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Drug Polymorphism: A Review

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Abstract

Formulators are charged with the responsibility of formulating a product which is physically and chemically stable, and bio-available. Solid-state properties including polymorphism, solvate and salt formation can have a profound impact on important properties (solubility & stability) that are essential for successful development of drug candidates. Crystallization of pharmaceutically active ingredients, particularly those that possess multiple polymorphic forms, are among the most critical and least understood pharmaceutical manufacturing processes. Many process and product failures can be traced to a poor understanding and control of crystallization processes. Most drugs exhibits structural polymorphism and it is desirable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real world storage conditions. There are occasional situations in which development of a meta-stable crystalline or amorphous form is justified to achieve the desired medical benefit. Such situation includes those in which faster dissolution rates or higher concentrations are desired in order to achieve rapid absorption and the efficiency or to achieve acceptable systemic exposure for low solubility drugs. This article briefly reviews the basic principle of polymorphism, different classes of phase transformations, the underlying transformation mechanisms with respective kinetic factors and hence the impact of polymorphism on pharmaceutical formulations.

Keywords: Bioavailability, Crystallization, Polymorphism.

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Introduction

It has been known since the middle of 18th century that many substances could be obtained in more than one crystalline form [1] but the subject of drug polymorphism has received extensive academic and industrial attention since the early pioneering reports of Aguiar and colleagues at Parke – Davis, in which effect of polymorphism on dissolution and bioavailability were highlighted for chloramphenicol palmitate [2,3]. It is the well-known fact that nature of structure adopted by a given compound on crystallization would have a profound effect on the solid-state properties of the system. It was found that various polymorphs could exhibit different solubilities and dissolution rates and these differences sometimes lead to the existence of non-equivalent bioavailabilities for different forms. Polymorphism in crystalline solid is defined as materials with the same chemical composition different lattice structures and/or different molecular composition [4,5,6,7]. Pseudopolymorphism is a term that refers to crystalline forms with solvent molecules as an integral part of the structure. [8,9] Knowledge of crystal structure has also been applied to further understand chemical stability and dehydration or solvent loss [9].

There is a renewed interest in polymorph; this is partly due to increased economic pressure faced by pharmaceutical companies and the greater awareness of the effect that polymorphs may have on the bioavailability, manufacturability and stability of the product. This is also reflected in regulatory recommendations with regard to polymorphism appearing in both ‘new drug application’ (NDA) and ‘abbreviated new drug application’ (ANDA) particularly those for solid dosage form [10,11,12].

Once the diversity of solid state form is known, a decision can be made as to which crystal form should be selected for further development during preclinical & clinical testing. This decision must ultimately be based upon the physico-chemical attributes of various crystal forms including their solubility and physical and chemical stability. Many drug candidates occur in number of polymorphic forms (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of polymorph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol Palmitate</td>
<td>2</td>
</tr>
<tr>
<td>Mefanamic acid</td>
<td>2</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>2</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4</td>
</tr>
<tr>
<td>Phenyl butazane</td>
<td>5</td>
</tr>
<tr>
<td>Sulfapyridine</td>
<td>7</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>2</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>3</td>
</tr>
<tr>
<td>Spiranolactone</td>
<td>6</td>
</tr>
<tr>
<td>Ritonavil</td>
<td>2</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>2</td>
</tr>
<tr>
<td>Enalapril maleate</td>
<td>2</td>
</tr>
<tr>
<td>Ranitidine HCL</td>
<td>2</td>
</tr>
<tr>
<td>Terazosin HCL</td>
<td>3</td>
</tr>
<tr>
<td>Tolsemide</td>
<td>2</td>
</tr>
<tr>
<td>Warfarin VA</td>
<td>2</td>
</tr>
<tr>
<td>Cefuroxime Axetil</td>
<td>2</td>
</tr>
<tr>
<td>Metaprotol tartarate paracetamol</td>
<td>2</td>
</tr>
<tr>
<td>2-Amino 5-Nitropyridine</td>
<td>3</td>
</tr>
<tr>
<td>Prednisolone tetra butylacetate</td>
<td>2</td>
</tr>
<tr>
<td>Primidone</td>
<td>2</td>
</tr>
<tr>
<td>Eztrene</td>
<td>3</td>
</tr>
<tr>
<td>Probucel</td>
<td>2</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Drug and their number of Polymorphs.

Aspects of Polymorphism

Structural aspects of polymorphism

An ideal crystal is constructed by the regular spatial repetition of identical structural units. In the structures of organic molecules, different modification can arise in two main distinguishable ways. One behavior is termed as packing polymorphism in which molecules exhibit as rigid grouping of atoms that may be stacked in different motifs to occupy the points of different lattices. The other behavior is termed as conformational polymorphism in which molecule is not rigidly constructed and can exist in distinct conformational states so that each of these
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conformationally distinct modifications may crystallize in its own lattice structure [13].

**Thermodynamics of polymorphism**

When a compound exists in various solid state forms two important questions to be considered are

1. What is their relative thermodynamic stability or the condition and direction in which a transformation can occur, and
2. How long it will take the transformation to reach equilibrium.

The main approach used to assess thermodynamic stability relationships of polymorphism are based on thermodynamics rules according to Burger and Ramberger [14] and free energy change temperature diagram. The former distinguishes between monotropic and enantiotropic systems while the later in addition to this allows for calculation of the transition temperature.

**Kinetics of polymorphism**

While the thermodynamics establishes the stability domain of the various solid states, a metastable domain once encountered, the kinetic pathway will determine which form will be created and for how long it can survive. It is essential to consider the structural elements of the molecular assembly processes that lead to crystallization and their control. Etter [15] considered the process of crystallization in terms of molecules arranging themselves into energetically suitable packing patterns by non-covalent forces especially hydrogen bonds. A major conclusion of the work was to establish a connection between the molecular assembly processes that precede nucleation and molecular arrays in the crystal states. These findings motivated investigations on the supramolecular aspects of crystallization processes and have found great utility in explaining the appearance or disappearance of polymorphs, [4] the role that solvents and additives have on the


Drug Polymorphism

directed nucleation of polymorphs [5,16,17] and the kinetic stability of metastable forms including amorphous solid [18].

Crystallization involves both nucleation and growth of a phase. Studies of growth kinetic and crystal morphology are useful in characterizing intermolecular interaction on specific crystal planes and as a consequence in identifying additives or solvents that may promote the crystallization of particular polymorph.

**Nucleation**

Nucleation mechanism can be divided into two main categories that are homogeneous and heterogeneous [19,20,21,22]. Homogeneous nucleation rarely occurs in large volume (quarter than 100 µl) since the solution contains random impurities that may induce nucleation [23,24].

A surface or interface of composition and/or structure different from the crystallizing solute may serve as nucleation substrate, by decreasing the energy barrier for the formation of a nucleus that can grow into a mature crystal. Nucleation that is promoted by crystals of crystallizing solute is known as secondary nucleation. These mechanisms are thoroughly described by Zettlemayer, [19] Mullin [20] and Myerson [22]. Nucleation mechanisms have been of great utility in controlling the nucleation and transformation of polymorphs and solvents, isolating metastable solid phases in confined space, [25] diverting nucleation of polymorphs using solid substrates that template certain crystal structure [26-28] and in controlling transformations during dissolution of metastable solid phases [29-31].

In recent years various new techniques for nucleations have been developed

**Newer techniques in nucleation**

Scientists have yet to achieve a satisfactory degree of control over polymorphism and in
particular there is no method to guarantee the production of even the most thermodynamically stable form of compound. Most difficult encountered task for pharmaceutical companies is finding all forms of a compound that can exist under ambient conditions. There are various recent developments in crystallization techniques that contribute towards this goal. [32] The various techniques developed in this regard are:

1. **High throughput crystallization methods**

   Are number of possible temperatures, concentrations and solvent combinations are often sampled in developing new polymorphs. In order to test thousands of conditions, a high throughput process of crystal growth and analysis has been developed [33]. Robotic liquid handling prepares individual solutions, which are subjected to various crystallization conditions. Crystals are screened by a combination of optical image analysis & Raman microscopy to differentiate polymorphs. The analysis of patterns of polymorph generation under a multitude of crystallization conditions provides a road map for generating the desired form [32].

2. **Capillary Growth Methods**

   Polymorphs generation from solution is dependent upon super saturation ratio. It is known that in order to access metastable forms of a compound, a high super saturation ratio is often required. Crystallization from capillaries is ideal for providing an environment with high super saturation because small volumes of solution isolates heterogeneous nucleants [22,23] and induce turbulence & convection. An additional advantage of this approach is that the crystals can be analyzed by Powder X-ray diffractometry (PXRD) in single X-ray diffraction.

3. **Laser induced nucleation**

   Non-Photochemical Laser Induced Nucleation (NPLIN) is a crystallization technique that has the potential to affect nucleation rate as well as polymorph produced. Initial experiments revealed a dramatic increase in nucleation rate for super saturated urea solution upon irradiation to plane polarized light [34]. This is proposed to occur by alignment of the prenucleating clusters in the applied optical field. Although this method has not yet been used in pharmaceuticals, the technique represents a promising area for polymorph solution and discovery.

   Heteronucleation on single crystal substrates: Organic and inorganic crystal substances have been used as substances to direct crystallization of many compounds by epitaxial mechanism. [35] In this process, the oriented growth of a substance on a surface occurs due to the alignment of their lattice parameters. Extension of this method, by employing a combinational library of surfaces, has been proposed for polymorph discovery [36,37].

4. **Polymer heteronucleation**

   The first combinational approach in controlling polymorphism that directly targets nucleation is polymer heteronucleation [28]. In this method compounds are crystallized in the presence of a chemically diverse library of polymer heteronuclei by solvent evaporation, cooling sublimation or other traditional crystallization techniques. The polymer acts as an additional diversity element to affect the crystallization outcome. This technique has the potential for controlling the formation of established forms as well as discovery of unknown polymorphs without prior knowledge of solid-state structure. Over 30 years of study on the solid state chemistry of carbamazepine has yielded three polymorphs. However a fourth polymorph [38]...
was discovered using polymer hetero-
nucleation that remarkably proved more
stable than the well-studied trigonal form
[39].

**Generation and Characterization of Polymorph**

**Generation of polymorphs** [1]

The primary method for production of
crystalline forms is slow solvent evaporation
of saturated solutions, with the rate of
evaporation being adjusted by empirical
means. Solvents routinely used for this
purpose are dipolar aprotic solvents like
dimethyl formamide, acetonitrile, dimethyl
sulphoxide, protic solvents like water,
methanol, Lewis acids like dichloromethane,
chloroform, Lewis bases like acetone, 2-
butanone, aromatic solvents like toluene,
xylene and non-polar solvents like
cyclohexane and hexane.

The process of solution mediated
transformation can be considered as the
result of two separate events, beginning with
dissolution of initial phase and completing
with nucleation and growth of final, stable
phase.

Another commonly used crystallization
method involves controlled changes in
temperature. Slow cooling of hot saturated
solution can be effective in providing crystals
if the compound is more soluble at higher
temperatures, while slow warming can be
used if the compound is less soluble at
higher temperatures. Sometimes it is
preferable to heat the solution to boiling, filter
to remove excess solute, and then quench
cool using an ice bath or even a dry acetone
bath.

Hydrates are usually obtained by
recrystallization from water. Trazodone
hydrochloride tetrahydrate was prepared by
dissolving the anhydrate in hot distilled water
[40].

**Phase transformation**

The active pharmaceutical ingredient (API)
and the excipients in a solid oral dosage
form may exist in different crystalline
modification or may be amorphous. When a
predefined solid phase of a drug substance
or crystalline excipient in a solid formulation
is subjected to a variety of processing
conditions during dosage form manufactur-
ing, many phase transformation may take
place including intervention among
crystalline, solvates/ hydrates and the
amorphous form [41].

During product development, one must
identify both the solid phases and recognize
the transitions among them under relevant
conditions. The stability relationship between
crystalline solid phases often changes
depending on the temperature, pressure and
relative humidity of the environment. The
knowledge of mechanism of phase
transformations is very helpful in identifying
the potential for such transitions and factors
affecting their kinetics. The four underlying
mechanism have been listed in the Table 2.

The stability relationship between a pair of
crystalline phases can be categorized as
monotropic or enantiotropic.

**Monotropy:** When a metastable polymorph
is there, a polymorphic transition to the
stable polymorph during processing can
proceed via all four mechanism enlisted
above. For an enantiotropic system, one
crystalline form is stable below the transition
temperature ($T_t$), while the other is stable
above $T_t$. Only one polymorph is stable
throughout the temperature range for a
monotropic system.

**Enantiotropy:** If the temperature does not
reach $T_t$ during heating, the system is
monotropic for practical purpose. However if
the temperature is raised above $T_t$,
crystalline transition between the two
phases can proceed via any of the four
mechanisms.
Table 2: Mechanisms of phase transitions

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Phase transition</th>
<th>Factors influencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid-state</td>
<td>Polymorphic transition Hydration/dehydration amorphous crystallization/vitrification</td>
<td>Environment (Temperature, pressure, relative humidity etc.), presence of crystalline defects, particle size and distribution and impurities.</td>
</tr>
<tr>
<td>Melt</td>
<td>Polymeric transitions, vitrification</td>
<td>Relative rates of nucleation, crystal growth, cooling and impurities and excipients.</td>
</tr>
<tr>
<td>Solution</td>
<td>Polymorphic transition Hydration/dehydration, amorphous crystallization/vitrification</td>
<td>Rate of solvent removal, ease of nucleation, processing conditions, undissolved solids and excipients.</td>
</tr>
<tr>
<td>Solution mediated</td>
<td>Polymorphic transition Hydration/dehydration amorphous crystallization/vitrification</td>
<td>Solubility and solubility difference between the phases, processing temperatures, contact surfaces, agitation and soluble excipients / impurities</td>
</tr>
</tbody>
</table>

Preventing and anticipating phase transformations in process of development

To anticipate and prevent phase transitions during manufacturing it is important to have a thorough understanding of crystals forms and the amorphous phase of an API and excipients as well as the interconversion mechanisms and processing options. Phase transition in crystalline excipients and their impact on product performance cannot be also ignored. Induced hardening is anticipated in tablets may lead to a decrease in dissolution rates during storage of formulations containing a high level of crystalline excipients such as mannitol. If process induced hardening is anticipate, variable product dissolution can be minimized through the use of intragranular and extra granular super disintegrants or by selecting an alternative excipients. [41] In designing manufacturing processes for solid dosage forms, process induced phase transformation can be anticipated based on preformulation studies. These transformations can be controlled and circumvented by selecting the appropriate process. Acetylsalicylic acid is known to be prone to hydrolysis. Reports indicate that when roller compacted acetyl salicylic acid is used in formulation; moisture uptake of formulation increases leading to increase in hydrolysis [42]. This increased moisture uptake was attributed to the presence of 10% amorphous acetylsalicylic acid, which was unintentionally generated during the roller compaction process.

Hydration and dehydration during wet granulation is probably most likely to result in phase changes via solution or solution mediated mechanism. These changes often occur when a compound forms stable hydrates at ambient conditions and when an anhydrous crystal form is supplied for granulation. In such cases solution mediated transformation to a hydrate can occur during granulation. Then depending on the speed and conditions of drying, the final phase can be the original anhydrous phase or a metastable anhydrate phase. For example, carbamazepine an anticonvulsant drug exists as three polymorphic anhydrate forms and as a dehydrate [43]. It is practically insoluble in water, is marketed as tablet with strength up to 400 mg [44]. For such compound wet granulation may be utilized to improve flow and compression properties of the formulation. One except that the poor solubility of carbamazepine should reduce the risk of solution mediated transformation. However Otsuka et al have demonstrated that solid phase transition can occur during wet granulation of this compound [45].
### Table 3: List of analytical techniques for polymorph characterization [41]

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder X-Ray diffractometry (PXRD)</td>
<td>Standard for phase identification, usually show significant difference among crystal forms</td>
<td>Interference from crystalline recipients</td>
</tr>
<tr>
<td>Single crystal X-ray diffractometry</td>
<td>Ultimate phase identification (ID) in depth understanding of structure</td>
<td>May be difficult to prepare single crystal</td>
</tr>
<tr>
<td>Differential scanning calorimetry (DSC)</td>
<td>Small sample size, information on phase transition, information on interference with recipients</td>
<td>No information on the nature of transition, interference from both crystalline &amp; amorphous recipients</td>
</tr>
<tr>
<td>Thermogravimetry Analysis (TGA)</td>
<td>Quantitative information on the stoichiometry of solvates / hydrates</td>
<td>Only useful for solvates / hydrates, interference from water containing excipients</td>
</tr>
<tr>
<td>Mid infrared (IR)</td>
<td>Complementary phase ID method, ability to show the different states of water, sample size can be very small if coupled with microscopy</td>
<td>Severe interference from moisture, interference from excipients, differences may be small</td>
</tr>
<tr>
<td>NCAR IR (NIR)</td>
<td>Complementary phase ID method, ability to penetrate through containers ability to show different states of water</td>
<td>Low intensity, differences may be very subtle interference from excipient</td>
</tr>
<tr>
<td>Raman</td>
<td>Complimentary phase ID method, small sample size, minimum interference from water</td>
<td>Interference from excipient</td>
</tr>
<tr>
<td>Solid state nuclear magnetic resonance (SSNMR)</td>
<td>Complimentary phase ID method, local environment of atoms</td>
<td>Relatively long data acquisition time</td>
</tr>
<tr>
<td>Polarized microscopy</td>
<td>Information on crystal morphology and size, qualitative information on crystallinity, Complimentary information on phase transition</td>
<td>Interference from excipient</td>
</tr>
<tr>
<td>Hot stage microscopy</td>
<td>Complimentary information on phase transition</td>
<td>Interference from excipient</td>
</tr>
<tr>
<td>Solvent sorption</td>
<td>Excellent for detection of low level of amorphous phase, defining the liability of hydrates</td>
<td>Interference from amorphous excipient, large hysteresis loop possible</td>
</tr>
</tbody>
</table>

**Characterization of polymorphs**

Once a variety of crystalline solids have been produced using a suitable polymorph protocol, it is very important to characterize these by proper techniques so that system can become better defined [2,46-49]. The list of various analytical techniques for characterization is as given in Table 3. The most definitive of all these technique is single X-ray diffraction because it directly determines differences in packaging and conformation of molecules. Moreover, intermolecular interactions in the solids are elucidated with atomic resolution providing a wealth of chemical data. The important feature of this technique is that it can rule out pseudopolymorphism.
In cases, where single crystals of sufficient quality for structural determination are not available solvates and hydrates can often be identified by Thermogravimetric analysis (TGA) or by spectroscopic technique such as infrared or Raman spectroscopy. Powder X-ray diffraction, the most reliable technique for rapid polymorph identification, cannot easily differentiate between true polymorph and pseudo-polymorphism [32].

**Polymorphism and Development of Formulation**

**Polymorphism and solubility**

Since different lattice energies (and entropies) associated with different polymorphs not only gives differences in physical properties but also exhibit different solubilities and dissolution rates [61] and these variation in solubility may have impact on absorption of drug from its dosage form. A solid having higher lattice free energy (i.e. a less stable polymorph) will tend to dissolve faster, since the release of higher amount of stored lattice free energy will increase the solubility and hence driving force for dissolution. The concept of solubility implies the process of solution has reached an equilibrium state such the solution has become saturated.

The most critical issue related to drug substance polymorphism is equilibrium solubility. Equilibrium solubility is the concentration of drug dissolved when there is an equilibrium between the solid drug substance and solution. Although drug dissolution testing is appropriate for drug product evaluation, equilibrium solubility is more reliable than dissolution rate for drug substance evaluation since dissolution rate is typically influenced by particle size and wettability [26]. The influence of wettability on the dissolution rate of pharmaceutical powders was studied by Lippold and Ohm [62]. It was determined that there is a correlation between wettability and dissolution rate. Particle size affects the rate of dissolution. Dissolution rate is proportional to the surface area and decreasing the particle size increases surface area.

Equilibrium solubility studies can be conducted to assess the affect of crystal structure or polymorphism. Particle size and wettability can be modified by processing parameters but equilibrium solubility is determined by polymorphic form. Equilibrium solubility should be assessed according to procedures recommended in the Biopharmaceutical classification system (BCS) guidance. According to BCS guidance, the definition of a highly soluble drug is one that has solubility in excess of highest dose strength in 250 ml in aqueous media through the pH range 1.0 – 7.5. For drugs that are highly soluble, the effect of polymorphism on bioavailability is not anticipated, and therefore, no controls on polymorphism should be required provided that drug product is manufacturable.

The most recent example of the impact of polymorphs on solubility and dissolution rate is the protease inhibitor Ritonavir. [63] A new thermodynamically stable form, form II was dissolved, two years after the launch of product using form I. The two crystals forms differ substantially in their physical properties such as solubility and dissolution rate.

The intrinsic solubility of a substance depends on the particular solid phase (solvate or anhydrate) that is present [64]. Since lattice energies of physical forms (amorphous, polymorphs of solvates) are responsible for the difference in solubilities and dissolution ratio, the largest difference in solubility is observed between amorphous and crystalline materials [65-67]. The solubility difference between different polymorphs is typically less than 10 times whereas the difference between amorphous and crystalline material can be up to hundred times.

Weather differences in the solubilities of various polymorphs will have an effect upon drug product, bioavailability/bioequivalence.
(BA/BE) is also dependent upon other factors that govern the rate and extent of drug absorption, including gastrointestinal motility and intestinal permeability. For a drug whose rate and extent of absorption is limited by its dissolution, large differences in the solubilities of various polymorphous forms are likely to affect BA/BE. On the other hand, for a drug whose rate and extent of absorption is only limited by intestinal permeability, differences in the solubilities of various polymorphs are less likely to affect BA/BE. Furthermore, when the solubilities of the polymorphic forms are sufficiently high and drug dissolution is rapid in relation to gastric emptying, differences in solubilities of the various solid-state forms are unlikely to affect BA/BE.

**Approaches to improve solubility of polymorphs**

**Single component system**

*Amorphous:* Pharmaceutical glasses or amorphous solids present an alternative approach to drug delivery because of their improved bioavailability compared to their crystalline counterparts. Amorphous solids lack the three-dimensional long-range molecular order characteristics of crystal but may exhibit short-range order [26, 68, 69]. Amorphous materials are further from equilibrium than crystalline materials, are higher energy states and as expected have faster dissolution rates and kinetics or metastable solubilities relative to corresponding crystals [67].

**Multicomponent system**

Multi-component systems are molecular assemblies composed of an API and a complementary molecule (neutral or charged) such as solvent excipients and other substances. These solid-state supermolecules are assembled from specific non-covalent interactions between molecules including hydrogen bonds, ionic, Van Der Waals and π – π interactions. Thus intermolecular interactions can be used as key molecular recognition in the design of amorphous or crystalline multi-component system and in characterization of structures. It is important to note that the amorphous and crystalline solids share the same intermolecular bonds and differ mainly in the range of disorder.

**Amorphous:** Multi-component system can be prepared as amorphous molecular dispersions. Homogeneous dispersion of API and other substances offer the advantages of the higher energy amorphous state, such as improved dissolution rates and bioavailability. Components used in formulation of solid dispersion include polymers such as PEG [70, 71], PVP [26, 72-76], PVA [77], PVP/VA copolymers [78, 79], cellulose derivatives [80, 81], polycrlylates and polymethacrylates [82, 83]. In contrast to single component amorphous solids, molecular dispersions can be designed with optimal stability and function. For instance relaxation times, molecular mobility and intermolecular interaction can be varied by choice of components [18, 178].

**Crystalline:** Crystal engineering offers a rational approach to the design of new composition and crystal structures. Covalent as well as non-covalent bond can be exploited in the design of supramolecular structures. Hydrogen bonded networks are the most commonly studied since a certain degree of reliability and predictability exists regarding the interaction of donors and acceptors [84].

**Co-crystals solvates:** The drug development process exposes pharmaceutical solids to solvents, organic and aqueous solvent during crystallization, wet granulation, storage and dissolution, that can lead to formation of solvated crystals by design or inadvertently. Crystalline forms of APIs with included solvent molecules differ in pharmaceutical performances, mechanical behaviour, stability, dissolution and often
from the unsolvated API crystal [85-87]. Choice of development of solvated or unsolvated form will depend on its pharmaceutical properties, how long it can survive and under what conditions. The propensity of an API molecule to form solvate has been related to molecular structures, hydrogen bond patterns and crystal packing [9, 86-89].

Chemical stability of polymorphs and amorphous forms

The polymorphs (or pseudopolymorphs) of some drug have shown to exhibit different chemical stability. Examples are carbamazepine [90], paroxetine maleate [91], indomethacin [92], methylprednisolone [93], furosemide [94] and enalapril maleate [95]. For example, the photo decay of form II of carbamazepine was 5 and 1.5 fold faster than form I and III, respectively [83]. In addition to change in the rate decay, polymorphism may also affect the mechanism of decay as observed in the reactivity of different polymorphs of cinnamic acid derivatives [96].

It is generally observed that the more thermodynamically stable polymorph is more chemically stable than a metastable polymorph. This has generally been attributed to higher crystal packing density of thermodynamically favored polymorph but current investigation suggests that other factors such as optimized orientation of molecules and H-bonding and non-hydrogen bonds in crystal lattice plays a more important role.

Indomethacin can exist as the metastable \( \alpha \)-form and thermodynamically favoured \( \gamma \)-form. Although the metastable \( \alpha \)-form has higher density, the \( \alpha \)-form rapidly reacts with ammonia vapour while the \( \gamma \)-form is inert to ammonia. The lower reactivity of indomethacin polymorphs is due to differences in crystal packing/hydrogen bonding [93].

The intrinsic difference in chemical stability between 2 polymorphs Ex. \( \alpha \)-\( \gamma \) indomethacin cannot be overcome, but less chemically stable polymorphs can often be formulated in a way, which results in acceptable shelf life. In comparison to crystalline polymorphs, the amorphous form of drug is generally accepted to be less chemically stable due to lack of 3-dimensional crystalline lattice, higher free volume and greater molecular mobility. As early as 1965, amorphous Penicillin G was shown to be less stable than crystalline sodium and potassium salts [97].

It should be pointed out that a major portion of any formulation effort is the choice of excipients and processes, which minimize the chemical instability of drug. If metastable polymorph (or amorphous form) is less chemically stable than the lowest energy form of the drug, than in many cases it will be possible to maximize the chemical stability of this metastable form through judicious formulation decision. [98-103] Thus reduced chemical stability of a metastable crystalline or amorphous form does not necessarily preclude its development as a product.

Mechanical properties of polymorphs and amorphous drug forms

Polymorphs can affect the mechanical properties of drug particles and thus may affect the manufacturability and physical attributes of tablets. For example, polymorphs of metaprotol tartarate [104] paracetamol [105-108], sulfamerazine [109], phenobarbitone [110], carbamazepine [111, 112] and phenylbutazone [113] have been shown to exhibit different mechanical properties. A common effect of polymorphism is alteration of powder flow due to the difference in particle morphology of two polymorphs. Polymorphs with needle or rod shaped particles may have poor flow compared to polymorphs with low aspect such as cubic habit or irregular spheres. The effect of polymorphism on other mechanical properties such as hardness, yield pressure,
elasticity, compressibility and bonding strength is more complex.

A simple general rule, although semi empirical proposed can be used to predict the effect of crystal packing of polymorphs on their compressibility and bonding strength [114-115]. The more stable polymorphs due to its higher packing density, is expected to form stronger interparticle bonds but is harder to deform [104,113,114]. Since an increase in the bonding surface area resulting from deformation of particles may have higher impact on tablet strength than interparticle bond strength, the more stable of two polymorphs may provide weaker tablets.

Factors other than those accounted for by the general rule proposed by Summers et al [113] may also affect the mechanical properties of two polymorphs. For example, the presence of slip planes in form I of sulfamecazine was found to be the reason for its higher plasticity than form II, the more stable form at room temperature [109]. This higher plasticity results in greater compressibility and tabletability.

For amorphous drug forms, mechanical properties may be different from those of crystalline drug due to the absence of long range packing. The mechanical attributes of amorphous forms are less well understood than those of crystalline polymorphs. The lack of information on mechanical properties of amorphous drugs may be due to the physical and chemical instability of these forms. One report comparing the mechanical properties of crystalline and amorphous forms of model drug has been published [115].

Differences in the mechanical properties of 2 polymorphs or amorphous vs. crystalline forms may or may not affect the manufacturability and physical attributes of tablets. For example, in the case of metaprotol tartarate, the differences in the mechanical properties of two polymorphs did not affect the bonding properties of tablets with relatively high drug loading [104].

In some cases the favourable mechanical properties of a polymorph, such a metastable, may be used to develop a more desirable process to manufacture tablets. For example, direct compression may be used to manufacture tablets with the more compressible orthorhombic form II of paracetamol instead of using more resource intensive granulation processes for monoclinic form I [105,108]. However, development of a metastable form for processing advantage should only be undertaken for drugs for which a complete understanding exists with respect to form dependent chemical stability, physical stability & most important bioavailability. This will typically be the case only for very old, highly studied drugs.

**Solvates and hydrates**

In general, the analysis provided above for the behaviour of polymorphs also applies to metastable solvates and hydrates. For example, the dissolution rate and solubility of drug can differ significantly for different solvates. Glibenclamide have been isolated as pentanol and toluene solvates, and these solvates exhibit higher solubility and dissolution rate than 2 non-solvated polymorphs [116]. In formulation of solvates (other than hydrates), the formulation must be careful to address the toxicity of the associated solvent, and carefully evaluate interactions of the drug and mobile solvent molecules with excipients on storage, which may result in compromised performance.

Similar to polymorphs in general the physical stability of hydrates and anhydrates forms may depend upon the relative humidity and/or temperature of the environment, and the most stable form may switch as the humidity / temperature is varied. Anhydrous to hydrate transitions can occur during dissolution at the drug / medium interface and can affect dissolution rate and bioavailability [117].

Regulatory Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications (ANDAs)

A sponsor of an abbreviated new drug application (ANDA) must have information to show that the proposed generic product and the innovator product are both pharmaceutically equivalent and bioequivalent and therefore therapeutically equivalent. Many pharmaceutical solids exist in several crystalline forms and thus exhibit polymorphism. Polymorphism may result in differences in physicochemical properties of active ingredient and variations in these properties may render a generic drug product to be bioequivalent to the innovator brand. For this reason, in ANDA careful attention is paid to the effect of polymorphism in the context of generic product equivalency.

Conclusion

The impact of drug substance and polymorphs on pharmaceuticals development revolves around solubility of the drug substance and dissolution of drug product. Once the existence of polymorphism has been identified through the literature, the drug substance available must be evaluated and formulations can be developed based on its solubility. In the case of compounds that have poor solubility, the formulation must be developed so that the effect of polymorphism on dissolution and bioequivalence can be minimized. For this, it is always advisable to identify the lowest energy crystalline polymorph of the drug candidate during development. If metastable or amorphous forms are used in the development of the drug product, it is possible to improve chemical stability of such forms through judicious choice of excipients and formulation processes.

References


44. Meyer MC, Straughn AB, Jarvi EJ, Wood GC, Pelsor FR, Shah VP. The bioinequivalence of...


73. Sekizaki H, Danjo K, Eguchi H, Yonezawa Y, Sunada H, Otsuka A. Solid-state interaction of


