ISSN: 0975-766X
CODEN: IJPTFI
Available through Online
www.ijptonline.com
Review Article

DRUG POLYMORPHISM: AN OVERVIEW

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Received on 02-01-2013 *Accepted on 17-01-2013*

Abstract

More than one third of drug in pharmaceutical industry show polymorphism. These polymorphic or crystalline drugs have their stringent and specific physicochemical properties. These stringencies regarding physicochemical properties make it difficult for the formulation of such drugs into suitable dosage form. Various methods are available for the improvement of physiochemical properties of these medicinal agents, but most of the time they fail to give the satisfied results. To resolve all these complications, the prior study of polymorphic properties can be very helpful. Crystalline drugs always have their thermodynamic as well as kinetic properties. As such these properties make them crystalline but at the same time these drugs get it difficult for ideal formulation. This review covers the information regarding drug polymorphism as detail as possible. The methods, newer techniques in the field of crystallization, sophisticated techniques for the characterization of crystal forms and the regulatory consideration have been discussed in detailed. The role of crystallization processes in pharmaceutical science and technology can be associated, both, with its influence on the solid-state properties of the drug substances and with an effect on drug product stability and performance. The concept of crystal and particle engineering applied to pharmaceutical substances requires, first of all, reproducibility and consistency of the solid-state properties.

Keywords: Polymorphism, thermodynamics, kinetics, co-crystals, characterization, regulatory aspects.

Introduction

Crystallization is the spontaneous arrangement of the particles in to a repetitive orderly array, i.e., regular geometric pattern[1]. When applied to solids, the adjective, *crystallin*e, implies an ideal crystal in which the structural units, termed *unit cells,* are repeated regularly and indefinitely in three dimensions in space. The common crystalline forms found for a given drug substance are polymorphism and solvates. Crystalline polymorphisms have the same chemical composition but different internal crystal structures and, therefore, possess different physic-chemical

properties. The different crystal structure in polymorphs arises when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. The occurrence of polymorphism is quite common among organic molecules[2]. *Polymorphism* in crystalline solid is defined as materials with the same chemical composition different lattice structure and/or different molecular composition[3]. Chemists and engineers in the pharmaceutical industry generally seek to deliver crystalline forms of their active compounds, mainly due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on purification and isolation of chemical substances. Increasing attention is now being paid to the impact of materials properties in drug discovery and early development as the drug compounds tend to be very valuable materials. The pharmaceutical industry's mission for the material is to rapidly advance development programs with good confidence that form and formulation problems are unlikely to arise and to maximize a compound's potential as a therapeutic. In keeping with the common goal of making better products, faster and cheaper, we propose a paradigm of pro-active material design in pharmaceutical research. Rather than settling for the physical forms that the pure compounds intrinsically display, we should be aiming to identify the physical / material properties required of the target drug and make crystalline forms to meet those needs[4]. Small molecules in the amorphous state are thermodynamically metastable compared with the crystalline phase. Therefore, this property results in crystallization during storage and handling of pharmaceutical products, such as post compression hardening of tablets, particle aggregation in dry powder inhalers, and structural instability in transdermal patches. Over 90% of all pharmaceutical products, such as tablets, aerosols, capsules, suspension and suppositories contain drug in particulate, generally crystalline form[87]. Polymorphism, which is produced when a compound crystallizes in a various solid phases that differ in crystal packing, is common among pharmaceutical compounds[5]. More than one-third of the drug in the pharmaceutical industry show polymorphic structures. A further one-third is capable of forming hydrates and solvates[6]. Crystal engineering approaches, which can potentially be applied to wide range of crystalline materials, offer an alternative and potentially fruitful method for improving the solubility, dissolution rate and subsequent bioavailability of poorly soluble drug[7]. One of the important objective of pharmaceutical technology is to secure the stability and effectiveness of pharmaceutical products[8].

Crystal habits

Crystal is a polyhedral solid with number of planar surfaces. A substance crystallizes in such a way that the angle between a given pair of faces is same in all specimens. It is the characteristic of a particular substance irrespective of

the relative sizes of faces. The shape and size of the crystals formed are markedly dependent on the conditions under which crystallization is carried out.

Columnar: - Rod like particles having a width and thickness exceeding that of needle type particles. The term prismatic may also be used. e.g. flurocortisone acetate

Blade: - Long, thin and flat particles, which can also be referred to as being lath shaped. e.g. Resorcinol

Plate: - Flat particles of similar length and width. They are also denoted as being lamellar or micaceous. e.g. Naphthalene

Tabular: - Flat particles of similar length and width, but possessing greater thickness and flakes. e.g. Tolbutamide

Equant: - Particles of similar length, width and thickness. e.g. Sodium chloride

Acicular: - Needle like prism[1]. e.g. Nalidaxic acid.

Solvates & 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. 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 anhydrites 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[3].

It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. 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 structure. Because solvates behave similarly to hydrates, common analytical technique can be used for characterization of solvates and hydrates.

Crystalline hydrates, based on their structure may be classified into three categories. The first category (class I) are the isolated site hydrates, where the water molecules are isolated from direct contact with other water molecules by intervening drug molecules, e.g., cephradine dehydrate. The second category (class 2) are channel hydrates where the water molecules included in the lattice lie in next to other water molecules of adjoining unit cells along the axis

of the lattice, forming channel through the crystal, e.g., ampicillin trihydrate. The channel hydrates can be sub classified in to two categories. One category comprises the expanded-channel or nonstoichiometric hydrates, which may take up additional moisture in the channel when exposed to high humidity and for which the crystal lattice may expand or contract as the hydration or dehydration proceeds effecting changes in the dimensions of unit cell, e.g., cromolyn sodium. The other subcategory comprises the planner hydrates, which are channel hydrates in which water is localised in a two-dimensional order, or plane, e.g., sodium ibuprofen, the third category (class 3) of crystalline hydrates are the ion-associated hydrates, in which the metal ions are coordinated with water, e.g., calteridol calcium. Various types of phase changes are possible in solid state hydrated or solvated systems in response to changes in environmental conditions, such as relative humidity, temperature and pressure. For example, some hydrated compound may convert to an amorphous form up on dehydration and some may convert from a lower to higher state of hydration yielding forms with lower solubility. Alternatively, a kinetically favoured but thermodynamically unstable form may be converted during pharmaceutical processing to a more stable and less soluble.

The phase transformation associated with exposure to water, such as during solubility measurement, wet granulation processes, dissolution studies and accelerated stability tests are likely to occur via solution mediation. The rate of solution-mediated transformation is proportional to the solubility of the species involved. Temperature, pressure and relative humidity may increase the rate of phase transformation of hydrates by inducing mobility in the system.

Apart from identifying and characterizing the phases during various stages of drug development, it is very important to gain an understanding of the dehydration/hydration mechanisms and kinetics. Nucleation is the most significant phenomenon in determining the transformation kinetics, that is, the rate of formation of new phases. The practical application of understanding the dehydration kinetics are mainly the determination f the condition for allowable exposure of bulk drug substance during development and processing, proper packing, allowable temperature ranges for shipping, storage, and labelling of the final product, and the initial selection of a form for development[2].

Predicting the formation of solvates and hydrates of a compound and the number of molecules of water and solvent incorporated in to the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favour the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, where as other crystal forms

are more stable in the presence of water and/or solvent. There may be too much possibility so that no computer programmes are currently available for predicting the crystal structures of hydrates and solvates.

The combined physical analytical techniques of thermogravemetry and infrared spectroscopy (TG/IR) can permit identification of the solvent incorporated into the crystal lattice. This combined technique has been used to study formulated products, like capsules and tablets[7].

Co-crystals

Pharmaceutical co-crystals can be defined as crystalline materials comprised of an active pharmaceutical ingredient (API) and one or more unique co-crystal formers, which are solids at room temperature. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. In contrast Dunitz defend the use of co-crystal as encompassing molecular compound, molecular complexes, solvates, inclusion compounds, channel compounds, clathrates and possibly other type of multi-component crystals[7]. Co-crystals can be constructed through several types of interaction, including hydrogen bonding, π-stacking, and van der Waals forces. Solvates and hydrates of the API are not considered to be co-crystals by this definition. However, co crystals may include one or more solvent/water molecules in the crystal lattice.

A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. Co crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts – this is an important feature, since Brønsted acid-base chemistry is not a requirement for the formation of a co-crystal[4].

An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability is through the application of crystal engineering of co-crystals, historically referred to as molecular complexes. Pharmaceutical co-crystallization is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The physicochemical properties of the API and the bulk material properties can be modified, while maintaining the intrinsic activity of the drug molecule. The intellectual property implications of creating co-crystal are also highly relevant[7].

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 behaviour 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 behaviour is termed as conformational polymorphism in which molecule is not rigidly constructed and can exist in distinct conformational states so that each of these conformationally distinct modifications may crystallize in its own lattice structure[3].

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[3].

The energy of interaction between a pair of molecules in a solid, liquid, or real gas depends on the mean intermolecular distance of separation according to Morse potential curve. For a given pair of molecules, each polymorph, liquid or real gas has its own characteristic interaction energies and Morse curve. These intermolecular Morse curve are similar in shape but have smaller energies and greater distance than the Morse potential energy curve for the interaction between two atom linked by a covalent bond in a diatomic molecule or within a functional group of a polyatomic molecule. The Morse potential curve is itself the algebraic sum of a curve for intermolecular attraction due to van der Walls forces or hydrogen bonding and a curve for intermolecular electron-electron and nucleus-nucleus repulsion at closer approach.

The convention employed is that attraction causes a decrease in potential energy, whereas repulsion causes an increase in potential energy. At the absolute zero of temperature, the pair of molecules would occupy the lowest or zero point energy level. The Heisenberg uncertainty principle requires that the molecule have an intermediate position at a defined momentum or energy. This indeterminate position corresponds to the familiar vibration of the molecules about the mean positions that define the mean intermolecular distance.

The sum of the individual energies of interaction between nearest neighbours, next nearest neighbours, and so on, throughout the entire crystal lattice, liquid, or real gas can be used to define the internal energy E (i.e., the intermolecular structure energy) of the phase. Normally the interactions beyond next nearest neighbours are weak enough to be approximated or even ignored. Because each polymorph has its own distinctive crystal lattice, it has its own distinctive Morse potential energy curve for the dependence of the intermolecular interaction energies with

intermolecular distance. The liquid state has a Morse curve with greater intermolecular energies and distances, because the liquid state has a higher energy and molar volume (lower density) than does the solid state[9].

Kinetics of polymorphism

During the 19th century, Gay Lussac observed that, during crystallization, an unstable form is frequently obtained first that subsequently transform into a stable form[10]. This observation was later explained thermodynamically by Ostwald[10, 11-14], who formulated the law of successive reactions, also known as Ostwald's step rule. This rule may be stated as, "In all processes, it is not the most stable state with the lowest amount of free energy that is initially formed, but the least stable state laying nearest in free energy to the original state[10].

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. 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[3].

An understanding of the kinetics of the crystallization process involves consideration of the various steps involved. In the first step (termed nucleation) tiny crystallites of the smallest size capable of independent existence (termed nuclei) are formed in the supersaturated phase. Molecules of the crystallizing phase then progressively attach themselves to the nuclei, which then grow to form macroscopic crystals in the process known as crystal growth, until the crystallization medium is no longer supersaturated because saturation equilibrium has now been achieved. If the crystals are now allowed to remain in the saturated medium, the smaller crystal, which have a slightly greater solubility according to the Thomson (Kelvin) equation[15, 16] tend to dissolve. At the same time, the larger crystal, which consequently have a lower solubility, tend to grow. This process of the growth of larger crystals at the expense of smaller crystals is sometimes termed Ostwald ripening.

The nucleation step is the most critical for the production of different polymorphs and is therefore discussed in some detail below. Nucleation may be primary (which does not require pre-existing crystals of the substance that crystallizes) or secondary (in which nucleation is induced by pre-existing crystals of the substance). Primary nucleation may be homogenous, whereby the nuclei of the crystallizing substance arise spontaneously in the medium in which crystallization occurs, or heterogeneous, whereby the nuclei comprise foreign solid matter, such as particulate contaminants (including dust particles or the walls of the container).

Heterogeneous (i.e., spontaneous) nucleation is a stochastic process that is governed by the algebraic opposition of a volume term that favours the accretion of additional molecules from the supersaturated medium and a surface term that favours the dissolution of the volume term that favours the dissolution of the molecular aggregates that would otherwise form nuclei[9].

Enantiotropy and monotropy

If one polymorph is stable (i.e., has the lower free energy content and solubility over a certain temperature range and pressure), while another polymorph is stable (has a lower free energy and solubility over a different temperature range and pressure), the two polymorphs are said to be enantiotropes, and the system of the two solid phases is said to be enantiotropic. For an enantiotropic system a reversible transition can be observed at a definite transition temperature, at which the free energy curves cross before the melting point is reached. Examples showing such behaviour include acetazolamide, carbamazepine, metochlopramide, and Tolbutamide[17, 18, 19].

Sometimes only one polymorph is stable at all temperatures below the melting point, with all other polymorphs being therefore unstable. These polymorphs are said to be Monotropes, and the system of the two solid phases is said to be monotropic. For a monotropic system the free energy curves do not cross, so no reversible transition can be observed below the melting point. The polymorph with the higher free energy curve and solubility at a given temperature is, of course, always the unstable polymorph. Examples of this type of system include Chloramphenicol Palmitate and metolazone[17, 18, 19].

To help decide whether two polymorphs are enantiotropes or Monotropes, Burger and Ramberger developed four thermodynamic rules[18]. The application of these rules was extended by Yu[19]. The most useful and applicable of the thermodynamic rules of Berger and Ramberger are the heat of transition rule and the heat of fusion rule. The heat of fusion rule states that, if an endothermic polymorphic transition is observed, the two forms are enantiotropes. Conversely, if an exothermic polymorphic transition is observed, the two forms are Monotropes.

The heat of fusion rule states that, if the higher melting polymorph has the lower heat of fusion, the two forms are enantiotropes. Conversely, if the higher melting polymorph has the higher heat of fusion, the two forms are Monotropes[9].

Different polymorphs differ in following physical properties[9]

- Packing properties
    - Density
    - Refractive index

- Conductivity (electrical & thermal)
- Hygroscopicity

- Thermodynamic properties
  - Melting temperature
  - Vapor pressure
  - Solubility
- Spectroscopic properties
  - Electronic transition (UV spectra)
  - Vibrational transitions (IR spectra)
  - Nuclear spin transition (NMR spectra)
- Kinetic properties
  - Dissolution rate
  - stability
- Surface properties
  - Surface free energy
  - Interfacial tension
  - Habit (i.e. shape)
- Mechanical properties
  - Hardness
  - Tensile strength
  - Compatibility (Tableting)
  - Handling, flow & blending properties

Mechanism of Crystal Formation

A) **Supersaturation**

When the solubility of a compound in a solvent exceeds the saturation solubility, the solution becomes supersaturated and the compound may precipitate or crystallize. Supersaturation can be achieved through:

1) Evaporation of solvent from the solution
2) Cooling of the solution, if the solute has a positive heat of solution.
3) Formation of a new solute as a result of chemical reaction.
4) Addition of a substance, which is more soluble in solvent than the solid to be crystallised.

In the absence of seed crystals, significant Supersaturation is necessary to initiate the crystallization through formation of nuclei. The rate of separation, particle size, uniformity and distribution depend on two successive largely independent processes, namely, Nucleation and Growth of nuclei[1].

B) **Nucleation**

Nucleation refers to the birth of very small bodies of a new phase within a homogenous supersaturated liquid phase. Nucleation is a consequence of rapid local fluctuations at the molecular level when molecules or ions or atoms are in random motion in any small volume. Initially several molecules or ions or atoms associate to form clusters. These are loose aggregates, which usually disappear quickly. However, when enough particles associate to form an embryo, there is a beginning of the lattice arrangement and formation of a new solid phase. In most of the cases, embryos have short lives dissolve as soon as they form. An embryo may grow to such a size that it is in thermodynamic equilibrium with the solution. The initially formed crystals are of molecular size, which are termed as *nuclei*. On certain occasions, the nuclei grow in dimensions that are limited by the amount of material available and thus form crystals[1].

The factors that influence nucleation, readily explains why and how the following factors determine the polymorph that crystallizes out:

- Solvent medium
- Supersaturation
- Temperature
- Impurities or additives dissolved
- Surface of the crystallization vessel
- Suspended particles
- Seed crystals.

Under appropriate thermodynamic conditions, a less stable polymorph may be converted into a more stable polymorph. The rate of conversion to the more stable polymorph is often rapid, if mediated by the solution phase or vapour phase. In these phases the less stable polymorph (having the greater solubility or vapour pressure) dissolves or sublimes, while the more stable polymorph (having the lower solubility or vapour pressure) crystallizes out. The rate of conversion to the more stable polymorph is usually slower, if the transformation proceeds directly from one solid phase to another. In this case, the mechanism of interconversion is likely to involve the following three steps:

1) Loosening and breaking of the inter molecular forces (not covalent bonds) in the less stable polymorph
2) Formation of the disordered solid, similar to the localised amorphous form.

3) Formation of the new intermolecular forces leading to crystallization of the more stable polymorph as the product phase[20].

In another words, the nucleation mechanism can be divided into two main categories that are homogenous and heterogeneous[21,22,23,24]. Homogenous nucleation rarely occurs in large volume (quarter than 100 µl) since the solution contains random impurities that may include nucleation[25,26].

A surface or interface of composition and/or structure different from the crystallizing solute may serve as a 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. Nucleation mechanisms have been of great utility in controlling the nucleation and transformation of polymorphs and solvents, isolating metastable solid phases in confined space[27], diverting nucleation of polymorphs using solid substrates that template certain crystal structure[28,29,30] and in controlling transformations during dissolution of metastable solid phases[31,32,33].

Newer techniques in nucleation

In recent years various new techniques for nucleation have been developed. Scientists have yet to achieve a satisfactory degree of control over polymorphism and in particular there is no method to guarntee the production of even the most thermodynamically stable form of compound. Most difficult encountered in this tasks 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[34]. 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[35]. 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[34].

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 Supersaturation ratio is often required. Crystallization from capillaries is ideal for providing an environment with high Supersaturation because small volumes of solution isolates heterogeneous nucleants[24,25] 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[36]. 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[37]. 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[38,39].

4) Polymer heteronucleation:

The first combinational approach in controlling polymorphism that directly targets nucleation is polymer heteronucleation. 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[40] was discovered using polymer heteronucleation that remarkably proved more stable than the well-studied trigonal form[41].

C) **Crystal growth**

Crystal growth is a diffusion process and surface phenomenon. From solution, solute molecules or ions reach the faces of a crystal by diffusion. On reaching the surface, the molecules or ions must be accepted by the crystal and

organised into the space lattice. This phenomenon continues at the surface at the finite rate. Neither the diffusion nor the interfacial step will proceed unless the solution is supersaturated[2].

METHODS FOR PREPARATION OF CRYSTAL FORMS

Organic medicinal agents that can exist in two or more solid phases often can provide some distinct advantages in particular application. Factors related to processing, such as powder flow characteristics, compressibility, filterability, or Hygroscopicity, may dedicate the use of one polymorph in preference to another. In other cases, a particular form may be selected because of the high reproducibility associated with its isolation in the synthetic procedure[9].

It is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future synthesis[9]. In 1990 Byrn and Pfeiffer found more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavaibility, ease of purification, preparation or synthesis, Hygroscopicity, recovery, or prevention of precipitation[42].

One question likely to arise during the registration process is "What assurance can be provided that no other crystalline forms of this compound exist?" it is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity. The condition under which different polymorphs are obtained exclusively or together also can provide very useful information about the relative stability of different phases and the methods and techniques that might be necessary to obtain similar structure of different chemical systems[9].

Following are the different methods employed to obtain different crystals forms.

A. Sublimation

On heating, approximately two-third of all organic compounds are converted partially from the solid to the gaseous state and back to solid, i.e. they sublime[43]. While strictly speaking the term sublimation refers only to the phase change from solid to vapour without the intervention of the liquid phase, it is often found that crystals are formed on cooler surfaces in close proximity to the melt of organic compounds when no crystals were formed at temperatures below the melting point.

The sublimation temperature and the distance of the collecting surface from the material undergoing sublimation have a great influence on the form and size of the crystals produced. The occurrence of polymorphic modifications depends on the temperature of sublimation. In general, it may be assumed that unstable crystals form preferentially at lower temperatures, while at higher temperatures stable forms are to be expected. Nevertheless, mixtures consisting of several modifications are frequently found together. It should be obvious that the sublimation technique is applicable only to those compounds that are thermally stable.

A simple test can be used to determine if a material sublimes. A small quantity (10-20 mg) of the solid is placed in a petri dish that is covered with an inverted watch glass. The petri dish is heated gently on a hot plate and the watch glass is observed to determine if crystals are growing in it. According to McCrone[44], one of the best methods for obtaining a good sublimate is to spread the material thinly over a portion of half-slide, cover with a large cover glass, and heat slowly using a Kofler block. When the sublimate is well formed, the cover glass is removed to a clean slide for examination. It is also possible to form good crystals by sublimation from one microscope slide to a second held above it, with the upper slide also being heated so that its temperature is only slightly below that of the lower slide. Cooling of the cover slip by placing drops of various low-boiling solvents on the top surface will cause condensation of the more unstable forms. On a larger scale, a glass cold finger or a commercial sublimator can be employed. Once crystals of various modifications have been obtained, they can be used as seeds for the solution phase crystallization of larger quantities[9].

B. Crystallization from a single solvent

Slow solvent evaporation is a valuable method for producing crystals. Solutions of the material being crystallize, preferably saturated or nearly so, are filtered to remove most nuclei and then left undisturbed for a reasonable period of time.

For the solvent to be useful for recrystallization purposes, the solubility of the solute should be on the order of 5-200 mg/mL at room temperature. If the solubility exceeds 200 mg/mL, the viscosity of the solution will be high, and a glassy product is likely to be obtained. A useful preliminary test can be performed on 25-50 mg of sample, adding few (5-10) drops of solvent. If the entire solid dissolves, the solvent will not be useful for recrystallization purposes. Similarly, high viscous solvents, and those having low vapour pressure (such as glycerol or dimethylsulphoxide) are not usually conductive to efficient crystallization, filtration, and washing operations. The solvents selected for

recrystallization should include any with which the compound will come into contact during synthesis, purification, and processing, as well as solvents having a range of boiling points and polarities.

The process of solution mediated transformation can be considered the result of two separate events,

(a) Dissolution of the initial phase

(b) Nucleation/growth of the final, stable phase.

If crystals do not grow as expected from saturated solution, the interior of the vessel can be scratched with a glass rod to induce crystallization by distributing nuclei throughout the solution. Alternatively, crystallization may be promoted by adding nuclei, such as seed crystals of the same material.

If two polymorphs differ in their melting point by 25-50^{0}C, for monotropic polymorphs the lower melting, more soluble, from will be difficult to crystallize. The smaller the difference between the two melting points, the more easily unstable or metastable forms can be obtained.

A commonly used crystallization method involves controlled temperature change. Slow cooling of a hot, saturated solution can be effective in producing crystals if the compound is more soluble at higher temperatures, alternatively slow warming can be applied if the compound is more 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 ice-acetone bath. High boiling solvents can be useful to produce metastable polymorphs.

The reason for using crystallization solvents having varying polarities is that molecules in solution often tend to form different types of hydrogen-bonded aggregates, and that these aggregate precursors are related to the crystal structures that develop in the supersaturated solution[46].

Some solvents favour the crystallization of a particular form or forms because they selectively absorbed to certain faces of some polymorphs, thereby either inhibiting their nucleation or retarding their growth to advantage of others.

Among the factors affecting the types of crystals formed are

a) The solvent composition or polarity

b) The concentration or degree of Supersaturation

c) The temperature, including the cooling rate and the cooling profile

d) Additives

e) The presence of seeds

f) pH, especially for salt crystallization

g) agitation

In determining what solvents to use for crystallization, one should be careful to select those likely to be encountered during formulation and processing, typically these are water, methanol, ethanol, propanol, isopropanol, acetone, Acetonitrile, ethyl acetate, and hexane[9].

C. Evaporation from a Binary Mixture of Solvents

If single-solvent solutions do not yield the desired phase, mixtures of solvents can be tried. Multicomponent solvent evaporation method depends on the difference in the solubility of the solute in various solvents. In this approach, a second solvent in which the solute is sparingly soluble is added to the saturated solution of the compound in good solvent. Often a solvent system is selected in which the solute is more soluble in the component with the higher vapour pressure. As the solution evaporates, the volume of the solution is reduced and, because the solvents evaporate at different rates, the composition of the solvent mixture changes.

Occasionally, crystals are obtained by heating the solid in one solvent and then pouring the solution into another solvent or over cracked ice[9].

D. Vapour Diffusion

In the vapour diffusion method, a solution of the solute in good solvent is placed in a small, open container that is then stored a larger vessel containing a small amount of miscible, volatile nonsolvent. The larger vessel (often a desiccator) is then tightly closed. As solvent equilibrium is approached, the nonsolvent diffuses through the vapour phase into the solution, and saturation or Supersaturation is achieved. The solubility of the compound in a precipitant used in a two-solvent crystallization method such as vapour diffusion should be as low as possible (much less than 1 mg/mL), and the precipitant (the solvent in which the compound is poorly soluble) should be miscible with the solvent and the saturated solution. The most frequent application of this technique is in the preparation of single crystals for crystallographic analysis[9].

E. Thermal Treatment

Frequently when using differential scanning Calorimetry as an analysis technique, one can observe an endothermic peak corresponding to the phase transition, followed by a second endothermic peak corresponding to melting. Sometimes there is an exothermic peak between the two endotherms, representing a crystallization step. In these cases it is often possible to prepare the higher melting polymorph by thermal treatment[9].

F. Crystallization from the Melt

In accordance with Ostwald's rule[47], the cooling of melts of polymorphic substances often first yields stable modification, which subsequently rearranges into the stable modification in stages. Since the metastable form will have the lower melting point, it follows that supercooling is necessary to crystallize it from the melt. After melting, ht system must be supercooled below the melting point of the metastable form, while at the same time the crystallization of the more stable form or forms must be prevented. Quench cooling a melt can sometimes result in formation of an amorphous solid that on subsequent heating undergoes a glass transition followed by crystallization[48].

G. Rapidly changing solution pH to precipitate Acidic or Basic substances

Many drug substances fall in the category of slightly soluble weak acids, or slightly soluble weak bases, whose salt forms are much more soluble in water. Upon addition of acid to an aqueous solution of a soluble salt of a weak acid, or upon addition of alkali to an aqueous solution of a soluble salt of a weak base, crystals often result. These crystals may be different from those obtained by solvent crystallization of a weak acid or weak base. Nucleation does not necessarily commence as soon as the reactants are mixed, unless the level of Supersaturation is high, and the mixing stage may be followed by an appreciable time lag before the first crystals can be detected. Well-formed crystals are likely to result in these instances than when rapid precipitation occurs[9].

H. Thermal Desolvation of Crystalline Solvates

The term "desolvated solvates" has been applied to compounds that were originally crystallized as solvates but from which the solvent has been removed generally by vaporization induced by heat and vacuum). Frequently, these "desolvated solvates" retain the crystal structures of the original solvate form and exhibit relatively small changes in lattice parameter. For this reason, these types have been referred to as pseudopolymorphic solvates. However, in instance where the solvent serves to stabilize the lattice, the process of desolvation may produce a change in lattice parameters, resulting in the formation of either a new crystal form or an amorphous form. These solvates have been referred to as polymorphic solvates.

The process of desolvating pseudopolymorphic solvates is similar, involving only two steps of

(a) Molecular loosening

(b) Breaking of host-solvent hydrogen bonds or association

Among the factors that influence the desolvation reaction are the appearance of defects, the size of tunnels in the crystal packing arrangement, and the strength of hydrogen bonding between the compound and its solvent of crystallization[49].

I. Growth in the Presence of Additives

The presence of impurities can have a profound effect on the growth of crystals. Some impurities can inhibit growth completely, and some may enhance growth. Still others may exert a highly selective effect, acting only on certain crystallographic faces and thus modifying the crystal habit. Some impurities can exert an influence at very low concentrations (less than 1 part per million), whereas others need to be present in fairly large amounts to have any effect[50].

A route to polymorph selection and stabilization is to employ additives or solvents (impurities), which have the ability to inhibit or interfere with the fastest growth directions of a stable polymorph over that of metastable form exhibited by the system. Such studies highlight the subtle role that growth conditions play in crystallization, and have direction ramifications for the supramolecular chemist engaged in crystal engineering[51].

Many studies have reported the role of additives in controlling the outcome of the crystallization process. Some of the preselected additives are capable of inhibiting the nucleation and/or growth of the unwanted polymorphs[52].

Additives can be designed to bind specifically to the surfaces of particular polymorphs and so inhibit their achieving the critical size for nucleation, allowing a desired phase to grow without competition[53]. Lahav and co-workers have shown additives at levels as low as 0.03% can inhibit nucleation and crystal growth of a stable polymorph, thus favouring the growth of a metastable polymorph. They also showed that it is possible to design crystal nucleation inhibitors to control polymorphism[54].

Crystallization in the presence of additives like surfactants and polymers is a relatively less explored area but is important for polymorphic screening of a compound during its developmental stage. Surfactants and polymers act by various mechanisms to influence either the growth or the nucleation phase, resulting in modification of either the polymorphic form or the crystal habit[55].

J. Grinding

Polymorphic transformations have been observed to occur in grinding of certain materials, such as sulfathiazole, barbital, phenylbutazone, cephalexin, Chloramphenicol Palmitate, indomethacin and chlorpropamide. Bryn[49] has stated that polymorphic transformations in the solid state require the three steps of

(a) Molecular loosening (nucleation by separation from the lattice)

(b) Solid solution formation

(c) Separation of the product (crystallization of the new phase).

Depending on the material of the conditions employed, grinding can result in conversation to an amorphous substance. With the exercise of care, different polymorphic forms can be obtained[9]. It is known that the polymorphic form of a drug substance is produced by the grinding of a single component, grinding it with some excipients[8].

METHODS OF CHARACTERIZATION OF POLYMORPHS

Certainly the most important aspect relating to an understanding of polymorphic solid and solvate species is the range of analytical methodology used to perform the characterization studies[56,57,58]. The importance of this area has been recognised from both scientific and regulatory concerns, so the physical methods have begun to come under the same degree of scrutiny as have the traditional chemical method of analysis.

The identification, characterization and quantification of crystal forms are becoming increasingly important within the pharmaceutical industry. A combination of different physical analytical techniques is usually necessary for this task[59].

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[60-64].

Of all the methods available for the physical characterization of solid materials, it is generally agreed that crystallography, microscopy, thermal analysis, solubility studies, Vibrational spectroscopy, and nuclear magnetic resonance are the most useful for characterization of polymorphs and solvates. However, it cannot be overemphasized that the defining criterion for the existence of polymorphic types must always be a non-equivalence of crystal structures. For compounds of pharmaceutical interest, this ordinarily implies that a non-equivalent x-ray powder diffraction pattern is observed for each suspected polymorphic variation. All other methodologies must be considered as sources of supporting and ancillary information; they cannot be taken as definitive proof for the existence of polymorphism by themselves alone.

In the present work, the practice of the most commonly encountered techniques performed for the solid-state characterization of polymorphic or solvate properties will be reviewed. No attempt will be made to summarize every recorded use of these methodologies for such work, but selected examples will be used to illustrate the scope of information that can be extracted from the implementation of each technique[9].

Following are the methods for characterization of polymorphs.

I. Crystallography: X-ray diffraction

A. Single Crystal X-ray Diffraction

B. X-ray powder diffraction

II. Morphology : Microscopy

A. Polarizing Optical Microscopy

B. Thermal microscopy

III. Phase transitions: Thermal methods of analysis

A. Thermogravemetry

B. Differential thermal analysis

C. Differential Scanning Calorimetry

IV. Molecular Motion: Vibrational Spectroscopy

A. Infrared Absorption Spectroscopy

B. Raman spectroscopy

V. Chemical environment: Nuclear Magnetic Resonance Spectroscopy

Table-1: Drug and their number of Polymorphs[8].

Drug	No. of polymorph
Chloramphenicol Palmitate	2
Mefanamic acid	2
Carbmazepine	4
Phenyl butazane	5
Sulfapyridine	7
Nabumetone	2
Terfenadine	3
Spiranolactone	6
Ritonavil	2
Lamivudine	2
Enalapril maleate	2
Ranitidine HCL	2
Terazosin HCL	3
Tolsemide	2
Warfarin VA	2
Cefurozime Axetil	2
Metaprotol tartarate paracetamol	2

2-Amino 5-Nitropyridine	3
Prednisolone tetra butylacetate	2
Primidone	2
Eztrene	3
Probucel	2
Ampicillin	3
Estradiol	4
Acetohexamide	2
Cefamandole nafate	2
Bupropion hydrochloride	2
Olanzapine	2
Famotidine	2
Taltirelin	2
2-acetamidobenzamide	2
Arteether	6
Benzimidazole	3
R-albuterol sulfate	2
Sitafloxacin	2
Pentoprazole	2

Table-2: Solvents often used in the preparation of polymorphs (9) (45).

Solvent	Boiling point (^{0}C)
Dimethylformamide	153
Chlorobenzene	132
Octane	126
n-butanol	118
Acetic acid	118
Toluene	111
Nitromethane	101
Water	100
Isooctane	99
Heptane	98.4
1-Propanol	97
1,2-Dichloroethane	83.5
2-Propanol	83
Acetonitrile	82
2-Butanone	80
Benzene	80
Butanone	79.5
Ethyl acetate	77
Ethanol	78
Isopropyl ether	68

Hexane	69
n-Hexane	69
Diisopropyl ether	68.4
Tetrahydrofuran	65
Methanol	65
Chloroform	61
Methyl acetate	57
Acetone	57
Methylene chloride	40
Dichloromethane	40
n-Pentane	36
Diethyl ether	35

Table-3: **List of analytical techniques for polymorph characterization (65).**

Technique	Advantages	Disadvantages
Powder X-ray diffractometry (PXRD)	Standard for phase identification, usually show significant difference among crystal forms	Interference from crystalline recipients
Single crystal X-ray diffractometry	Ultimate phase identification (ID) in depth understanding of structure	May be difficult to prepare
Differential scanning Calorimetry (DSC)	Small sample size, information on phase transition, information on interference with recipients	No information on the nature of transition, interference from both crystalline & amorphous recipient
Thermogravemetric analysis (TGA)	Quantative information on the stoichiometry of solvates/hydrates	Only useful for solvates/hydrates, interference from water containing excipients
Mid infrared (IR)	Complimentary phase ID method, ability to show the different states of water, sample size can be very small if coupled with microscopy	Severe interference from moisture, interference from excipients, difference may be small
NCAR IR (NIR)	Complimentary phase ID method, ability to penetrate through containers, ability to show different states of water	Low intensity, differences may be very subtle, interference from excipients
Raman	Complimentary phase ID method, small sample size, minimum interference with water	Interference from excipients
Solid state nuclear magnetic resonance (SSNMR)	Complimentary phase ID method, local environment of atoms	Relatively long data acquisition time
Polarised microscopy	Information on crystal morphology and size, qualitative information on crystallinity, Complimentary information on phase transition	Interference from excipients
Hot stage microscopy	Complimentary information on phase transition	Interference from excipients

Solvent sorption	Excellent for detection of low level of amorphous phase, defining the liability of hydrates	Interference from amorphous excipients, large hysteresis loop possible

REGULATORY CONSIDERATION

In ANDA, careful attention is paid to the effect of polymorphism in the context of generic product equivalency[3]. In the case of a new drug substance, it is important that polymorphism data be generated prior to the initiation of pivotal clinical studies and primary stability batches. Companies have experienced market shortage because they have observed unpredicted changes in polymorphic form, which ultimately resulted in problematic quality release and stability testing (i.e. dissolution) of the finished dosage form. Generic drug manufacturers have the benefit of a large amount of information that is known before bulk drug manufacturers even begin their synthesis. Prior to developing the drug product, the recall history for the branded product is known.

The impact of drug substance polymorphs on generic pharmaceuticals development revolves around solubility of the drug substance and dissolution of the drug product. Once the existence of polymorphism has been identified through the literature, the drug substance available must be evaluated. Based upon the solubility of the drug substance, formulations can be developed. 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. Drug substance polymorphism is an old issue that organic chemists have had to deal with since they first crystallized a compound. Although this is an unavoidable reality of organic compounds, there is no affect on the ability of the generic pharmaceutical scientist to be able to formulate a manufacturable and bioequivalent product[66].

Pre-formulation and formulation drug development stages are associated with manufacturing control, characterization and optimization of solids. Pre-formulation concerns “rational, science-based requirements for drug substances and excipients”.[67]

The drug substance section of an NDA must contain specifications related to purity, solubility, crystal properties, morphology, particle size and surface area. Both drug substance and drug product sections of NDA require detailed investigation into the influence of structure on stability, in order to avoid negative recrystallization phenomena, and also into the relationship between structure and drug release rate. An NDA also requires complete proof of structure on all crystalline drug candidates, preferably from single-crystal structural data. Often, a growth technique will have to be developed to produce single crystals, which may prove a challenging task for large molecular substances or

substances with low solubility. If production of single crystals is difficult, X-ray powder diffraction will have to be used to assure crystal and solid-state phase identity. Additional requirements are imposed on chiral drugs, which may possess different pharmacological and toxicological effects depending on their enantiotropic form. These requirements consist of identification of enantiomeric composition and (optical) purity, resolution (if the drug is used in a single enantiomeric form) and the confirmation of enantiomeric stability in formulation[68].

The potential impact of changing crystal properties during late-stage drug development, in terms of both cost and product delay has led to specific guidelines on the control of physicochemical properties according to the NDA requirements and further inspections. These guidelines have been developed as a result of collaboration between regulators, industry and academia[69-70] and presented in the form of algorithms. The four types of solid-state phases identified according the FDA charts are polymorphs, solvates (e.g. hydrates), desolvated solvates (pseudopolymorphs) and amorphous compounds. The crystallization process must be controllable with respect to the solid form produced. Once the properties of these solid forms are identified using appropriate analytical techniques and these properties are different, control and specification procedures should be defined to ensure consistency and stability of the product. Extended international guidelines have been formulated as collaboration has grown between different regulatory organizations through the International Conference on Harmonization (ICH). The standards of potency, purity and other physicochemical properties and the standard analytical methods for most commonly used drugs and drug products are given in pharmaceutical compendia such as the United State Pharmacopoeia (USP) and British Pharmacopoeia (BP). The above regulations, combined with internationally accepted manufacturing rules covering current good manufacturing practices (cGMP) make the crystallization process among the most important industrial and regulatory recognized issues in pharmaceutical development[71].

Conclusion

The role of crystallization processes in pharmaceutical science and technology can be associated, both, with its influence on the solid-state properties of the drug substances and with an effect on drug product stability and performance. The concept of crystal and particle engineering applied to pharmaceutical substances requires, first of all, reproducibility and consistency of the solid-state properties.

References

1. C. V. S. Subrahmanyam, A. Setty Thama, S. Sarasija, V. Kusum devi. Pharmaceutical Engineering Principle and practices; Vallabh prakashan (2005).
2. S. R. Vippagunta, H. G. Brittain, D. J. W. Grant, *Crystalline Solids,* Advanced Drug Delivery reviews, 2001, 48, 3-26.
3. M. Saifee, N. Inamdar, D. L. Dhamecha, A. A. Rathi, *Drug Polymorphism: A Review*, International journal of Health Research, 2009, 2(4): 291-306.
4. M. L. Peterson, M. B. Hickey, M. J. Zaworotko, O. Almarsson, *Expanding the scope of crystal Form Evaluation in Pharmaceutical Science*, J Pharm Pharmaceut Sci, 2006, 9 (3): 317-326.
5. J. S. Park, H. W. Kang, S. J. Park, C. K. Kim, *Use of CP/MAS solid state NMR for the characterization of solvate molecules within estradiol crystal forms*, European Journal of Pharmaceutics and Biopharmaceutics, 2005, 60, 407-412.
6. M. Sheikhzadeh, S. Rohani, M. Taffish, S. Murad, *Solubility analysis of busprione hydrochloride polymorphs: Measurement and prediction,* International Journal of Pharmaceutics, 2007, 338, 55-63.
7. N. Blagden, M.de Matas, P. T. Gavan, P. York, *Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates,* Advanced Drug Delivery Reviews, 2007, 59, 617-630.
8. E. Yonemochi, S. Kitahara, S. Maeda, S. Yamamura, T. Oguchi, K. Yamamoto, *Physicochemical properties of amorphous clarithromycin obtained by grinding and spray drying*, European journal of Pharmaceutical Sciences, 1999, 7, 331-338.
9. H. G. Brittain, S. R. Bryn, E. F. Fiese, J. W. Grant David, J. K. Guillory, K. R. Morris, M. J. Pikal, Polymorphism in Pharmaceutical Solids, Marcel Dekker Inc., 2008.
10. A. R. Verma, P. Krishna, Polymorphism and polytypism in crystals, John Wiley, New York, 1966, pp 15-30.
11. W. Ostwald, Lehrbuch der Allgemeinen Chemie, 2, W. Engelmann, Leipzig, Germany, 1896, pp.444.
12. W. Ostwald, Z. Physik, Chem., 1897, pp 289-330.
13. W. Ostwald, W. Engelmann, Grundriss der Allgemeinen Chemie, Leipzig, Germany, 1899.
14. J. W. Mullin, Crystallization, 3d ed. Butterworth Heinemann, London, UK, 1993, pp. 172-201.
15. P. W. Atkins, Physical Chemistry, Oxford Univ. Press, Oxford, UK, 1978, pp. 194, 563-566, 658-660.

16. D. J. W. Grant, H. G. Brittain, Solubility of Pharmaceutical Solids, Chapter 11 in Physical Characterization of Pharmaceutical solids, Marcel Dekker, New York, 1995, pp. 321-386.
17. S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg, G. Poochikian, Pharm. Res., 1995, 945.
18. A. Burger, R. Ramberger, Mikrochim. Acta [Wien], II, 1979, 259-271, 273-316.
19. L. Yu, J. Pharm. Sci., 84, 1995, 966-974.
20. D. B. Black, E. G. Lovering, J. Pharm. Pharmacol., 29, 1977, 684.
21. A. C. Zettlemoyer, Nucleation, Marcel Dekker, New York, 1969. p 1-70,109.
22. J. W. Mullin, Crystallization, Butterworth-Heinemann, Oxford, 1992, p 172-206.
23. O, Sohnel, J. Garside, Precipitation: Basic Principles and Industrial Applications, Butterworth-Heinemann, Oxford, 1992, p 1-5.
24. A. S. Myerson, Handbook of Industrial Crystallization, Butterworth-Heinemann, Boston, 2002, p 67.
25. J. H. Perepezko, Nucleation reactions in undercooled liquids. Mater Sci Eng A 1994, 178: 105– 111.
26. J. H. Perepezko, Kinetic processes in undercooled melts. Mater Sci Eng A 1997, 226: 374– 382.
27. L. J. Chyall, J. M. Tower, D. A. Coates, T. L. Houston, S. L. Childs, *Polymorph generation in capillary spaces: the preparation and structural analysis of a metastable polymorph of Nabumetone*, Crystal Growth, Des 2002, 2: 505– 510.
28. L. S. Taylor, G. Zografi, *Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions*, Pharm Res, 1997, 14: 1691–1698.
29. M. D. Ward, *Bulk crystals to surfaces: combining Xray diffraction and atomic force microscopy to probe the structure and formation of crystal interfaces*, Chem Rev, 2001, 101: 1697– 1725.
30. M. D. Lang, A. L. Grzesiak, A. J. Matzger, *The use of polymer heteronuclei for crystalline polymorph selection*, J Am Chem Soc, 2002, 124: 14834–14835.
31. N. Rodrýguez-Hornedo, D. Murphy, *Surfactant facilitated crystallization of dehydrate carbamazepine during dissolution of anhydrous polymorph*, J Pharm Sci 2004, 93(2): 449-460.
32. D. Murphy, F. Rodrý´guez-Cintro´n, B. Langevin, R. C. Kelly, N. Rodrý´guez-Hornedo, *Solutionmediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder*, Int J Pharm, 2002, 246: 121– 134.

33. N. Rodrýguez-Hornedo, D. Lechuga-Ballesteros, H. J. Wu, *Phase transition and heterogeneous/epitaxial nucleation of hydrated and anhydrous theophylline crystals,* Int J Pharm, 1992, 85: 149– 162.
34. B. R. Spong, C. P. Price, A. Jayasankar, A. J. Matzger, N. R. Hornedo, *General principles of pharmaceuticalsolid polymorphism: a supramolecular perspective*, Adv Drug Delivery Rev, 2004, 56: 241–274.
35. M. L. Peterson, S. L. Morissette, C. McNulty, A. Goldsweig, P. Shaw, M. Lequesne, J. Monagle, N. Encina, J. Marchionna, A. Gonzalez-Zugasti, J. Gonzalez Zugasti, A. V. Lemmo, S. J. Cima, M. J. Cima, O. Almarsson, *Iterative high-throughput polymorphism studies on acetaminophen and an experimentally derived structure for form III,* J Am Chem Soc, 2002, 124: 10958–10959.
36. B. A. Garetz, J. E. Aber, N. L. Goddard, R. G. Young, A. S. Myerson *Nonphotochemical, polarizationdependent, laserinduced nucleation in supersaturated aqueous urea solutions*, Phys Rev Lett, 1996, 77: 3475–3476.
37. D. E. Hooks, T. Fritz, M. D. Ward, *Epitaxy and molecular organization on solid substrates,* Adv Mater, 2001, 13: 227– 241.
38. M. D. Ward, *Organic crystal surfaces: structure, properties and reactivity,* Curr Opin Colloid Interf Sci, 1997, 2: 51– 64.
39. C. A. Mitchell, L. Yu, M. D. Ward, *Selective nucleation and discovery of organic polymorphs through epitaxy with single crystal substrates,* J Am Chem Soc, 2001, 123: 10830–10839.
40. M. D. Lang, J. W. Kampf, A. J. Matzger, *Form IV of carbamazepine*, J Pharm Sci, 2002, 91:1186–1190.
41. A. L. Grzesiak, M. Lang, K. Kim, A. J. Matzger, *Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I.* J Pharm Sci, 2003, 92: 2260–2271.
42. S. R. Byrn, Personal Communication, October 2, 1996.
43. M. Kuhnert-Brandstatter, Thermomicroscopy in the analysis of Pharmaceuticals, Pergamon Press, Oxford, 1971.
44. McCrone, S. R. Jr, Fusion methods in Chemical Microscopy, Interscience, New York, 1957.
45. D. Choquesillo-lazarte, J. M. Garcia-Ruiz, *Poly(ethylene) oxide for small-molecule crystal growth in gelled organic solvents*, Journal of Applied Crystallography, 2011, 44, 172-176.

46. S. R. Byrn, R. R. Pfeiffer, G. Stephenson, D. J. W. Grant, W. B. Gleason, Chem Materials, 1994, 6, 1148.

47. W. Ostwald, Z. Phys. Chem., 1897, 22, 289.

48. B. Peffenot, G. Widmann, Thermochim, Acta, 1994, 234, 31.

49. S. R. Byrn, Solid state Chemistry of Drugs, Academic Press, New York, 1982.

50. J. W. Mullin, Crystallization, 3d ed., Butterworth-Heinemann, Oxford, 1993.

51. N. Blagden, R. J. Davey, R. Rowe, R. Roberts, *Disappearing polymorphs and the role of reaction by-products: The case of Sulphathiazole*, Int J. Pharm., 1998, 172, 169-177.

52. W. Z. Ostwald, Studies on formation and transformation of solid materials, Phys. Chem., 1897, 22, 289-330.

53. L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil, L. J. W. Shimon, M. Lahav, L. Leiserowitz, Angew. Chem., Int. Engl., 1985, Ed., 24, 466.

54. I. Weissbuch, L. Addadi, M. Lahav, Leiserowitz L., Science, 1991, 253, pp637.

55. S. Kumar, G. Chawala, A. K. Bansal, *Role of additives like polymers and surfactants in the crystallization of Mebendazole*, The Pharmaceutical Society of Japan, 2008, 128(2) 281-289.

56. H. G. Brittain, S. J. Bogdanowich, D. E. Bugay, J. DeVincentis, G. Lewen, A. W. Newman, Pharm. Res., 1991, 8, pp963.

57. H. G. Brittain, Physical Characterization of Pharmaceutical Solids, Marcel Dekker, New York, 1995.

58. T. L. Threlfall, Analyst, 1995, 120, pp2435.

59. S. Agatonovic-Kustrin, T. Rades, V. Wu, D. Saville, I. G. Tucker, *Determination of polymorphic forms of Ranitidine-HCl by DRIFTS and XRPD*, Journal of Pharmaceutical and Biomedical Analysis, 2001, 25, 741-750.

60. A. J. Aguiar, J. Krc, A. W. Kinkel, J. C. Samyn, *Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol Palmitate*, J Pharm Sci, 1967, 56, 847– 853.

61. H. G. Brittain, Polymorphism in Pharmaceutical Solids, Marcel Dekker, New York, p 1999.

62. L. Yu, S. M. Reutzel, G. A. Stephenson, *Physical characterization of polymorphic drugs: an integrated characterization strategy*, Pharm Sci Technol Today, 1998, 1, 118– 127.

63. J. Bernstein, Polymorphism in Molecular Crystals, Oxford University Press, New York, 2002.

64. S. R. Byrn, R. R. Pfeiffer, G. Stephenson, D. J. W. Grant, W. B. Gleason, *Solid-state pharmaceutical chemistry*, Chem Mater, 1994, 6, pp1148–1158.

65. G. G. Z. Zhang, D. Law, E. A. Schmitt, Y. Qiu, *Phase transformation considerations during process development and manufacture of solid oral dosage forms,* Adv Drug Delivery Rev, 2004, 56, pp371– 390.
66. D. A. Snider, W, Addicks, W. Owens, *Polymorphism in generic drug product development,* Advanced Drug Delivery Reviews, 2004, 56, pp391-395.
67. FDA Division of Product Quality, http://www.verity.fda.gov
68. B. Shekunov, Yu, P. York, *Crystallization processes in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth, 2000, 211, pp122-136.
69. SSCI Analytical and Custom Research Services, http://www.ssci-inc.com
70. S. R. Byrn, R. R. Pfeiffer, G. Stephenson, D. J. W. Grant, W. B. Gleason, Chem. Mater, 1994, 6, pp1148.
71. Code of Federal Regulations, Title 21, Food and Drugs, Parts 210 and 211, 1992.

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