

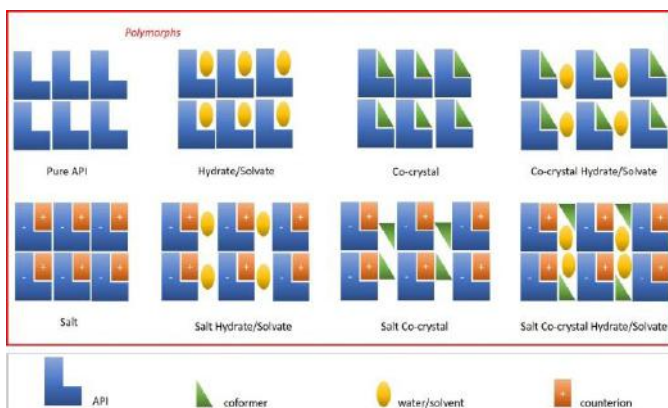


# Pharmaceutical Solid-state Forms

Solid form is a general term that refers to both crystalline and amorphous materials. The solid form will impact active pharmaceutical ingredient (API) development properties such as solubility, dissolution rate, stability, hygroscopicity, and bioavailability.

Crystalline forms can include polymorphs, hydrates, solvates, salts, and cocrystals (Figure 1). It should be noted that there are two commonly accepted pharmaceutical definitions of polymorph. The Food and Drug Administration (FDA) definition of a polymorph includes hydrates, solvates, and amorphous materials [1]. The purist definition, from solid-state pharmaceuticals, defines a polymorph as forms with the same chemical composition- two anhydrides are polymorphs or two monohydrates are polymorphs, but an anhydrate and a monohydrate are not polymorphs. It is important to understand how the term is used in publications and documentation.

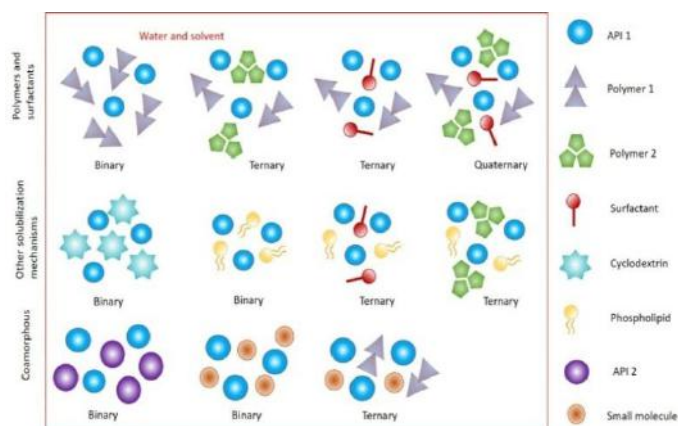
As shown below, there are neutral and charged crystalline materials and polymorphs are possible for all of these solids. In the diagram below, the term polymorph is used as forms with the same chemical composition.



**Figure 1.** Schematic of pharmaceutical crystalline forms

Amorphous materials can include amorphous drug substance, amorphous solid dispersions, and co-amorphous (Figure 2) [2,3]. Amorphous drug substances exhibit high apparent solubility but low physical and chemical stability. In order to improve stability and maintain the high apparent solubility, amorphous dispersions have been produced with polymers. The goal of the polymer is to form a miscible solid (one

phase containing the amorphous API and polymer) which decreases or prevents crystallization in the solid state and in solution [4,5]. Surfactants may also be added to form ternary or quaternary systems. The term amorphous solid dispersion



**Figure 2.** Schematic of pharmaceutical amorphous forms

has also been used for other solubilization mechanisms such as complexation (cyclodextrins) and micelle formation (phospholipids). While these systems are called dispersions, it is important to note the unique mechanism so appropriate studies can be performed to obtain a better understanding of the overall system. Co-amorphous systems have been introduced that originally contained two API molecules and have been expanded to include an API and a small molecule, such as amino acids [6]. Other reports include ternary systems containing multiple components, such as API, small molecule and polymer [7] or two APIs and a polymer [8]. For all amorphous systems, it is important to note that water and solvent content will affect the glass transition ( $T_g$ ) and stability. Therefore, initial solvent content and hygroscopicity will be important when developing these materials.

