# 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 pharmaceutics, defines a polymorph as forms with the same chemical composition- two anhydrates 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.

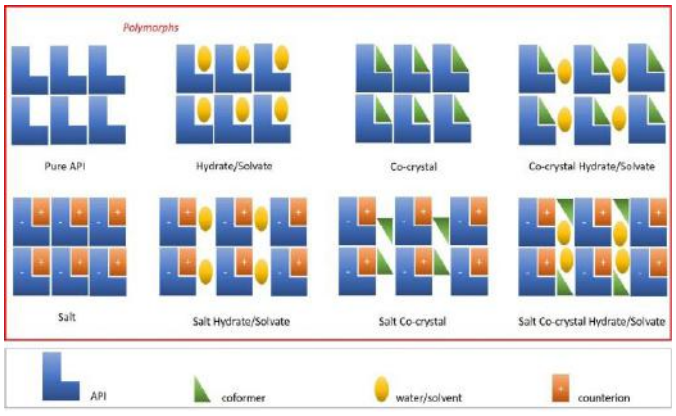


***Figure 1.*** Schematic of pharmaceutical crystalline forms

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

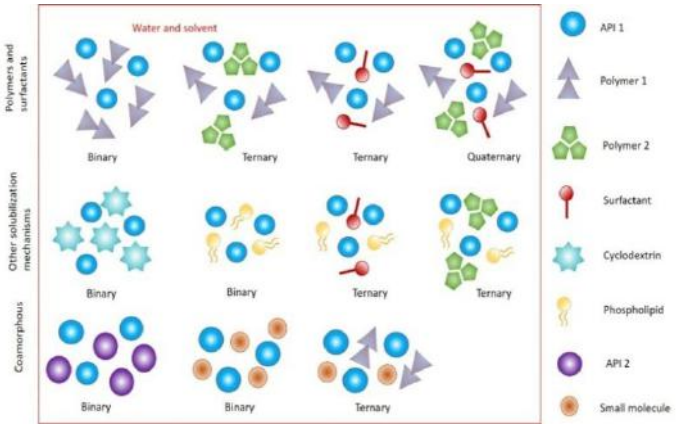


***Figure 2.*** Schematic of pharmaceutical amorphous forms

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 (Tg) and stability. Therefore, initial solvent content and hygroscopicity will be important when developing these materials.

Solid forms can be found during early and late development through screening studies [9] or through unwanted process induced transformations during processing of the API or drug product [10,11]. A variety of characterization methods are available to identify a new form and include x-ray powder diffraction (XRPD) to determine crystallinity or amorphous nature, spectroscopic methods (IR, Raman, and NMR) to identify different forms and interactions between molecules, differential scanning calorimetry (DSC) to obtain melting point and phase transformations upon heating, and thermogravimetric analysis (TGA) to find total volatile content, and vapor sorption to determine water uptake and form changes with relative humidity (RH) . Additional properties need to be considered when selecting the best form for development and these can include solubility, dissolution rate, chemical and physical stability, and bioavailability. Other properties may be needed depending on the dosage form and development plan [12].

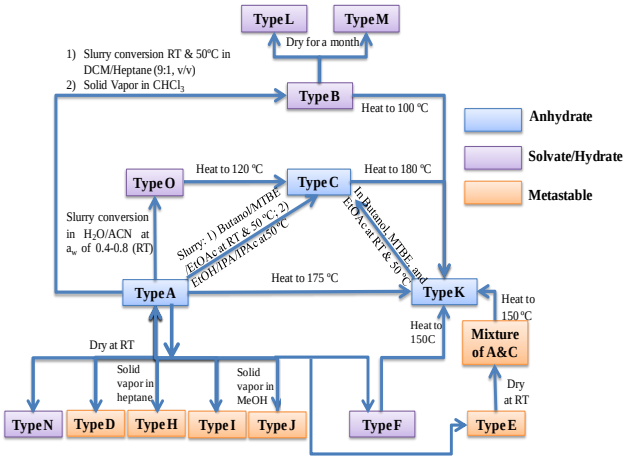


***Figure 3.*** Schematic showing relationship of solid forms for a compound.

Solid form studies will help velop an understanding of the solid form landscape and provide a "road map" of possible form transformations that may occur upon processing or during development (Figure 3). An example of a road map based on a polymorph screen is given below. Form changes under a variety of conditions are easily visualized. Based on this diagram, processes can be developed that will produce the desired form and avoid conditions that may produce other known forms.

## Summary

- Form changes during the drug development process need to be evaluated on a case by case basis.
- Changes during early development are relatively common, but changes in later development may significantly increase the time and cost of development.
- Understanding possible forms and selecting the best form early in the process can help streamline development

## References

1. Food and Drug Administration (FDA) International Conference on Harmonization (ICH) Guideline Q6A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm)

2. Pharmaceutical Amorphous Solid Dispersions, 2015, Wiley and Sons, New York, edited by A. Newman,

3. A. Newman, K. Nagapudi, R. Wenslow. "Amorphous Solid Dispersions: A Robust Platform to Address Bioavailability Challenges" Ther. Deliv. 2015, 6, 247-261

4. A. Newman, E. Munson "Characterizing Miscibility in Amorphous Solid Dispersions". Amer. Pharm. Rev.2012, April, 92-98.

5. A. Newman, G. Knipp, G. Zografi "Assessing the Performance of Amorphous Solid Dispersions". J Pharm Sci .2012,101(4), 1355-1377

6. S.J. Dengale, H. Grohganz, K. Löbmann, T. Rades, Recent advances in coamorphous drug formulations, Adv. Drug Deliv. Rev. 100 (2016) 116–125.

7. Q. Lu, G. Zografi. Phase Behavior of Binary and Ternary Amorphous Mixtures Containing Indomethacin, Citric Acid, and PVP. Pharm Res 1998, 15, 1202- 1206.

8. M.K. Riekes, A. Engelen, B. Appeltans, P. Rombaut, H.K. Stulzer, G. Van den Mooter. Pharm. Res. 2016, 33, 1259-1275.

9. A. Newman. Specialized Solid Form Screening Techniques. Org. Proc. Res. Dev. 2013, 17, 457-471

10. G.G.Z Zhang, D. Law, E.A. Schmitt, Y. Qiu. "Phase Transformation Considerations During Process Development and Manufacture of Solid Oral Dosage Form" Adv. Drug Delivery Rev. 2004, 56, 371-390.

11. K.R. Morris, U.J. Griesser, C.J. Eckhardt, J.G. Stowell. Adv. Drug Delivery Rev. 2001, 48, 91-114.

12. "Solid Form Changes During Drug Development: Good, Bad, and Ugly Case Studies" A. Newman, R. Wenslow. AAPS Open, 2016, 2(1), 1-11