

Preformulation: Emphasis on Solid State Characterization and Its Implications on Pharmaceutical Development

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INTRODUCTION

Preformulation in pharmaceutical development plays very important role in successful making of any drug into its drug product. Elaborative pre-formulation investigation in early development program helps to avoid drug product failures [1]. From the pre-formulation perspective selection of solids state form and right choice of formulation type is very critical, because it can significantly affect the drug product property including chemical stability, solubility, bioavailability, etc [2]. Leading to major regulatory, legal and commercial implications. Most often seen in early development program primary goal is to move forward drug candidate into clinical trial [3]. During this development phase, target is to achieve desirable bioavailability but the long-term physical, chemical, and solid-state properties are simply overlooked. Which could have serious implications when drug reaches in next phase to develop a prototype formulation in short period of time? Based on published literature and author's experience suggestion is that once a new chemical entity is found in early discovery showing desired pharmacological responses in pre-clinical trials, then drug should be tested for its solid-state and preformulation properties. In preformulation the drug is investigated alone or in combination with excipients. The main goal is to gain comprehensive understanding of a drug substance or drug product intermediate to evade any undesirable surprises in advanced developmental stages [4].

To start with, preformulation study involves study of essential physicochemical and solid-state properties of the drug before beginning of dosage form development. Findings from these studies can be very useful for the formulators to understand the intrinsic properties of the drug and what needs to be done in order to design a desired formulation with desirable solubility, dissolution, bioavailability, physical-chemical, solid-

state stability and processability [5-10]. Furthermore, different types of excipients are also studied in combination with drug to understand the behavior of the molecule in presence of inert material [11]. In this editorial note we intend to provide a general methodology for conducting preformulation studies and brief discussion on solids-state property, and its importance in pre-formulation studies.

PREFORMULATION STUDY

Preformulation collectively involves the understanding of drugs' intrinsic property, solid-state property, kinetic effect on solubility and bioavailability, etc. This can be studied in parallel or in sequential order. Study order and techniques used may vary from lab to lab because it is dependent on the scientist's opinion and availability of required instruments or equipment [12]. Based on our experience we are suggesting following order to conduct pre-formulation testing. To mention this order is subject to vary depending on the different factors including but not limited to potency and therapeutic class of the drug. Preformulation studies can be categorized into four main categories.

Physical and chemical property evaluation

1. Melting Point
2. Solubility studies
 - Organic solvents, kinetic and equilibrium studies in physiological pH buffers and biorelevant media [13]
 - Effect of temperature, pH-solubility profile, dissolution rate constant, common ion effect and similar studies [14,15]
 - a. Partition co-efficient (Log P)
 - b. Dissociation constant (pKa) [6]
 - c. Stability studies (e.g., solution state, forced degradation studies) [10,16-20]

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Solid-State property evaluation [4]

1. Solid form investigations and selection
 - Polymorphs/pseudo-polymorphs
 - Salts and cocrystals
 - Amorphous form
2. Solid-state stability at different storage condition

Bulk properties [21]

- a. Particle size and particle shape
- b. Micromeritic properties
 - Bulk, tapped, and true density.
 - Powder flow properties
 - Compaction studies
- c. Drug-excipient compatibility studies
- d. Drug product risk assessment studies for the intended pharmaceutical unit operations

Optional preformulation studies [5,22]

- a. Computational materials science
 - Screening counterions for salt/co-crystal formation
 - Polymorph predictions
 - Predicting the mechanical properties
 - Solubility predictions
- b. Single crystal determination
- c. Quantifying the different solid forms of a particular salt using a mathematical model

SIGNIFICANCE OF SOLID-STATE CHARACTERIZATION

For the flow Solid form selection plays pivotal role in commercial pharmaceutical product development. Ideally, selection of thermodynamically most stable form for the final formulation should be preferred in order to avoid the potential risk associated to product failure. Significant number of recently discovered molecules is BCS class II and IV, resulting in poor aqueous solubility. Poor solubility is biggest hurdle in product development for most of the recently discovered molecules. To improve the aqueous solubility different enabling technologies are being used including solid-lipid nanoparticles, self-micro emulsifying (SMEDDS), self-nano emulsifying (SNEDDS), liposomes, complexation, solid dispersion, eutectics, and nanosuspensions [15,23-25]. However, most of these enabling technologies either results in amorphous material or solution state material which may lead to potential problems by lowering physical and chemical stability. Few such examples are discussed later in this section.

Nanoparticle formulation is very famous and widely studied for their different application including kinetic solubility enhancement and permeability in some cases. The technical difficulty with the use of nano formulations is maintaining constant nanometer size range of the particles [26]. Because

of the nanometer size, particles have higher surface area and surface energy leading to ripening and causing agglomeration between the particles over the period of time. Therefore, in nanoparticle-based formations it is imperative to characterize the solids' property in terms of particle morphology, particle size distribution, and form stability.

Another common approach to improve the aqueous solubility is to make amorphous material. Thermodynamically, amorphous material has higher kinetic solubility caused by absence of long-range order, essentially requiring less energy to dissolve the solids. However, amorphous material has higher free energy which potentially could lead to recrystallization. Therefore, in amorphous formulation keeping amorphous state is key and difficult. One such example is high hygroscopicity of amorphous material may acts as a plasticizer and increased chemical reactivity, which may cause recrystallization of amorphous material over the period of time. To mitigate the risk of recrystallization, use of solid dispersion technique is widely preferred. In solid dispersion drug is molecularly dispersed with polymer which inhibits the recrystallization by lowering drugs' molecular mobility caused by steric hinderance or increased viscosity. However, these approaches are meant for inhibiting or mitigating risk of recrystallization for a period of time and at a given condition. Therefore, it is very important to use solid-state characterization techniques to confirm the solid state. The best approach to determine and confirm the amorphous state of the material is by X-ray diffraction and differential scanning calorimetry.

Recently, because of limited stability of amorphous materials, nanoparticles, etc. industry is inclining towards using alternative solid-state forms such as salts and co-crystals. Compared to amorphous state, salts or co-crystals may have lower solubility but it tends to have better solid-state and chemical stability. Drugs which have ionizable species are preferred choice for the salt form, while non-ionizing drug candidate are the preferred choice for the co-crystal. Published literature suggests that one drug candidate can form different salts or co-crystals and may have different physical-chemical properties. Therefore, selection of best alternative form needs in-depth form screening analysis. This indicates that solid state characterization is very imperative.

Drug or excipients solid state property is central in defining product stability or efficacy; therefore, it is critical to sustain consistent solid-state form from drug product development to its storage period. However, as cited earlier having higher kinetic energy could lead to solid-state transformations, and it is not rare to see such occurrences during pharmaceutical processing or storage. Solid state transformation results in pure phase or the mixture of solid forms which essentially lead to solubility change and bioavailability. Generally, mixture of forms is outcome of such transformation, one such example is occurrence of hydrate-anhydrate mixtures caused because of routine manufacturing processes. Pharmaceutical manufacturing involves several unit operations including milling, granulation,

drying, tablet compression, and coating, this involves high thermal and mechanical stresses, exposure to solvents, which may induce solid-state transformations. To make good quality, robust, reproducible process, and product assessment of solid-state forms during manufacturing and storage is critical. If pharmacologically accepted, then early detection and quantification of transformations will help to set the acceptable limit of such changes.

SOLID-STATE CHARACTERIZATION TECHNIQUES

Moving solid state characterization earlier and earlier in drug discovery helps to achieve developable physically and chemical stable solid form. It is recommended that depending on the level of understanding required, data from two or more techniques are required to establish the relationship between the solid states. 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). Process monitoring and control (PAT) tools including Raman spectroscopy, near-infrared spectroscopy (NIR), and blaze imaging techniques are mainly used for the in-process monitoring. In this editorial we have briefly discussed about the most commonly used solid-state characterization technique.

Differential scanning calorimetry (DSC) measurement provides sufficient information to characterize the chemical purity, solid-state stability, determining solvates, and finding relationship between the polymorphs. Three major thermal events from DSC are endotherm (melting or desolvation or dehydration), exotherm (recrystallization), and glass transition (amorphous). Relationship between the polymorphs can be established by comparing the melting temperature and melting enthalpy of each thermal event [27]. This gives the basic understanding about the enantiotropic vs. monotropic behavior of the material. Risk of salt disproportionation as a function of temperature can also be characterized. Reversible heat flow shows the glass transition event for amorphous material which could be very useful in determining the potential temperature range where material may or may not have tendency to recrystallize. Most often data from DSC is correlated with the thermogravimetric analysis (TGA) in determining the amount of solvent/water present in the material. DSC and TGA are generally performed in temperature range of -20°C to 300°C with a repeatability of $\pm 0.1^\circ\text{C}$.

X-ray powder diffraction (XRPD) is most preferred technique to establish if the material is amorphous or crystalline, and if it is crystalline then it is pure form or the mixture of forms. Diffraction studies provide the unique pattern for each form except for isostructural materials. This is fast and non-destructive technique. X-ray powder diffraction (XRPD) studies are generally carried out to determine a distinct crystalline form in the 2 θ -range of 2°-40° for small molecules. Method development becomes very important for qualitative and quantitative analysis of undesired

crystalline form in the material. Recent literature suggests that XRPD technique can be successfully used to quantify and confirm the content of active pharmaceutical ingredient in presence of the excipients.

Raman and Fourier Transform Infrared (FTIR) are the commonly used spectroscopic methods to differentiate different crystalline (one form vs. between the forms) and amorphous solid forms. These techniques can be used offline as well as inline measurement. *In situ* analysis helps in process optimization to reject the undesired crystalline form during the robust crystallization process development [28]. Near Infrared (NIR) spectroscopy has been used to monitor the wet granulation process during the fluid bed granulation process to obtain uniform quality and size granules for further tableting process. Solid-state nuclear magnetic resonance (NMR) can be useful in identifying the number of asymmetric units in the unit cell along with the stoichiometric of salt, co-crystal, hydrate and/or solvate.

CONCLUSION

Preformulation studies are essential for the long-term clinical success of potential drug candidate. Early involvement of preformulation and solid-state characterization can help to find suitable solid form and best drug delivery approach. In addition, solid-state characterization plays important role in early drug discovery phase to find thermodynamically stable polymorph which can be further promoted to as a lead candidate and avoid any failures caused by the metastable form. 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 cost-effective and good quality product. Alternative solid form such as salts and co-crystals instead of amorphous materials could be the best approach to achieve good aqueous solubility, and better chemical and solid-state stability.

CONFLICT OF INTEREST

We have no conflict of interests to disclose and the manuscript has been read and approved by all named authors.

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