Microcalorimetry and routine control of amorphous content, validation examples

Stephanie Monnier, Thomas Buser, Danielle Giron, Michael Mutz
Novartis Pharma AG, Chemical and Analytical development, Basel

Unit operations involving solids such as milling, micronisation, drying… can induce the formation of a amorphous phase in crystalline materials. The presence of amorphous parts in a drug substance could have a significant impact on its dissolution behaviour, bioavailability and toxicity. Moreover, as the amorphous phase is an unstable state it could convert to a more stable crystalline state which leads to a decrease of dissolution, bioavability and an increase of particle size. In the same way, it is likely that reactions take place in the more disordered amorphous regions of the solid. According to the storage temperature and the relative humidity (RH), the amorphous phase can evolve towards various crystalline varieties.

Detection and quantification of the amorphous content in a sample is therefore very important for the drug substance as well as for the excipient. For optimisation of the production process and for quality control a robust and sensitive method to quantify amorphous phase in the sample is required. Although several analytical methods can be applied (XRPD, DSC, DVS, RAMAN, heat of solution…) one of the most sensitive method is isothermal microcalorimetry. This method is generally applied by subjecting samples to various relative humidity, but any organic vapour can be employed and have a similar effect on the recrystallization behavior of amorphous parts.

The present work focuses on the development and validation of isothermal microcalorimetry methods for quantification of amorphous part in drug substances as routine analysis. Typical examples will be presented to emphasize the importance of the selection and optimisation of the solvent vapour used to induce spontaneous recrystallization of the amorphous part. The validation of quantitative method of amorphous material including the determination of the limit of detection and the limit of quantification will be discussed.