An Example of Crystal Polymorphism in Pharmaceutical Development

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It has been recognised that crystal polymorphism is an important factor related to the physico-chemical and biological properties of drug substances and formulations. There are several examples from the pharmaceutical industry where the appearance of a new crystal form significantly affected the performance of a product, sometimes with serious clinical effects. Important legal factors related to patent issues are also involved since the appearance of a new crystal structure is usually not covered by patent [1].

In this presentation, a specific problem related to crystal polymorphism in pharmaceutical development is presented. The drug as received from the production site was shown to be in a pseudo-stable state and no transformation was observed in long-term stability studies of pure form or when the drug was part in a formulation. However, a subsequent alteration of a crystallisation step in the production line radically affected the stability of the apparently stable polymorphic form. Transformation to a more stable polymorpic structure was observed with lots produced after this change in the production line.

Efforts were made to elucidate the cause of this lowering of stability. For this purpose a method based on isothermal microcalorimetry was developed with which the polymorphic conversion could be measured on-line. The drug subtance, which is hydrophobic, was dispersed into water to form a slurry whereafter the heat production was measured during the course of transition. This provided a convenient tool with which stabilising factors of the non-stable polymorphic form could be studied directly.

The slurry-process can be viewed as a solvent mediated polymorphic transition and the microcalorimetric measurements provided insight into the nature of the process. In the presentation a discussion about the transition mechanism will also be presented.

References

[1] N. Hall. *Predicting Polymorphism*. Pharmaceutical Formulation & Quality, February/March 2000.