

Thermal Analysis of Drug Hydrates – Problems and Solutions

U. J. Griesser

Institut für Pharmazie, Universität Innsbruck, Innrain 52, A-6020 Innsbruck

About one third of the drug compounds show the ability to form crystalline adducts with water, called hydrates. The importance of hydrates in industrial pharmacy is pointed out by the fact that most of these compounds are used and manufactured in the hydrate form rather than in the anhydrous state. This is obvious as water is involved in many manufacturing steps and a hydrate is usually the thermodynamically stable form in an aqueous medium.

Thermal analytical techniques hold a key position in the characterization of hydrates but due to the increased number of phase changes (desolvation, melting, solid-solid transformation) and the high potential of forming a variety of different product phases upon heating (polymorphs, hydrates with lower stoichiometry, amorphous form etc.), complex solid state reactions mechanism may occur. Thus the thermal analysis of hydrates can be a particular analytical challenge and it is essential to apply a variety of experimental conditions and to combine thermal methods with other analytical techniques such as x-ray powder diffraction or moisture sorption studies.

This presentation is an approach to summarize and classify main factors that determine the thermal behavior of stoichiometric hydrates. The reflections are based on the studies (preferentially hot stage microscopy, differential scanning calorimetry and thermogravimetry) of a number of different hydrates with different chemical structures.

In order to understand the thermal behavior of hydrates it is advantageous to consider a) the stability of the hydrate in a dry atmosphere, b) the particle size and c) the water solubility. For hydrates that lose the water under dry conditions the atmosphere (*e.g.* sample in hermetically sealed or open container), the heating rate and the particle size are crucial parameters for the observed behavior upon heating. Hydrates of highly water-soluble compounds generally tend to melt congruently whereas less soluble or insoluble compounds often show incongruent or no melting. The analysis of single crystals is important to clear up the mechanism and kinetic control of a dehydration reaction. Since hydrates are binary crystals their basic thermodynamic picture is given by a binary *T-c* phase diagram between water and the compound. Such phase diagrams are accessible by DSC for isochoric conditions but, however, are rarely observed for hydrates. Finally it will be shown that also the formation of a particular anhydrous form or a mixture of polymorphs is strongly depending on the dehydration conditions and that a goal directed thermal characterization of a hydrate requires an adequate experimental strategy.