Co-crystals

A pharmaceutical co-crystal is a crystalline form that can be used to change pharmaceutical properties, such as solubility, dissolution, stability, hygroscopicity, or bioavailability. Co-crystals can be used in early development for animal pharmacokinetic studies, in human clinical trials, and in marketed products.

A pharmaceutical co-crystal is a molecular complex that contains the neutral active pharmaceutical ingredient (API) along with additional neutral non-toxic molecular species (guest or coformer) in the same crystal structure [1]. The primary bonding in a co-crystal consists of hydrogen bonding, pi stacking, or van der Wals interactions (there is no transfer of a proton as observed in salts). There is a continuum between salts and co-crystals and determination of proton transfer and the designation of salt vs co-crystal can be difficult for some systems. Co-crystals can contain water or solvent in the lattice to produce a hydrate or solvate (Figure 1). Hydrates can be used for drug products, and most solvates will be an issue during crystallization. Salt co-crystals are also possible where three components are present in the lattice- free acid/base, counterion, and neutral guest [2]. Hydrates and solvates are also possible for salt co-crystals.

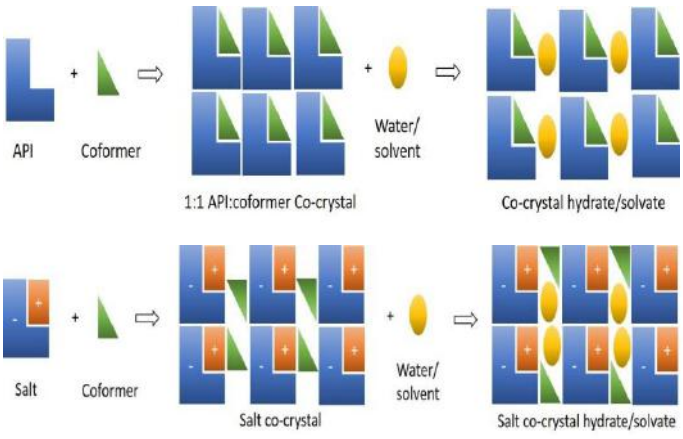

Figure 1. Schematic of co-crystals and salt

Co-crystals have been shown to change the properties of an API, including solubility, dissolution, bioavailability, hygroscopicity, and stability [1]. A co-crystal screen can be performed to find different co-crystals [3] and the first step is to compile a list of possible guests to include. Pharmaceutically acceptable guests, such as counterions used in salt screens, are initially considered, but other compounds from the GRAS (Generally Recognized as Safe) and EAFUS (Everything Added to Food in the United States) lists can also be considered, especially if the co-crystal is being used as an intermediate in the synthesis. As with salts, the toxicity of the guests will need to be evaluated based on loading, dose, and duration of therapy. Co-crystals need to be characterized to determine crystallinity, hydration/solvation state, and interactions [4,5]. Based on the screening and characterization results, a co-crystal will be selected based on the needs of the project, including the desired properties (solubility, dissolution, etc) and dosage form requirements.

Polymorphs of co-crystals are also possible and a polymorph screen should be performed on the selected co-crystal to find the thermodynamically stable form, as well as hydrates, solvates, and metastable forms (Figure 2). Dissociation of the co-crystal into the individual components (API and guest) can occur in the solid state or in solution [6], therefore, it is important to understand this aspect of the co-crystal early in development. It is also possible to produce unwanted co-crystals in liquid formulations with common excipients [7].

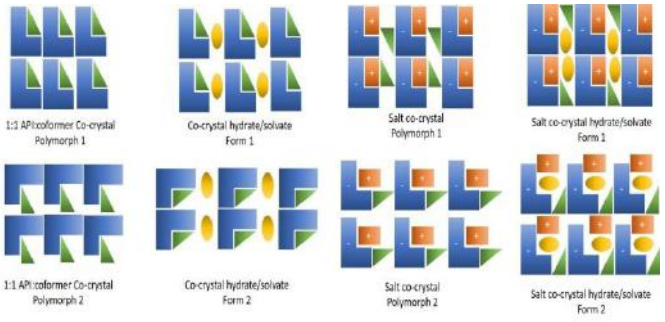

Figure 2. Schematic of polymorphs of co-crystals and salt co-crystals.

The FDA has issued a revised co-crystal guidance stating that an API designated to be a pharmaceutical co-crystal will have a regulatory classification similar to that of a polymorph of the API [8]. This is similar to the European Medicines Agency (EMA) co-crystal guidance [9]. Drug products that are designed to contain a new co-crystal will be developed ogous to a new polymorph of the API. Different co-crystals of a salt API (salt co-crystals) will be treated as a polymorph of that salt. As applicable, the pKa rule and/or orthogonal characterization data will be used to provide supporting evidence for each case. A co-crystal that is composed of two or more APIs (with or without additional inactive coformers) will be treated as a fixed-dose combination product and not a new API.

According to the guidance, data on the dissociation of the cocrystal before absorption is needed. While there are currently no marketed products containing APIs labeled as co-crystals, it is possible that there are "weak salts" on the market that are likely co-crystals. It has also been suggested that the marketed product Depakote® is a co-crystal of sodium valproate and valproic acid even though it was not previously designated as a co-crystal [10]. A large number of co-crystals currently in early and late development are expected to make it to market now that there is more clarity around the regulatory path needed for development. As with all solid forms, co-crystals can be patented as part of an intellectual property (IP) strategy for pharmaceutical compounds.

Summary

- Co-crystals and salt co-crystals are additional crystalline form that can be used to change the properties of an API, such as solubility, dissolution, and bioavailability.
- Co-crystals can exist as polymorphs, solvates, and hydrates, and characterization data are needed to identify the crystalline forms and the relationships between the forms.
- The new FDA guidance classifies co-crystals of an API similarly to a polymorph of th API.
- Co-crystals and salt co-crystals are patentable and can be added to the IP strategy of an API.

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