Investigation of relaxation kinetics of hydrophobic drug substances upon micronisation

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Micronised drugs for dry powder formulations are mostly produced by air jet milling. This causes changes in the structure on the surface of the particles, often leading to a partial transformation into a metastable crystalline or even amorphous form. The subsequent relaxation of the drug substance to a more stable form can cause variability in process behaviour and pharmaceutical performance. For this reason drug substances are usually conditioned after micronisation. To control and optimise this conditioning process it is desirable to understand the crystallisation kinetics of the drug substance in different vapour environments.

Kinetic studies have been carried out by dynamic gravimetric vapour sorption. Budesonide was selected as a model drug substance and its crystallisation with ethanol vapour has been investigated. After determination of the glass transition and crystallisation point (as a function of temperature and vapour pressure) the crystallisation kinetics were studied under defined conditions by monitoring the change in mass. Crystallisation kinetics of budesonide were compared to the relaxation of the more hydrophilic compound salbutamol sulphate under controlled humidity and temperature. In addition, the energetic relaxation of budesonide under defined humidity conditions has been investigated. For the latter surface energy measurements were carried out.

Modelling shows that budesonide crystallises in a single-step reaction as a one-step process. This suggest just one stable reaction product (crystalline form). The data further allow for a prediction of the crystallisation time under the conditions given. Unlike salbutamol there is no moisture-induced crystallisation with humidity although surface energy data suggest a energetic relaxation of budesonide and a change in the acid-base properties, possibly linked to a re-orientation of surface groups.

It can be concluded that the exact knowledge of the crystallisation kinetics and the transition points allows for an accurate and time-optimised conditioning process. This avoids potential relaxation problems during manufacturing and storage.