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POLYMORPHISM

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1. INTRODUCTION

It had been known since the middle of the 18th century that many substances could be obtained in more than one crystal form, and so the properties of these solids were studied to the fullest extent possible with the characterization tools (e.g., crystal morphology and melting phenomena) available at that time. Eventually the work of Von Laue and Bragg on the diffraction of X-rays by crystalline solids led to the development of technology that could be used to directly study the structures of such materials and to provide the structural justification for the phenomenon that became known as polymorphism.[1]

1.1 Definition

Polymorphism is the ability of a solid material to exist in more than one form or crystal structure. Polymorphism can be found in any crystalline material including polymers, minerals, metals, and is related to allotropy, which refers to elemental solids.[2]

'Polymorphism' comes from the Greek word, *Polus* = many and *morph* = shape. Thus it is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice. It essentially means that in different polymorphs, the same molecule exists in different ways. If this difference is because of packing, it is termed as packing polymorphism and if it is due to difference in conformation, it is called conformational polymorphism.

As a result of polymorphism, molecules have different arrangements in the unit cell of its crystal and thus display different physical properties. These include different packing properties, thermodynamic properties such as solubility, free energy, melting point, spectroscopic properties, kinetic properties such as dissolution rate, stability, and mechanical properties such as hardness, compatibility, tableting, tensile strength, etc. Polymorphism is very important in those areas of chemical research where full characterization of a material has a pivotal role in determining its ultimate use, e.g. in pharmaceutical, pigment, agrochemical, explosive and fine chemical industries.[3]

1.2 Types of polymorphs

Polymorphs are of two types:

a) Enantiotropic polymorph: It is the one which can be reversibly changed into another form by altering the temperature or pressure.
E.g. sulphur.

b) Monotropic polymorph: It is the one which is unstable at all temperatures and pressures.
E.g. glyceryl stearates.[4]

1. History

With the discovery by Bragg that one could use the angular dependence of scattering of X-rays from a crystalline solid to determine the structure of that solid, structural science has played a large role in the fields of chemistry and physics. Very early in the 19th century, it had become known that many compounds were capable of exhibiting the phenomenon of dimorphism, and could be crystallized into solids having different melting points and crystal habits. For example, the α and β forms of potassium ethyl sulfate were found to exhibit different solubilities and eutectic temperatures in their phase diagram. The existence of a thermally induced phase transition between the anhydrous and monohydrate forms of 5-nitrosalicylic acid was deduced from the temperature dependence of its solubility.

As the techniques of structure elucidation grew in their sophistication, the crystallographic basis of dimorphism became firmly established. The X-ray crystallographic technique enabled workers to determine the dimensions and angles associated with the fundamental building blocks of crystals, namely, the unit cell. At the same time it also became recognized that crystalline solids were not limited to one or two crystal forms, and that many solids were capable of being isolated in multiple crystalline forms.

During the very first series of studies using single-crystal X-ray crystallography to determine the structures of organic molecules, Robertson reported the structure of resorcinol (1,3-dihydroxybenzene). This crystalline material corresponded to that ordinarily obtained at room temperature, and was later termed the α -form. Shortly thereafter, it was found that the α -form underwent a transformation into a denser crystalline modification (denoted as the β -form) when heated to about 74°C, and that the structure of this newer form was completely different. The α –form features a relative open architecture that is maintained by a spiraling array of hydrogen bonding that ascends through the various planes of the crystal. The effect of the thermally induced phase transformation is to collapse the open arrangement of the α -form by a more compact and parallel arrangement of the molecules in the β -form. This structural change causes an increase in crystal density on passing from the α -form (1.278 g/cm^3) to the β -form (1.327 g/cm^3).

The term "polymorphism" has come to denote those crystal systems for which a substance can exist in structures characterized by different unit cells, but where each of the forms consists of exactly the same elemental composition.[5]

Phase Transition in Tin

It is interesting to note that polymorphism has left an impression even on the history of our world. Polymorphism has a link with Napoleon Bonaparte, the French military and political leader. In the chilling winter of 1812, the highly decorated and shining buttons on the uniform of Napoleon's soldiers crumbled to dirty grey and the soldiers believed that it is the wrath of God; their morale became so low that they faced a pathetic defeat at the gates of Moscow.

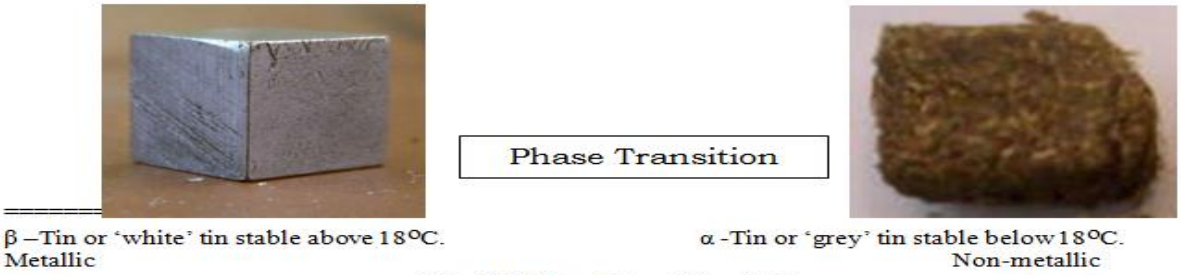

Fig: 2.1 Phase Transition in Tin

The scientific reason for the crumbling of the buttons is interesting. At subzero temperatures of Moscow, the metallic white tin underwent a polymorphic transition to the stable but non-metallic grey tin, thus reducing the decorum of the mighty soldiers.[3]

Polymorphism has contributed too much variability in product performance in pharmaceutical, chemical and food industry and continues to pose a challenge to pharmaceutical scientists in producing drugs of consistent quality. It also provides a unique opportunity, to engineer solids having 'tailor made' properties.

Surprisingly, a very large number of chemical entities exhibit the phenomenon of polymorphism. 70 per cent of barbiturates, 60 per cent of sulfonamides and 23 per cent of steroids exist in different polymorphic forms. Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic or inorganic, can crystallize in different solid forms.[6]

In January 1998, the worldwide pharmaceuticals manufacturer Drugs Inc. released their new Wonder Drug on the US market. Hailed as the new leader for over-the-counter pain control, the drug was successfully launched and enjoyed considerable market growth during its first six months on the market.

In July 1998, Pills PLC released a rival product Fantastic Drug. Claiming similar properties to Wonder Drug, it was sold at two thirds of the price. Drugs Inc.'s hold on the market was gradually eroded, as consumers turned to Pills PLC's cheaper alternative. Drugs Inc. were forced to cut their price, but Pills PLC retaliated by cutting prices still further until Drugs Inc. were no longer willing to follow.

Dr Andrews and Dr Brown, who were working for Drugs Inc. at the time, were given the task of analyzing Pills PLC's new Fantastic

Drug. As they suspected, Fantastic Drug was nothing other than a different crystalline polymorph of Wonder Drug.

Patents on drug molecules are taken out on their crystalline forms, in addition to the molecules themselves. Believing there to be only two crystalline forms of Wonder Drug, Drugs Inc. had only covered themselves for those forms. Thus, by finding a new polymorph, Pills PLC had effectively stolen Drugs Inc.'s years of research and investment, and Drugs Inc. had no legal comeback.[7]

2. Influence of Polymorphism On Product Quality And Performance

Different polymorphs have different arrangements of atoms within the unit cell, and this can have a profound effect on the properties of the final crystallized compound. The action of a drug can be affected by the polymorphism of the drug molecules. Different polymorphs can have different rates of uptake in the body leading to lower or higher biological activity than desired. In extreme cases an undesired polymorph can even be toxic.[7]

Polymorphs possess different physical and chemical properties. These properties can have a direct impact upon drug substance processability, drug product manufacturability, and drug product quality/ performance, such as stability, dissolution, and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, which may result in product development delay and commercial production. As a result, pharmaceutical solid polymorphism has received much scrutiny throughout various stages of drug development, manufacturing, and regulation. For these reasons it is essential that during drug product development and abbreviated new drug application (ANDA) regulatory review, close attention be paid to pharmaceutical solid polymorphism.[8]

2.1 Effect on Solubility, Dissolution, Bioavailability (BA)/ Bioequivalence (BE)

One of the principle regulatory concerns with regard to pharmaceutical solid polymorphism is based on the effect that it may have upon drug product bioavailability/ bioequivalence (BA/BE), particularly for solid oral dosage forms. This stems from the fact that the differing lattice energies of the various polymorphic forms will give rise to differences in their apparent solubilities and dissolution rates. Typically, solubility differences between crystalline polymorphs will be less than several-fold, while hydrates generally exhibit lower aqueous solubilities than the anhydrous crystalline form. Amorphous forms can have solubilities several hundred times that of the crystalline counterparts. When differences in the solubilities of the various polymorphs are sufficiently large, this may alter the drug product *in vivo* dissolution and hence impact drug product bioavailability. An example, where polymorphism has been associated with differences in drug product bioavailability, comes from the classic work of Aguiar on chloramphenicol palmitate, in which Form B was shown to exhibit greater oral absorption than Form A due to its enhanced solubility.

From an FDA perspective, because drug product BA/BE depends upon several factors that influence the rate and extent of drug absorption, such as gastrointestinal motility, drug dissolution, intestinal permeability, and metabolism, a multi-faceted approach is essential in making a rational assessment of the relative risk of the effect that an inadvertent change in polymorphic form would have on drug product bioavailability. In this context, concepts from the biopharmaceutical classification system (BCS) provide a scientific framework for regulatory decisions regarding drug polymorphism. For drugs exhibiting poor aqueous solubility and high intestinal permeability (BCS Class II), it would be anticipated that dissolution would be the rate-limiting step to drug absorption and it may even be possible to establish an *in vivo–in vitro* correlation. Hence, for such BCS Class II drugs such as carbamazepine, one would anticipate that differences in the solubilities of the various polymorphic forms have the potential to affect drug product BA/BE. In such a situation, because of the relatively high risk that a change in polymorphic form will impact bioavailability, it would be important to incorporate suitable controls on polymorphic forms. Conversely, for drugs that exhibit high aqueous solubility and high intestinal permeability (BCS Class I), or high aqueous solubility and low intestinal permeability (BCS Class III), dissolution would likely proceed rapidly and not be the rate-limiting step to drug absorption. Hence, rapidly dissolving immediate release solid oral dosage forms of such high solubility drugs, such as metoprolol tartarate (BCS I) or ranitidine hydrochloride (BCS Class III), would, in effect, resemble oral solutions *in vivo*. For such drug products, clearly the relative risk of an unintentional change in polymorphic form to affect bioavailability would be quite low. In such a situation it may not be necessary to incorporate controls on polymorphic forms.[9]

2.2 Effect on Stability

An additional concern with regard to pharmaceutical solid polymorphism is the effect that it may have upon drug product stability. This is based upon differences in chemical reactivity between the various polymorphic forms. This stems from various reasons, including differences in thermodynamic stability of the crystal lattices, differing micro-environments of reactive functional groups within the crystal lattice, and greater molecular mobility seen for amorphous forms. These differences in chemical reactivity present concerns as a change to a chemically reactive polymorphic form may result not only in an undesired loss of drug product potency but might also generate elevated levels of degradation impurities. Nonetheless, because drug product stability depends upon not only the intrinsic chemical reactivity of the drug substance polymorphic form but also on other factors, including formulation, manufacturing process, and packaging, many of these facets should be incorporated into the scheme of making a rational determination as to what the relative risk a change in polymorphic form would have upon drug product stability.

Such an approach of assessing the effect of polymorphic forms on drug product stability is nicely illustrated in the case of enalapril maleate. Enalapril maleate is known to

exist in two polymorphic modifications (I and II) with Form II being the more thermodynamically stable. Both forms exhibit similar properties, as exemplified by their similar solubilities, dissolution characteristics, heats of solution, IR and Raman spectra, and DSC thermograms. Interestingly, although tablets manufactured via wet granulation using Form I of enalapril maleate and one molar equivalent of sodium bicarbonate are quite stable, tablets manufactured from Form II give rise to unacceptably high levels of the diketopiperazine degradation impurity. Hence, with the given drug product formulation, an inadvertent change in polymorphic form would negatively impact drug product stability, and it would be important to incorporate controls on the drug substance polymorphic forms. Conversely, tablets manufactured via wet granulation from either Form I or II and two molar equivalents of sodium bicarbonate are equally stable. For such a drug product formulation, as there is low risk that a change in solid- state form will impact upon drug product stability, it would not be necessary to incorporate controls on the polymorphic form for incoming batches of the bulk drug substance.[9]

2.3 Effect on Manufacturability

A final concern with regard to pharmaceutical solid polymorphism is the effect that it may have upon drug product manufacturability. This is based upon differences in mechanical properties and crystal morphologies between various forms, which may impact powder flow and tablet compressibility. Because product manufacturability depends not only upon the intrinsic mechanical properties and morphologies of the drug substance polymorphic form, but also upon the formulation and manufacturing process, ultimately it is manufacturability of drug product that is the most relevant measure of quality, and it is from this perspective that one can make a rational assessment of the risk a change in polymorphic form will have upon product manufacturability. This approach of assessing the effect of polymorphic forms on drug product manufacturability is nicely illustrated by paracetamol (acetaminophen). Paracetamol exists in two stable polymorphic modifications (I and II). By virtue of their differing mechanical properties, Form II is compressible and suitable for the manufacture of tablets via direct compression, whereas Form I does not possess such compression properties.[13] Hence, with paracetamol tablets manufactured by direct compression, there is a risk that an inadvertent change to a polymorphic form will impact drug product manufacturability. To maintain a robust manufacturing process, it would be important to incorporate suitable controls on the polymorphic form of incoming batches of the bulk drug substance. Conversely, by using a wet granulation process in tablet manufacture, the original processing deficits of Form I are "masked", and hence tablets can readily be manufactured from either form. Clearly, for such a process it may not be essential to incorporate controls on the drug substance polymorphic form.[9]

3. Generation of Polymorphs

It is essential to determine the range of crystalline forms that are accessible to a potential drug substance and to determine which of the various forms will be the one used in products used in pivotal trials. To answer this question, investigators must conduct whatever studies might be required to evaluate the full range of possible polymorphs.

Table 4.1: Solvents routinely used to isolate compound polymorphs and solvates.

Solvent	Boiling point (^{0}C)
Dipolar aprotic	
Dimethyl formamide	153
Acetonitrile	81
Dimethyl sulfoxide	189
N-methyl pyrolidinone	80
Protic	
Water (various pH values)	100
Methanol	65
Acetic acid	115
Ethanol	78
i-Propanol	82
n-Propanol	97
n-Butanol	118
Lewis acidic	
Dichloromethane	40
Chloroform	61
Lewis basic	
Acetone	56
2-Butanone	80
Tetrahydrofuran	66
Ethyl acetate	77
Methyl butyl ether	56
Aromatic	
Toluene	111
Xylene	140
Pyridine	115
Non-polar	
Hexane	69
Cyclohexane	81

The first and primary method for production of polymorphs entails slow solvent evaporation of saturated solutions, with the rate of evaporation being adjusted by empirical means. Examples of solvents routinely used for such work are listed in Table 3.1 together with their boiling points. The process of solution-mediated transformation can be considered the result of two separate events, beginning with dissolution of the initial phase, and completing with nucleation and growth of the final, stable phase. If two polymorphs differ in their melting points by 25.50^{0}C, for monotropic polymorphs the lower melting, more soluble, form will be difficult to crystallize. The smaller the difference between the two melting points, the easier can it be to obtain the unstable or metastable forms.

Another commonly used crystallization method involves controlled changes in temperature. Slow cooling of a hot, saturated solution can be effective in producing 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 ice- acetone bath.

There are situations where kinetics determines the course of crystallization, and thermodynamics becomes of secondary consideration. For example, Ostwald's Law of Stages states that, ''when leaving an unstable state, a system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy.'' This form then transforms to the next most soluble form through a process of dissolution and crystallization. For crystals whose formation is dominated by kinetic factors, it is essential to isolate the metastable form from the crystallization solvent by rapid filtration so that subsequent phase transformation would not occur.

During the characterization of solids obtained from solvent crystallization studies, one finds that thermal treatment may be a means to produce new crystal forms. For instance, when using differential scanning calorimetry as an analysis technique, one can observe an endothermic peak corresponding to a 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.

In accordance with Ostwald's rule, the cooling of melts of polymorphic substances ordinarily yields the least stable modification, which subsequently rearranges into the stable modification in steps. Since the metastable form will have the lower melting point, it follows that supercooling is necessary to crystallize it from the melt. After melting, the 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.[1]

4.1 Solvatomorphs

Substances often crystallize containing water orsolvent molecules located at specific sites in the crystal lattice, defining new crystalline forms known as solvatomorphs. Since water is a pharmaceutically acceptable solvent, hydrate species are of primary importance to drug development. The variety of hydrates that can exist has been summarized. Most solvatomorphs form with an integral number for the solvent/molecule ratio, but this is not always the case.

In the simplest type, water is bound to inorganic cations as part of a coordination complex. This type of water is denoted as water of crystallization and is common for inorganic compounds. For example, nickel sulfate forms a well defined hexahydrate, where the waters of hydration are bound directly to the Ni (II) ion. Well-defined multiple hydrate species can also form with organic molecules, where the water molecules bridge unit cells in the overall structure. Finally, water molecules can exist in a semispecific manner, lining cavities within the crystal structure. This last hydrate type is often termed a channel hydrate.

Typically, hydrates are obtained by recrystallization from water. For example, trazodone hydrochloride tetrahydrate was prepared by dissolving the anhydrate in hot distilled water, allowing the solution to remain at room temperature overnight, and storing the collected crystals at 75% relative humidity and 25^0C until they reached constant weight. Hydrates can sometimes be obtained by suspending the anhydrous material in water, a process that is analogous to Ostwald ripening. For instance, aqueous suspensions of anhydrous metronidazole benzoate are metastable, and storage at temperatures lower then 38^0C leads to monohydrate formation accompanied by crystal growth. The exposure of an anhydrous powder to high relative humidity often yields the formation of new hydrate forms. For example, the experimental anticholesterol compound SQ-33600 was found to form a multitude of hydrate forms on exposure to various relative humidity environments.[1]

4. Characterization of Polymorphs

There are a number of methods for characterizing the solid state properties of pharmaceutical solids, such as optical and electron microscopy, X-ray analysis, infrared (IR) and Raman spectroscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Thermal methods, such as TGA or DSC, have limited accuracy due to the small weight fraction of the mobile solvent. Single-crystal X-ray analysis is generally used to understand the crystal packing of individual molecules within a crystal lattice. However, X-ray crystallographic analysis cannot usually detect solvent molecules, which are essential for growing high-quality single crystals of sufficient size as a meta-stable form. In addition, most of these techniques are unsuitable for studying amorphous compounds. Solid- state NMR spectroscopy is also a powerful technique for analyzing the structural, chemical and physical properties of pharmaceutical solids.[10]

5.1 Differential Scanning Calorimetry (DSC)

In DSC, which is the most widely used technique for thermal characterization of pharmaceuticals, the analyte is subjected to a controlled temperature program and the temperature and the heat flow associated with a thermally induced transition is measured.

The basic principle behind a change in the baseline of a

typical DSC plot (power vs. temperature), signifying a thermal event, is a change in the heat capacity of the system under investigation. The basic equation describing the relationship between the heat flux (*Q*) associated with a thermal event and the heat capacity (*Cp*) of the system under investigation is given by: $(dQ/dt)=C_p(dT/dt)$

Where d*Q*/d*t* represents power at the constant heating or cooling rate, d*T*/d*t* .DSC plots are obtained as the differential rate of heating [in units of watts (joules/second) or calories/second] against temperature, and thus represent direct measures of the heat capacity of the sample. The area under a DSC peak is directly proportional to the heat absorbed or evolved by the thermal event, and integration of these peak areas yields the heat of reaction (in units of calories/seconds · gram or joules/seconds · gram).

In a typical DSC application, the sample is encapsulated in a pan and the lid is crimped, where the lid can be crimped either in a non-hermetic or in a hermetic (airtight) manner. In the hermetically crimped pan, a pinhole can be made in the lid to relieve pressure during the acquisition of the DSC curve. To minimize the head space, the lid can be inverted and then hermetically crimped.

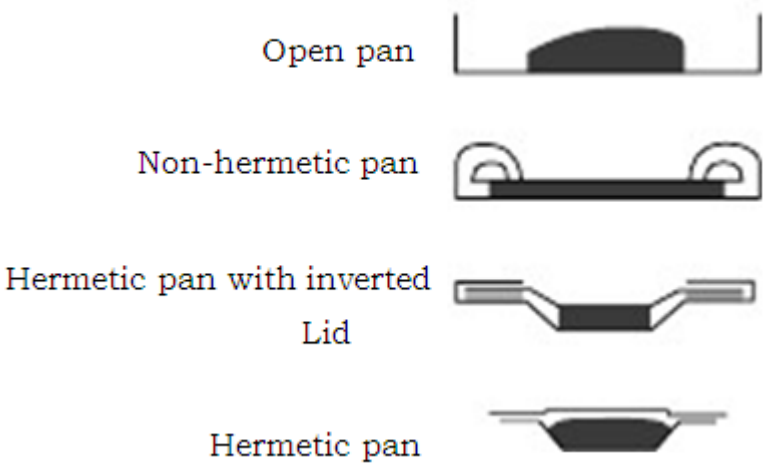

Fig. 5.1: Diagrammatic representation of different DSC pan congurations.

The pan configuration can influence the outcome of a DSC experiment. This is especially true for solvates, because the desolvation kinetics, as well as the physical form of the product phase, can be profoundly influenced by the sample environment. In an open pan, there is no physical barrier to the escape of liberated solvent, and the purge gas (typically nitrogen) will facilitate removal of the liberated solvent. The reasonably unrestricted nature of a non- hermetically crimped pan will also permit ready escape of the liberated solvent. At the other extreme, the liberated solvent cannot escape in a hermetically crimped pan. In a sealed pan with a pinhole, the rate of vapor loss will become appreciable only when the vapor pressure exceeds atmospheric pressure. Different pan configurations, which result in varied desolvation conditions, have been used to generate different polymorphs of anhydrous carbamazepine and trehalose from their respective hydrates.

Pressure DSC (PDSC) enables DSC experiments to be carried out at elevated pressures as high as 1000 psi. PDSC is useful for the separation of overlapping dehydration and vaporization events that are observed following the dehydration of hydrates. Although the temperature of dehydration is likely to be unaffected by pressure, the boiling temperature of water is pressure dependent and can be ascertained from the Clausius–Clapeyron equation. In addition, the potential interaction of the liberated water with the anhydrous product phase can also be ascertained. Han and Suryanarayanan used PDSC to successfully resolve overlapping dehydration and vaporization transitions observed when carbamazepine dihydrate was heated (Fig. 5.2,). The conventional DSC of carbamazepine exhibited two overlapping endotherms over the temperature range of 85°C to 100°C, attributed to dehydration followed by vaporization, which were followed by the melting of non-solvated carbamazepine around 189°C. When the pressure was increased, only a single endotherm attributable to dehydration was observed at approximately 90°C.

Interestingly, several thermal events were observed between the dehydration and the melting temperatures.

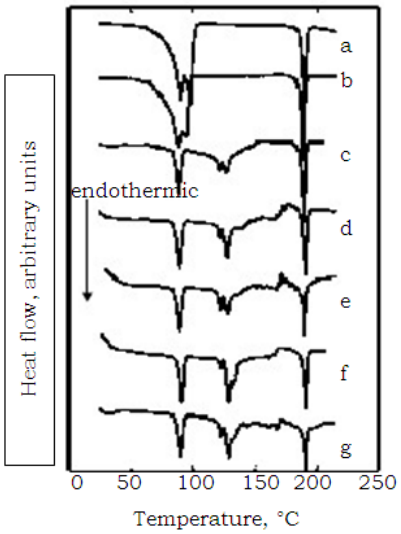

Fig. 5.2: DSC of carbamazepine dihydrate at different pressures: (a) ambient pressure in conventional DSC cell, (b) ambient pressure in PDSC cell, (c) 100 psi, (d) 200 psi, (e) 300 psi, (f) 400 psi, (g) 600 psi.

A limitation of DSC is that although it reveals the existence of thermally induced transitions, the nature of these transitions can be difficult to determine. In an effort to simulate the PDSC experiments, Han and Suryanarayanan heated carbamazepine dihydrate in a "sealed" environment. Following dehydration, the released water caused an increase in pressure by being retained in the holder, although the pressure was uncontrolled. As shown in the Fig. 5.3, the carbamazepine polymorphic transitions were further characterized by VT-XRD. The formation of β -carbamazepine at ~90°C was evident in the diffraction patterns on the basis of peaks observed at scattering angles of 13.1, 15.3, and 18.7° 2θ*)*. Based on the disappearance of the characteristic peaks of carbamazepine dihydrate (at 8.9 and 12.3° 2θ), dehydration appeared to be complete by 100°C. Around 160°C, several characteristic peaks of γ -carbamazepine were observed, indicating a β → γ solid–solid phase transition. Based on the decrease in the intensities of the β -carbamazepine peaks, and the increase in the intensities of the γ -carbamazepine peaks, the β → γ phase transition was accelerated as the temperature was increased to 180°C. These VT-XRD results aided in the interpretation of the DSC results. When DSC was conducted under elevated pressure, usually four endotherms were observed. The first endotherm at ~90°C, as explained earlier, is attributed to dehydration. The two overlapping endotherms at ~120°C and 125°C are attributed to the β → γ carbamazepine phase transition and to the vaporization of water. The melting of γ -carbamazepine occurred at ~189°C. This scheme is illustrated in Figure 4 (*lower panel*) and shows the transitions of carbamazepine dihydrate at ambient and elevated pressures.[5]

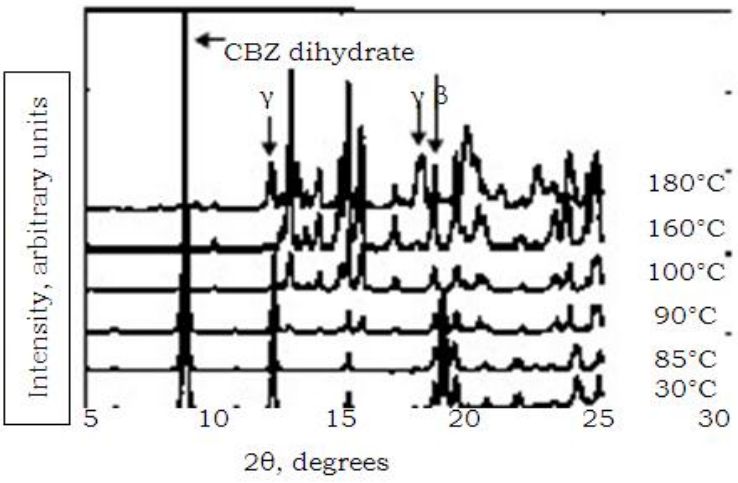

Fig. 5.3: VT-XRD of carbamazepine dihydrate. Peaks characteristic of the dihydrate as well as anhydrous β and γ forms are shown.

5.2 Thermogravimetry

Thermogravimetry (TG, and also known as thermogravimetric analysis or TGA) is a technique where one uses a very sensitive balance to continuously determine the weight of the analyte as a function of temperature or time. This simple technique provides valuable information that can aid in the identification and characterization of the thermal events associated with thermally induced reactions of solvates. For example, several hydrates of nedocromil sodium were identified and profiled using TG as one of the characterization tools. As the sample was heated, the weight loss occurred in a stepwise fashion, which facilitated calculation of the hydrate stoichiometries based on the percent weight loss at each step.

There are different ways in which water can associate with solids. In authentic hydrates, water is incorporated in the crystal lattice, whereas in amorphous and partially crystalline materials, water can associate with disordered regions in the lattice. Water can also be adsorbed and also exist as "bulk water" in incompletely dried solids. TG analysis can also be used to distinguish between some of these states of water in solids. Compared with dehydration, desorption (adsorbed as well as bulk) typically occurs at lower temperatures, although these two processes can overlap. As shown in Fig. 5.4, for carbamazepine dihydrate, when the TG experiment is carried out under isothermal conditions, there can be.

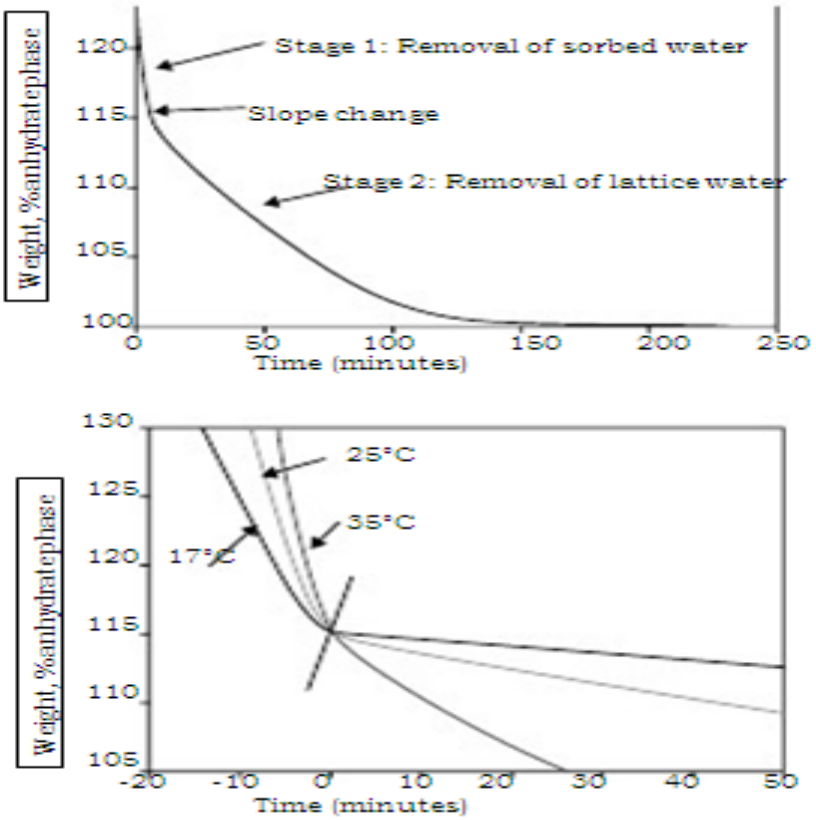

Fig. 5.4: (top panel) Dehydration of a wet sample of carbamazepine dihydrate at 0% RH (25°C). The plotted sample weight is based on the dry sample weight after complete dehydration. The first and second stages of dehydration are separated by the point of slope change. (Bottom panel) Effect of temperature on desorption and dehydration kinetics of carbamazepine dihydrate shown at three representative temperatures.

TG analysis performed under isothermal conditions can be used to study the kinetics of phase transitions in solvatomorphs. Alkhamis carried out model-independent isoconversional analysis of the isothermal desolvation of the monohydrate and ethyl acetate solvate of fluconazole. One potential shortcoming of this technique is that a separate and direct technique might be required to confirm the cause of weight loss. In order to address this inadequacy, the TG instrument can be interfaced with additional instrumentation capable of identifying the vapour released upon heating. For example, TG has been used in combination with infrared absorption spectroscopy to understand the thermal behavior of a hydrate. In this study, two different thermal events resulting in weight loss were shown to be due to separate dehydration and decomposition processes.[5]

5.3 Single-Crystal X-Ray Diffraction:

Structural information derived from an XRD study of a single crystal is the most fundamental description of a polymorph or solvatomorph, and helps to explain its physical properties.

Generally, polymorphic structures can be classified into one of two main categories. The first is associated with molecules that can only exist as a rigid grouping of atoms that can be stacked in different motifs to occupy the points of different lattices (i.e., packing polymorphism). One of the best-known instances of packing polymorphism is the allotropic system of carbon, namely graphite and diamond. As shown in Fig. 5.5, in diamonds each carbon atom is tetrahedrally surrounded by four equidistant neighbors, and the tetrahedra are arranged to give a cubic unit cell. Graphite is composed of planar hexagonal nets of carbon atoms, which can be arranged to yield either a hexagonal unit cell (the α -form) or a rhombohedral unit cell (the β -form).

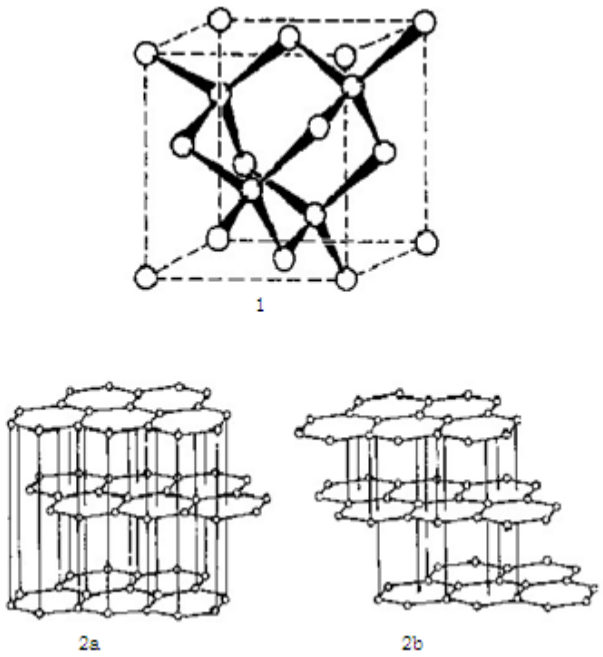

Fig. 5.5: Crystal structure of (1) diamond, showing the tetrahedral coordination of each carbon atom. Also shown are the crystal structures of the two polymorphs of graphite, specifically (2a) the hexagonal α -form, and (2b) the rhombohedral β -form.

The other category is associated with molecules that are capable of existing in conformationally different arrangements, each of which can crystallize in its own characteristic structure. This latter behavior has been termed conformational polymorphism, and the probucol system represents an extreme example of a compound where the polymorphism arises from the packing of different conformers. Although both polymorphs were found to be monoclinic, the unit cells belonged to different space groups and the molecular conformations of the title compound were quite different. In form II, the C–S–C–S–C chain is extended, and the molecular symmetry approximates C2v. This symmetry is lost in the structure of form I, where the torsion angles about the two C–S bonds deviate significantly from 180°. The extended conformer was shown to be less stable relative to the bent conformer, as simple grinding was sufficient to convert form II into form I.

The analysis of single-crystal XRD data is divided into three parts. The first of these is the geometrical analysis, where one measures the exact spatial distribution of X-ray reflections and uses these to compute the size and shape of a unit cell. The second part entails a study of the intensities of the various reflections and uses this information to determine the atomic distribution within the unit cell. Finally, one looks at the X-ray diffraction pattern to deduce qualitative information about the quality of the crystal or the degree of order within the solid. This latter analysis may permit the adoption of certain assumptions that may aid in the solving of the crystalline structure.

Crystallographic characterization of the physical form of an API may be used to understand its performance during pharmaceutical processing. One well-known case is that of polymorphic forms I and II of acetaminophen (also known as paracetamol). Monoclinic acetaminophen form I cannot be formulated into tablets by direct compression, but the presence of slip planes (illustrated in Fig. 5.6) in the orthorhombic form II allows its direct compression due to a plastic deformation process. This property is an immense advantage considering that direct compression is a cost-effective and time- efficient method of tablet production.[5]

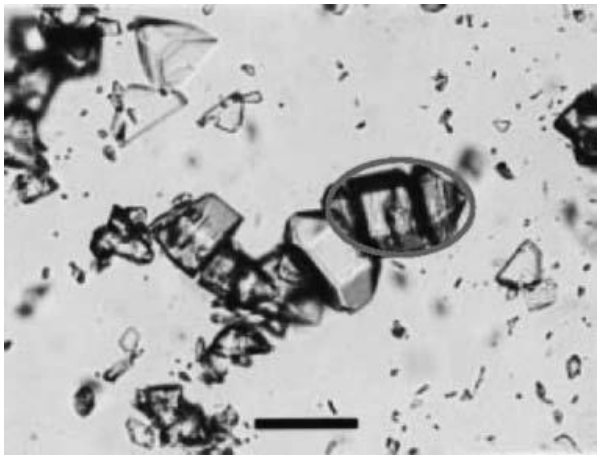

Fig. 5.6: Pressure-induced formation of cleavages (indicated in circle) in an acetaminophen form II crystal perpendicular to its length, showing the evidence of the existence of slip planes.

5.4 X-Ray Powder Diffraction

A properly prepared sample of a powdered solid will present a substantially random selection of all possible crystal faces and the diffraction patterns will therefore provide information regarding all possible spacings (atomic or molecular) in the crystal lattice. To measure a powder pattern, a randomly oriented powdered sample is prepared in an effort to expose all the planes in the lattice. The scattering angle is determined by slowly rotating the sample and measuring the angle of diffracted

X rays (typically using a scintillation detector) with respect to the angle of the incident beam. Alternatively, the angle between sample and source can be kept fixed, while moving the detector to determine the angles of the scattered radiation. Knowing the wavelength of the incident beam, the spacing between the planes (identified as the *d* -spacings) is calculated using Bragg's Law.

The XRD pattern will therefore consist of a series of peaks detected at characteristic scattering angles. These angles, and their relative intensities, can be correlated with the computed *d* -spacings to provide a full crystallographic characterization of the powdered sample. After indexing all the scattered lines, it is possible to derive unit cell dimensions from the powder pattern of the substance under analysis. For routine work, however, this latter analysis is not normally performed, and one typically compares the powder pattern of the analyte to that of reference materials to establish the polymorphic identity. Because every compound produces its own characteristic powder pattern owing to the unique crystal structure, powder XRD is clearly the most powerful and fundamental tool for polymorphic identity of an analyte.

The United States Pharmacopeia contains a general chapter on XRD, which sets the criterion that identity is established if the scattering angles in the powder patterns of the sample and reference standard agree to within the calibrated precision of the diffractometer. It is noted that it is generally sufficient that the scattering angles of the ten strongest reflections obtained for an analyte agree to within either ± 0.10 or ± 0.20° 2θ, whichever is more appropriate for the diffractometer used. Older versions of the general test contained an additional criterion for relative intensities of the scattering peaks, but it has been noted that relative intensities may vary considerably from that of the reference standard, making it impossible to enforce a criterion based on the relative intensities of corresponding scattering peaks.

For identification purposes, it is usually convenient to identify the angles of the 10 most intense scattering peaks in a powder pattern, and to then list the accepted tolerance ranges of these based on the diffractometer used for the determinations. Useful tabulations of the XRD patterns of a number of compounds have been published By Koundourellis and coworkers, including 12 diuretics, 12 vasodilators, and 12 other commonly used drug substances.

There are countless examples that illustrate how powder diffraction has been used to distinguish between polymorphs. It is safe to state that one could not publish the results of a phase characterization study without the inclusion of XRD data. Nowhere is this more crucial than in intellectual property controversies, where the different XRD patterns of polymorphs are used for patentability purposes. For example, two polymorphic forms of ibandronate sodium have been the subject of two United States patent applications, and although the XRD patterns of these are somewhat similar (Fig. 5.7), a sufficient number of differences in scattering peak angles exist so as to permit their identification. In the patent applications, some of the claims define the two polymorphs on the basis of five characteristic XRD scattering peaks, which enables one to tabulate the data and determine whether or not a given sample of ibandronate sodium is within the scope of these XRD claims.

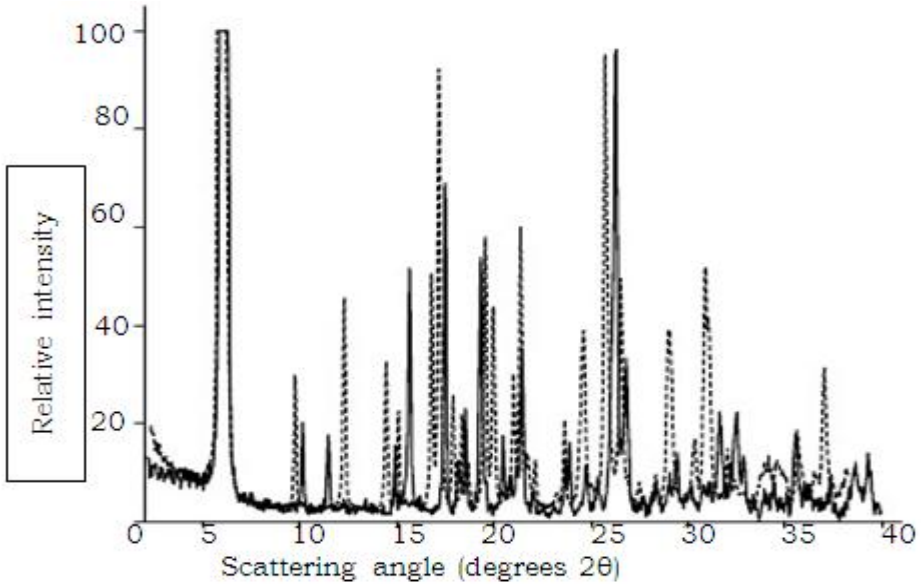

Fig. 5.7: X-ray powder diffraction patterns of ibandronate sodium, Form A (*solid trace*) and Form B (*dashed trace*).

Once the characteristic XRD patterns of one or more analytes have been established, it is usually possible to develop methods for phase quantification. The methodology is based on the premise that each

component will contribute to the overall scattering by an amount that is proportional to its weight fraction in a mixture, and that the powder pattern of each analyte contains one or more peaks whose scattering angle is unique to that analyte. Quantitative analysis typically requires the use of reference standards that contribute known scattering peaks at appropriate scattering intensities. This can be achieved through the use of internal standards, where one would mix reference materials such as elemental silicon or lithium fluoride into the sample matrix.

Although simple intensity correction techniques can be used to develop suitable quantitative XRD methods, the introduction of more sophisticated data acquisition and handling techniques can greatly improve the quality of the developed method. For instance, improvement of the powder pattern quality through use of the Rietveld method has been used to evaluate mixtures of two anhydrous polymorphs of carbamazepine and the dihydrate solvatomorph. The method of whole pattern analysis developed by Rietveld has found widespread use in crystal structure refinement and in the quantitative analysis of complex mixtures. Using this approach, the detection of analyte species was possible even when their concentration was less than 1% in the sample matrix. It was reported that good quantitation of analytes could be obtained in complex mixtures even without the requirement of calibration curves.

Well-characterized and stable (both physically and chemically) Standard Reference Materials are available from the National Institute of Standards and Technology (NIST). These materials are used both to calibrate powder XRD equipment and to measure the instrument sensitivity. Silicon powder (SRM 640c) is typically used for the calibration of *d* -spacing or line position, and also can be used as an internal reference for quantitative applications. NIST SRM 674b is a set of four metal oxides (CeO_2, Cr_2O_3, TiO_2, and ZnO) that are also used as internal standards in quantitative work.

The use of parallel beam optics as a means for determining the polymorphic composition in powder compacts has been evaluated. In this study, compressed mixtures of known polymorphic composition were analyzed in transmission mode, and the data processed using profile fitting software. The advantage of using transmission, rather than reflectance, was that the results were not sensitive to the geometrical details of the compact surfaces, and that spurious effects associated with preferential orientation were minimized.

The effects of preferred orientation in XRD analysis can be highly significant, and are most often encountered when working with systems characterized by plate like or tabular crystal morphologies. A viable XRD sample is one that is free from the deleterious effects of preferential orientation, and any sample packing effect that serves to introduce a non-random pattern of crystal faces can strongly affect the observed intensities and any quantitative results. The problem has been investigated for the three needle-like polymorphs of mannitol, and it was found that through the use of small particles, the preferential orientation effects were held to a minimum, enabling quantification of the polymorphs around the 1% level.

The use of powder XRD has been investigated to determine whether one may use pattern indexing as another tool for polymorph screening studies. In this work, data were collected on six compounds using two diffractometers that employed transmission geometry, primary monochromatic radiation, and a position sensitive detector. The data were found to exhibit good angular resolution, and therefore lattice parameters were easily obtained using the indexing program

DICYOL-91. The extent of preferred orientation in each pattern was estimated using the DASH implementation of the March–Dollase function. It was concluded that the combination of experimental techniques used would be highly effective compared to just one technique that would require a large number of samples per day with the aim of obtaining the type of high-quality data necessary for pattern recognition and indexing.

Practical complications associated with preferential orientation effects have been discussed in detail. A number of sample-packing methods were considered (vacuum free-fall, front-faced packing vs. rear-faced packing, etc.), but the best reduction in preferential orientation was achieved by using materials having small particles that were produced by milling. Through the use of sieving and milling, excellent linearity in diffraction peak area as a function of analyte concentration was attained. The authors deduced a protocol for development of a quantitative XRD method consisting of (a) calculation of the mass attenuation coefficient of the drug substance, (b) selection of appropriate diffraction peaks for quantification, (c) evaluation of the loading technique for adequate sample size, (d) determination of whether preferred orientation effects can be eliminated through control of the sample particle size, (e) determination of appropriate milling conditions to obtain reproducibility in peak areas, and (f) generation of calibration curves from physical mixtures.[5]

5.5 Infrared Absorption Spectroscopy

The acquisition of high-quality infrared spectra on solid materials has been made possible using Fourier transform technology, because the use of this methodology minimizes transmission and beam attenuation problems. Essentially all FTIR spectrometers use a Michelson interferometer, where infrared radiation entering the interferometer is split into two beams: one of which follows a path of fixed distance before being reflected back into the beam splitter, and the other traveling a variable distance before being recombined with the first beam. The recombination of these two

beams yields an interference pattern, where the time-dependent constructive and destructive interferences have the effect of forming a cosine signal. Each component wavelength of the source yields a unique cosine wave, having a maximum at the zero pathlength difference (ZPD) and which decays with increasing distance from the ZPD. The radiation in the central image of the interference pattern impinges on the detector, and intensity variations in the recombined beam become measurable manifest as phase differences. If the component cosine waves can be resolved, then the contribution from individual wavelengths can be observed. The frequency domain spectrum is obtained from the interferogram by performing the Fourier transformation mathematical operation.

Numerous modes of sampling may be used with FTIR spectrophotometers, although only a few of these are appropriate for the study of polymorphs and solvatomorphs. Probably the most useful sampling method for the study of polymorphs and solvatomorphs uses attenuated total reflectance accessories. In the attenuated total reflectance (ATR) technique, infrared radiation is passed through a crystal at an angle less than the critical angle, which causes the light to undergo total internal reflection. At each such reflection, the radiation penetrates a small distance beyond the crystal surface, and if an analyte is in physical contact with the crystal, then the internally reflected energy will be attenuated at those frequencies corresponding to changes in molecular vibrational states. The advantage of the ATR approach is that it requires effectively no sample preparation, because one simply clamps the analyte onto the surface of the crystal with moderate pressure to ensure a sufficient degree of optical contact. Because the internal reflectance process does not permit the infrared beam to pass very deeply into the sample, it is typical to determine the composition of an analyte up to a sampling depth in the range of 5 to 10 μm.

Not surprisingly, the sensitivity of infrared absorption spectroscopy to subtle changes in crystal structure have led to its application in a wide variety of investigations of polymorphic solids, often in conjunction with Raman spectroscopic studies. For example, FTIR spectra of different polymorphs of mepivacaine hydrochloride were obtained in Nujol mulls and via ATR sampling, with the ATR method providing better distinction between the polymorphs. This has been illustrated in Fig. 5.8, where the infrared absorption spectra of mepivacaine hydrochloride (Form-II) is seen to be superior when obtained using the attenuated total reflectance sampling mode as opposed to a Nujol mull. When coupled with artificial neural network methods, a diffuse reflectance FTIR spectroscopic method was developed that permitted the simultaneous quantification of three polymorphs of carbamazepine in ternary mixtures.

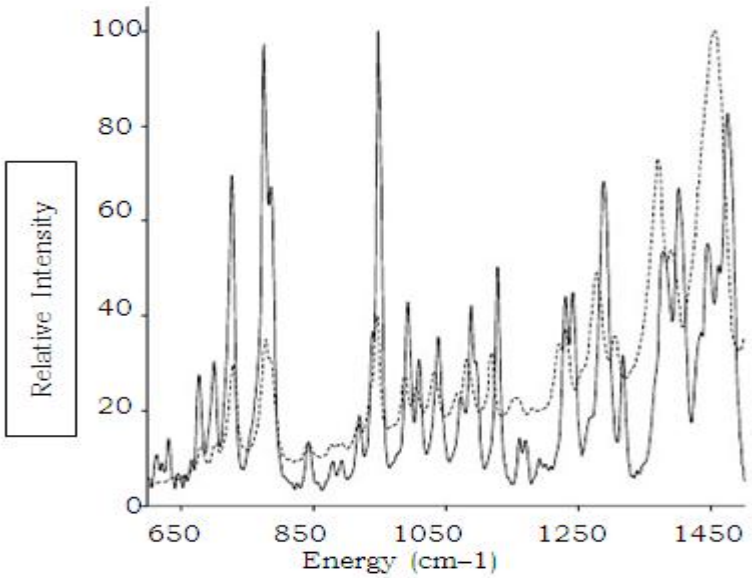

Fig. 5.8: Infrared absorption spectra of mepivacaine hydrochloride, Form-II, obtained using the attenuated total reflectance (*solid trace*) and Nujol mull (*dashed trace*) sampling modes.

FTIR–ATR spectroscopy was used to characterize the salt- induced crystallization of a metastable polymorph of flufenamic acid, and to characterize the product obtained after a subsequent interface- mediated polymorphic transition. The FTIR–ATR method was also used to characterize the fluconazole products obtained using the supercritical antisolvent process, with the technique being able to identify the polymorphic forms produced as a result of variation of operating conditions such as temperature, pressure, and solvent type. Three concomitant polymorphs of 1,3-bis (*m* -nitrophenyl) urea had been reported in 1899 as yellow prisms (the α -form), white needles (the β -form), and yellow tablets (the γ -form), and FTIR microscopy was used during a more detailed investigation of the system. In this work, complete assignments for the absorption bands

associated with hydroxyl, amide, nitro, and benzene-ring functional groups were developed in order to obtain a deeper understanding of the conformational differences in the molecules constituting the various crystal forms.

Five differently colored solid-state forms of 5-methyl-2-[(2- nitrophenyl) amino]-3-thiophenecarbonitrile, where the color of the polymorphic crystal forms is related to changes in the energies of molecular orbitals of the systems have been studied using infrared absorption spectroscopy. The spectra for three of the solid-state forms were characterized by frequency shifts originating from the structural differences, with the nitrile stretching frequency varying by approximately 10 cm –1 each for the yellow, orange, and red solid- state forms of the compound. In a study of the amorphous salt formed by the co-precipitation of cimetidine and diflunisal, solid-state infrared absorption spectroscopy was used to prove the existence of the salt species. The prominent carbonyl absorption band observed at 1650 cm –1 in crystalline diflunisal could not be observed in the spectrum of the amorphous salt, but a new peak was noted at 1580 cm –1 that was assigned to an asymmetric stretching mode of a carboxylate group.

5.6 Solid-State NMR Spectroscopy

The two enantiotropic polymorphs of {4-(4-chloro-3 fluorophenyl)-2-[4-(methyloxy) phenyl]-1, 3-thiazol-5-yl} acetic acid were studied by ^{1}H, ^{13}C, ^{15}N, and ^{19}F solid-state NMR spectroscopy (SSNMR spectroscopy). A thorough SSNMR spectroscopy study was used to help understand the structures of each polymorph determined by X-ray diffraction. The solid-state transition temperature of the polymorphs was ~ 30°C. Form I was thermodynamically more stable below 35°C, but form II was more stable to milling and had lower hygroscopicity. The single-crystal structure of form I was determined, but form II did not produce suitable single crystals. The structure of form II was determined using XRPD, and various SSNMR spectroscopy analyses were used to provide additional restraints for the structure determination. Two 2D NMR pulse sequences that rely on dipolar coupling, ^{1}H DQ-BABA (double quantum back-to-back) and ^{1}H– ^{13}C HETCOR (heteronuclear correlation), were used to determine conformational features of both polymorphs. The 2D PASS (phase-adjusted spinning sidebands) pulse sequence was used to determine chemical shielding tensors (CSTs) for ^{13}C resonances of form II to help refine the calculated structure. The orientation dependence of chemical shielding anisotropy (CSA) is useful in providing unique structural details to support diffraction analyses. The authors suggest that, with additional work on other polymorphs, it may be possible to use SSNMR spectroscopy rather than the Burger–Ramberger IR rule for predicting the relative stability of polymorphs. The degree of peak overlap in the spectral region sensitive to hydrogen bonds is not nearly the problem for SSNMR spectroscopy as it is for IR spectroscopy. This study is an excellent example of using multinuclear, multidimensional SSNMR spectroscopy as a powerful technique to thoroughly characterize polymorphs. However, many of the analyses and the interpretation require a high level of expertise in NMR spectroscopy.

Maccaroni et al studied the solid-state form interconversions for two linezolid (Fig. 5.9) polymorphs by ^{13}C SSNMR, XRPD, and thermal methods. Most of the SSNMR peaks were assigned for the two polymorphs by comparison to the ^{13}C NMR assignments of linezolid in a $CDCl_3$ solution. However, this procedure will not necessarily lead to correct assignments for the solid state unless the conformations are very similar. It appears that the spectra of both polymorphs were acquired with the same parameters (e.g., contact time, pulse delay, number of scans), but form IV obviously has a longer 1H T_1 relaxation time based on the much lower signal-to-noise ratio in the spectrum (Fig. 5.9). The peak widths also are somewhat broader for form IV, which may result from unresolved peaks of two very similar molecules per asymmetric unit, as the authors state. The authors also note that the lowest frequency methyl carbon resonance of form IV is split into two peaks (nearly overlapping), which may be consistent with two molecules per asymmetric unit. However, this could also be explained by conformational exchange due to restricted rotation about the amide bond, which is quite well known for liquid state NMR spectroscopy. The small symmetrical splitting of C2 (~ 170 ppm) in form II is likely due to conformational exchange rather than coupling to 14N, because the quadrupolar broadening effect is not very large at this field strength (~ 9.4 T), and only some peak broadening is likely to be observed instead. The 13C-14N coupling usually produces asymmetrical splitting at lower field strengths where it is more readily observed. The 19F atom directly bonded to the aromatic carbon (C9) produced significant broadening for this peak in the spectrum of form II due to the relatively strong scalar and dipolar coupling. The C8 resonance also shows broadening as do the C7 and C10 peaks to a lesser extent (Fig. 5.9). This is because 19F decoupling is not commonly used simultaneously with 1H decoupling for 13C CP/MAS (cross-polarization/magic angle spinning) SSNMR spectroscopy unless the spectrometer and probe are specifically designed to do so. The MAS speed would need to be much faster than 7 kHz to reduce ^{19}F–^{13}C dipolar coupling significantly. The effect of 19F coupling shows that for form II, C9 should be assigned to the broader peak at 154.9 ppm, and C6 should be assigned to the peak at 157.2 ppm. The C6 and C13–C16 resonances were apparently not observed for form IV supposedly because of broadening due to their proximity to oxygen and nitrogen in the molecule. However, the assignments for the C6 and C9 resonances are also swapped for form IV, which means that the C9 resonance is broadened (by 19F coupling) into the baseline noise in this spectrum that already has a very low signal-to-noise ratio relative to the spectrum of form

II (Fig. 5.9). This alternative interpretation of the spectrum of form IV is supported by the missing C13–C16 resonances (also broad in the spectrum of form II), which are likely broadened due to inefficient ^{1}H decoupling. Although the experimental details for the SSNMR spectroscopy data acquisition are very minimal in this report, it is quite likely that the older continuous wave ^{1}H decoupling scheme rather than one of the modern modulated decoupling methods was used to acquire the SSNMR spectra. The contact time (1 millisecond) is also relatively short, and may partly account for the low sensitivity of some quaternary carbons in the spectrum of form IV. The difficulties in correctly interpreting SSNMR spectra to compare solid forms can be reduced by using modern fast MAS and modulated decoupling or simultaneous ^{1}H and ^{19}F decoupling along with efficient CP. One or more of the various spectral editing methods would have been particularly useful in confirming the assignments in this case.[5]

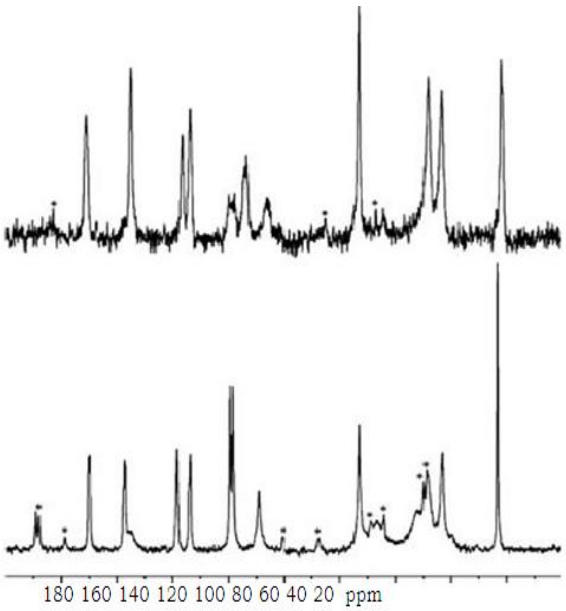

Fig. 5.9: 13C CP/MAS spectra of linezolid form II (*bottom*) and form IV (*top*) obtained at 9.4 T and 7 kHz MAS. Asterisks indicate spinning sidebands.

Polymorph Screening

In the absence of solvents and humidity, the thermodynamically stable polymorph is the only one that is guaranteed not to convert into another polymorphic form. This is why this form is most often chosen for the drug product. The disadvantage of the thermodynamically stable form is, of course, that it is always the least soluble polymorph and therefore has the lowest bioavailability. But in most cases this is a small price to pay for the very large advantage of absolute kinetic stability. Differences in the solubility of various polymorphs are typically lower than a factor of 2 but sometimes as much as a five-fold difference can be observed. In cases where several enantiotropically related forms exist and where the transition temperature is around room temperature, the choice may be difficult, but it is based on the same criteria as for all solid forms. The kinetics of interconversion from one form into the other and the reproducibility of producing consistently the same ratio of polymorphs are important.

In a few cases, a metastable form might be preferable, normally for one of the following reasons:

1. Too low a solubility (and bioavailability) of the stable form;
2. High dissolution rate needed for quick-relief formulations;
3. Manufacturing difficulties;
4. Intellectual Property issues;
5. Chemical instability of the thermodynamically stable form due to topochemical factors.

If the solubility of the stable polymorph is critically low and no salt is feasible, several options exist. Liquid-like formulations (emulsions, microemulsions, liposomal formulations) or soft gelatin capsules filled with solutions of the drug in a non-aqueous solvent may be used. Alternatively, a metastable solid form, a solvate or a co-crystal might be selected for development. If a solid form with a higher solubility than the thermodynamically stable form is desired, it is often better to use the amorphous form rather than a metastable polymorph, provided that the glass transition temperature (*T*g) of the amorphous form is sufficiently high. Firstly, the amorphous form often has a ten- fold or higher increased solubility relative to the stable form, while metastable polymorphs typically have a less than a two-fold higher solubility, as mentioned above. Secondly, it is normally impossible to stabilize a metastable form reliably by excipients, since they can only interact with the surface of the crystals of the metastable drug substance. This will change the surface free energy, but for crystal sizes larger than some tens of nanometers, the contribution of the surface free energy to the total free energy is negligible. The best way to stabilize a metastable form kinetically is to ensure the absence of any seeds of the stable form because such seeds have a very large effect on the kinetics of transformation. The amorphous form, however, can be stabilized, for example, by creating a solid dispersion with a polymer. Such dispersion will be highly kinetically stable if two conditions are fulfilled: if it remains in the glassy state under the storage conditions, thus blocking all translational diffusion, and if the drug substance molecules are molecularly dispersed within the matrix. In any case, irrespective of whether a crystalline or disordered metastable form is to be developed, very careful kinetic stability studies will be necessary. For amorphous solids, particular attention has to be paid to the lowering of the glass transition temperature due to humidity.

1. In some instances, quick onset of action of a drug is of particular importance. In such cases, metastable forms with a higher dissolution rate may accelerate

the uptake of the drug and may therefore act faster.

2. Different polymorphs will also have different mechanical properties, such as hardness, powder flow properties, compressibility and bonding strength. A well-known example is acetaminophen (also known as paracetamol), where the thermodynamically stable form (monoclinic form I) cannot be compressed into stable tablets while the metastable form II (orthorhombic) can as it shows more favorable properties with respect to plastic deformation. In very rare cases, this might lead to a decision to develop a metastable form.
3. If the thermodynamically stable polymorph is protected by patents, while other forms are free, the respective drug substance can be marketed as a metastable form without obtaining a license from the patent owner.
4. Generally, the thermodynamically most stable polymorph is also the most stable chemically. This has been attributed to the fact that its density is typically higher, but it could also be explained by its lower free energy. Only in extremely rare cases, where the arrangement of atoms in the stable polymorph favors an intermolecular chemical reaction, could its chemical stability be lower. In such cases, development of a metastable form might be advisable.

Since different solid forms have different properties and may have different bioavailabilities, it is definitely advisable to select the final form together with the accompanying formulation before carrying out pivotal clinical studies. It is, therefore, critical to have at least identified the thermodynamically stable form along with important hydrates by the end of Phase I at the latest. Accordingly, by that time a polymorphism screening that is primarily designed to identify these forms with a large probability should have been completed. Owing to economic reasons and the expected attrition rate of up to 90% of potential drug candidates after this stage, a full polymorphic screening, which identifies all relevant metastable forms as well, may need to be deferred. However, this should only be the exception because knowledge of metastable phases, thermodynamic stability as a function of temperature and conditions for solvate formation is crucial for the design of crystallization and formulation processes.

While the kinetic stability of dry metastable forms is not much influenced by additives, as mentioned above, additives and impurities can influence their kinetic stability in solutions and suspensions by affecting both nucleation and growth rates. Therefore, a polymorphism screening that is performed with an early batch of drug substance still containing many impurities may provide different results from a screening performed with a later, purer batch. In particularly unfortunate cases, important forms may not be discovered in the initial screening. Therefore, it is highly advisable to repeat at least a limited polymorphism screening with a batch of drug substance produced with the final GMP procedure, which has the impurity profile of the product to be marketed.

Clearly, the unexpected appearance of a new form at a late stage can be disastrous. A very well publicized example is that of ritonavir (Norvir). When it was launched on the market, only form I was known. One marketed formulation consisted of soft gelatin capsules filled with a nearly saturated solution of form I. About two years after market introduction, some capsules failed the dissolution test due to precipitation of a new, thermodynamically more stable form of ritonavir (form II). The solubility difference between forms I and II is about a factor of 5, which is unusually high. In the end, the original formulation had to be taken off the market, and a new formulation had to be developed with considerable effort and expense.[38] While this is certainly an extreme case, there are many instances of new polymorphs appearing in Phase II and Phase III studies, leading to considerable difficulties.[11]

Legal Aspects Associated With Polymorphism

The commercial arena, especially the pharmaceutical companies, has recently faced many complex legal issues arising from polymorphism. Most of these issues are concerned with patent cases.

The most famous case is the Zantac patent case, which is concerned with the solid-state form of Glaxo's major drug, ranitidine hydrochloride, for the treatment of peptic ulcers. This is a polymorphic drug capable of adopting two crystal structures. A process resulting in the crystallization of Form I was patented in 1978; two years later a more stable crystalline Form II appeared which was also patented and which subsequently became the active ingredient for Zantac formulations. When the patent expired in 1995, other generic companies also came in this field and subsequent legal battles resulted.

The second case is of Novartis patent case, which was dealt in Madras High Court. This case is about a lifesaving cancer drug 'Gleevac' containing imatinib mesylate. Gleevac offers a cure to the life threatening form of the cancer 'chronic myeloid leukemia'. Novartis invented imatinib in 1992 and patented it in 1993 in US and other countries. The company applied for a patent in India in 1998 for β- crystalline form of imatinib mesylate, which led to a legal scrutiny of Patents Act 1970.[3]

CONCLUSION

The primary goal of any pharmaceutical company is to manufacture a drug product that conforms to reproducible quality standards. Central to this goal for solid products is selection of an active pharmaceutical ingredient (API) solid form that will remain unaltered throughout processing, shipping, storage, and product life.

For the most part, it is desirable to identify and select the most thermodynamically stable phase as early as possible (preferably during the first scale-up of drug substance production) so that all downstream toxicology, pharmacokinetics, and clinical studies may be conducted using the form likely to be present in the commercial product. Far-sighted drug development will also consider the impact of processing on the properties of various excipients included in formulations, where subtle (or significant) changes to their solid forms may also result in unexpected or unpredictable performance attributes of the drug product. In the end, multidisciplinary studies that investigate the likelihood of form changes any time during the handling of formulation materials is important to ensure the consistency of the final drug product. Fortunately, the wide variety of available characterization methods makes it possible to detect even very subtle changes in solid materials as they are processed. A successful approach to problem solving will require collaborative research by process, formulation, and analytical scientists. Although problems in development can often occur at the most inconvenient time, the judicious use of information previously gathered from properly designed studies, and rigorous efforts to embrace more complete materials understanding adopted by worldwide regulatory bodies, should lead to ever-improving development patterns that enable higher quality pharmaceutical products.

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