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SOLID STATE CRYSTALLINITY, AMORPHOUS STATE, AND ITS IMPLICATIONS IN THE PHARMACEUTICAL PROCESS

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ABSTRACT

Many drugs exist in crystalline solid form due to reasons of stability and ease of handling during the various stages of drug development. Crystalline solids can exist in the form of polymorphs, solvates or hydrates. Phase transitions such as polymorph inter-conversion, formation of hydrates, desolvation of solvates, and conversion of the crystalline to amorphous form may occur during various pharmaceutical processes. This could change the dissolution rate and transport characteristics of the drug. The current focus of research in the area is to understand the origins of polymorphism at the molecular level, and to predict and prepare the most stable polymorph of the drug. The aim of this review is to understand the recent development in the area of solid state crystallinity, amorphous state and to address the current challenges faced by pharmaceutical formulation, process development scientists and to anticipate future developments.

INTRODUCTION: Many compounds of pharmaceutical interest can exist in more than one crystalline form. The structure of a given crystal may be assigned to one of the seven crystal systems, to one of the 14 Bravo's lattices, and to one of the 230 space groups compiled in the International Tables for Crystallography [1-3]. The common crystal forms are polymorphs and solvates. Polymorphs have different internal crystal structures and therefore possess different physicochemical properties.

Solvates, also known as pseudo polymorphs, are crystalline adducts containing solvent molecules within the crystal structure, in either stoichometric or non-stoichometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug. If the entrapped solvent is water, it is termed as a hydrate. Adducts frequently crystallize more easily because two molecules can often can bond together with less difficulty than a single molecule. Desolvated solvates are less ordered than their crystalline counterparts and are difficult to characterize, because analytical studies indicates that they are unsolvated materials (or anhydrous crystal forms) [4].

Significance of Solid State Crystallinity: Various crystal forms and solvates differ in crystal packing and /or molecular conformation as well as in lattice energy and entropy. This can cause significant differences in their physical properties such as density, hardness, tableting, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, color, and other thermodynamic and kinetic properties [5].

Differences in the physical properties of various solid forms have an important effect on the processing of the drug substances into drug products. The differences in solubility may have an implication on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules [6-7]. For approval of a new drug FDA insists on appropriate analytical procedures to detect polymorphism, hydrates and amorphous forms; and also stresses the importance of controlling the crystalline forms during the various stages of drug product development [4].

Pharmaceutical Processing and Phase Transformation: Various pharmaceutical processes during drug development significantly influence the final crystalline form of the drug in the dosage form. Processes such as lyophilization and spray drying may lead to the formation of an amorphous form of the drug, which tends to be less stable and more hygroscopic than crystalline products. Processing stresses such as drying, grinding, milling, wet granulation, oven drying and compaction are reported to accelerate the phase transition in pharmaceutical solids [8].

The presence of a metastable form during processing or in the final dosage form often leads to instability of drug release as a result of phase transformation [9]. The factors affecting the rate and mechanism by which crystals formed are; stability, supersaturation and desupersaturation occurrence, diffusivity, temperature and the reactivity of surfaces towards nucleation. The various forces responsible for holding the organic crystalline solids together, such as non-bonded interaction and hydrogen bonding have been discussed by Byrn *et al.,* and Etter [2, 10].

Recent Advances in the Prediction, Identification and Characterization of Polymorphs: The single most valuable piece of information about the crystalline solid, including the existence of polymorphs and solvates is the molecular and crystalline structure, which is determined by single crystal X-ray diffractometry and powder X-ray diffractometry [11]. It will give a fingerprint of the

solid phase and sometimes used to determine crystal structure as established by spectral methods such as Fourier transform infrared absorption spectroscopy, Fourier Transform Raman spectroscopy, Solid state nuclear magnetic resonance spectroscopy and UV-VIS spectroscopy. Thermal methods such as Differential scanning spectroscopy (DSC), thermal gravimetric analysis (TGA) and optical microscopy using hot stage are also used for further characterization [12].

Modulated DSC in combination with DSC and optical microscopy are able to identify the glass transition temperature (Tg) of amorphous forms with much greater clarity and allows unique insights into the glass transition and polymorphic behavior of drug substances [13]. Solid state ^{13}C NMR in conjunction with techniques known as high power proton decoupling, cross polarization (CD), and magic angle spinning (MAS), offers information not obtained readily by other techniques.

Two dimensional NMR and total suppression of spinning side bands pulse sequences are also used as powerful methods for analyzing the differences in the chemical environment and is finding increased application, like discovering variation in the hydrogen bonding network and molecular conformation among polymorphisms.

Polymorphic Forms: Based on differences in the thermodynamic properties, the polymorphs are classified as either enantiotropes or monotropes, depending upon whether one form can transform reversibly into another or not. In an enantiotropic system, a reversible transition between polymorphs is possible at a definite transition temperature below melting point. In a monotropic system, no reversible transition is observed between the polymorphs below melting point. Four reversible rules have been developed to determine qualitatively the enantiotropic or monotropic nature of the relationship between polymorphs [14-15]. These rules are the heat of transition rule, heat of fusion rule, infrared rule and density rule. The plotting of Gibb's free energy difference, ΔG, against the absolute temperature, T, given the most complete and quantitative information on the stability relationship of polymorphs with the most stable polymorph having the lowest Gibbs free energy [16]. ΔG between the polymorphs may be obtained using several techniques operating at different temperatures such as solubility and intrinsic dissolution rates [17].

Extrapolating ΔG to zero gives an estimate of the transition temperature, from which the existence of monotropy or enantiotropy is inferred. Another approach to establish the order of stability among various polymorphs has been studied using pressure versus temperature plots, e.g., for sulfanilamide and piracetam [18]. This approach is based upon Ostwald's principle of least vapor pressure according to which the stable polymorph exhibits the lowest vapor pressure.

Organic molecules are capable of forming different crystals lattice through different mechanisms such as packing and conformational polymorphism. In packing polymorphism, the rigid molecules can be assembled into different three dimensional structures through the invocation of different intermolecular mechanisms. Conformational polymorphism occurs when a non-conformationally rigid molecule can be folded into different arrangements, which can subsequently be packed into alternative crystal structures[2].

The conformational polymorphisms of the two forms of piroxicam pivallate have been described in literature [19]. The inclusion of different solvent molecules in a crystal lattice can lead to the existence of different packing pattern, and has also been found to influence the molecular

conformation of paroxetine HCl in two solvate forms [20].

Phase Transformation in the Solid State: Understanding the kinetics and mechanism of phase transformation in the solid state is of significant practical importance. This is because the sudden appearance or disappearance of a crystalline form can threaten process development, and can lead to serious pharmaceutical consequences if the transformation occurs in the dosage forms. To explains the mechanism of solid phase transition, four steps have been proposed; molecular loosening in the initial phase, formation of intermediate solid solution, nucleation of the new solid phase and growth of a new phase.

A number of spectroscopic techniques have been used to study the processes associated with a polymorphic transition of 2 (2, 4- dinitrobenzyl) - 3-methyl pyridine [21]. The two inter-converting structures coexisted over a temperature range of 8-9^{o}C. In prediction of polymorphs the main challenge in managing the phenomenon of multiple solid forms of the drug is the inability to predict the number of forms that can be expected on a given case. Accurate theoretical prediction of polymorphs from studies of molecular dynamics and crystal structure generation would be of outstanding importance in drug research [18].

More research is being directed towards developing computational tools to understand the nature of polymorphism and to predict polymorphic forms at an early stage in the drug development processes. The polymorphic prediction from molecules simulation is currently the only commercial software package that predicts the possible polymorphs of an organic compound from its molecular structure [22-24]. Many studies have reported the role of additives in controlling the outcome of the crystallization process. For the first time, the rate of reaction byproduct on controlling the polymorph appearance of sulfathiazole has been reported [25].

Solvates and Hydrates: It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates [26]. The water molecule, because of its small size, can easily fill structural voids and because of its multidirectional hydrogen bonding capability is also ideal for linking a majority of drug molecules into stable crystal structures. It is the activity of water in the medium that determines whether a given hydrate structure can form.

Solvates may be formed when a pure organic solvent or a mixture of solvents is used as the solvent for crystallizing the compound. Crystalline hydrates based on their structure may be classified into three categories. The first category (class 1) are the isolated site hydrates where the water molecules are isolated from direct contact with other water molecules by interacting drug molecules, e.g., cephradine dihydrate. Class II are channel hydrates where water molecules included in the lattice lie next to other water molecules and adjoining unit cells along an axis of the lattice, forming channels through the crystal e.g., ampicillin trihydrate.

It is subdivided into an expanded channel or non-stoichometric hydrates e.g., cromyln sodium. The other one is planar hydrate which are channel hydrates in which water is localized in a two dimensional order or planar e.g., sodium ibuprofen. The third category of crystalline hydrates are the ion associated hydrates, in which the metal ions are coordinated with water e.g. calteridol calcium [27-28]. Stoichometric hydrate forms pose a special challenge in dosage form development due to the unpredictability of water content in the crystals [29-30].

Phase Transformation in Hydrates: The phase transformation associated with exposure to water, such as during solubility measurements, wet granulation processes, dissolution studies and accelerated stability tests are likely to occur via solution mediation. Solution mediated phase transformations depend upon the solution phase to provide the mobility necessary to rearrange the most stable form and hence are faster than solid state transformations. Pressure and relative humidity may increase the rate of phase transformation of hydrates by inducing mobility in the system. This transformation has been reported for many hydrate systems such as theophylline crystals, eprosartan mesyalte and nedocromil sodium [9, 31-32]. Apart from identifying and characterizing various stages of drug development, it is very important to gain an understanding of the dehydration/hydration mechanism and kinetics. Many models have been developed to account for the dehydration kinetics of crystalline hydrates [33].

Phase Transformation during Processing of Hydrates and Solvates: The effects of pharmaceutical processing on the crystalline state of drug polymorphs and solvates have been discussed recently by Brittain and Fiese [8]. The exposure to changes in temperature, pressure, relative humidity and communition are encountered during processes such as drying, granulation, milling and compression. The stresses applied to crystals during pharmaceutical processing can cause defects in their crystal lattice, and contribute to lattice disorder, thus affecting the physical properties of the resulting powder [34].

The effect of roller compaction on lattice defects and phase changes has been examined for aspirin [35]. Thermal activation, like mechanical activation during processing, also results in a high energy state of crystals that may reorganize into different lattice arrangements resulting in a phase change. The effects of low temperature, such as during freeze drying, on the crystalline form of the drug has also been studied. The formation of new mannitol hydrate during freeze drying has been reported [36]. The formation of crystalline hydrate by an excipient during freeze drying may have several practical consequences, such as the difficulty of removing bound water from the crystal lattice can significantly limit the drying rate while the residual water that is not removed by freeze drying may be a potential threat to product stability if it is released during storage. Spray drying has been shown to lead to loss of crystallinity in materials by a combination of processes involving rapid solidification of dissolved materials and solid state transition due to milling effects in the atomizer.

Spray drying leads to conversion of a crystalline phase to an amorphous state, because the amorphous state is metastable with respect to the crystalline form. The amorphous materials being in a thermodynamically metastable state susceptible to reconversion to the crystalline state affects many physicochemical characterization of the drug. The phase transformations can occur within the effective life of the pharmaceutical processing resulting in loss of quality and potency in the products.

Quantitative Method of Analysis: Because the physical form of a drug can impact pharmaceutical drug product performance, one may need to develop a quantitative method to monitor the production process and ensure that the active pharmaceutical ingredient (API) remains within manufacturing control limits and the drug product performance is not compromised. To meet regulatory requirements for drug product registration flow charts were constructed for investigators to use as guidelines for characterizing compounds under development [4, 39]. An estimation of the degree of crystallinity of a sample before and after processing poses one of the larger challenges facing the pharmaceutical field. Powder

X-ray diffractometry is still the commonly used method for detecting the degree of crystallinity though this method suffers from the same limitation due to peak broadening, amorphous halo, and preferred orientation, all of which make interpretation and quantitation difficult. DSC is not a sensitive method for measuring crystallinity due to crystallization of the amorphous content at elevated temperatures and the effect of differences in heat capacity. Solution calorimetry has been proposed as the accurate method for analysis of percent crystallinity [4, 37-38].

A decrease in the endothermic enthalpy of solution indicates a decrease in the crystallinity of the sample. X-ray powder diffraction has been used extensively for quantitative analysis of mixtures of crystal forms and to lesser extent the determination of the degree of crystallinity. There are two primary methods for quantification, using either individual peaks or the whole patterns to establish the relationship between phase composition and the intensity of individual peaks or of patterns of the phases being quantified.

The primary assumptions of the diffraction method relay on the particle size to be sufficiently small so that extinction and microabsorption effects are negligible. The potential of phase interconversion while reducing particle size is of major concern. Sonication is a good method for monitoring a less stable phase in its native state during particle size reduction. With this approach, a solvate can be stabilized by using its solvent of crystallization such as if the form is metastable and non-solvated, it is best to use a non-solvent such as octane.

The non-solvent reduces the potential for phase inter-conversion to the more stable form by minimizing the rate of solvent mediated transformations. An additional method of overcoming preferred orientation is to mix the sample with an inert amorphous component[40]. This is highly convenient in the pharmaceutical industry, as typically one will examine the previously defined active pharmaceutical either as a mixture of polymorphic forms or as a mixture of the crystalline and amorphous phase (both having a simple linear intensity proportionality to concentration). Alternatively, one may encounter a mixture of hydration/solvation state, in which cases the intensity would not necessarily be directly proportional to concentration. When quantifying polymorphic composition of a drug substance in a formulation, one makes standard mixtures of two polymorphic forms added to a constant amount of excipients.

The sample's mass absorption coefficient is constant and a linear relationship results from a plot of peak intensity and polymorphic composition. The overall intensity of the peaks associated with the API will be reduced, since it is diluted relative to pure API. Consequently, the range of quantification is reduced and detection limit higher than for quantitative methods of formulated products relative to pure API methods. Some methods use direct analysis of an individual phase concentration based upon intensity of the single peak relative to its pure phase intensity.

Other methods refer the analytes intensity to an internal standard, while still others rely on a change in diffraction response as a result of spiking or dilution of the sample. Single line methods generally require less knowledge about the phases to be quantified than whole pattern methods. The latter will often be the most sensitive approach, since the method may be developed to quantify based on the intensity of only the most intensive peak of the diffraction pattern.

However, such methods suffer from greater variability due to the influence of factors such as preferred orientation, but are the least

sophisticated methods and are often ideally suited only for long term quality control applications. In whole powder pattern decomposition methods (WPDD), the integrated intensity parameter, unit cell parameters and the peak profile parameters as refined by least square fitting procedures along with or overall scale factors relating to the individual phases. There are number of different background function and profile function to describe the diffraction profile [41].

Quantification of Degree of Crystallinity: The assessment of crystallinity by analytical techniques depends on just how the technique detects the organization of molecules in the solid pharmaceutical for e.g., X-ray diffraction measurement of crystallinity requires ”long range” ordering of molecules whereas solid state NMR is more sensitive to local or “short range” order, approximately 100 versus 5A^{o}, respectively [45]. Furthermore, the amorphous component of the pharmaceutical may actually be due to disorder of the crystal lattice itself, i.e., consistent with the single state model, rather than a distinct separate phase as the dual state model of crystallinity [42].

Takashi *et al*. investigated the effect of grinding and drying on the solid state stability of ampicillin trihydrate [43]. The effect of removal of water from ampicillin trihydrate structure resulted in the chemical instability of the drug. This is due to the hydrolytic solid state reaction in the impaired crystal lattice. They quantified the degree of crystallinity by rationing the peak area under the diffraction peaks to the total area of the diffraction pattern. A linear correlation curve was observed between concentration and peak area divided by the total area of diffraction.

Kaneniwa *et al*. examined the effect of grinding in a centrifugal ball mill or the transformation of polymorph of chloramphenicol using XRD [44]. They used the ratio of two peaks representing individual crystalline phases. Both FTIR-spectroscopy and XRD methods were developed to quantify the degree of crystallinity of cefazolin sodium [45]. FTIR method used the intensity ratio of a peak representative of the crystalline and amorphous phases, respectively versus a reference peak where intensity was independent of the crystalline state of the substance. X ray powder diffraction method used standard mixtures of amorphous and crystalline forms to generate a calibration curve. Crystallinity was measured by integrating the intensity of X-ray scattering of the crystalline region of the sample, the area of the sharp above the “amorphous halo”, versus the integrated intensity of the entire diffraction pattern.

Qualitatively, the crystalline and amorphous phases can be readily obtained by solid state NMR spectroscopy whereas discrete, sharp signals are typically observed in solid sate NMR spectra for molecules in crystalline environments. Amorphous components will give rise to broad resonances due to the distribution of all possible molecular conformation and/or orientation in the non-crystalline solid.

Phase Transformation during Manufacturing Process: In the last two decades, there has been significant emphasis on the characterization and control of the crystal form of the active pharmaceutical ingredient or bulk drug [2, 4.] The characterization and control of the crystal form of API throughout processing and in the final dosage form is drafted within the regulatory agencies (e.g., ICH Q6A) [46]. Subjecting a crystal form of a bulk drug in a formulation to a processing unit operation induces some stress into the system.

This stress may be thermal, mechanical, or result from interaction with a second factor (e.g., solubilization or moisture). When the stress is dissipated, the system may relax back to the

original equilibrium position. This trapping and relaxation constitutes the mechanism for the transformations. First, the stress may move the system to a point to the phase space where the new form is the most stable, and becomes metastable only when the stress is removed (e.g., in tableting). Second, the stress may serve to kinetically produce a metastable phase that is not the most thermodynamically stable form (e.g., the formation of a metastable polymorph like a hydrate that occurs during a wet granulation-drying process).

Phase Transformation during Processing: The transformation of the pharmaceutical materials can be classified simply as solid-solid (phase transition, deformation), solid-liquid (mostly crystallization), or solid-gas (sublimation, condensation). Solid state reactions can occur where the drug substance is intrinsically chemically reactive or unstable. It can occur in any of the following ways: acceleration due to interaction with excipients, processing effects, or due to the presence of amorphous materials.

Solid state reaction can be understood in terms of a four step process;

(i) Loosening of molecules at the reaction site

(ii) Molecular change

(iii) Solid solution formation and

(iv) Separation of the product. It is often clear that solid state degradation of pharmaceuticals is often related to molecular mobility [47-49].

In addition, Ahlneck and Zografi have suggested that water absorption enhances the molecular mobility of pharmaceutical solids, perhaps explaining the enhanced chemical reactivity of these materials in the presence of water [50]. Solid state reactions can include oxidation, cyclization, hydrolysis, and deamidation. Solid state NMR offers several attractive approaches to study of the molecular mobility of solids. Excipients present in formulated products may not be directly involved in the degradation mechanisms, but presence of water can contribute to the solid state reaction. Solid state reaction in formulation can include tranacylation, Maillard browning reaction, and acid base reaction.

Tablet mixtures containing aspirin and drugs with easily acylated functionalities react to give acyl compounds and salicylic acid. Troup and Mitchner reported the reaction of phenylepherine hydrochloride with acetyl salicyclic acid [51]. Wirth et al showed that lactose and fluoxetine hydrochloride reacted to form colored pigments via the Mallard reaction. A particularly interesting example of solid- solid acid base reaction is the stability of effervescent tablets and the reaction of ibuprofen with magnesium oxide [52].

Amorphous Substances: In case of pharmaceutical materials, the amorphous substances have many useful properties like higher solubility, dissolution rate, and better compression characteristics than corresponding crystals. The amorphous solids are generally less stable physically and chemically than corresponding crystals. The amorphous solids can be produced by standard pharmaceutical processes and are the common form of certain materials (e.g., proteins, peptides, some sugars and polymers). The preparation of amorphous solids is straightforward for some materials (good glass formers) but difficult for others (poor glass formers). Processes that introduce mechanical or chemical stress (e.g., grinding, milling, and wet granulation) can render crystalline materials fully or partially amorphous.

Characterization of Amorphous Materials: There are a variety of physical techniques utilized for

characterizing amorphous solids. These include XRD, molecular spectroscopy, DSC, Isothermal calorimetry, DEA, DMA, Dilatometry, TSC etc. It offers several types of information like structure, thermodynamics, changes, and multi-component systems. The structure of amorphous solids is usually described as possessing crystals like short range molecular rearrangement, but lacking long range order. If crystallization is avoided, many liquids of pharmaceutical relevance vitrify at a temperature (Tg) approximately 2/3 to 4/5 of the crystalline melting point, Tm.

Modulated DSC and can be used to separate reversing and non-reversing components at a glass transition (e.g., in a spray dried lactose), a beneficial utility in the assignment of glass transitions that are weak or overlap with other thermal events [53]. Apart from quench cooling, a melt miscible impurity may be introduced to inhibit crystallization [54]. Crystallization of carbohydrates and derivatives, which are common pharmaceutical excipients, presents a special challenge. Xylitol, for instance, is crystallized initially as a more stable polymorph, with the metastable form being impossible to make again [55].

Stabilization of Amorphous Materials: The stabilization of amorphous solids is multifaceted including i) stabilization of labile molecules (e.g., proteins and peptides through additives). Freezing and drying are essential steps in the preparation of protein and peptide formulations and in the preservation of organisms. ii) The prevention of crystallization of excipients that must remain amorphous for their intended function [56].

Vitrification based stabilization relies on the immobilization and isolation of labile substances. In vitrification based stabilization strategies, Tg provides a concrete guide to the selection of stabilizers and storage temperatures. It has been observed that the proteins, peptides and organisms can be effectively protected against freezing and drying damages when they are co-processed with certain excipients, typically carbohydrates and its derivatives (e.g., sucrose, trehalose, mannitol, sorbitol etc.) [57-60]. Moreover, the storage at appropriate temperature, the use of antioxidants, buffer, preservatives etc is very critical in pharmaceutical processing of amorphous solids.

CONCLUSION: The solid state form can drastically change the physiochemical properties of a pharmaceutical product. It may change its effectiveness, stability and suitability for a particular formulation. The ultimate goal of solid form screening is to identify and to select the optimal solids for the intended use. The solid state behavior of the drug plays an important role during the entire shelf life of a drug, from invention to the life-cycle management stage.

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