Chapter 1

General Principles of the Pharmaceutical Solid State

1.1 Introduction

The solid state, based on the order of molecular packing, can be classified into two major sub-phases: the crystalline and amorphous state (Cui, 2007).

The crystalline state, perhaps the most well-known solid sub-phase, is usually the preferred form, since it can be reproduced reliably and details surrounding its physical properties are well defined. However, the current trend of moving towards APIs (active pharmaceutical ingredients) that are more hydrophobic, lipophilic or even practically insoluble has prompted the development of amorphous or metastable forms to compensate for bioavailability issues, for these forms are widely known to possess higher solubility and dissolution rates (Cains, 2009).

The molecules of each crystal are held together via weak inter and intra-molecular forces (for example, hydrogen or van der Waals bonds), which are unique for every crystal form, displaying different free energies as exemplified by many of its physical properties such as solubility, chemical stability, melting point, density etc. (Hilfiker *et al.,* 2006). A crystalline solid can exist in a variety of interchangeable states including polymorphs, solvates and hydrates. What is of major interest to both academia and industry is the ability to quantify, control and predict these transformations (Heng & Williams, 2011).

Insufficient understanding of the solid-state properties of pharmaceutical polymorphism has in some cases led to unexpected setbacks for companies and seemingly random alterations in stability properties during manufacturing proceedings and storage. A well-known example is the case of ritonavir, where conformational polymorphism was found, with two unique crystal lattices, having different solubility properties (marketed as Norvir® by Abott Laboratories) (Chemburkar *et al.*, 2000; Bauer *et al.*, 2001). A sudden spark of interest in the last few decades was triggered by this phenomenon and deservedly so. A thorough understanding of the solid state is a prerequisite for incorporating the most suitable polymorphic form into the drug product. This information not only creates intellectual property opportunities for the pharmaceutical company, but could also provide enhanced drug properties to the advantage of the patient (Hilfiker *et al.,* 2006).

In the crystalline state, the molecules arrange in a highly regular fashion, displaying both short and long-range order. In this way crystalline molecules can pack more tightly and

efficiently, thereby reducing their molar volume. This results in a lower potential energy level. By contrast, amorphous materials (also known as glasses), lack the long-range molecular order found in crystals. They do however possess a certain degree of local or short-range order. More importantly, this lack of order is associated with all the other differences in the amorphous state, including greater intermolecular distance, high molecular mobility and free energy levels with reference to the crystalline phase. Therefore, crystals are considered as being thermodynamically more stable than amorphous or disordered states, and molecules tend to pack into crystals in an attempt to lower their free energy levels (Cui, 2007; Petit & Coquerel, 2006).

From a manufacturer's viewpoint, stability issues are generally of greater concern, and a less soluble form is deemed necessary for the absolute kinetic stability of a compound to be guaranteed. Products containing the stable form of a drug always exhibit lower solubility and have higher activation barriers to dissolution, but on the other hand they are least likely to transform inadvertently during manufacturing or subsequent storage (Cains, 2009).

The vast majority of drug products and excipients are in the solid phase, mainly because they present with higher chemical stability than in solution. However, as we can see the solid-state has many variables of which we must acquire knowledge and without which progression from the research to the formulation phase cannot commence (Griesser & Stowell, 2003).

1.2 Phases

A phase represents the tangible part of a system that is internally homogenous and can be separated physically from the other constituents in a system by the phase boundary (Ymén, 2011).

Gas, liquid and solid are the most frequently encountered phases. Different approaches can be used to differentiate between phases including: intermolecular distance, molecular motion, order of molecular packing and potential energy state (figure 1.1). These differences are generally progressive: the most distinctive is the intermolecular distance, then molecular motion; molecular packing being the most subtle one. All of these result in difference in potential energy. Therefore the difference in the energy state is an inherent feature for different phases. This has pharmaceutical significance since energy differences could have an influence on the solubility, bioavailability and stability of a compound. Hence, an

understanding of phase behaviour and in particular the energy state of the target compound is crucial (Cui, 2007).

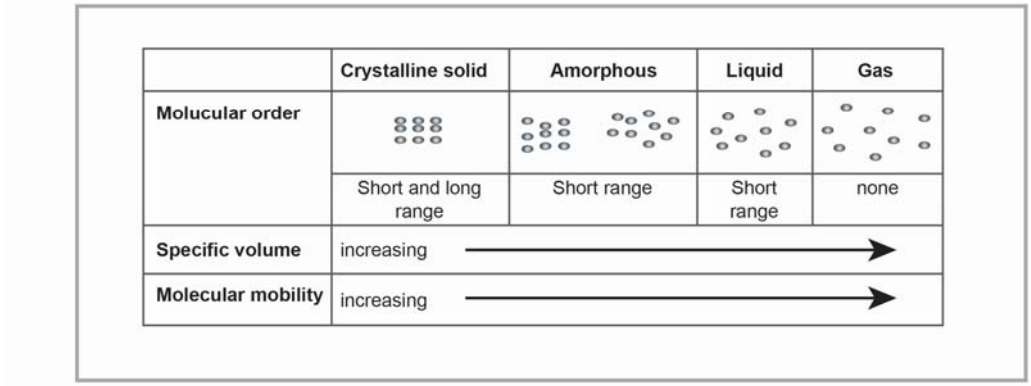

Figure 1.1 Comparison of molecular order, specific volume and molecular mobility in different phases (Adapted from Taylor & Shamblin, 2009).

1.2.1 Energy landscapes

The concept of energy landscapes provides a functional approach to complex phenomenology, representing the potential energy of a phase as a function of its molecular coordinations (position, conformation, orientation) (Cui, 2007; Debenedetti & Stillinger, 2001).

Molecular interaction in gases are minimal, therefore the potential energy state of the phase will not be influenced by changes in molecular coordination. When compared to the liquid state, where intermolecular distance is somewhat reduced, minute changes in the potential energy may be observed upon alteration of molecular coordinations (figure 1.2A). Temperature reduction to the supercooled region further reduces the intermolecular distance and there is concomitant increase of molecular interaction. At this point, changes in molecular coordination cause greater energy turmoil in the system as stronger molecular interactions are not so easily overcome and potential energy fluctuation becomes more eminent. As depicted in figure 1.2C, at this stage of cooling the liquid starts exhibiting structural dissimilarities, and "preferred" coordinations where lower potential energy is reflected, become evident. Cui (2007) believes that this is due to a degree of local order that emanates from directional intermolecular interactions. As the temperature approaches the glass transition temperature (figure 1.2D), structural dissimilarity becomes even more

apparent. When sufficient time is allowed, energy variations may form local areas that display higher energy levels compared to the bulk liquid, resulting in the formation of nuclei, or small molecular clusters that are represented in figure 1.2D by sharp discontinuities (Y & Z). Other molecules can now start to adhere to these clusters, or "crystal forming" coordinations, allowing crystal growth to take place. A schematic representation of crystal growth shows the molecular flux of molecules from higher energy coordinations into energy dips, or basins Y and Z. This process does not require as much energy as nucleation and is therefore usually not the rate-limiting step. All crystals, because of their highly ordered crystal lattice structures, are represented (see figure 1.2E crystals I and II) by sharp narrow discontinuities at specific "crystal-forming" coordinations and will occur at no other coordination sites. Because these sharp dips possess lower energy levels than those presented by disorderly states, they are always indicated in energy landscapes by sharp energy dips (Cui, 2007).

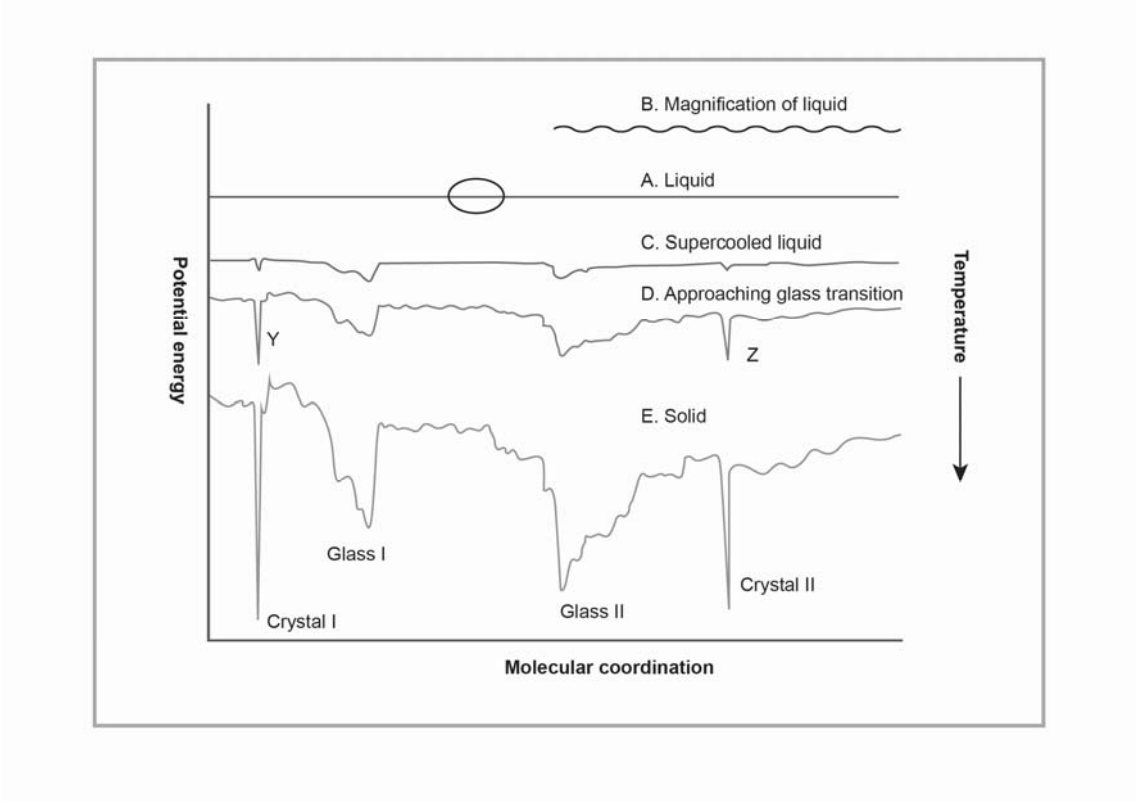

Figure 1.2 Energy landscapes of liquid and solid phases. Crystalline polymorphs are indicated as sharp energy dips and amorphous states as broad energy basins (Adapted from Cui, 2007).

A simplified representation of how crystallisation occurs can be represented effectively by the redistribution of molecular coordinations along an energy landscape (see figure 1.3). As mentioned, structural heterogeneity is already evident in the supercooled state of a liquid. Molecules have a tendency to seek out areas where potential energy is lower or "preferred' coordinations (e.g. W, X, Y and Z in figure 1.3A). At the supercooled state, the energy difference does not greatly differ between crystal-forming coordinations (Y and Z) and other energy basins (W and X). Since the crystal-forming coordinations are always narrow in comparison to other energy basins, the molecules are more likely to distribute to broader energy basins (W and X). Molecular flux is indicated in figure 1.3A by solid dots that flow to energy minima W and X, as indicated by the arrows (Cui, 2007).

Upon further cooling the energy difference between crystal forming coordinations (Y and Z) and the other energy basins (W and X) increases. Figure 1.3B shows that the change in flux as indicated by the arrows is then redirected to the energy basins Y and Z. However, for the molecules to move to these crystal-forming coordinations, the energy barrier between the energy basins needs to be overcome i.e. these molecular redistributions need kinetic energy and molecular mobility. Kinetic energy is dictated by temperature and since the highly supercooled liquid has a very low kinetic energy and molecular mobility slows down, molecular redistribution to crystal forming coordinations becomes a time-consuming process. Thus, crystallisation relies on local energy variations of the bulk liquid to create areas where higher kinetic energy causes molecular coordinations to be "pushed" over the energy hindrances, into the crystal-forming coordinations (Cui, 2007).

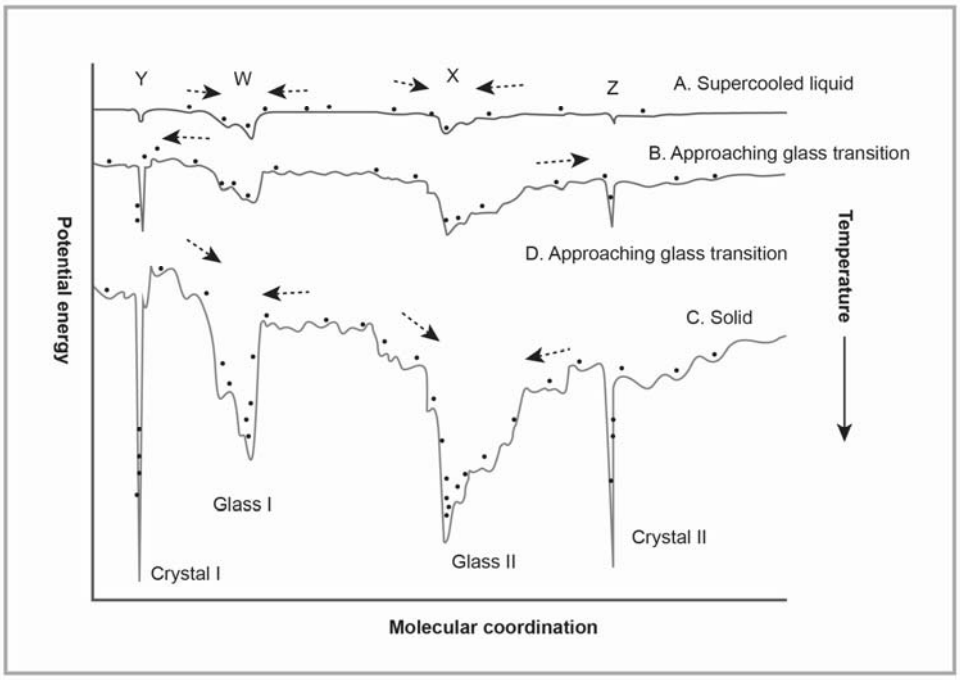

Figure 1.3 Dynamic redistribution of molecular coordinations in different stages. Molecular coordinations are represented by solid dots (Adapted from Cui, 2007).

1.3 The crystalline state

The Gibbs free energy, without which phase transition cannot occur, is the impelling force that initialises crystallisation. Crystallisation is driven by the attempt to keep the Gibbs energy to a minimum, also striving to adhere to several energy-minimising demands that include: (a) molecular conformation in the lowest energy state (b) charge imbalances being minimal (c) maximising the packing density (Ymén, 2011).

There are various methods for preparing different crystal forms of a substance. The most common method employed by pharmaceutical sciences is to crystallise from different solvents under a range of temperature regimes. At first a supersaturated solution is prepared. Following this, the supersaturation is discharged by either slow or rapid cooling of the solution, addition of an anti-solvent to induce precipitation, chemical reaction between two or more soluble species or variation of pH to produce a less soluble acid or base (Brittain *et al.,* 2009; Rodríguez-Hornedo & Murphy, 1999).

1.3.1 Crystal structure

Crystals are solids characterised by their morphology. They usually have well-defined crystal structures (faces and shapes) that characterise the entire sample. In order to understand the macroscopic crystal and its underlying array of atoms and molecules we first need to grasp the concept of unit cells and lattices (Gilmore, 2011).

Every crystal consists of a three-dimensional translational repetition of a basic structural motif. This motif can comprise one or more atoms, a molecule or an arrangement of molecules or a combination of these. In the pharmaceutical sciences, motifs are generally two or more molecules that may additionally have a salt former or solvent bound to them. If one were to construct a parallelepiped containing such a motif and it has the ability to propagate in three dimensions to generate a macroscopic crystal, this parallelepiped is called a unit cell. An infinite number of unit cells can be tightly packed in three dimensions in order to form a crystal lattice. This is achieved by placing a point in the corner of each unit cell. A crystal lattice will be observed as a regular three-dimensional arrangement of points such that each lattice point has an identical environment with respect to the basic motif and other lattice points. The basic parallelepiped is called the unit cell and its geometry is defined by lengths of the three axes (a,b,c) and the angles between them (α,β,γ) (Gilmore, 2011).

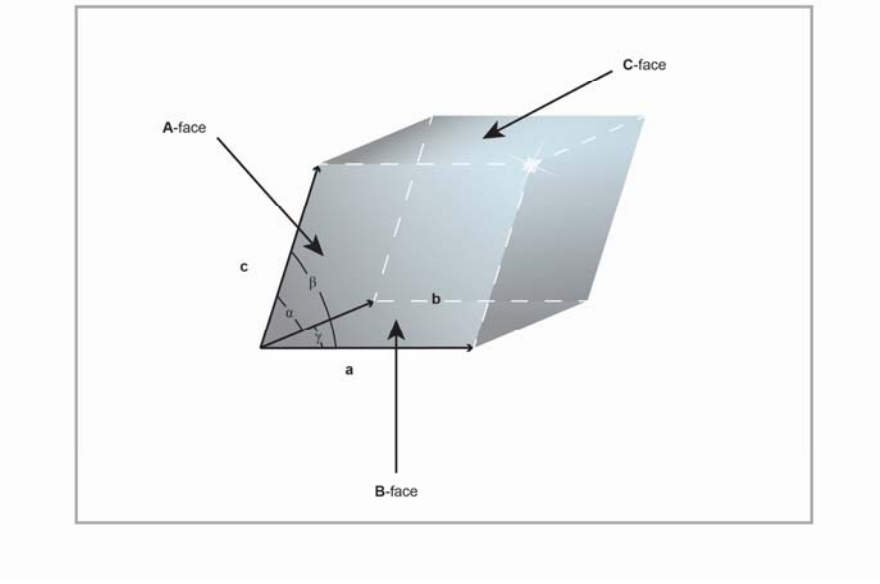

Figure 1.4 The unit cell with unit cell axes and angles indicated (Adapted from Gilmore, 2011).

Symmetry is a characteristic of cells and lattices. As shown in table 1.1 there are seven basic crystal systems, each defined by its own symmetry elements and cell conditions. In this example the rotational symmetry is examined by searching for the *n*-fold rotational axis where the unit cell is rotated 360/*n* about this axis resulting in a lattice identical to the initial one. The unit cells most commonly found in pharmaceuticals are triclinic, monoclinic or orthorhombic (Gilmore, 2011).

Table 1.1 The seven crystal systems, their unit cell, their rotational symmetry and the constraints on the unit cell dimensions (Gilmore, 2011)

Cell	**Rotational symmetry**	**Cell conditions**
Triclinic	None	$a \neq b \neq c$; $\alpha \neq \beta \neq \gamma \neq 90$
Monoclinic	2-fold parallel to b-axis	$a \neq b \neq c$; $\alpha = \beta = 90$
Orthorhombic	2-fold parallel to a, b and c-axes	$a \neq b \neq c$; $\alpha = \beta = \gamma = 90$
Tetragonal	4-fold parallel to c-axis	$a = b \neq c$; $\alpha = \beta = \gamma = 90$
Trigonal/rhombohedral	3-fold parallel to (***a*** **+** ***b*** **+*c*)**	$a = b = c$; $\alpha = \beta = \gamma$ (unrestricted)
Hexagonal	6-fold parallel to c-axis	$a = c$; $\alpha = \beta = 90$; $\gamma = 120$
Cubic	3-fold along the cube diagonals	$a = b = c$; $\alpha = \beta = \gamma = 90$

1.3.2 Nucleation and crystal growth

Several steps precede the crystal-forming stage from a supersaturated solution, of which the first is termed nucleation, where tiny crystallites known as nuclei are formed in the supersaturated solution. Thereafter, molecules progressively attach themselves to these nuclei, forming clusters. In order for these clusters not to disintegrate, the critical nuclei size of the particles needs to be reached (Brittain *et al.*, 2009; Grant, 1999.) Furthermore, depending on the size of the surface area of the particle compared to its total size, a specific

energy input is needed for crystallisation to proceed and ultimately grow to macroscopic size range or until the solvent saturation equilibrium is reached (Brittain *et al.,* 2009; Ymén, 2011).

Nucleation may be primary; where initially no crystals are present in the solution or secondary; where some nuclei will form as a result of pre-existing crystals that scatter to form new crystals or as a deliberate seeding technique added to the solvent. Primary nucleation may be homogeneous, in which nucleation manifests spontaneously in a medium, or heterogeneous, in which foreign matter acts as an interface for nucleation (Lohani & Grant, 2006).

The change in free energy associated with nucleation (ΔG_{TOT}) from a homogeneous solution is given by:

$$\Delta G_{TOT} = \Delta G_S + \Delta G_V$$

where ΔG_S represents the surface excess free energy and ΔG_V, the volume excess free energy, both of which are functions of the particle radius. ΔG_S is a positive quantity, as surface formation absorbs energy and ΔG_V is a negative quantity as bulk formation of a particle releases energy (Ymén, 2011). This implies that ΔG_S and ΔG_V represent two opposing algebraic factors, represented in figure 1.5 by an inverted Morse curve, where the resulting free energy curve has a maximum corresponding to the critical radius (r_{CRIT}) of the nucleus (Brittain *et al.*, 2009; Grant, 1999). The free energy of the critical nucleation may also be calculated using the following equation:

$$\Delta G_{CRIT} = 4\pi\sigma r_{CRIT}^{2}/_{3}$$

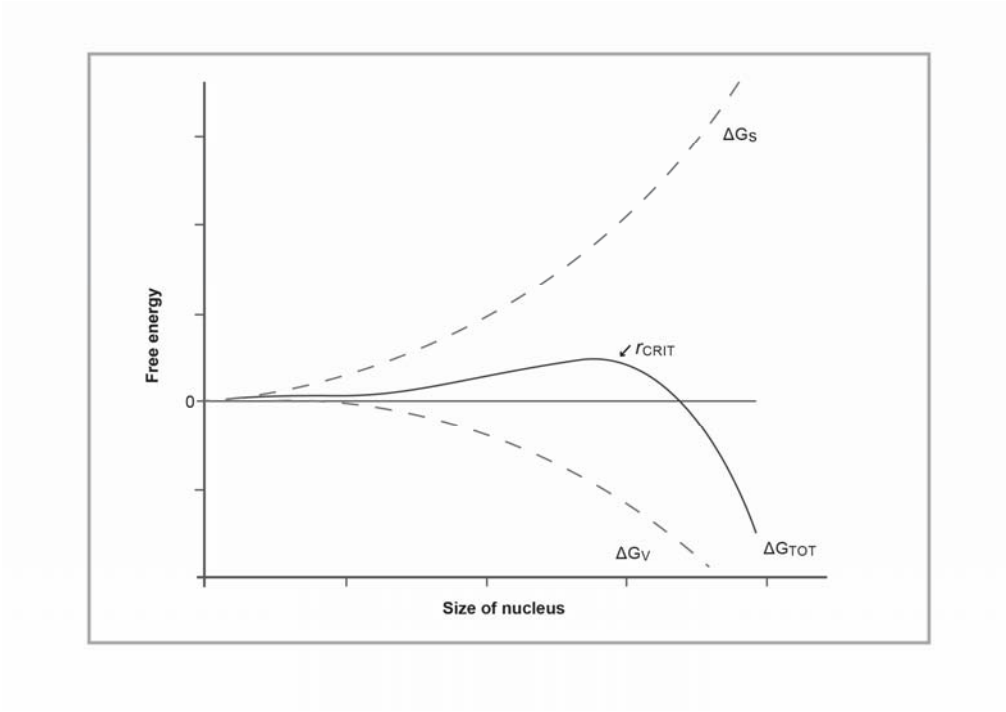

Figure 1.5 Dependence of the surface free energy (ΔG_S) and the volume free energy (ΔG_V), also illustrating the existence of the critical nucleus having a diameter equal to r_{CRIT} (Adapted from Brittain *et al*., 2009).

Homogeneous nucleation is therefore seen as a randomised process determined by two opposing factors that involves a volume term, in which molecular adduction from the supersaturated medium is favoured and a surface term where dissolution of molecular clusters are favoured. In the supersaturated medium, molecules will aggregate in an attempt to lower the Gibbs free energy under the influence of the volume term (Brittain *et al*., 2009).

Crystal size and the number of crystals obtained are highly dependent on the level of supersaturation i.e. high supersaturation yields many small crystals whereas lower supersaturation yields fewer but larger crystals (Ymén, 2011; Lu & Rohani 2009). In another instance, larger crystals will grow at the expense of smaller, higher energy crystals. Smaller crystals have higher energies because of a higher surface:volume ratio and will dissolve on account of the growth of the larger, lower energy crystals because of higher apparent solubility rates. This process is called the Ostwald ripening (Ymén, 2011; Gu *et al*., 2001).

1.4 Polymorphism

Polymorphism has been described comprehensively and from various perspectives by different authors. Although no one definition can encapsulate them all, a concise definition

of polymorphism, regarding the pharmaceutical industry, is the potential of a pharmaceutical substance to crystallise in different ways, having significantly different crystal lattice structures but are chemically equivalent with regard to bonding sequence and types of atoms. These structural differences come as a result of different molecular conformations, hydrogen bonding and molecular packing (Ymén, 2011).

1.4.1 Packing and conformational polymorphism

The ideal crystal is defined by identical structural units occurring at regular spatial intervals throughout the crystal lattice. Modifications in structures of organic molecules can occur as a result of two different mechanisms: packing and conformational polymorphism. Packing polymorphism occurs where conformationally rigid molecules are stacked in different motifs that occupy different positions in the crystal lattice. Conformational polymorphism is described as conformationally flexible molecules that exist in distinguishable conformational states, which may crystallise into its own lattice structure *(*Saifee *et al*., 2009).

Although they have similar chemical composition, the differences in internal crystal lattice structure cause polymorphs to have different physical and chemical properties, including spectroscopic, thermodynamic, kinetic, mechanical, packing and interfacial properties (Yu *et al.,* 2003; Holzgrabe *et al*., 1999). In the liquid and vapour phases though, these differences are no longer observed (Lohani & Grant, 2006).

The case of ritonavir, a protease inhibitor, is one of the most celebrated recent examples of how the existence of different crystal forms can have dramatic effects on commercial pharmaceuticals (Bauer *et al*., 2001; Chemburkar *et al.*, 2000). The different crystal lattice energies displayed by two conformational polymorphs (form I and form II) of ritonavir, led to different equilibrium solubilities, affecting the drug product in such a way that the manufacturer was forced to recall the original formulation from the market (Chemburkar *et al.*, 2000).

In 1996 the product marketed as Norvir®, containing a novel protease inhibitor for the treatment of acquired immunodeficiency syndrome (AIDS) was released by Abbot Laboratories. It was available in two dosage forms; an oral liquid and the semi-solid capsules, both containing ritonavir in ethanol/water-based solutions (since ritonavir is not bioavailable from solid formulations). The ICH (International Committee on Harmonization) guideline states: “For a drug product that is a solution, there is little scientific rationale for polymorph control” (quoted by Bauer *et al*., 2001), therefore meticulous control over the crystal form was not required. Moreover, during the developmental stages of the compound,

only one crystal form, form I, was identified. Norvir® capsules were produced in 240 lots without any indication of stability problems, until mid-1998, when several lots of capsules were found to deviate from the dissolution requirements. Upon further examination using XRPD and microscopy, a new form with markedly reduced solubility characteristics compared to form I was discovered. Within weeks the new form referred to as form II started appearing in both bulk drug and formulation areas. The decreased solubility of this form meant that although the formulation was saturated with respect to form I, it was 400% supersaturated with respect to form II. In addition, Norvir® oral solution could not be stored between the previously acceptable temperatures of 2-8ºC, without the risk of crystallisation. It therefore necessitated the reformulation of the drug product and incorporation of the dramatically less soluble form II. Form II was also found to be thermodynamically the more stable form and unusually difficult to crystallise.

The sudden appearance and dominance of this form, together with its unique properties not only temporarily threatened the supply of this life-saving treatment for AIDS but led to the late stage pharmaceutical product failure for the pharmaceutical company (Bauer *et al*. 2001). This highlights the importance of the enumeration of all possible forms of a drug product during the research and developmental stages.

1.4.2 Generating different crystal forms

There are various methods for yielding different polymorphs. The most commonly used technique involves crystallising the API in various organic solvents (Ymén, 2011; Cains, 2009). Although this kinetic phenomenon is not entirely understood, Bernstein *et al.* (1999) theorised possible reasons for its occurrence: (a) activation energy required for primary nucleation is different for each solvent (b) molecules of a pharmaceutical substance undergo different conformational changes in each solvent (c) proportions of solvent-solute and solute-solute interactions differ when the solubility varies in different solvents. As a general rule, if conducted under mild conditions with a moderate driving force, slow crystallisation and transformation processes are more likely to produce stable polymorphs. Conversely, if rapid processes are employed involving extreme or dynamic conditions the formation of the metastable or amorphous forms is favoured. Figure 1.6 uses this principle to portray the relative stability of a selection of methods (Cains, 2009).

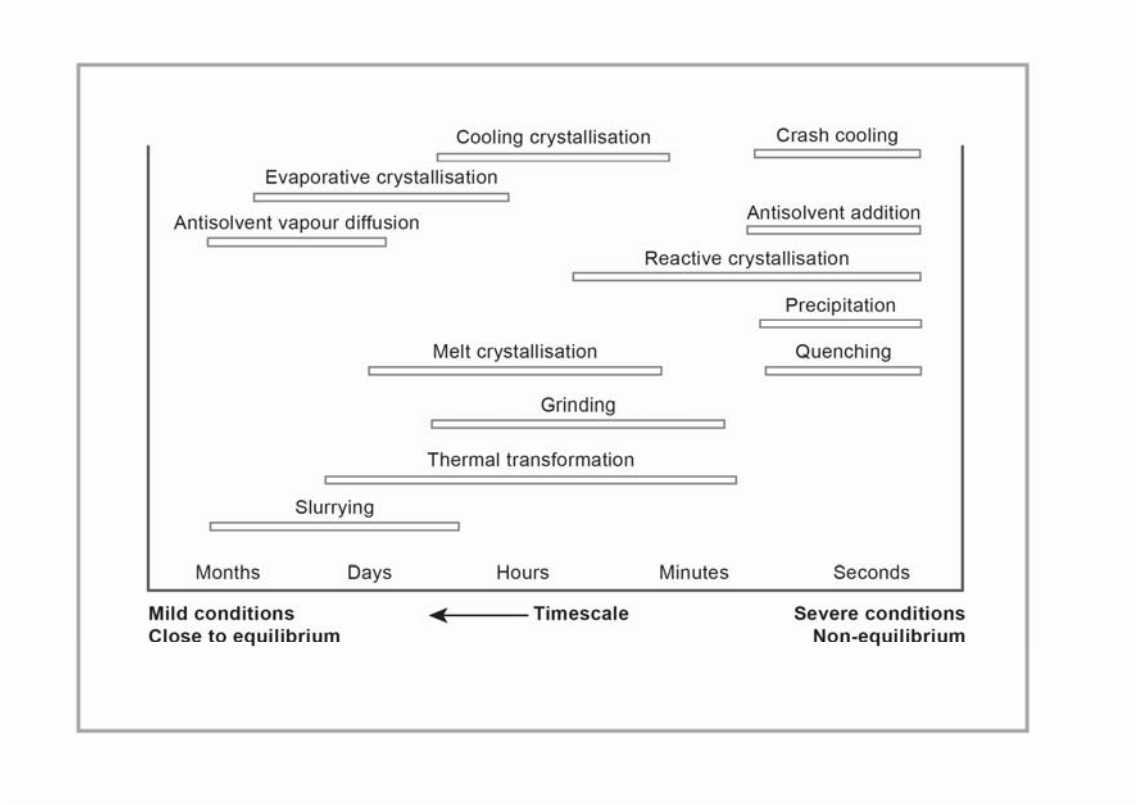

Figure 1.6 Methods for producing different crystalline forms (Adapted from Cains, 2009).

The main problem with polymorphism is that it is not possible to guarantee the most stable form under a certain set of conditions. Instead, having found several polymorphs, testing can only provide the form that is more stable than the others for the given experimental conditions. Therefore, one can never rule out the possibility of another, more stable polymorph appearing and if this polymorph is so dominant that the old polymorph can never again be produced, the situation could become problematic (Dunitz & Bernstein, 1995).

Since disappearing polymorphs are monotropic (irreversible transitions), it is best to choose a form that seems thermodynamically stable. This is usually confirmed by the presence of reversibility or enantiotropy (Ymén, 2011).

1.4.3 Polymorphic nature and thermodynamic stability

The difference in Gibbs free energy ΔG_c during the crystallisation process at a constant pressure and temperature (usually ambient conditions) is given by:

$$\Delta G_c = \Delta H_c - T\Delta S_c$$

where, the enthalpy and entropy differences are represented by ΔH_c and ΔS_c respectively. The formation of the stable crystal form is driven by the attempt to keep ΔG_c to a minimum, whilst irreversible thermodynamics is driven by the attempt to maximise the entropy rate, leading to the formation of the metastable form. The rate at which excess energy is applied to the system determines the equilibrium composition of the polymorphic mixture (Lu & Rohani, 2009).

Meanwhile, the Gibbs free energy difference between polymorphs (ΔG_t) determines the relative thermodynamic stability of polymorphs and the system's ability to undergo spontaneous transitions at constant pressure and temperature:

$$\Delta G_t = \Delta H_t - T\Delta S_t$$

Enthalpy difference between different crystal forms is given by ΔH_t, which emulates lattice energy differences and entropy difference, ΔS_t, measures the entropy difference between different crystal forms, and relates to disorder/randomness and lattice vibrations. In a dimorphic system spontaneous transformation from one phase into another can commence when $\Delta G_t < 0$. If $\Delta G_t = 0$, the Gibbs free energy between the two phases is in equilibrium (Lu & Rohani, 2009).

1.4.3.1 Enantiotropy and monotropy

Polymorphs can be either enantiotropically (reversible solid-solid transition) or monotropically (irreversible solid-solid transition) related, in accordance with the thermodynamic relationships (Saunders & Gabbot, 2011; Morris *et al*., 2001). Burger and Ramberger (1979) developed four rules, namely: the heat of transition rule, the heat of fusion rule, the infrared rule and the density rule. These rules aid in predicting the relative thermodynamic stability and the nature of the polymorphic system.

After successful implementation of these rules and after the polymorphic nature of the system has been determined, the next goal will be to define the domain in which a substance is thermodynamically stable or metastable. Plotting the Gibbs free energy difference ΔG against the absolute temperature (T) remains one of the most effective ways of doing so. The relative stability of a polymorph depends greatly on its free energy value in such a way that the polymorph that possesses a lower free energy is the thermodynamically

stable polymorph. Under a certain set of conditions, there can only be one stable polymorph and all the others are designated as metastable (Vippagunta *et al.,* 2001).

Figure 1.7 depicts energy-temperature diagrams of a single component and a dimorphic system. In figure 1.7 (a) the free energy curve of the liquid intersects the free curve of the polymorphs before the equilibrium temperature (T_t) is reached, showing a monotropic relationship between polymorphs. In this system one polymorph is always stable below the melting point (T_m) of both polymorphs. As illustrated, polymorph B has a higher free energy than polymorph A at all temperatures below $T_{m,A}$, i.e. $G_A<G_B$. As a result an exothermic transition from polymorph B to the more stable polymorph A can occur spontaneously at all temperatures. Furthermore, when the crystallisation rate is higher than the rate of solid-state transformation, there is a possibility for crystallisation of two forms (Lu & Rohani, 2009).

A system displaying enantiotropic behaviour is illustrated in figure 1.7 (b) and (c). In this system the free energy curve of the liquid line and the free energy curve of the polymorphs converge beyond the T_t. Below $T_{t,\ A\text{-}B}$, polymorph A is stable and possesses a lower free energy than that of B, i.e. $G_A<G_B$. Therefore, a spontaneous transition from polymorph B to polymorph A can occur. Conversely, above $T_{t,\ A\text{-}B}$, polymorph B has a lower free energy than polymorph A, which allows polymorph A to undergo a spontaneous endothermic reaction into the more stable polymorph B. Figure 1.7 (c) illustrates how solid-state transformation may be obstructed by steric hindrance, causing the thermodynamic equilibrium temperature (i.e. theoretical transition temperature) $T_{t,\ A\text{-}B}$, to differ from the actual transition temperature $T_{t,\ R}$ (Lu & Rohani, 2009).

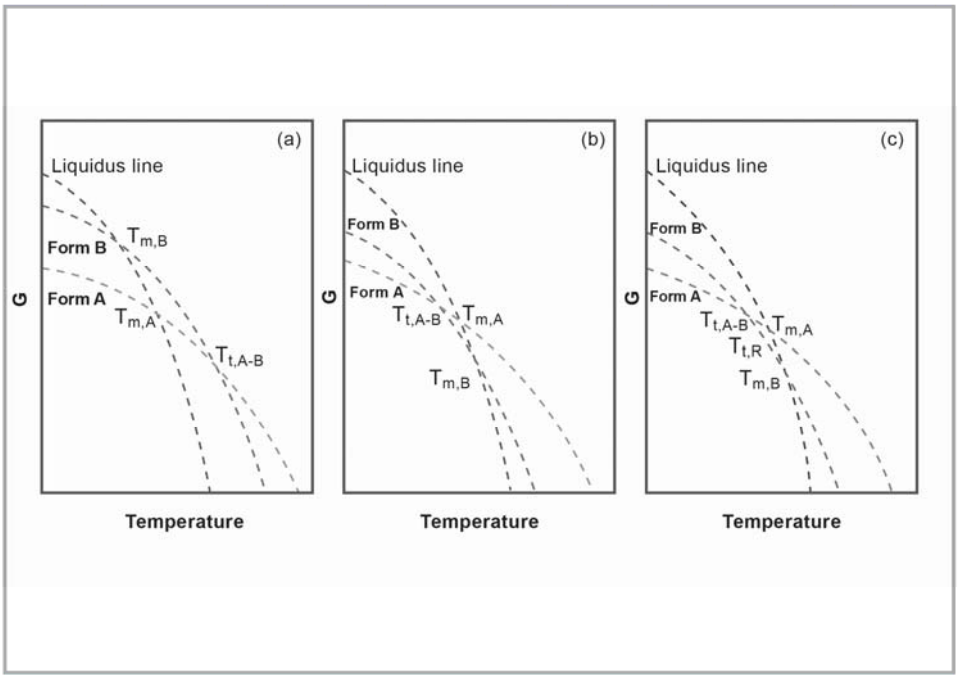

Figure 1.7 Plots of the Gibss free energy curves for dimorphic systems: (a) monotropic (b) and (c) enantiotropic (Adapted from Lu & Rohani, 2009).

1.4.3.2 The metastable state

As indicated by the energy-temperature diagrams, at a specified temperature, only one polymorph can be thermodynamically stable (except at the transition temperature). The stable form will, under the specific conditions, also be the least soluble form (Byrn *et al*., 1999). All the other forms can be regarded as metastable with respect to the stable form. The existence of the metastable state is however of a temporary nature and will over time convert to the stable form. This conversion is produced by the metastable states tendency to lower its free energy and convert to the thermodynamically stable form (Lohani & Grant, 2006).

The lower solubility of the stable form may influence the pharmacological utility in such a way that it may be beneficial to formulate selectively a product containing the metastable form, in which case the energy-temperature or pressure-temperature forms the basis for the formulation strategies (Bernstein, 2002).

When choosing the most appropriate polymorphic form to incorporate into the drug product, there are several thermodynamic considerations. The polymorph displaying greater physical and chemical stability is generally the preferred form. On the other hand there are several reasons for choosing the thermodynamically metastable polymorph including greater solubility and bioavailability. To avoid unforeseen late-stage product failure, the most stable polymorphic form is usually preferred (Saunders & Gabbot, 2011; Lu & Rohani, 2009; Yu *et al.,* 2003).

Throughout the industry and experimental practice, the metastable form is frequently observed to appear initially where after it will convert to a more stable form. Ostwald studied this phenomenon and concluded that (quoted by Lu & Rohani, 2009) "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".

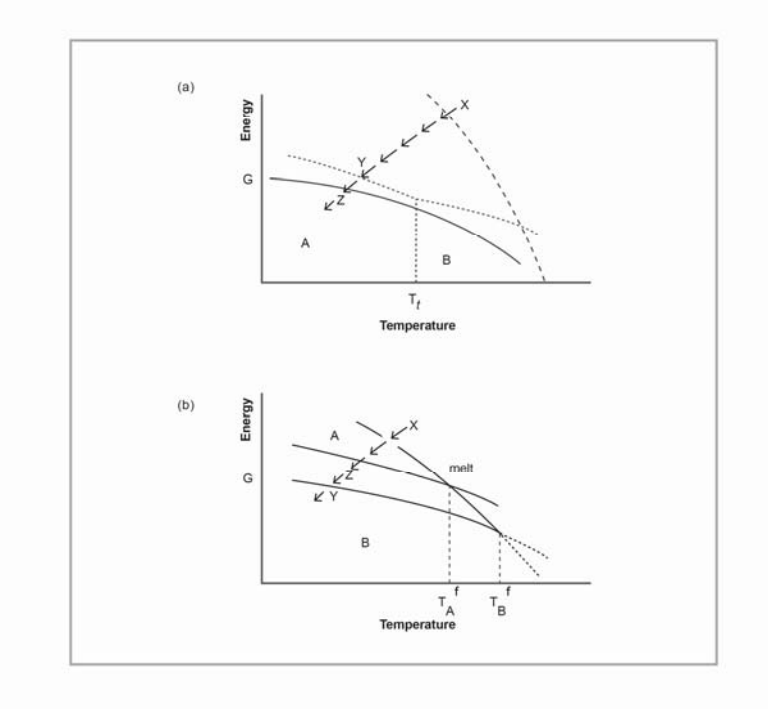

Figure 1.8 Relationship between the Gibbs free energy (G) and the temperature (T) for two polymorphs for (a) an enantiotropic system and (b) a monotropic system where it is cooled initially from point X. The arrows indicate the direction of change (Adapted from Grant, 1999).

According to Ostwald's step rule, as a system cools down, the Gibbs free energy will be lowered as the temperature drops. In figure 1.8 (a), if the system reaches point Y, the preferred polymorph will be B, as this form is the least stable form and resides nearest to the

original state when their Gibbs free energies are compared. If the system in figure 1.8 (b) is initially represented by point X, cohering to that of an unstable liquid or vapour or to a supersaturated solution, when it reaches point Z, then polymorphic form B will be preferred above form A according to this rule (Grant 1999).

Although this is a useful practical rule, it is based on the thermodynamics and crystallisation kinetics under specific experimental conditions and is therefore not universally valid (Bernstein, 2002; Grant, 1999).

1.4.4 Significance of polymorphism

Dissimilarity of the physical and chemical properties of different polymorphs has instigated regulatory authorities to require solid-state characterisation of pharmaceuticals (Strachan *et al*., 2005; Caira, 1998). These properties primarily affect the stability, processability, bioavailability (BA) and bioequivalence (BE) of a substance. Therefore strict monitoring and control over all phases of drug-development should be maintained to ensure the quality, safety and efficacy of the API in its final dosage form (Saunders & Gabott, 2011).

Depending on stability relationships between polymorphs, manufacturing processes such as milling, wet granulation spray drying, micronisation, drying and compaction could cause phase transitions. When preparing samples prior to analysis, it should therefore not be ground or milled as this could affect the properties of the sample. Environmental conditions such as humidity and temperature can also induce inadvertent polymorphic transitions (hydrate formation or solid-solid phase transformation). The relative stability of polymorphs, applied stress and kinetic activation barriers for phase conversion will in most cases project the extent of a conversion. Nonetheless, if controlled and well understood, phase conversions are not of serious concern when they form part of validated manufacturing processes and where the bioavailability and bioequivalence of the final drug product are satisfactory (Saunders & Gabbott, 2011; Yu *et al.,* 2003).

1.4.4.1 Bioavailability and bioequivalence

When considering a generic drug, the Food and Drug Administration (FDA) must determine whether a drug is bioequivalent to that of the reference listed drug (RLD). Different polymorphs, as mentioned, may exhibit different dissolution rates and apparent aqueous solubility rates. When the values differ substantially, the polymorph will potentially exert

altered bioavailability and therefore formulation of a bioequivalent product using a different polymorph could prove a difficult task (Yu *et al.,* 2003).

Figure 1.9 represents how different crystal lattice structures may influence the dissolution of two polymorphs, leading to changes in bioavailability of a substance.

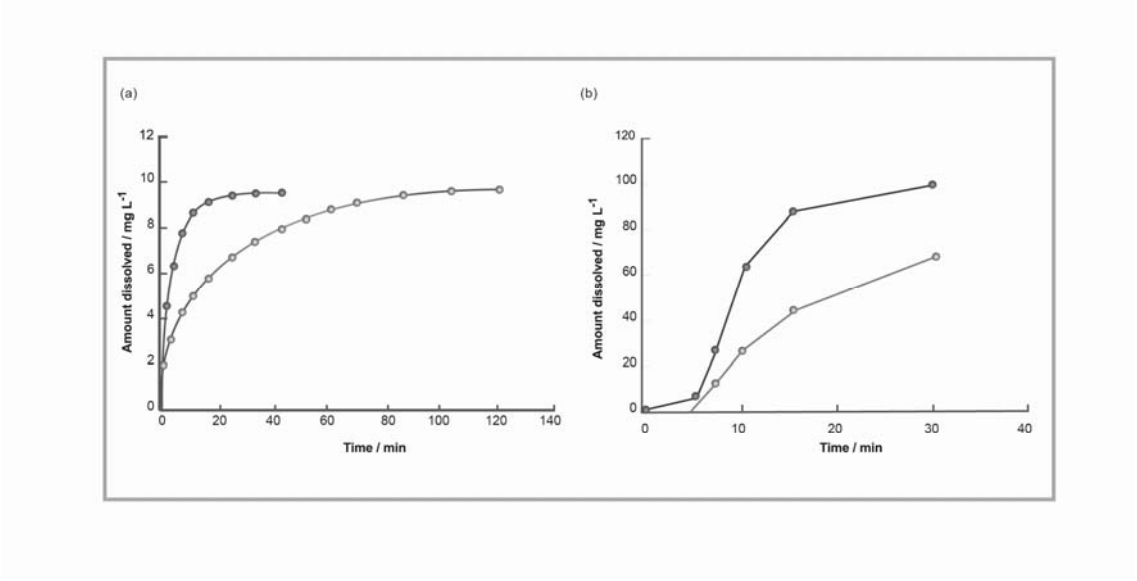

Figure 1.9 Dissolution curves of two crystalline modifications (A and B) of a drug candidate and the corresponding curves of the drug products consisting of capsules containing A and B. a – drug substance form A: -●- form B: -○-; b- capsules form A: -●- form B: -○- (Giron, 2001).

Solubility can be defined as the saturation concentration of a drug in a fixed amount of solvent under specified pressure and temperature. Solubility tests are usually performed using the equilibrium solubility method to determine the aqueous solubility of a drug. The solubility is measured by the maximum concentration obtained through dissolution of an excess amount of the solid in an aqueous medium. For metastable forms of a drug this might not be the preferred method, as the possibility exists for solvent mediated conversions to the stable form to occur during experimental proceedings. In this case the intrinsic dissolution method will be a more suitable option.

Solubility is often the rate-limiting factor for oral absorption. If, however, the dissolution rates are sufficiently high for each of the relevant polymorphs, regulatory concerns regarding bioavailability are minimal (Snider *et al.,* 2004; Yu *et al.,* 2003).

Apparent solubilities and dissolution rates can offer valuable insight into potential discrepancies during generic drug testing and can be indicative of possible phase transformations and inter-polymorphic differences (Yu *et al.,* 2003).

Although, there have been instances that have proved that differences in solubility of polymorphs do not necessarily lead to bio-inequivalence. The rate and extent of oral absorption are also dependent on physiological factors (permeability, metabolic stability) and not just on dissolution rate (Amidon *et al*., 1995; Yu *et al*., 2002). This was proven to be the case with two bioequivalent polymorphs (polymorph I & II) of ranitidine, where the rate-limiting factor is the intestinal permeability. This, however, is not the case with carbamazepine, where the rate-limiting factor for oral absorption is dissolution. Kobayashi *et al*. (2000) determined that polymorphic forms I & III and the dihydrate are not bioequivalent.

When addressing the issue of "sameness" between the RLD and the generic, regulatory authorities have concluded that there are other factors also governing drug stability and performance and not only the solid-state properties of the active ingredient. Applicants of ANDA (abbreviated new drug applications) have to prove that the proposed pharmaceutical product is bioequivalent to the RLD and meets the standards for identity and stability.

Therefore polymorphism itself does not directly determine whether the drug product is the "same" as the RLD, but the potential impact it has on its physical and chemical properties makes it a subject to which close attention should be paid during regulatory review (Yu *et al.,* 2003).

1.4.4.2 Processability

Polymorphs of organic molecules crystallise into different crystal structures to create more than one distinct crystal species. They may therefore substantially differ in terms of physico-chemical and mechanical properties both of which affect compaction behaviour. In three separate studies done by Summers *et al.* (1977), Ragnarsson and Sjogren (1984) and Kopp-Kubel *et al.* (1992) different polymorphs showed to have different mechanical property behaviours including tensile strength of compacts and yield stress. Their results show that on each occasion less stable polymorphs are more easily deformed, have a lower yield pressure and weaker compressibility and compactibility properties, making them less favourable choices for tabletting (Roberts, 2011).

In another study done by Roberts and Rowe (1996), involving enantiotropic pairs carbamazepine (III/I), sulphathiazole (III/I) and sulphanilamide (β/γ), a mechanical property

used in powder compaction called the Young's modulus, E, was used to compare the elasticity and stiffness of the different forms (Table. 1.2)

On each occasion the more stable form was reported to display the highest lattice energy as observed by the heat of solution, heat of fusion and true density shown in the table 1.2, which is consistent with the thermodynamic rules of Burger (1982) for enantiotropic systems.

From the results we can see that the thermodynamically stable form has both the higher yield strength and Young's modulus (Roberts & Rowe, 1996).

Table 1.2 Thermodynamic and mechanical properties of carbamazepine, sulphathiazole and sulphanilamide polymorphs (Roberts, 2011)

Drug	Form	ΔH fusion (kJ mole^{-1})	ΔH solution (kJ mole^{-1})	Young's modulus (GPa)	Yield stress (MPa)
Carbamazepine	III	29.39	24.15	13.2	123
Carbamazepine	I	26.20	21.05	3.7	37
Sulphathiazole	III	29.47	25.53	14.6	90
Sulphathiazole	I	27.75	22.19	10.6	87
Sulphanilamide	*β*	22.26	19.61	10.7	138
Sulphanilamide	*γ*	20.81	17.32	6.3	119

1.5 Solvatomorphism

A pharmaceutical substance may be exposed to solvent molecules or vapour during the various stages of processing. It is during this processing that solvent molecules may, to some extent, become entrapped within a solid (Griesser, 2006). Polymorphism has been described as crystal systems of the same elemental composition defined by different unit cells. When the elemental composition changes by solvent inclusion into the unit cell, Brittain *et al*. (2009) refer to the term solvatomorphism, a term that denotes a solvate or a hydrate (when the molecular adduct is water).

Classification of solvatomorphs is based on the ratio between solvent and drug molecules and can be either stoichiometric, where a definite ratio exists between solvent and molecules, or non-stoichiometric, where this ratio may vary continuously or over a given range (Brittain *et al*., 2009). Griesser (2006) further identified that solvent inclusion into non-stoichiometric solvatomorphs may be present in either an interstitial or substitutional mode.

Possible reasons for studying solvatomorphism have been pointed out by Byrn *et al*. (1999):

1) The solvatomorph may be the penultimate solid form of the drug substance.
2) The solvatomorph could be specifically chosen for recovery and purification.
3) The solvatomorph could be characterised by a crystal morphology that facilitates performance of a step in a manufacturing process.
4) The solvatomorph could be the only crystalline form suitable for crystal structure determination of the drug substance by means of single-crystal X-ray diffraction study.
5) The solvatomorph could constitute new intellectual property, and thus be patentable.

1.5.1 Hydrates

Water is undoubtedly one of the most commonly encountered solvent inclusions, with an estimated one third of all drug substances capable of forming hydrates (Stahl, 1980). The small size of a water molecule as well as its inherent ability to form hydrogen bonds makes it an unrivalled solvate former (Griesser, 2006). Although, the mere presence of water in a system is not enough evidence to suspect hydrate formation, as some compounds do not form hydrates even though they are soluble in water. The determining factor is the activity of water in the crystallising medium (Vippagunta *et al*., 2001).

Throughout the developmental processes possible changes in the hydration state of substances and excipients and its pharmaceutical impact are of major interest. Depending on the thermodynamic stability of a substance, hydration or dehydration may occur in response to environmental conditions, processing, or naturally over time (Morris & Rodrìguez-Hornedo, 1993).

The physico-chemical stability of a hydrate is often the first consideration during pre-formulation. Upon dehydration a crystal may more or less retain its original crystal structure or in some cases may lose its crystallinity and convert to the amorphous form. In addition to

physical changes, a substance may undergo chemical changes or even become chemically labile. Cephradine dihydrate becomes amorphous after dehydration and undergoes subsequent oxidation. Other compounds may convert from a lower to higher hydration state, which will often yield a form with lower solubility (Brittain *et al.*, 2009).

Since formation of new hydrated phases has the same ability to influence bioavailability, toxicity, stability and processing as polymorphism, the ICH decision tree considers hydrate formation as part of the investigation of the physical properties of a drug substance (Giron *et al.*, 2002).

Three categories of crystalline hydrates have been proposed (Morris & Rodrìguez-Hornedo, 1993):

1) Isolated site hydrates: where water molecules are isolated from direct contact with one another by intervening drug molecules.
2) Channel hydrates: where water molecules included in the lattice lie next to other molecules of adjoining unit cells along an axis of the lattice, forming “channels” through crystals.
3) Metal ion-associated hydrates: where water molecules are bound directly to a metal ion, either as part of a coordination complex in the case of transition metal ions, or through strong ionic bonds as in the case of alkali earth ions.

1.5.2 Solvates

As described, a solvate is a crystal lattice host comprised of unsolvated molecules into which solvent molecules are incorporated (Haleblian, 1975). Thermodynamically unstable solvates are often a result of kinetics, where an unstable anhydrate attempts to stabilise itself by adding solvent molecules to its structure. Exposing a metastable ansolvate to solvent vapour or to slurry it quickly in a solvent are typical methods for preparing unstable solvates. When crystallisations evaporate too quickly, unstable solvates may also appear (Ymén, 2011).

Solvates can only be thermodynamically stable, when in a certain temperature range and when in contact with its solvent. Therefore all solvates are thermodynamically unstable when exposed to air. On the contrary, hydrates are able to persist in the metastable state in low relative humidities and anhydrates at high relative humidities for prolonged periods. Solvates usually live in parallel with a thermodynamically stable ansolvate, so that at a low

solvent activity the latter is more stable, whereas at high solvent activities solvate stability is higher. This means that in air a hydrate may be stable at a high relative humidity, whereas its corresponding anhydrate is stable at low relative humidities. It is assumed that solvates exist when solvent molecules are incorporated into the crystal lattice where packing between pharmaceutical molecules is insufficient and solvent molecules compensate by filling the voids (Ymén, 2011).

Therefore, solvent molecules lend stability to the crystal lattice, by imposing stronger molecular interactions between molecules or between planes of molecules. There are two primary ways to accomplish this; one where solvent molecules assume isolated positions in a crystal structure and the other is where lattice positions assemble solvent molecules along channels in the structure (Brittain *et al*., 2009).

The intrinsic dissolution rate of solvatomorphs compared to that of their unsolvated counterparts is generally different because of different solubility rates. The same applies to their stability profiles when compared at different temperature and vapour pressures (Brittain & Grant, 1999).

This shows how molecular adducts influence intermolecular interaction and physical properties of the crystal and that each solvate or hydrate has a unique set of values for internal energy, enthalpy, entropy and Gibbs free energy and thermodynamic activity (Lohani & Grant, 2006). These differences may influence the formulation, processing and stability under various storage conditions of the drug compound and also the pharmaceutical product (Roberts, 2011).

1.6 The amorphous or glassy state

According to Yu (2001), amorphous pharmaceutical solids are of interest because of its apparent higher solubility and faster dissolution rate when compared with the crystalline counterparts. However, decreased physical stability has been reported because of excess properties of enthalpy and Gibbs free energy, that are responsible for the detrivication (crystallisation) tendency of the amorphous state, which endows the desirable property of high solubility (Kaushal & Bansal, 2008). Hence, stability is of great concern when developing these drugs, for they have shown not to be in thermodynamic equilibrium and depend on several factors including time, temperature, percentage relative humidity (%RH) and T_g of the solid (Heng & Williams, 2011).

1.6.1 The generation of amorphous materials by cooling of a melt

Amorphisation of materials is generally achieved through spray drying (Yu, 2001), rapidly cooling a melt (Forster *et al.,* 2001) or freeze drying (Craig *et al*., 1999*)*. The quench cooling technique can also be applied, but it is not preferred as pharmaceuticals frequently decompose near or at melting point (Saunders & Gabbot, 2011).

Although many techniques are employed to render a substance fully or partially amorphous, most texts refer to the method of rapidly cooling of the melt. Figure 1.10 illustrates the fundamental differences between the formation of the crystalline and the amorphous form (Hancock & Zografi, 1997; Craig *et al*., 1999).

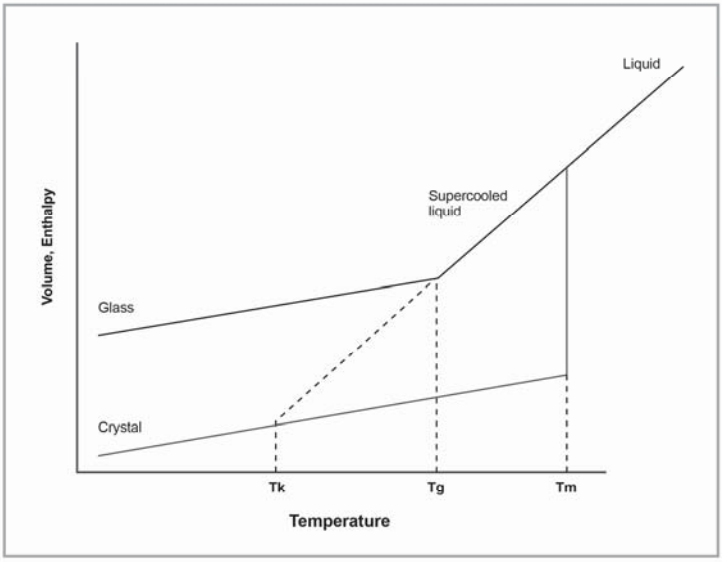

Figure 1.10 Schematic illustration of the change in volume or enthalpy with temperature for a material undergoing crystallisation or a glass transition (Adapted from Hancock & Zografi, 1997).

Temperature decrease of the liquid form of a crystalline substance to the melting point (T_m), without supercooling, will result in a transition to the crystalline state. The temperature region below T_m is considered to be the thermodynamically stable state regarding non-crystalline substances. An exothermic transition occurs as a result of the decrease in both specific volume and enthalpy (H), caused by the sudden contraction (with the exception of water) of the system and decrease in free volume associated with crystallisation (Craig *et al*., 1999; Hancock & Zografi, 1997).

For glass-forming materials, the cooling process is too fast for crystallisation to occur. This is either ascribed to the unfavourable circumstances created due to the molecular size and shape or the rapid cooling rate. Cooling below T_m of the material causes no discontinuity in enthalpy or volume, instead the system forms a supercooled liquid (Craig *et al*., 1999).

Upon further cooling, a point is reached where the material becomes "frozen" into the glassy state. Hence, a defining characteristic of the glassy state is the lack of translational and rotational motions, with primarily vibrational motions taking place below the glass transition (T_g). However, bonding between the molecules remains essentially the same with reference to the liquid state (Craig *et al*., 1999).

Amorphous substances lack the abrupt discontinuity that occurs at the melting point of the substance if represented by a time vs. temperature plot (Giron, 2001). Instead, a step in the heat capacity, which is a derivative of enthalpy with respect to temperature ($(\partial H/\partial T)_p$) signals the glass transition temperature. Therefore the transition is dependent on molecular mobility with no associated heat transfer for the process (Craig *et al*., 1999).

The glass transition temperature varies depending on the rate of cooling, with slower cooling rates, resulting in a lower value for T_g, as indicated by figure 1.10. Slower rates give molecules more time to pack efficiently which leads to a lower T_g. As mentioned, at temperatures below the glass transition temperature (T_g) the molecules of the substance are configurationally solidified, whilst in the temperature range above T_g the behaviour of the substance resembles that of elastomers, displaying a certain degree of flow called the rubbery state (Heng & Williams, 2011).

The term glass and amorphous material are often used interchangeably, which is quite confusing if one wants to distinguish it from a supercooled and a normal liquid. In fact, all three can be classified as amorphous, which means that they all lack the long-range order found in crystals and they all lack sharp peaks (distinct "halo" pattern) when compared by means of XRPD analysis (Ymén, 2011).

1.6.2 The measurement of T_g bydifferential scanning calorimetry (DSC)

There are a number of available methods by which the glass transition temperature may be studied, but for purposes of this study the focus will be on thermal methods and more specifically DSC. This technique provides the simplest way of determining the T_g, by measuring the change in heat capacity associated with this transition (Craig *et al*., 1999).

Figure 1.11 represents an idealised sketch of a typical glass transition, with the response to the heat signal expressed in terms of the heat capacity changes. The T_g is the temperature at which the heat capacity is midway between the liquid and the glassy state (Wunderlich, 1990). It is determined by extrapolation of the C_p (or power) plots for the glass and the liquid/rubber state, with T_g given as the midpoint between the two lines. T_b denotes the beginning of the transition, whereas the extrapolated onset temperature is T_1. Similarly, T_2 denotes the extrapolated endpoint and T_e represents the end of the transition. The use of parameters such as T_b and T_e may be limited in practice because of the problems associated with defining the beginning and the end of this transition. An important observation is that the value of T_g varies with the cooling and the heating rate. As illustrated by figure 1.11 a faster cooling rate will produce a higher value of T_g than with slower rates (Richardson & Savill, 1975).

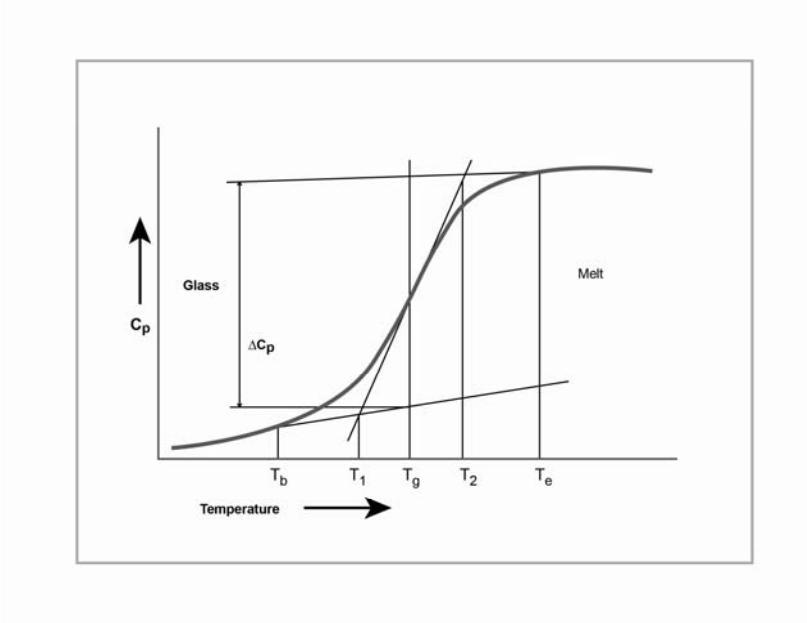

Figure1.11 Schematic representation of the change in heat capacity through the glass transition, indicating the various parameters that may be used to express the glass transitional behaviour (Adapted from Wunderlich, 1990).

Therefore the development of quality control tests often presents a formidable challenge, as contrary to the melting point which is independent on the heating rate, the T_g varies depending on the method of measurement as it is a reaction to a heating or cooling signal (Craig *et al*., 1999).

This difficulty may be overcome by using the fictional temperature T_f, which indicates the temperatures where the extrapolated enthalpies above and below the T_g are equal. Because the T_g is a kinetic event, it is highly dependent on the heating and cooling setting of the temperature programme. The true measurement of T_g is however only dependent on the condition under which formation occurs i.e. cooling in the case of quenching. The DSC technique is a dynamic technique constituting the experimental differences caused by the heating rate. Consequently analysis will give a dynamic glass transition, with the possibility of leading to experimental and molecular timescale differences. This value will therefore not be the 'true" value of T_g but a dynamic glass transition dependent on heating rate. The measurement of the fictional temperature was suggested by Richardson and Savill (1975) to rule out this problem. Employing this parameter could be useful in establishing reproducible quality control protocols (Craig *et al*., 1999).

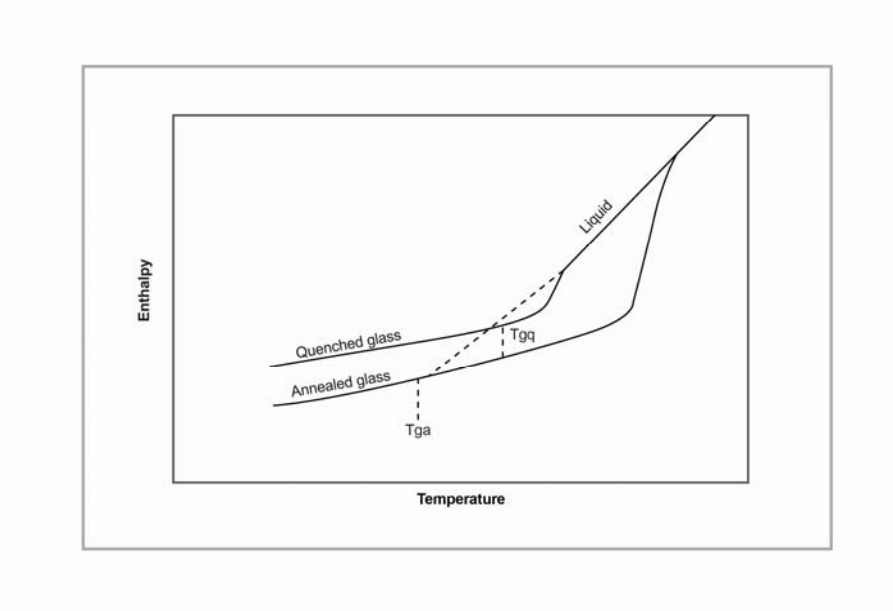

Figure 1.12 Schematic representation of the fictional temperature, showing the extrapolation of the enthalpy curves below and above T_g for a quenched (T_{gq}) and the annealed (T_{ga}) glass (Adapted from Richardson and Savill, 1975).

Another problem with measurement of the T_g is the presence of relaxation endotherms, which can be seen on the thermogram as a shift on the baseline, rendering the value of T_g very difficult to quantify. Especially for multicomponent or complex structures, it may be extremely difficult to differentiate between the melting point and the glass transition temperature (Craig *et al*., 1999).

The relaxation endotherm may be a result of two different processes. Firstly, a mismatch between the heating and cooling rate i.e. a slow cooling rate and a fast heating rate. A higher heating rate causes the material to overheat briefly because molecules of the glass cannot achieve the motion needed for glass transition within the timescale of the experimental heating rate (Wunderlich, 1990). The superheated glass will revert back to the liquid line in the enthalpy curve once relaxation times lower to the order of the heating rate. This is observed as an overshoot and subsequent recovery in the baseline of the enthalpy curve and displays a characteristic endothermic peak on the C_p curve. Another reason is that glasses are not in thermodynamic equilibrium and structural relaxation may occur over time. This causes the enthalpy and volume of the material to decrease, and could also produce the relaxation endotherm, for the same reasons as above (Craig *et al*., 1999).

Controlling the thermal history of a product could provide a solution to this problem. This normally involves a heating and subsequent cooling run which removes some annealing effects. For certain components this might not be the most suitable option as heating could cause irreversible changes to the material. Alternate approaches involve the use of a modulated DSC. It has a significant advantage over the conventional DSC as it allows the separate view of the relaxation endotherm and the glass transition (Craig *et al*., 1999).

Consistency regarding the preparation of a sample is of the utmost importance, if experimental reproducibility is to be achieved. This particularly relates to the type of pan and residual solvent present in the sample (Craig *et al*., 1999). It is also preferable to conduct T_g measurements on cooling cycles, for the liquid sample is in equilibrium whereas the amorphous sample is in a non-equilibrium state at the beginning of the experiment. This explains the lack of reproducibility of the glass heating cycle when compared to the cooling cycle. As pointed out though, complex substances such as freeze-dried systems might not be able to withstand a heating cycle and hence they are not suitable candidates for this method of standardisation (Wunderlich, 1990).

1.6.3 The effect of plasticisers on the value of T_g

The addition of plasticisers or guest molecules (for example moisture sorption during storage at elevated relative humidities) into the matrix can have a detrimental effect on the stability of an amorphous pharmaceutical product as it lowers the T_g. Plasticisers are small molecules that act as an impurity by embedding themselves between the molecules of the amorphous substance. This has serious implications for an amorphous product, as storage above the

T_g may increase molecular mobility and the crystallisation potential of the amorphous substance (Saunders & Gabbot, 2011; Reutzel-Edens & Newman, 2006). This accelerated conversion to the crystalline form, can be explained by the Gordon-Taylor equation (Giron, 2001):

$$T_g = w_1 T_{g1} + K w_2 T_{g2} / w_1 + K w_2$$

Relative to the crystalline state, amorphous materials are considerably more hygroscopic (Hancock & Zografi, 1997). This tendency is mostly due to the absorption of water into the solid with the determining factor being the sample mass rather than the dependence on surface area as seen in crystalline materials. According to the Gordon-Taylor equation, the increase in the water concentration leads to the lowering of T_g. Therefore, at any given temperature, water uptake could cause a glass to convert to the rubbery state, with major implications on stability and detrivication (Craig *et al*., 1999).

1.6.4 Structural heterogeneity and relaxation of amorphous materials

One of the most significant features of the amorphous sub-phase is the fact that some molecules may have higher energy levels than others and therefore lack the uniformity of their crystalline counterparts (Shamblin *et al.,* 2000). As a result some molecules appear to be less stable than the bulk average, having a substandard physical and chemical stability. Therefore it is logical that the normal characterisation techniques that aim to detect various bulk properties of a substance will not sufficiently project the physical stability of an amorphous system. These characterisation techniques include the use of spectroscopic, thermal and other modern characterisation methods (Cui, 2007).

As discussed in paragraph 1.2.1, a variation of the cooling rate causes molecules to redistribute along different positions in an energy landscape. A slower quenching rate allows for the redistribution to energy minima, lowering the overall potential energy of the amorphous system, whereas faster quenching allows less time for this redistribution to take place and the subsequent amorphous system presents with higher overall potential energy. Other techniques may also be applied to generate this kind of result which leads to the

conclusion that the obtained energy levels of the amorphous state are in fact process dependent (Cui, 2007).

In figure 1.3C, we see that the molecules of a substance may be distributed over a range of molecular coordinations, each presenting its own potential energy, some with higher energy values than others. Over time, these higher energy level molecules may redistribute to the coordinations with lower potential energy values through molecular movements. This process of gradually lowering energy levels of the amorphous system is called structural relaxation. Over time, as indicated by the arrows in figure 1.3C, molecules will redistribute towards the energy minima denoted as glass I and II. In the process, the amorphous system's energy level starts decreasing, through continuous release in the form of heat until the system ultimately falls into the energy megabasins (glass I or II). As the energy of the system slowly decreases, the molecular movements will also gradually slow down. It is therefore safe to say that the amorphous structure is constantly changing, and altering its energy levels. Bearing this in mind, the structure of an amorphous system and the energy levels are said to be "process and time dependent" (Cui, 2007).

1.7 Conclusion

"In fact the whole existence of a drug is affected by the properties of the solid form, and the final goal of solid form development is to find and select the solid with the optimal characteristics for intended use" (Hilfiker *et al.*,2006).

To find the desired drug for incorporation into the solid form, one will have to scrutinise all aspects relating to thermodynamics and kinetics before a satisfactory and reproducible form can be obtained. Preliminary investigations of solid-state behaviour, especially in the research phase are increasingly being done for better understanding of successful formulation and subsequent delivery of an API. An integrated approach for identifying the optimal solid form for intended use is therefore needed to make successful predictions on solid-state behaviour and product life cycle management. A particularly useful way of generating this kind of information is to study the energy-temperature diagrams of polymorphs to determine stability aspects of the obtained forms (Hilfiker *et al*., 2006).

The enumeration of all possible solid forms of an API, especially in the developmental stages can add significant value to product life cycle management, and in addition create intellectual property opportunities for companies (Florence, 2009).