PO7

Thermogravimetry as routine analysis, determination of Accuracy

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Thermogravimetry is a very efficient technique in pharmaceutical development since the dynamic method allows to follow every process correlated with change of mass in a very broad range of temperature. The advantages of automatic instruments in development is obvious since different conditions can be chosen for each sample. Sensitive instruments allows limits of quantitation in the range of 0.1% with less than 1 mg sample. The use of the technique as routine for release and stability testing in GMP conditions was possible when automatic instruments allowed that the sample does not lose volatile impurities nor absorb moisture before the measurement. The TGA instruments used in the laboratory are built in such a way that samples are introduced in sealed pans and that a pin hole is made just at the beginning of the measurement. Pharmacopeas (Ph. Eur., J. Ph., USP) describe the technique, therefore it is now used in production in replacement of the 'loss on drying' test. We described in References 1, 2 examples of calibrations and examples of validation in accordance to ICHQ2.
The validation of the method should demonstrate the repeatability, the intermediate precision and the robustness of the method.
According to ICH accuracy can be demonstrated by comparison with other validated techniques. But if the samples do not contain sufficient amount of volatile impurities, spiking experiments covering the range of the specifications should be performed.
Examples of accuracy obtained by comparing results of thermogravimetry with results of GC for residual solvents and Karl Fischer are adequate if the TG values of batches are >0.3%.
For the other cases spiking experiments with solvent or water revealed serious instrumental hurdles. In addition the solvent is only adsorbed on the surface and not encaged as it often the cases for organic substances. Several hydrate-standards were tested: the temperature range of the lost of crystal water should be lower than the melting-degradation temperature of the substance to be validated. Experiments with lactose monohydrate revealed very promising results. Lactose monohydrate is proposed for adequate accuracy testing for substances with decompositon temperatures > 180°C.

References:

1) Giron, D., Characterization of pharmaceuticals by thermal analysis. Am. Pharm. Rev. **2000**, *3 (2)*, 53-61 and *3 (3)*, 43-53.
2) Giron, D., Thermal Analysis of Drugs and Drug Products, in *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., **2002,** Swarbrick, J. and Boylan, J.C., eds, Marcel Dekker, p.2766-2793.