The use of organic vapour atmospheres to quantify amorphous content in pharmaceutical substances by isothermal microcalorimetry.

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Most unit operations (milling, micronisation, drying…) involving solids can induce the formation of a finite amount of 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 will 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.[1]

Detection and quantification of the amorphous content in a sample is therefore very important for the drug substance as well as for the excipient. A sensitive method to detect and quantify the amorphous content is isothermal microcalorimetry. This method is generally applied by subjecting samples to various relative humidity, but any organic vapour can be employed and should have a similar effect on the recrystallization behavior of amorphous parts.[2]

The present communication focuses on the investigation of the recrystallization of hydrophobic compounds by using organic vapors. In the light of these considerations the influence of 3 organic solvents (MeOH, EtOH and THF) as plastifier for drug substances has been investigated by means of DSC and TGA. The obtained results are compared with those obtained in presence of relative humidity. It is shown that organic solvents cause a more important decrease of the glass transition temperature, which is believed to be a prerequiste for recrystallization.

For analytical purposes, the start of recrystallization is a critical criteria for sensitivity and time of analysis. Mixtures of organic solvent and water offer the possibility to optimise the analysis procedure. The method applied for a drug substance will be presented.

1: V. ANDRONIS, G. ZOGRAFI; *Pharmaceutical Research*, Vol. **15**, N° 6, pp. 835-842, 1998
2: H: AHMED, G. BUCKTON, D: A: RAWLINS; *Int. J. of Pharma.*, **130**, pp. 195-201, 1996