Efficient use of TG-MS Coupled Technique in Pharmaceutical Development

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TG analysis is well used in pharmaceutical development for the study of pseudo-polymorphism, for the determination of the volatile impurities in release and stability studies of drug substance as well as for the compositional analysis of drug products. The on line detection and identification of all volatiles by MS add an high value for the speed of analysis and for the quality of the delivered information which are needed in early development.
Three types of applications are given. The first type of application deals with the proper detection of solvates which are often formed in crystallisation processes. For the first substance a stable anhydrous form or a metastable hydrate may be obtained in the crystallisation mixture ethanol-water. In acetone a solvate is obtained. For the second substance many solvates were formed and two anhydrous forms were identified. The choice of the solvent, ethyl acetate, was mandatory for a reproducible manufacture of the anhydrous form. The solvent may be also bounded in channels and upon storage water may replace the solvent. TG-MS is very useful for the detection of such cases.
TG is applied routinely for the determination of the volatile impurities and replaces the classical test of loss on drying at constant temperature where the conditions of drying are often dependant on the particle size and on the amount of substance. Since the method is dynamic, the TG curve gives reliable results with very small amounts of material. The method should be validated in order to demonstrate that all solvents are determined. TG-MS allows to identify the steps where solvents are evolved. For a substance crystallised in a mixture water/acetone, the solvent acetone is encaged in the drug and is evolved only during the melting. Since decomposition occurs during the melting process, residual solvent acetone is not accurately determined by thermogravimetry. Other examples include the identification of different solvents in a substance, the detection of residual methylene chloride in a microsphere formulation and the determination of the steps where water and acetic acid are evolved in a peptide. A further example deals with a change of the drying process by comparing two batches of a hygroscopic drug. Both batches contain water. Ethanol is present only in the new batch.
TG-MS allows the accurate study of the decomposition during the melting or after the melting of substances as for example butylhydroxytoluene. Decompositions with formation of water and CO2 are easily determined as demonstrated for a malonate salt of a drug substance with formation of the base.