Co-Crystals of Active Ingredients: Solid State Properties for New Drug Products

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US regulations and EU regulations for the approval of drug products based on different solid state forms like salts, co-crystals, solvates, polymorphs and others seem to be on the way of harmonization. Whereas the first drafts of FDA (2013) [1] and EMA (2014) [2] defined co-crystals in different ways with strong impacts for registration, the new FDA draft guidance (2016) [3] discusses co-crystals in the same direction as the EMA white paper. This improves the potential use of co-crystals of active pharmaceutical ingredients (APIs) in drug products. The proposal is to consider co-crystals as analogous to a new salt (EMA) or polymorph of the API (FDA), respectively.

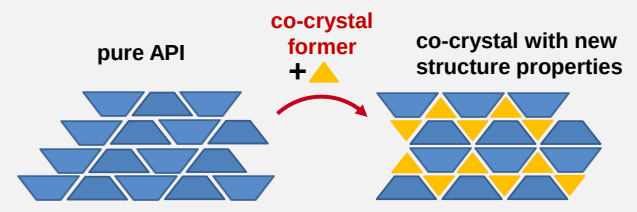

Figure 1: Co-crystal formation by placing API and a co-crystal former in the same crystal structure.

A co-crystal consists of at least two components that are solid at room temperature (Figure 1), for pharmaceutical use at least one of the components being the API. In contrast to salts, that since ever are used in drug products, at least one of the components in a co-crystal is not ionized, so that the concept can also be used for APIs that cannot be ionized. Co-crystals are new solid state forms that have new physical properties and can be patented. Properties that formulation scientists like to modify are, among others, solubility, bioavailability, hygroscopicity, chemical stability, purification and flowability.

Very few drug products containing a co-crystal of an API are in the market today. And so far no second generation drug product that makes use of better solid state properties of an API co-crystal compared to the established API has been commercialized. FABAN®, an agrochemical formulation of a co-crystal of two well known active ingredients, shows which improvement new products with optimized solid state properties can achieve.

A harmonization regarding co-crystals for pharmaceutical industry should lower the barriers to use co-crystallization for better drug products. Second generation drug products may be smaller due to higher API concentration, have higher safety due to lower drug load, consist of easier formulation, have easier processing or lower requirements regarding storage. Examples of API co-crystals that improve poor solid state properties of APIs and their potential for new drug products will be discussed.

[1] FDA; Guidance for Industry; Regulatory Classification of Pharmaceutical Co-Crystals, **2013**. [2] EMA; Reflection paper on the use of cocrystals and other solid state forms of active substances in medicinal products, **2014**. [3] FDA; Guidance for Industry; Regulatory Classification of Pharmaceutical Co-Crystals, **2016**.