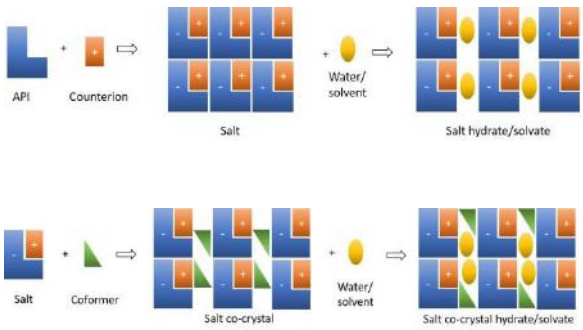
Salts

A pharmaceutical salt is a crystalline form that is commonly used to change pharmaceutical properties, such as solubility, dissolution, stability, or bioavailability. Salts can be used in early development for animal pharmacokinetic studies, in human clinical trials, and in marketed products.

A pharmaceutical salt is an acid:base complex that contains the active pharmaceutical ingredient (API) along with additional non-toxic molecular species in the same crystal structure [1]. Proton exchange between the acid and base will produce the salt. Crystalline salts can also contain water or solvent in the lattice to produce a hydrate or solvate (Figure 1). Hydrates can be considered for development into a drug product. Most solvates will not be considered for further development, but need to be investigated for other processes such as crystallization or formulation development. Salt co-crystals are also possible where three components are present in the lattice- free acid/base, counterion, and neutral guest. Hydrates and solvates are also possible for salt cocrystals.

Figure 1. Schematic of salts and salt cocrystals.



Salts can change the properties of a compound, such as improved solubility or dissolution rate [2,3]. A number of factors should be considered when developing salts that are associated with physical form or development (Figure 2). A variety of counterions can be used for the salt screen and the properties below should be considered when compiling the initial list of counterions [4]. Every salt screen/selection [5] is different-the properties of the molecules, the dosage form to be developed, the time frame involved, and other specific issues will all result in a very tailored program for that molecule.

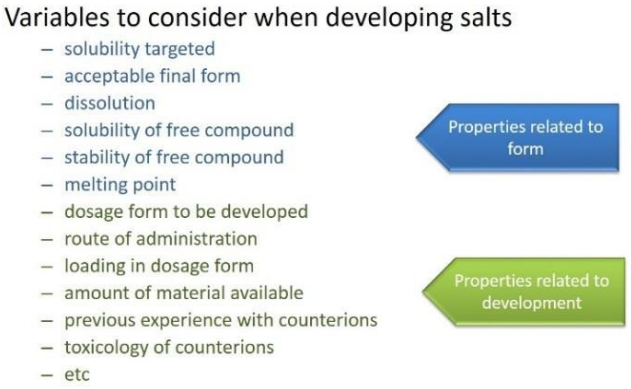
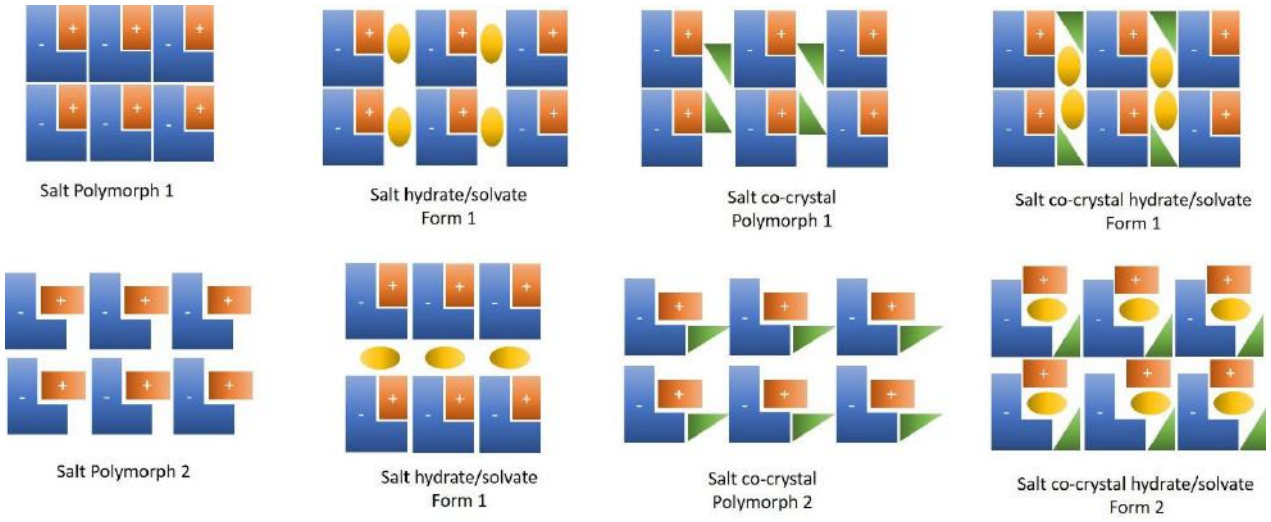


Figure 2. Variables to consider when developing salts related to form and development

Once a salt is selected it is essential to perform a polymorph screen on that salt to determine the most thermodynamically stable form, as well as possible hydrates, solvates, and metastable forms that may impact other development steps (Figure 3). Characterization will be needed to identify crystalline salt forms and quantitative methods to determine the form purity may be needed during development [6] Properties that can change with the salt form include solubility, dissolution rate, bioavailability, hygroscopicity, melting point, and physical and chemical stability [1]. Unwanted properties, such as hygroscopic behavior or dissociation of the salt into the respective acid and base in the solid or in solution [7], need to be determined early in development to prevent major issues during processing.

Figure 3. Schematic of polymorphs of salts and salt co-crystals.



Summary

- Salts and salt co-crystals are additional solid forms pharmaceutical scientists can use to change properties of an API.
- Salts and salt co-crystals can exhibit polymorphism and polymorph screening should be performed to find stable, metastable, hydrated, and solvated salt forms.
- Issues, such as disproportionation and hygroscopicity, need to be investigated for salts.

References

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