

Problems encountered in case of compounds having a low enantiotropic transition

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Rapid recognition of the form that is thermodynamically stable under a range of relevant temperatures and water vapor pressure is required during the early stage of a product development. For this purpose, a polymorphism screening is performed to detect the most suitable crystalline form for further development. The study and the understanding of the relationships existing between the forms are very important to develop a robust manufacturing process. The aim of this presentation is to focus on the problems that can occur when a compound presents a low enantiotropic transition.

The presence of two polymorphic forms of a drug substance has been observed during polymorphism screening. A study of the relationship existing between the two polymorphic forms shows an enantiotropic transformation of modification A into modification B which was observed at about 40°C from the DSC curve. A complete reversibility of the enantiotropic transformation was confirmed by DSC measurement. The substance has a strong tendency to form solvates either by equilibration or by crystallization experiment with various solvents such as acetone, dichloromethane, tetrahydrofurane, acetonitrile, dimethylformamide, methylethylketone. All of these crystalline forms have been characterized by the usual analytical techniques such as XRPD, FT-IR, thermal analysis (DSC and TG) and electronic microscopy. From these experiments no spontaneous conversion of solvated forms into modification A was observed. In addition, DSC curves of solvated forms show a melting onset temperature corresponding to modification B observed after desolvation which occurs sometimes at high temperature.

Based on these observations, the solvent used during the manufacturing process of the drug substance has to be selected carefully.