delivery of the desired/selected solid form.

Polymorphism is known since over 180 years[2] and can have major impacts on the performance of a final drug product as different polymorphs exhibit different physical properties (e.g. melting point, solubility hence bioavailability,…). During the last years, the focus in solid form screening moved from thermal methods to solvent based techniques which can be automated rather easily.[3] Nevertheless thermal analysis still plays a major role in the solid form development cycle, e.g. in developing a correlation diagram of the observed solid forms. DSC measurements are crucial to understand phase transitions,[4,5] defects in crystals[6] and are a simple way to determine the presence of a low temperature polymorph. DSC experiments can also be used as a preparative technique to produce high temperature modifications in analytical amounts to further analyse the modification by XRPD or spectroscopy. Simple experiments allow to analyse the enantiotropic or monotropic relationship between different solid forms. In addition TG analysis coupled to evolved gas analysis help to better understand the stability of hydrates or solvates.

A special case is the analysis of amorphous material. Thermal analysis is a valuable tool to understand the behaviour of amorphous material or amorphous fractions during heating and also to determine the effect of tempering on the glass transition. Using mid-pressure pans the influence of humidity or solvent vapour pressure on the glass transition can be detected. To circumvent a recrystallization in many cases the amorphous API is stabilized by embedding into a polymer matrix. DSC analysis is one method to determine the miscibility of the API and the polymer[7] next to other techniques like AFM.

Thermal analysis is still a powerful screening technique and a key solid-state analytical technique which is used during the whole drug development process. The generated data is essential for the right solid form selection to prohibit future problems during manufacturing or shelf life with respect to the selected solid form.



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