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Short Communication Open Acces

# Solid State Characterization and Pharmaceutical Development

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## ABSTRACT

Pharmaceutical materials solid-state property plays a critical role from early discovery to finalizing the formulation type. Pharmaceutical material exists in a crystalline or amorphous state. The crystalline state generally shows a high melting point, less hygroscopic, low solubility, lower bioavailability, and higher Physico-chemical stability compared to the amorphous material. A major concern in the pharmaceutical industry is the selection of solids state forms for the final formulations. This is because it can significantly affect the drug product quality in terms of Physico-chemical stability, processibility, solubility, bioavailability, and having regulatory, legal, and commercial implications.

## Keywords:

Pharmaceutical materials; Crystalline; Hygroscopic

## Introduction

Pollution Intermolecular force differences can result in significant variation of the physicochemical properties between different solid-state forms of pharmaceuticals. Particle morphology, mechanical properties including powder flow ability, and compressibility are greatly influenced by the molecular packing of the crystal. The thermodynamically stable crystalline form shows a higher melting point form, lower solubility, and dissolution rate since it has higher intermolecular forces compared to metastable or amorphous form [1-4].

## Short Communication

Bahir Solid-state failure of ritonavir marketed formulation brought the attention of regulatory agencies and the scientific community about the potential need of organized decision-making tree to determine and established the best suitable solid form of the particular drug in a given condition [5-7]. As mentioned in many published literatures that solid form is important in pharmacology because an insoluble solid-state form may give undesired outcomes and lowering the efficacy, and potency of the drug. Secondly API manufacturing is also very important because regulatory agencies required information on which solid-form is being manufactured and supplied. To get the same solid form from batch-to-batch manufacturing it is important to establish properties such as solubility in crystallizing solvent, metastable limit, and other solid-state properties to make a robust manufacturing process. It is imperative to establish the solid-state properties of the drug used in the formulation in early developmental research to circumvent drug as well as drug product failure. Therefore, in addition to traditional analytical tests such as chromatography, UV-spectroscopy, and dissolution testing it is important to include solid state characterization analytical techniques in decision making process [8-15]. These solid-state properties information will help the chemists and formulation scientists to assemble necessary information and develop a robust, most efficient process to design crystallization process and drug delivery system, respectively.

## Significance of Solid-State Characterization

A solid form of the API plays a decisive role in the development of a commercial pharmaceutical product [16,17]. The formulator perspective's first choice is a selection of thermodynamically most stable form for the final formulation development to lower the potential risk associated with product stability. Most of the new drugs fall in the BCS class of II and IV because of poor water solubility, which ultimately causes a lower dissolution rate and that may not be adequate to achieve good bioavailability. Therefore, to achieve a certain level of the drug in the blood different enabling technologies Solid-lipid nanoparticles, self-micro emulsifying (SMEDD), self-nano emulsifying (SNEDD), liposomes, complexation, solid dispersion, and nanosuspensions being used to increase the apparent solubility of the drug [18-20]. However, most of the enabling formulations have their limitation and potential challenges leading to their inherently lower physical and chemical stability.

For example, the high hygroscopicity of amorphous material may lead to increased chemical reactivity and the propensity to crystallize, since the absorbed moisture acts as a plasticizer. The stability of amorphous material is improved by making solid dispersion where the drug is molecularly dispersed with the polymer and the polymer acts as crystallization inhibitor either because of steric hindrance or viscosity. In these approaches, physical stability is often a concern, however, since crystallization of the drug during storage would

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negatively impact the solubility and intended therapeutic efficacy of the product.

A second such example is nanoparticle formulation since the nanoparticles have higher surface energy which leads to its potential to increase the individual particle size by ripening or agglomeration over the period. This indicates that because of the high free energy environment drug in the formulation may not be stable during the intended downstream process or the storage time. Unlike small organic drug molecules, in the solid protein formulations, the excipient's solid-state form plays a crucial role in product stability and performance. To stabilize the protein formulation interactions with stabilizing excipients are very important that can occur only when the excipient and protein molecules both are in the same amorphous phase. Therefore, in protein formulation protein aggregation and loss of therapeutic activity are mainly caused due to the crystallization of stabilizing excipient.

Drug or excipients solid-state forms are critical in defining product stability or efficacy; therefore, it is important to maintain consistent solid-state form through the drug product processing steps. However, as mentioned earlier having higher kinetic energy could lead to solid-state transformations, and it is not uncommon to see such incidences during pharmaceutical processing or storage. The solid-state formation could result in getting a pure phase of one form or a mixture of forms. Most commonly a mixture of forms is seen as a result of such transformation, one such example is an occurrence of hydrate-anhydrate mixtures caused because of routine manufacturing processes. Pharmaceutical manufacturing involves several unit operations including milling, granulation [21], drying, tablet compression [22], and coating; this involves high thermal and mechanical stresses, exposure to solvents, which may induce solid-state transformations. Unlike drugs, excipient manufacturing is not strictly controlled leading to different solid states between the manufacturers. To make good quality, robust, reproducible process product assessment of solid-state forms during manufacturing and storage are imperative. If pharmacologically accepted, then early detection and quantification of transformations will help to set the acceptable limit of such changes. Process analytical technology (PAT) tools are important to discover such solid-state transformations during the process and help to control and optimize the processes to make a cost effective and good quality product.

## Solid-State Characterization Techniques

Solid-state characterization of the pharmaceuticals is essential in drug discovery as well as in preformulation studies. Literature suggests that moving solid-state characterization earlier and earlier in drug discovery ensures that a developable solid form is physically and chemically stable. In solid-state characterization, an important goal is identifying the differences between amorphous and crystalline materials.

Several solid-state characterization techniques are used to analyze pharmaceutical materials. Generally, data from two or more techniques are required to establish the relationship between the solid-state, and the choice of technique is depending on the level of understanding required. The most commonly used methods for solid-state characterization have been X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapor sorption (DVS), mid-infrared spectroscopy and microscopy and solid-state nuclear magnetic resonance (ss-NMR). Other routine techniques which are mainly used as process monitoring and control (PAT) tools are Raman spectroscopy, near-infrared spectroscopy (NIR), and Blaze imaging techniques. The top six analytical techniques are briefly discussed later.

The long-range order of molecular packing can be easily observed with XRPD [23,24]. Crystalline material powder pattern will show sharp intense peaks in diffractogram unlike amorphous which only shows halo because of the lack of in-phase reflections from crystal planes. A different crystalline form of the same material will show a unique powder pattern which helps to determine the phase purity of the material. The second most important analytical tool could be differential scanning calorimetry (DSC) in which crystalline material will show sharp melting endothermic event, unlike amorphous material which will only show glass transition temperature (Tg) [25]. However, sometimes finding Tg of the amorphous material may need some modifications in DSC experiments involving slow ramp rate or changes in the modulation temperatures. Secondly, DSC can be very useful in determining the enantiotropic or monotropic relationship between two crystalline forms of the same material [26].

## Conclusion

Most often DSC data is correlated with the TGA data to determine if the resultant crystalline form is solvated, hydrate or anhydrate. The water activity or DVS data helps to determine the stability of the solid form under different equilibrium relative humidity conditions. Vibrational spectroscopy mainly is routinely used in crystallization because of its ability to distinguish two crystalline forms dues to the differences in intermolecular bonding. A polarized microscope (PLM) is a quick test to find if the material is amorphous or crystalline, under PLM crystalline material will show birefringence which will be absent in amorphous material. However, PLM alone is not useful in distinguishing different crystalline forms of the same material unless they have specific crystal morphology.

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