Determination of amorphous content: Comparison of microcalorimetry, DSC and X-ray diffraction

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In the manufacture of drug substances or in the processing of pharmaceutical solids degrees of disorder through the formation of defects and amorphous regions are often observed. The amorphous state is mostly detected after lyophilization, spray drying or milling. It results in an higher energy state than the crystalline state. This can result in more advantageous properties such as enhanced dissolution rate or better tabletting properties. It can also give rise to increased chemical instability and difficulties for mixing and milling. Solid-state transformation upon storage is the most inconvenient property since the driving force is the kinetic, which is often difficult to maintain as slow as possible. Furthermore depending of the conditions metastable or stable forms may result. Amorphous forms are hygroscopic and absorbed water plays the role of plasticizer, resulting to the lowering of the glass transition. It results an accelerated process of crystallization.

Therefore it is necessary to develop analytical techniques able to determine the batchwise quality of drug substances, excipients and drug products..

Two drug substances have been studied by using different analytical methods. The first substance is available as hydrochloride and as base. The analytical parameters of the microcalorimetric method are discussed and results given.For the hydrochloride the X.ray diffraction results are given.

For the second drug substance, the amorphization by milling or spray drying was observed by the crystallization peak of the DSC curve. X-ray diffraction and DSC are compared. First results of solution calorimetry and microcalorimetry are discussed.

For the three compounds X-ray diffraction is quite reliable, precise and easy to be used in ranges 10-100% amorphous content. With microcalorimetry 1% of amorphous form can be determined if crystallization can be induced by temperature and moisture. The crystallization peak in DSC can also detect levels of amorphous forms in the 1% range.

For all techniques the transformation of the amorphous form into the crystalline state is an artifact to be taken into account in all measurements, making difficult comparison of same samples.