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Physical and Chemical Aspects of Pharmaceutical Solids: Fundamentals of Polymorphs, Hydrates and Solvates

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Crystal polymorphs are solid phases of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state. Solvates form when the solvent is incorporated in the crystal structure of a compound; hydrates form when water is the solvent of crystallization. The potential effects of crystal polymorphism and hydration on the quality and performance of drug products is widely recognized by the pharmaceutical industry. Investigations of crystal polymorphism and hydration are usually conducted early in drug development to optimize the physical properties of a pharmaceutical solid. Although the thermodynamically most stable crystal form is generally selected for commercial development to mitigate the risk of undesired phase transformations, form selection oftentimes involves a compromise among different physical properties of various drug crystal forms. Controlling polymorph (or hydrate) appearance must be accomplished through careful evaluation of both thermodynamic (tendency toward the formation of more stable crystal forms) and kinetic parameters (which lead to the formation of metastable forms) in the crystallization process. In this presentation, fundamental aspects of polymorphs and solvates (hydrates) will be explored. Particular attention will be given to the structure and stability relationships between polymorphs and hydrates, kinetic vs. thermodynamic transitions, and the impact of polymorphism and hydration on the chemical and physical stability of an active pharmaceutical ingredient.