

Chapter 1

Theory and principles of the solid-state properties of pharmaceuticals

1.1 Introduction

All matter that occupies space and has mass consists of atoms, which in turn form molecules of varying size and composition. These atoms or molecules exist in phases of either gas, liquid or solid. On a macroscopic level molecules exist in the form of phases. An understanding of phases is considered fundamental to the field of pharmaceutical sciences. The phase present under specific conditions is dependent on factors including temperature and pressure. The different ways in which molecules link with each other will lead to differences in their orientation as well as differences in intermolecular distances. Ultimately these differences will lead to different phases with different energy levels (Cui, 2007).

The solid phase is the most common phase within the pharmaceutical industry. It is a well-known fact that the solid phase can present in a multitude of forms. In other words, although consisting of the same atomic or molecular composition, a given compound can exhibit an array of different packing conformations and subsequently have very different internal structures. It is this occurrence that can give a solid form different physical and chemical properties (Cui, 2007).

The solid phase is a collective term for two major differences in terms of molecular packing and it is considered imperative to distinguish between the two subphases of the solid phase. The first being the crystalline form. This form is well-known and is identified by the aggregation of the molecules in a definitive order. The crystalline form not only exhibits short-range order of molecules but also long-range order. The other subphase is the amorphous form, which presents only with short-range order.

Solid-state chemistry is the main focus in this study, though not at all the only focus point, as described by Byrn (1982), is a very broad branch of science encompassing such areas as physical pharmacy, industrial pharmacy and includes molecular aspects of solid-state reactions, kinetics of these reactions and stability of solids.

From the fact that the study of the solid-state properties of active pharmaceutical compounds encompasses such a wide array of aspects, it is considered important to

give some background information before discussing the solid-state and polymorphism as a research field. Therefore, the terms used to describe these different forms that solids can be found in as well as the principles governing them, will be described in this chapter.

1.2 Background information

1.2.1 Phases and forces

Of the forces involved in forming solids the strongest are intramolecular forces known as covalent bonds. These bonds hold the atoms together that form the molecules. On the other hand, intermolecular forces can be classified as hydrogen, Van der Waals and electrostatic forces. In general, hydrogen bonding is considered the strongest intermolecular force (Byrn *et al.*, 1999).

A phase is defined by Findlay (1938) as any part of a system that is disconnected from the rest of the system by a boundary, is physically dissimilar from the other parts in the system and is homogenous.

If this definition is considered, one will find that for any substance there can only exist one gaseous phase and one liquid phase, because these will each be disconnected from the other parts of the system, will be homogenous and physically dissimilar from other parts in the system. However, the case of solids is somewhat different since solids can consist of more than one crystalline form and each of these should be an individual phase as they are not homogenous, are physically dissimilar and are most probably separated by a distinctive boundary. An example of this is the various crystal forms of ice (Glasstone, 1948).

If one considers a solid that consists of a mixture of two polymorphic forms (see section 1.3), it contains two phases, but if there is only one homogenous form, it is one phase. This becomes quite tricky because now one has to regard the term homogenous (i.e. uniform throughout) within the confines of the molecular structure and also consider which dimensions will be used. This idea of being uniform throughout will be more difficult to define with ease when one reaches the molecular level (Bernstein, 2002). This is especially true for amorphous substances (see section 1.4.2).

The boundaries between phases mentioned earlier are interrelated with the scale at which one observes a phase. This is true because of the homogeneity that can be observed macroscopically when for instance, one looks at a solution consisting of two different molecules. At a macroscopic level above micrometers in this case, the whole looks like one phase, that of a liquid. When looking closer though, at the level of molecules, one will find either one molecule or the other. This makes the solution look much less homogenous. To resolve this, one should mention at what scale one is referring to when using phases as boundaries. For this reason terms like microphases or nanophases are sometimes used, but not without causing some confusion (Cui, 2007).

A liquid can have slight differences in density within itself and even a gas may contain regions with collisions happening more frequently than within others. This makes the term 'homogenous' when considering a phase seem a bit confusing, but this heterogeneity existing within a phase is important to keep in mind when one tries to explain the ambiguous phase known as the amorphous phase (see section 1.4.2) (Aasland & McMillan, 1994).

The phase rule

The phase rule is simply stated as:

$$F = C - P + 2 \quad \text{(Equation 1.1)}$$

Where F is the number of degrees of freedom of the system, C is the number of components, and P the number of phases of a system in equilibrium (Glasstone, 1948).

The number of components is the number of independently variable constituents or independent species that can define all the various phases in a system that is in equilibrium. Water can be used as an example where there can exist solid, liquid and vapour phases all of which consisting of the same water molecules and are thus considered to be one component (Bernstein, 2002).

The number of degrees of freedom or variance is the number of variable factors in a system that needs to be made constant for the condition of the system at equilibrium to be defined. These factors include pressure, temperature, concentration, etc. If for instance there is only one phase and one component in a system as in the case of a

gas, there will exist two degrees of freedom. For a system with one component and two phases there will exist one degree of freedom as in the case of a gas and a liquid. If there is only one component and three phases no degrees of freedom will exist, as is the case for water at the well-known triple point (Bernstein, 2002).

The relevance of having knowledge of phases and the practical importance thereof within the pharmaceutical industry lies within the fact that phases exist with different intermolecular distances and molecular orientations that almost always lead to different energy levels. The difference in energy levels can possibly create pharmaceutically relevant differences in the physico-chemical properties of active pharmaceutical ingredients (APIs). These physico-chemical properties include the solubility and stability of substances and can possibly affect other properties such as bioavailability (Cui, 2007).

The most important aspect to realise here is that no destruction or alteration of the molecules themselves is necessary (covalent bonds are not broken) for phase transitions to take place. This means that by altering the phase in which molecules are found, one can change the physico-chemical properties of substances without altering their pharmacological effects, unlocking seemingly endless possibilities in the field of pharmaceutical research (Cui, 2007). Figure 1.1 displays the summarised general differences of intermolecular distance, molecular motion, order of molecular packing, and potential energy states between the various phases.

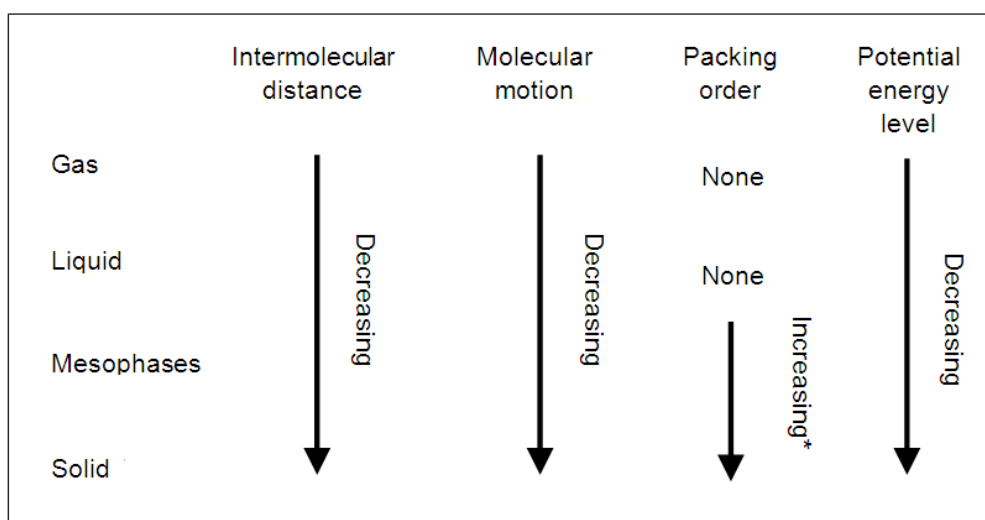


Figure 1.1 Differences among the common phases. *In this figure the solid phase refers only to crystalline solids, because amorphous solids lack long-range order (Adapted from Cui, 2007).

The molecular motions mentioned here can be grouped into large-amplitude molecular motions, consisting of rotational, translational and conformational motions and small-amplitude molecular motions which consist of vibrational motion. All three of these large-amplitude motions can be found in gases and liquids, but in crystalline solids only the small-amplitude vibrational motions occur. The presence or absence of these large-scale motions (relative to the scale of molecular movements) can be used to categorise phases (Cui, 2007).

The potential energy level is thus a consequence of the combination of all the following factors: intermolecular distance, molecular motion and packing order (Cui, 2007).

1.2.2 Solid-state reactions

In this section the focus will be on the reactions that take place within the solid-state. These reactions can be used to explain such phenomena as phase transformations, polymorphic transformations, desolvation and others.

As stated by Galway and Craig (2007) the Arrhenius equation (Equation 1.2) is well-known or more importantly by and large accepted to adequately represent reactions in crystals adequately. This can, however, complicate things when the assumption is made that the absolute reaction rate theory can be used to explain solid-state reactions and that the reactions happen through a transition state of this nature or by means of an activated complex. This model is based on the theory that interactions or collisions between precursor molecules, that move about at random, are the cause for chemical changes to take place. This theory obviously cannot fit the reactions taking place within a crystal because the precursor molecules are in a static condition.

It makes more sense to explain the reaction by making use of the theory that the precursor molecules or atoms are in the immediate vicinity of one another or what is described by Galway & Craig (2007) as a contact zone of heightened reactivity that serves as an interface between the reactants for the reaction to take place. It is here that chemical changes take place and events such as crystal growth can occur (see section 1.3.2).

1.2.3 Energy landscapes

An elegant way to explain the state of potential energy or free energy found in substances is by making use of what is called energy landscapes. Energy landscapes are a depiction of potential energy plotted in the y-axis against molecular coordination plotted in the x-axis (Figure 1.2. is an example) (Cui, 2007).

The potential energy as mentioned earlier is influenced by the intermolecular distance and packing order of molecules. These factors can be represented by molecular coordinations consisting of position, orientation and conformation of molecules. Molecular positions represent the intermolecular distances while molecular coordinations represent the packing order of molecules (Cui, 2007).

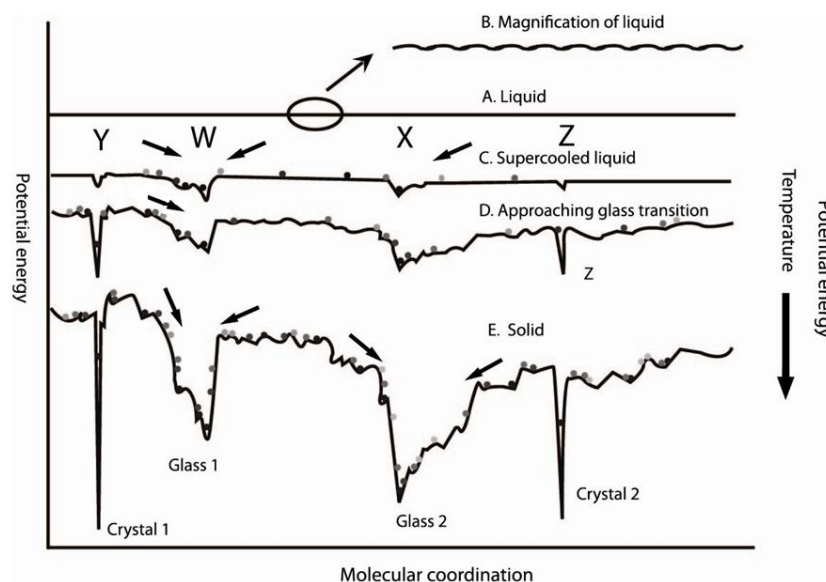


Figure 1.2 Representation of an energy landscape of liquid and solid phases that shows the dynamic rearrangement of possible molecular coordinations. (A) Liquid phase at higher temperature at which the changes of energy with differences in molecular coordination is slight; (B) magnified view of liquid, in which it is possible to see the slight energy changes; (C) the liquid is supercooled at this temperature, which is slightly below the melting point. Energy basins can be seen here as a result of heterogeneity; (D) deeply supercooled liquid at a temperature approaching the glass transition temperature. The sharp dips (Y and Z) represent crystal forming coordinations and are much deeper when compared to the energy basins (W and X), as a result of their higher stability and they represent thermodynamically more favourable molecular coordinations; (E) solid states. The sharp dips represent

crystalline polymorphs and broad basins represent amorphous states. The darker dots represent the coordinations that will be found and the lighter dots represent the dynamic redistribution of the coordinations by moving across the energy landscape as the result of interactions and changes in energy levels. The arrows show the directions these dots (favoured coordinations) will tend to move in, as the downhill of the energy landscape. The dots redistribute to the dips but can move out of the shallower basins X and W by structural relaxation. If the temperature of the system is decreased, the dips become deeper and redistribution will not take place as easily. If the temperature is very low the dots will stay in the dips and redistribution will not take place (E). If the temperature is increased though (E to D and D to C) the dots will be able to redistribute, but this will occur with greater ease from the shallower dips of Glass 1 and 2 than from the deeper dips of crystal 1 and 2 depicting the relaxation from a glass form compared to the phase transformations of crystalline solids (Adapted from Cui, 2007).

Considering all abovementioned facts it is clear that the science involving the solid-state of compounds is vast and that pharmaceutical scientists should consider numerous factors during research and development phases. Figure 1.3 provides a diagram that describes the field of solid-state in a simplistic manner.

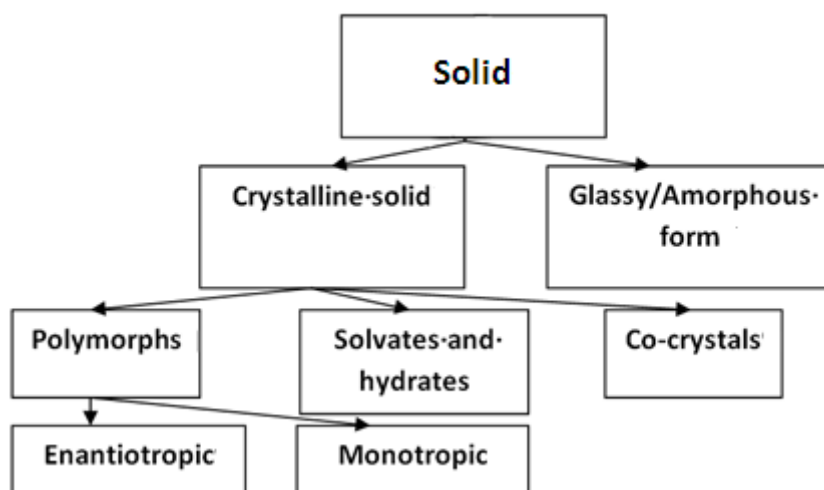


Figure 1.3 Schematic representation of the various solid-states.

The next section of this chapter will discuss the various facets of the solid-state of pharmaceutical ingredients in detail.

1.2.4 Thermodynamics and kinetics

The well-known Arrhenius equation is used to describe kinetic behaviour resulting from temperature changes and given here is a common form of this equation:

$$k = Ae^{-Ea/RT} \quad (\text{Equation 1.2})$$

where k is the specific reaction rate, A is the constant known as Arrhenius factor/frequency factor, Ea is the activation energy, R is the gas constant, and T is absolute temperature (Martin, 1993).

This model represents a change in form from a less thermodynamically stable to a more stable form. In order for this change to occur an energy barrier must first be overcome. This energy barrier usually consists of kinetic factors and is termed the activation energy (Ea) and is overcome by means of an increase in what is known as Gibbs free energy (Craig & Reading, 2007).

To explain the free energy that exists in a solid phase a depiction can be made with the Helmholtz relationship

$$A = E - TS \quad (\text{Equation 1.3})$$

Where E is the internal energy, T the absolute temperature, and S the entropy (Bernstein, 2002).

E can be considered as isothermally available energy and TS as isothermally unavailable energy (Martin, 1993).

If one considers this system to be at absolute zero, TS will be zero as well. This would make the Helmholtz free energy equal to the internal energy of the solid. This implies that the solid will be in the most stable form at absolute zero (i.e. having the lowest possible internal energy). If, however, the temperature of this system is increased, the entropy caused by various modifications and polymorphic forms will influence the free energy. This means that various modifications will alter the free energy when considered as a function of temperature. This influence on the free energy by different polymorphic forms is represented by the curves A_I and A_{II} in Figure 1.4 (Bernstein, 2002).

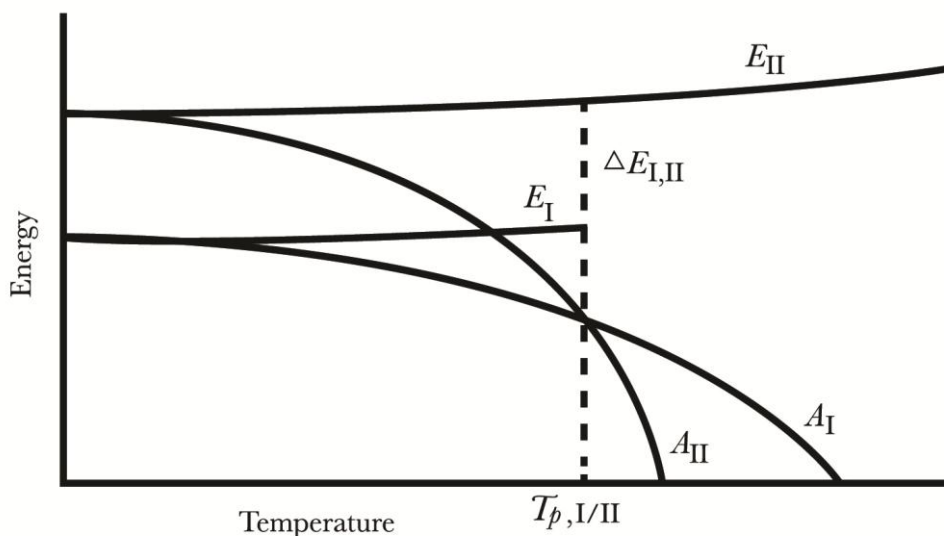


Figure 1.4 Diagram showing energy versus temperature curves for two polymorphs I and II. A is the Helmholtz free energy and E is the internal energy. Form I is assumed to be the stable form at room temperature (Adapted from Bernstein, 2002).

Here the endothermic energy needed for a phase transition to occur (i.e. activation energy) can be seen. The two forms have different free energies at all temperatures except at the point where they cross. This is the transition temperature $T_{p,I/II}$. At this point they have equal free energies, but internal energies differ and it is this difference in internal energy ΔE that needs to be breached for the phase transition to occur (Bernstein, 2002).

Gibbs free energy:

$$G = H - TS \quad (\text{Equation 1.4})$$

In this case E is replaced by the enthalpy H, and A is replaced by G, the Gibbs free energy.

The diagrams based on the Gibbs free energy are popular because it summarises a lot of information on the interrelationships of various polymorphic forms in a single graph. An example of one of these energy versus temperature graphs can be seen in Figure 1.5 (Bernstein, 2002).

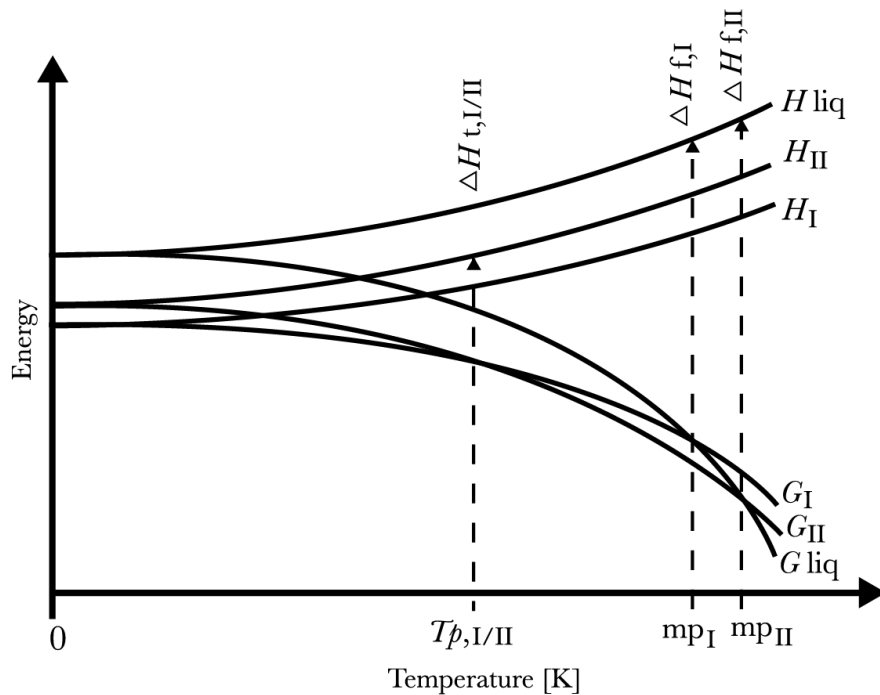


Figure 1.5 Energy versus temperature diagram of a dimorphic system. G represents the Gibbs free energy and H the enthalpy. This diagram depicts an enantiotropic system, where form I is the stable form below the transition temperature (Adapted from Bernstein, 2002).

If one compares Figures 1.4 and 1.5 there are two extra curves, that of the H_{liq} curve which can be found above the two solid curves (H_I and H_{II}), and the G_{liq} curve. If one can determine the heat capacity (C_p) at constant pressure, it is possible to create an H versus temperature diagram and vice versa. This is done by making use of

$$\left(\frac{\delta H}{\delta T}\right)_p = C_p \quad \text{(Equation 1.5)}$$

This fundamental relationship in equation 1.5 of the heat capacity and enthalpy is shown in Figure 1.6. In this plot one can see that the heat capacity of an ideal crystal at 0 K will be zero as is described by the third law of thermodynamics (the crystal must show the greatest orderliness at this temperature) as seen in the slope (Bernstein, 2002).

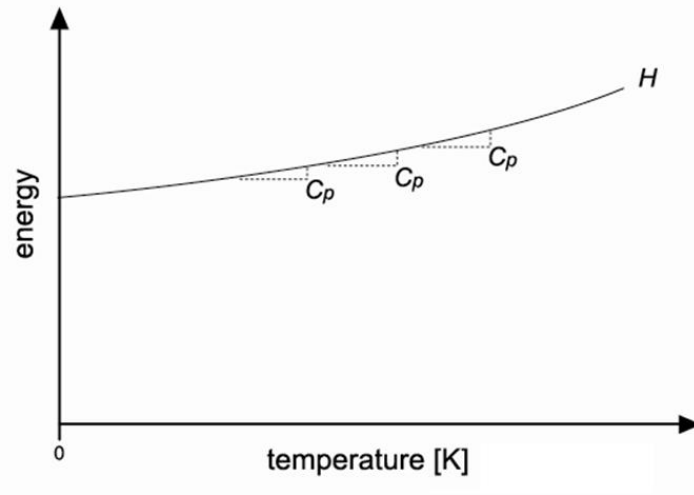


Figure 1.6 Energy versus temperature diagram displaying the relationship between heat capacity (C_p) and enthalpy (H) (Adapted from Bernstein, 2002).

When looking at the Gibbs free energy in relation to temperature a partial derivative at constant pressure can be written as follows:

$$\left(\frac{\delta G}{\delta T}\right)_p = -S \quad \text{(Equation 1.6)}$$

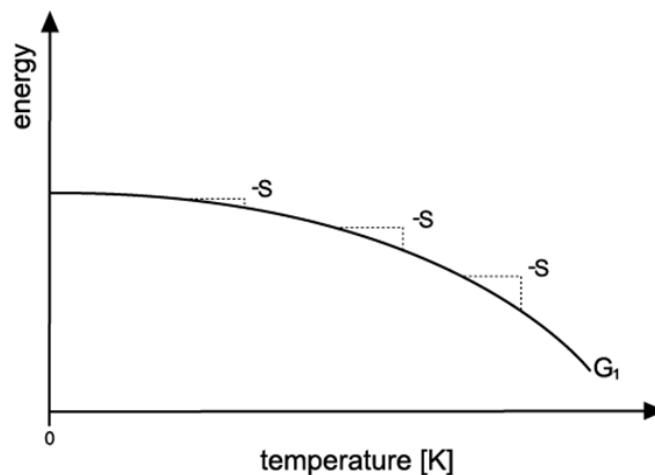


Figure 1.7 An energy temperature diagram that depicts the course of a G-isobar where S is entropy (Adapted from Grunenberg *et al.*, 1996).

From Figure 1.7 one can see that S will always be positive and G will persistently decrease, where intersections of the G isobars in Figure 1.5 represent phase transition points (Bernstein, 2002).

This, as described by Ymén (2011), shows that kinetics will be the determining factor in the phase of a substance and not thermodynamics in the instance where a metastable form does exist. A metastable form is known as a substance that is not the most stable form, but to reach a stable form the activation energy must first be reached for the transformation to take place (this is explained in more detail in section 1.3.2.1).

Activation energy can be increased though, when phase transitions are driven at a rate that will lead to the super-cooling or super-heating of the substance. This shows that activation energy is not a constant. The example used by Ymén (2011) is that of a solution being evaporated very rapidly so that crowding appears. In this instance the molecules might be too close together for the conformations that would have occurred at lower rates of evaporation to take place and would not be packed in the same way in the crystal lattice. This leads to an increased activation energy and can even lead to the formation of a glass (Ymén, 2011).

For a stable form to change into a metastable form it has to go through the liquid state, as in the case of a solution, melt or vapour state as is the case in recrystallisation from solution, quench cooling a melt or sublimation recrystallisation/vapour deposition respectively (See sections 1.5, 1.6 and 3.3) (Griesser & Stowell, 2003).

Enthalpy/ heat content

Stated in a basic way enthalpy (H) is a degree of bonding measured in the bound state of molecules, be it for a liquid, gas or a solid. This study focuses mainly on the solid-state, so enthalpy will be explained by making use of a description in this state. A consequence of increasing temperature in a solid is the corresponding increase in volume of the unit cell (see section 1.4.1.2 and Figure 1.16). This inevitably leads to a decrease in bond strength between molecules that will be directly proportional to the increase in temperature. This proportionality is, however, broken when phase transitions occur. Phase transitions cause jumps because of bonds being broken or weakened and is termed latent heats of transition (Ymén, 2011).

Gibbs free energy (G) is a term that combines entropy and enthalpy to explain phase transitions.

A process in which a phase transition occurs from state 1 to state 2 at constant temperature is defined by the following equation:

$$\Delta G = G_2 - G_1 = \Delta H - T\Delta S \quad (\text{Equation 1.7})$$

This equation shows how enthalpy drives a system to equilibrium by tending to reach a minimum value whereas entropy drives a system to equilibrium by tending to reach a maximum. For a system that is not in equilibrium without a change in temperature or pressure, a spontaneous transformation to a system in equilibrium can only be reached when the transformation results in a negative value for ΔG . Stated differently at equilibrium $\Delta G = 0$ and for a spontaneous transformation to occur $\Delta G < 0$ (Ymén, 2011).

Entropy

Entropy (ΔS) is a term for the disorder or randomness in a system and is measured in J/degree. At a temperature of 0 K there should be no entropy and the entropy will increase with an increase in disorder. If temperature, pressure and the Gibbs free energy remain constant a phase transition can be described by the following equation:

$$\Delta S = \Delta H/T \quad (\text{Equation 1.8})$$

This shows that an increase in enthalpy or rather an uptake of heat when going from the low temperature to the high temperature phase will be precisely matched by an increase in entropy. If, however, the temperature does not stay constant, the randomness or rather the accessible number of energy states in a system (as a result of various modifications of molecules etc.) will increase with an increase in temperature. This means that an increase in temperature will increase the entropy in the system (Ymén, 2011).

The total entropy is thus mainly influenced by the thermal motion of atoms (dynamic disorder) and the amount of molecules that can be found in what is referred to by Ymén as, (2011) “erroneous lattice positions” (static disorder) (Ymén, 2011).

The order of phase transitions

Before discussing the different kinds of phase transitions that are possible it is important to note that when considering the solid-state, kinetics can be much more difficult to describe than when considering the matching liquid reactions. These

kinetics are also regularly only partly of one order and partly of a different order and makes it difficult to place them as either zero-order, first order, etc. (Byrn, 1982).

Different kinds of phase transitions can occur and the first transition to be explained is called a first-order phase transition. A first order phase transition is defined by Reading and Craig (2007) as a process whereby the derivative of the change in Gibbs free energy (ΔG) with respect to temperature (T) is not equal to zero, i.e.,

$$(\delta\Delta G/\delta T) \neq 0 \quad \text{(Equation 1.9)}$$

There is thus a change in temperature dependence of free energy that happens during this change in state from solid to liquid.

$$(\delta\Delta G/\delta T) = (-\Delta S) \neq 0 \quad \text{(Equation 1.10)}$$

What this implies is that in first order transitions, the transition takes place at a specific temperature that is not influenced by the rate of cooling or heating. Melting is an example of a first order phase transition which is frequently studied by means of DSC which will be discussed later (See section 2.2.1) (Reading & Craig, 2007).

When looking at this process of melting from a thermodynamics perspective, it can be seen as the change in Gibbs free energy being zero at the point of melting because of an increase in both enthalpy and entropy. The event of melting will take place if the Gibbs free energy for the liquid phase is lower than the Gibbs free energy for the solid phase of the material, leading to the spontaneous phase transition (Saunders & Gabbott, 2011).

Heat capacity

Heat capacity can be explained by making use of a theoretical DSC run (see section 2.2.1). When the experimental temperature is running below which any thermal events take place in the sample being investigated, the heat flow or energy needed for the temperature in the sample to be increased to a value equal to that of the temperature increase brought about by the heating program, can be plotted as a baseline. This is called the heat capacity (C_p) of the sample. The energy needed to increase the temperature of the sample by 1K is denoted by this parameter. It can be written as the following equation

$$dQ/dt = C_p \cdot dT/dt \quad \text{(Equation 1.11)}$$

where dQ/dt is the heat flow and dT/dt is the heating rate. (This equation appears again in section 2.2.1 as equation 2.2 but is used there to explain the principles of DSC) (Reading & Craig, 2007).

At this point one should note that the heat capacity of the system is directly related to the baseline. When, however, a thermal event occurs, this direct relationship between the baseline and the heat capacity is reshaped as a result of the latent heat tied to events such as melting, crystallisation, glass transition, etc. which can be identified by a shift in baseline or a peak on the DSC run (See section 2.2.1) (Craig, 2006).

A second-order phase transition is defined by Reading and Craig (2007) as a process whereby the derivative of the change in free energy is zero but the second order derivative is non-zero, i.e.,

$$(\partial^2 \Delta G / \partial T^2) = (-\Delta C_p / T) \neq 0 \quad (\text{Equation 1.12})$$

Here the transition is a step change in the heat capacity of the sample as a function of temperature.

Second-order transitions are difficult to see with regular optic methods and this is also why in some texts the term pseudopolymorph is used. The birefringence (see section 2.3.2) of these crystals will change though, when this transition takes place and makes it possible to view by means of crossed polarisers (see section 2.3.3) (Bernstein, 2002).

Glass transition (T_g) (see section 1.4.2.4) is usually reckoned to be an example of a second-order phase transition. Though when considering the definition it does not completely fit, because T_g is a piecemeal transition taking place over a range of 10 degrees or more and is a kinetic event of which the position will shift depending on the rate of heating or cooling (Reading & Craig, 2007).

1.3 Polymorphism

The term polymorphism, from the Greek words “poly” meaning many and “morph” meaning form, is used to indicate the diversity that can be found in nature. Finding a definition for polymorphism that is all-inclusive and everyone can agree on, like many terms in chemistry, would be very difficult. Stated very simply in chemistry specifically, the term is used for the occurrence of at least two different possible

arrangements of solid-state crystal structures from the same molecule (Bernstein, 2002). As stated by Saunders and Gabbott (2011) the term allotropy is used when describing packing variations that occur in elemental solids such as the packing of carbon to form graphite as well as diamonds. Polymorphism is related to allotropy but in this case instead of elements being packed in different ways, it is molecules.

1.3.1 Structural origin of polymorphism

The mechanisms that alter crystal structures and lead to polymorphs are packing polymorphism and conformational polymorphism. Packing polymorphism describes the mechanism where molecules are packed in three-dimensional structures without conformational alterations taking place, where conformational polymorphism explains the packing when conformational alterations do take place. If, however, different isomers such as geometric isomers or tautomers crystallise and result in the formation of different polymorphs, the term configurational polymorphism is used. This is not considered to be actual polymorphism, seeing as though the molecules involved are not exactly the same. A clear distinction can sometimes be difficult to make between conformational and packing-polymorphism because of various conformations with the same crystal lattice or the same conformation with different lattices. It is thus most often the case in organic molecules that polymorphism is a combination of conformation and packing arrangements (Lohani & Grant, 2006).

Ymén (2011) states that if the molecule is very rigid chances are the packing of the molecule is the only difference between polymorphs. If, however, the molecule is more flexible, conformational variations can occur that will most probably cause variations in packing therefore creating different polymorphs as a result of the combination of these factors.

As was explained in the previous paragraphs, polymorphic forms differ only in their supramolecular arrangement and not in their chemical composition. This means that they are thus indistinguishable when in liquid or vapour forms (Griesser & Stowell 2003).

The differences between polymorphs is, as described earlier, the various interactions between the molecules making up these crystal lattices namely the non-covalent interactions such as hydrogen bonds, Van der Waals forces, $\pi - \pi$ stacking, and electrostatic interactions (Lohani & Grant, 2006).

These non-covalent interactions play a key role in the way heat dissipates through the crystal lattices. This means that each polymorph, having a unique combination of interactions between its molecules comprising the crystal lattice, will have a unique and characteristic heat capacity (C_p) (see section 1.2.4) (Grunenberg *et al.*, 1996). This makes it possible for one to distinguish between different polymorphs by determining their different heat capacities.

1.3.2 Crystallisation of polymorphs

The process of crystallisation takes place in a combination of steps. These steps include nucleation, crystal growth and Ostwald ripening. The polymorph formed and its nature depends upon the nucleation and crystal growth from the solution (Lohani & Grant, 2006).

1.3.2.1 Kinetics versus thermodynamics of polymorph formation

To illustrate the energy involved in the formation/crystallisation of different polymorphic forms from a saturated solution, the traditional energy-reaction coordinate diagram (Figure 1.8) is used. In this figure one can see the changes in free energy starting from a highly saturated solution (G_0) and then crystallisation takes place resulting in two different crystal modifications where form I has the lower free energy ($G_{II} > G_I$) (i.e. is more stable) than form II. The peak in the figure represents the activation energy needed for this transformation to take place and is influenced by the rates of formation (Bernstein, 2002).

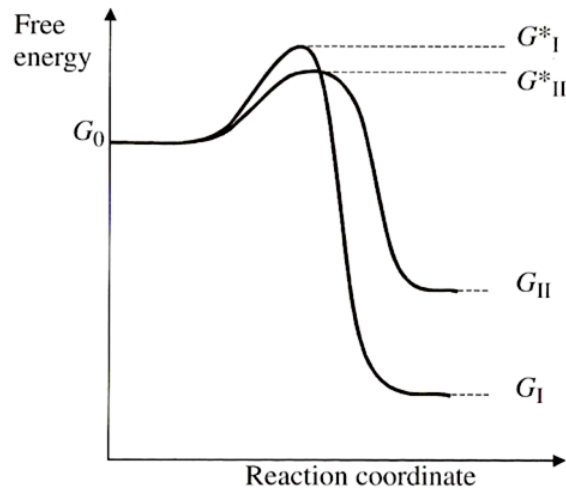


Figure 1.8 Scheme of the reaction coordinate for crystallisation in a dimorphic system, showing the activation barriers (*) for the formation of polymorphs I and II, where G is the Gibbs free energy (Adapted from Bernstein, 2002).

This activation energy is needed for nucleation to take place from which growth can follow. According to Bernstein (2002), the best model for predicting critical sizes of molecular assemblies is the kinetic theory of nucleation created by Volmer in 1939 (Volmer, 1939).

With this theory it is possible to determine the minimum size of a molecular assembly needed to obtain stability and from which growth can occur. It was also noted that the higher the saturation, the smaller this minimum would be. With this theory it was also made possible to predict which crystal modification would form under specific conditions. If various polymorphs were to form aggregates and nucleation took place at the same rates, the only factor influencing the probability of a polymorph forming would be the free energies existing in the various forms. This is, however, most often not the case and thermodynamic properties such as temperature, degree of supersaturation (i.e. a solution in which the amount of dissolved material exceeds the amount that will dissolve under the ambient conditions at which the system is held), etc. play a role in which polymorphic modifications would form (Bernstein, 2002).

The model created by Volmer accepts that for nucleation to occur, a critical cluster size (r_c) (with r being the mean radius of molecular assemblies) is needed. To determine the total free energy of a cluster (ΔG_{Total}) is to calculate the algebraic sum of a volume free energy term (ΔG_{Volume}) that drives the aggregation of molecules and

the surface free energy term ($\Delta G_{\text{Surface}}$) that drives the dissolution of molecular clusters (Lohani & Grant, 2006).

This is represented in equation 1.13:

$$\Delta G_{\text{Total}} = \Delta G_{\text{Surface}} + \Delta G_{\text{Volume}} = 4\pi r^2 \gamma + \left(\frac{-4\pi r^3 kT \ln \sigma}{3v} \right) \quad (\text{Equation 1.13})$$

$$\Delta G_c^* = \left[\frac{16\pi \gamma^2}{3(kT \ln \sigma)^2} \right] \quad (\text{Equation 1.14})$$

Where r is the mean radius of the cluster, k is Boltzmann's constant, T is absolute temperature, γ is the interfacial free energy between the nucleus and the super saturated solution, σ is the supersaturation ratio (the ratio of solute concentration in the super saturated solution to that in the saturated solution), v is the molecular volume, and ΔG_c^* is the free energy barrier to nucleation (Lohani & Grant, 2006).

When cluster formation begins and the critical cluster size is not yet reached ($r < r_c$), the clusters will tend to dissolve as the surface free energy will be stronger than the volume free energy. If the level of supersaturation is high enough though, cluster growth will be favoured as the necessary force to overcome the disruptive surface free energy will be provided by the supersaturation. As the crystal grows and eventually reaches the critical cluster size ($r = r_c$), a balance is reached between the surface and volume free energies. When this occurs the free energy of the cluster is at a maximum and at this point the activation free energy of nucleation is attained and from here crystal growth can take place.

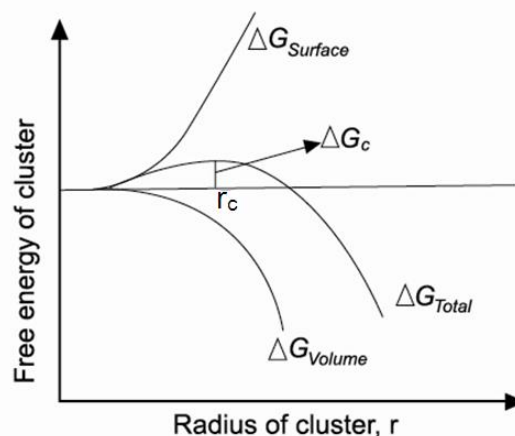


Figure 1.9 Plot to portray the changes in Gibbs free energy of clusters that occurs when molecular aggregation takes place that can result in nucleation. Where r is the mean radius of the cluster, r_c is the critical cluster size, ΔG_c^* is the free energy barrier

to nucleation, ΔG_{Total} is the total free energy of a cluster, ΔG_{Volume} is the volume free energy, $\Delta G_{\text{Surface}}$ is the surface free energy term (Lohani & Grant, 2006).

From equation 1.14 it is possible to see which factors influence crystal growth and how they influence it.

Not going into too much detail, one can see that it is impossible to predict the modifications that will form by either kinetics or thermodynamics, but that both play a major role and must be considered in creating polymorphs. Long before the nucleation theory though, as early as 1897 Ostwald had experimentally realised this and this can be seen in what is known as Ostwald's step rule (see section 1.3.2.3) (Bernstein, 2002).

1.3.2.2 Nucleation of polymorphs

From the previous section one should keep in mind that in a supersaturated solution, tiny nuclei also known as seeds can form from which crystal growth can take place. This is called nucleation and can be categorized into primary and secondary nucleation. The former takes place with the absence of any crystals in the solution and the latter takes place when crystals are already present either by accident or purposefully added to serve as seeds.

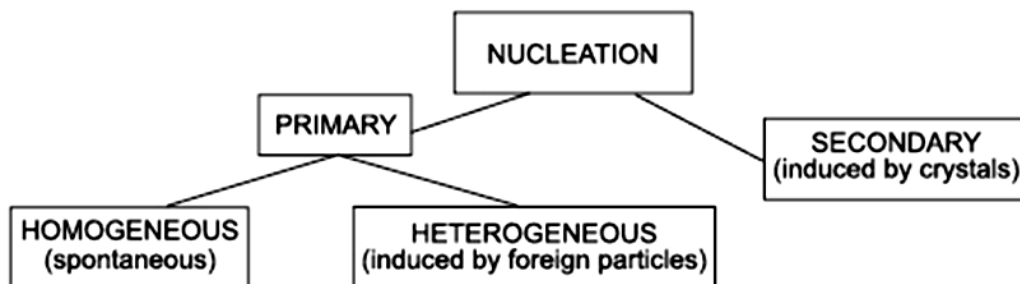


Figure 1.10 Diagram showing various nucleation pathways (Adapted from Bernstein, 2002).

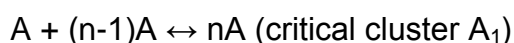
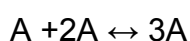
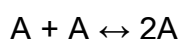
When primary nucleation spontaneously takes place in the bulk of a solution it is referred to as homogenous nucleation and when it takes place on surfaces of containers or foreign particles it is called heterogenous nucleation. Homogenous

nucleation is driven by the thermodynamic process of lowering the free energy of the system as was described in the previous section (Lohani & Grant, 2006).

Homogenous nucleation

Homogenous nucleation occurs because of molecules inside a homogenous supersaturated solution that move around freely and sometimes collide with one another. When these collisions occur it is possible for the molecules to bind by means of interactions between them. By the continued occurrence of these collisions and intermolecular bonding the bonded molecules will attach to more and more molecules and thus create a bigger cluster of molecules (r) (Ymén, 2011).

Bimolecular additions take place in steps as indicated below until a critical cluster is created from which nucleation can take place.



After this step nucleation can take place. These clusters A_1 to A_n can also be found in the starting conditions of systems such as solutions or melts. There will exist a constant competition of equilibria where each of these clusters are prospective polymorphic crystal modifications (Bernstein, 2002).

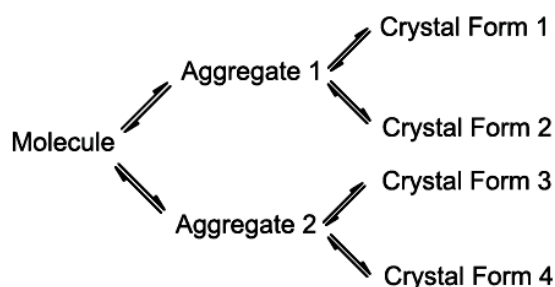


Figure 1.11 Diagram showing the pathways of molecules forming various aggregates that eventually result in different crystal forms (Adapted from Etter, 1991).

Here the clusters are described as aggregates that have the basic form of the eventual crystals. This is because the intermolecular forces that formed the aggregate will most likely be the same as the forces causing crystal growth to the surfaces of these aggregates. After this nucleation has taken place for a certain polymorphic form the equilibrium of this system will be directed in support of this form at the cost of all other forms. In this case the competition between kinetic and thermodynamic factors will be what determines which modifications will form. This will mean that the resultant form will not necessarily be the most stable form, but could simply be the form that was the fastest to create an aggregate large enough for nucleation. This, however, does not mean that only one form can be created at certain fixed conditions. If there are multiple forms that can be formed at specific conditions and have free energies that are close to each other, more than one form can exist simultaneously. These are termed concomitant polymorphs (Etter, 1991).

1.3.2.3 Ostwald ripening

Ostwald's step rule describes that when a material leaves a certain state to transform into a more stable one, it will not always transform into the most stable state under the current ambient conditions, but rather the state that is formed with the smallest loss of free energy or in other words the closest state of energy that it can transform into. This should be seen more as a guideline than a rule because exceptions do occur from time to time (Bernstein, 2002).

1.3.3 Enantiotropy and monotropy

A simplistic way to describe enantiotropic and monotropic polymorphs is by making use of the explanation by Craig (2007) that states that in the case of a polymorph with two enantiotropic forms, one or the other will be stable at a specific temperature and pressure. For a monotropic polymorph on the other hand, there will only be one most stable form and this is not dependent on temperature (i.e. will be the most stable form at any temperature).

When energy is brought into the equation, this difference can be seen when considering the temperature-dependant correlation between the free energy of the various forms. Represented in Figure 1.12 is a temperature termed T_0 at which both

enantiotropic forms will have the same free energy (i.e. $G_A = G_B$) and will be a temperature lower than the melting point of both forms.

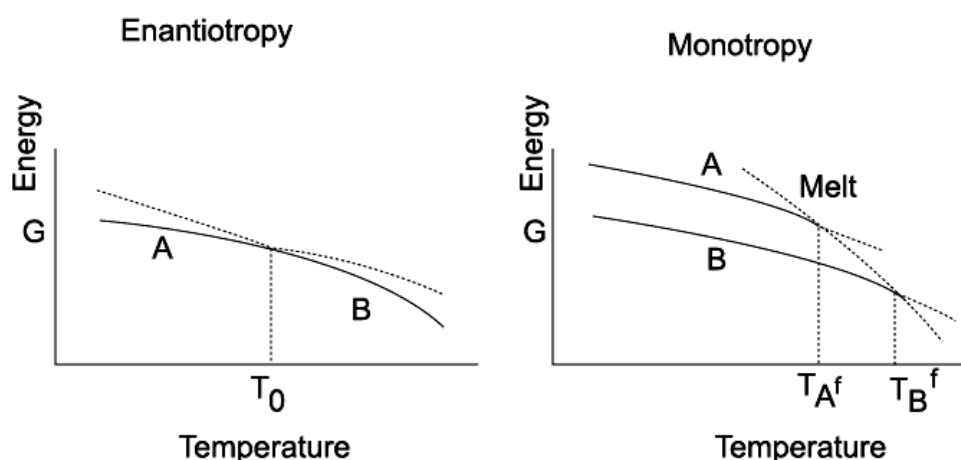


Figure 1.12 Relationship between Gibbs energy and temperature for two modifications in the cases of enantiotropy (left) and monotropy (right). Where A and B represent the different polymorphic forms, G represents the Gibbs free energy, T_0 represents the temperature at which both forms have the same free energy, T_A^f and T_B^f are the temperatures where form A and B melts respectively (Adapted from Giron, 1995).

When looking at the free energy over temperature graph the two forms will cross at this point and form A and B will be in equilibrium. At no other temperature will the free energy be the same and thus only one form or the other is most stable at a given temperature above or below T_0 as can be seen by the solid line in Figure 1.12. This means that the less stable form can spontaneously transform into the more stable form. (Exothermically from form B to A below T_0 because $G_A < G_B$ and endothermically from form A to form B above T_0 because $G_A > G_B$). When considering monotropic polymorphs this free energy will always be lower for the one form and the free energy over temperature graph will not show a temperature at which two polymorphs have the same free energy. This means that one form, the one with the highest free energy (A) will always be metastable when compared to the other form (B) with the lower free energy and form A will thus be energetically driven to transform into form B ($G_A > G_B$) (Craig, 2007).

The thermodynamic stability of polymorphs are thus directly related to their Gibbs free energies. Different polymorphs are ranked and labelled according to their stabilities and this can be determined by measuring their solubilities at a given temperature. This solubility measurement will lead to the same ranking when using any solvent (Ymén, 2011).

There is no unified means of labelling polymorphs and various forms can be seen in literature (e.g. I, II, III...; A, B, C...; α , β , γ) and sometimes the same polymorphic forms are even given different names by different discoverers (Kratochvíl, 2011).

In solubility studies done at different temperatures, the curves for two enantiotropic forms of a polymorph will cross at phase transition points. This is true because the Gibbs free energies and also the solubilities of the polymorphs will be identical at the solid-to-solid phase transition point (Ymén, 2011).

1.3.3.1 Heat of transition rule

If an endothermic phase transition takes place, a thermodynamic transition point can be found below this temperature and the two polymorphs will be enantiotropically related. If an exothermic phase transition takes place, there will not be a thermodynamic point below this temperature. This means that the two polymorphs will either be monotropically related or they are enantiotropically related but the thermodynamic transition point is simply at a higher temperature than the transition temperature that was experimentally observed (Lohani & Grant, 2006).

In certain cases it is possible that polymorphic conformation can make this rule invalid, though the rule was experimentally shown to be accurate in 99% of the circumstances tested by Burger and Ramberger (1979). This rule is represented visually in Figure 1.13.

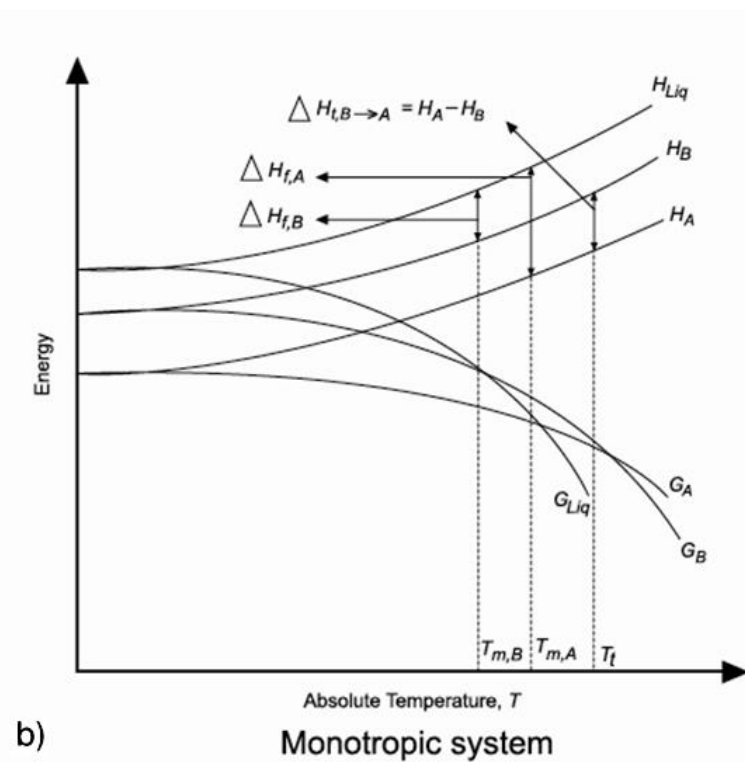
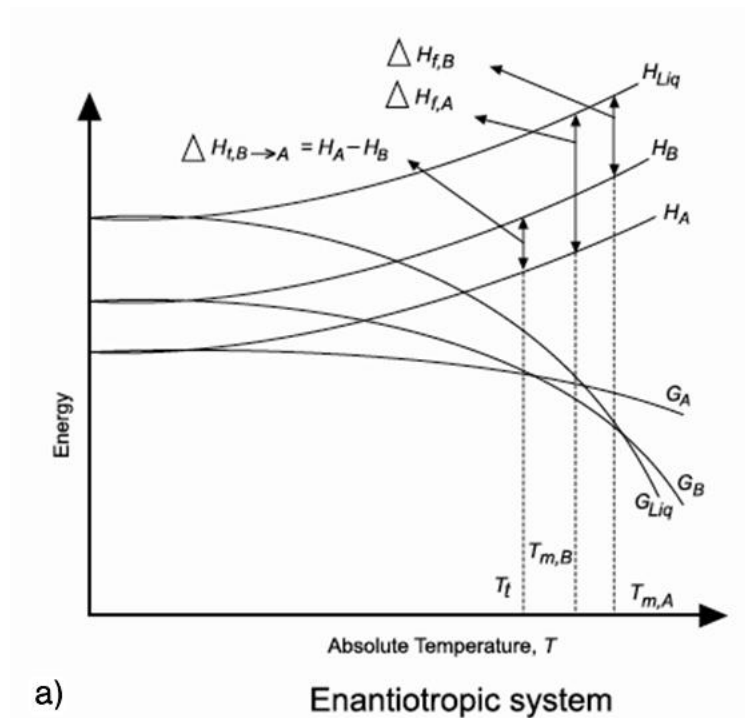


Figure 1.13 Energy-temperature plots for enantiotropic (a) and monotropic (b) systems. Where G is the free energy, H is the enthalpy, T is the temperature, subscripts A, B and Liq are for polymorph A, polymorph B and the liquid phase respectively. Subscripts f, t and m, refer to fusion, transition point, and melting point, respectively (Adapted from Lohani & Grant, 2006).

When a solid is heated gradually an increase in thermal motion will occur and consequently its density will decrease. If heated to a temperature at which transition takes place, more drastic changes such as conformational changes, molecular rotation or translation, or a mixture of these will occur (Ymén, 2011).

1.3.3.2 Density rule

When considering the packing of molecular crystals it will make sense that the crystals with the highest density should have the best packing formation and should thus be bound with the lowest free energy (Byrn, 1982).

Byrn (1982) describes this phenomenon by making use of the heat of sublimation by stating that the heat of sublimation and the approximated melting point of various polymorphs will increase with an increase in packing density. This will cause the densest polymorph in a series of polymorphs to be the most stable form.

This is not always the case though because of different intermolecular interactions, and can be explained by making use of what is called the density rule. Lohani *et al.* (2006) describe this rule as being based on Kitaigorodkii's principle of closest packing for molecular crystals. It states that when considering a non-hydrogen-bonded system at absolute zero, the most stable polymorph will be the one with the highest density, because of the many Van der Waals interactions between molecules in the system. Hence, this rule explains that with the most efficient packing one will see the lowest free energy. When on the other hand hydrogen bonds are to be found, they might compensate for the lower amount of Van der Waals interactions and then making a less dense polymorph, the one with lower free energy and thus also the more stable polymorph (Lohani & Grant, 2006).

1.3.3.3 Infrared rule

When considering different polymorphs of the same substance, each having hydrogen bonds between molecules in their crystal lattices, the infrared rule as stated by Lohani and Grant (2006) can be used to explain the entropy involved in these systems as follows: The polymorph which has more bond stretching may be assumed to have a higher level of entropy, this is because of the bond stretching vibrations that are thought to be weakly coupled to those in the rest of the molecule.

1.3.4 Solvates, hydrates and co-crystals

A solvate is a solid in which a solvent is incorporated into or accommodated within the crystal structure. Being the smallest solvent and having an astonishing ability to form hydrogen bonds, it makes sense that water is the solvent found most often as solvate and when water is the solvent the solvate is referred to as a hydrate. The difference between a solvate and a co-crystal is that if the components of the compound under investigation are isolated and one of the components is a liquid at room temperature it is a solvate and if both are solid it is a co-crystal (Griesser, 2006).

Some solvates/hydrates are formed by the solvent/water molecules simply filling voids that are left when the pharmaceutical crystals are packed in a way that leaves gaps (Ymén, 2011). If these voids are closed off from the outside to form a three-dimensional cage, it is termed a clathrate, which literally means “cage” (Griesser, 2006).

If, however, pharmaceutical crystals have unsaturated hydrogen bonding positions it is possible for the solvent/water molecules to bind to them, creating a crystal with lower lattice energy and thus creating a more stable crystal modification (see explanation in section 1.4.1). The latter case is an example of a stoichiometric solvate/hydrate (see section 1.3.4.2) (Ymén, 2011).

If no interaction exists between the solvent/water molecules and the crystalline lattice the term adventitious hydrate/solvate is used, these are not considered true hydrates/solvates. In this case the solvate/hydrate will be non-stoichiometric (Anderton, 2003).

Stoichiometry and non-stoichiometry:

In stoichiometric solvates/hydrates a fixed ratio of pharmaceutical active ingredient molecules and water/solvent molecules should exist, but in the case of non-stoichiometric hydrates/solvates the ratio is variable and the amount of water/solvent molecules and coincidentally the stability (as mentioned earlier) is dependent on the temperature and the partial pressure of the solvent in the environment. This ratio can be determined by means of single crystal X-ray diffraction analysis (Griesser, 2006).

Because the solvent/water molecules in stoichiometric solvates/hydrates play a structural role in these compounds (Figure 1.14), desolvation/dehydration can lead to the collapse of the structure and even lead to the formation of an amorphous solid. Desolvation/dehydration of non-stoichiometric compounds will simply result in a non-solvated/anhydrous version of the same compound because the molecules are not tightly bound and do not play a role in the lattice structure of the solvate/hydrate (Kratochvíl, 2011).

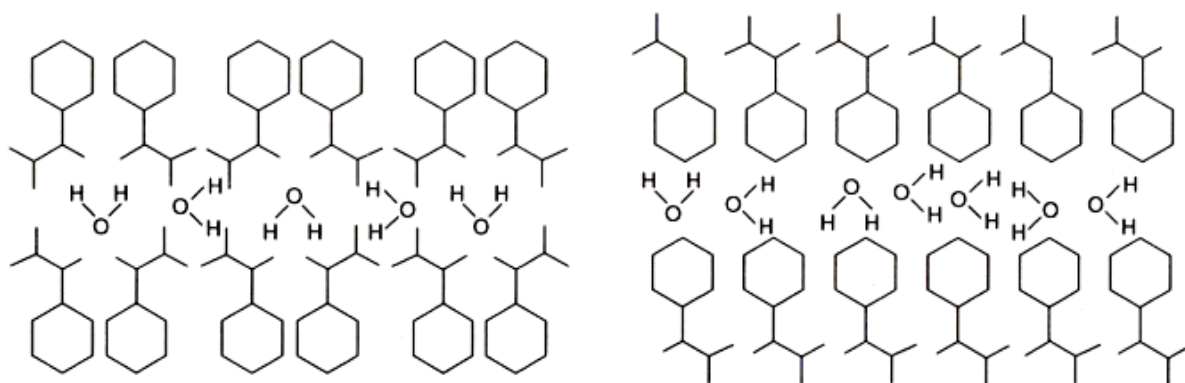


Figure 1.14 Schematic representation of a stoichiometric hydrate with a regular hydrogen bond network (left) and non-stoichiometric hydrate with water molecules in cavities (right) (Kratochvíl, 2011).

Some compounds are stable enough to form anhydrous crystals or crystals without solvent molecules in its lattice even in an environment of pure solvent (Ymén, 2011).

1.3.4.1 Effects of solvates, hydrates and co-crystals on properties of pharmaceutical solids

When considering the solubility of solvates and hydrates it is regularly the case that solvates can enhance aqueous solubility while hydrates are more prone to decrease the aqueous solubility (Griesser, 2006).

If the guest molecules (the molecules that are not part of the crystal lattice of the raw material) in co-crystals are water-soluble, they will usually lead to enhanced aqueous solubility. Other than these guidelines for solubility, general rules are not commonly found and each solvate, hydrate and co-crystal should be analysed individually for determination of relevant properties (Cui, 2007).

Solvates are most stable in an environment of its solvents and when a solvate is taken out of the solvent, the partial pressure of the solvent becomes essentially zero except in the case of a hydrate, where moisture in the atmosphere plays a role. This means that the solvate will tend to transform into a more stable form if not kept in the solvent (Griesser, 2006).

1.4 Solid-state properties

As is the case in this study, solid-state properties are essential when dealing with poorly water-soluble substances. For an API to pass through membranes and have an effect, it must first be freed from the drug product, and then dissolve in the body fluids. With dissolution being a crucial step in the functioning of the API and the dissolution being dependent on the molecular, supramolecular and particulate features of the API, the value of these properties become unmistakably cardinal.

The intrinsic solubility or thermodynamics of solubility of a drug substance is governed mostly by its molecular and supramolecular features, whereas the kinetics of solubility or the rate of dissolution is governed by the particulate characteristics such as particle size and crystal habit (Griesser & Stowell, 2003).

1.4.1 Crystallinity

As was described in the previous sections, with an increase in temperature, molecular mobility increases. The reverse for this is also true. As is explained by Ymén (2011), the molecular movements in a liquid will decrease when the liquid is cooled. When the liquid is cooled at a slow rate it is very likely for crystallisation to occur at the freezing/ melting point. If the rate of cooling is not slow enough however, the crystallisation might only occur at temperatures below this point and is even truer for bigger molecules. This is because of bonds being formed between molecules. When these bonds are strong enough to stop translational motion, crystallisation occurs. When the cooling rate is too fast the bonds will not have completely formed and this is why crystallization might only occur below the freezing/melting point. Though translational motion is ceased, vibrational/rotational motions are still possible (e.g. in glasses (see section 1.4.2)) (Ymén, 2011).

This process of crystallisation lowers the entropy by decreasing the dynamic and static disorder in the system and releases the latent enthalpy of crystallisation. When

this enthalpy is released, an exothermic event can be seen when using a DSC (see section 2.2.1). A more accurate determination of the onset of crystallisation or otherwise known as freezing point can be acquired by means of melting point analysis when a sample is heated because of the super-cooled state at which crystallisation usually occurs (Ymén, 2011).

The clear difference between crystals and liquids is the absence of translational motion, which is also true for amorphous or glassy substances. The difference is that crystals have long-range order whereas liquids and amorphous/ glassy substances do not have this long range-order (Ymén, 2011).

The long-range order refers to the periodic repetition of molecules in three dimensional space throughout hundreds and thousands of molecules starting at “neighbouring” molecules and then propagating through the rest of the phase. Short-range order on the other hand only follows a pattern of molecular coordination up to a few neighbouring molecules and then the pattern disappears with no periodic repetition (Cui, 2007).

The following figure (1.15) displays the long range and short range order found in solids.

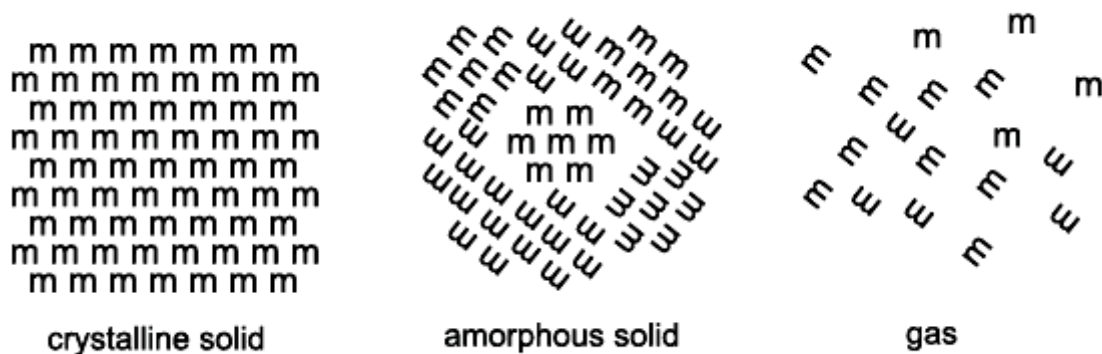


Figure 1.15 A graphic representation of short and long-range order found in solids and in a gas with (m) representing a molecule (Adapted from Yu, 2001).

The most thermodynamically stable crystal structure under specific conditions will be formed as a result of minimisation of the Gibbs free energy in the system (as was explained in section 1.2.4). The three main factors driving this energy-minimisation, according to Ymén (2011), is (a) the energy of molecular conformations striving to

reach a minimum, (b) charge imbalances striving to reach a minimum and (c) packing density striving to reach a maximum.

These factors can be combined in various ways, but there will only be one way in which the most stable form can be packed under specific conditions (Ymén, 2011).

The following section was explained by the density rule in section 1.3.3.2, but in this example the focus is on the directionality of the forces being described and this is why some information is repeated. When molecules are packed together be it by cooling, fast or slow evaporation or any other method, the molecules will strive to reach the highest packing density or stated differently, will try to minimise empty space. In the case of a substance that tends to form glasses rather than crystalline structures, these molecules will pack very closely together because of Van der Waals forces, without forming strong intermolecular bonds. This will leave the molecules densely packed in a non-directional way (Ymén, 2011).

If, however, the molecules have unsaturated charges, they will not merely pack closely together, but will move about so as to have the unsaturated charges between molecules form bonds such as hydrogen bonds. Here directionality is embedded into the structure of the crystal because of the molecules having to align in certain directional formations for these hydrogen bonds to form, in order to minimise the charge imbalances. When looking at this from the perspective of density, one will find that the density of the crystals that have many hydrogen bonded molecules would be lower than when packed at dispersion bond distances such as those of Van der Waals forces. This then seemingly contradicts the idea of the molecules striving to pack with a maximum density. This can be explained by noting that the driving force of minimisation of unsaturated charges i.e. forming of hydrogen bonds is a stronger driving force than that of maximisation of density (Ymén, 2011).

This makes much more sense if one considers the strength of these forces. According to Ymén (2011), medium strength hydrogen bonds are 10 to 100 times stronger than a Van der Waals bond (ca 0.2 kcal/mole).

This explains why crystals with directionality (long-range order) in their lattices should be more stable than glassy or amorphous molecular compositions (lacking long-range order) and also why by manipulating the way molecules are packed in

crystal lattices one can alter physico-chemical properties of pharmaceutical substances.

One example of polymorphs where the more stable polymorph at room temperature is the one with the lower density is that of resorcinol (Byrn, 1982).

1.4.1.1 Crystal habits

When creating crystals one can often find that the morphology or habits (i.e. shape) of these crystals differ as a result of the various conditions employed to attain these crystals. This, however, does not mean that there is a difference in the pattern by which the molecules in the crystals are packed. It is possible that they can have the exact same internal molecular arrangement in their lattices while having any number of varying crystal habits (Griesser & Stowell, 2003).

Because of this identical arrangement of molecules in a crystal, one will find that these various habits will have identical single crystal and powder diffraction patterns when examined by means of X-ray diffraction analyses. However, different pharmaceutical properties can be found as a result of differences in the crystal faces that are developed (Byrn, 1982).

The conditions that can influence the habit of crystals that are formed are the level of saturation, the rate at which cooling takes place and agitation of the solution. An example used by Byrn (1982) is that of naphthalene crystals. When formed by rapid cooling they have thin plate-like structures and when they are formed by a method of slow evaporation they form compact crystals (Byrn, 1982).

As was mentioned earlier, the habits and sizes of crystals can influence the kinetics of solubility or the rate of dissolution and these were examined in this study.

Other pharmaceutical properties of crystals that can be altered by crystal habits, that have significance in pharmaceutical applications, are those of suspension syringeability and that of tableting behaviour. Neither of which are analysed in this study, but are mentioned here for the sake of completeness (Byrn, 1982).

1.4.1.2 Crystal lattice and unit cells

Crystals can be envisioned as a translational replication of a three-dimensional structure or structural basic motif. This motif can consist of atoms, molecules or sometimes pharmaceutical molecules in combination with solvents, as is the case with solvates (see section 1.3.4), among other possibilities. This motif is termed a unit cell (Figure 1.16) and is the smallest part of a crystal that represents the pattern of molecular arrangement throughout the whole crystal. To create a crystal lattice one can place points at each corner of a unit cell. The surroundings of each of these points will be identical and will be a replication of the environment within each unit cell when envisioning the surrounding molecular packing and incorporating the motif and lattice points. The lattice, therefore, creates a parameter and consists of dimensions a , b and c and angles α , β and γ as represented in Figure 1.16 (Gilmore, 2011).

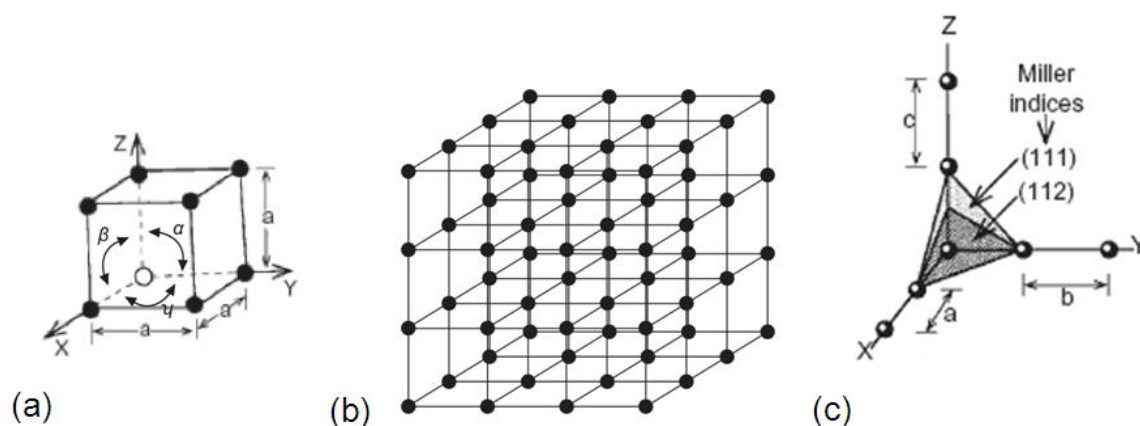


Figure 1.16 Depiction of a cubic unit cell (a) an example of a lattice (b) and the nomenclature of lattice planes (c) (Adapted from Mattox, 2010).

1.4.2 Glassy and amorphous states

As early as 1932 a fairly realistic model of a glass lattice was described by W.H. Zachariasen. Zachariasen (1932) made the observation that there were similarities between the mechanical properties of a glass and that of the related crystal. For this to be true he then concluded that the underlying “building blocks” of each should thus have similar structural energies and should be bound without expending more energy. By further inspection he found that the underlying “building blocks” nearest

each other had only faint variations in bond lengths (~1%) and bond angles (~1°). This meant binding with almost identical energies was possible when relating the amorphous lattice with that of the crystalline one.

This idea is almost correct as can be seen in the statement by Yu (2001) that for amorphous and crystalline phases the immediate environment of a molecule can be very nearly the same or even in some cases indistinguishable.

This was, however, only true for local distribution of atoms up to the second or third coordination sphere. From the next coordination sphere onward the differences became very large (Suga, 2011). This plainly shows that in a glass only short-range order is maintained while longer-ranged order is lost (Suga, 2011).

When the X-ray powder diffraction patterns (see section 2.5) of glasses are examined they show spectral broadening and the diffraction patterns appear as broad and featureless due to the lack of long-range order (as can be seen in Figure 2.8) (Griesser & Stowell, 2003).

Differences in properties of amorphous solids and crystalline solids by which they can be distinguished are for example, particle shape, birefringence and fracture mechanism (Saunders & Gabbott, 2011).

1.4.2.1 Molecular aspects of glasses/ amorphous solids

If one were to rapidly decrease the temperature of a solution or melt where stable nuclei have not yet formed, the viscosity could increase to a level where large-amplitude motions appear to cease. At this stage the molecular movements will seem to be “frozen” and the liquid will transform into a solid termed a glass (as was depicted by the basins in Figure 1.2 in section 1.2.3) (Cui, 2007).

The changes taking place gradually when cooling super-cooled liquids are exactly the same as the changes taking place when cooling a melt at a temperature higher than the freezing/melting point for the same substance. This is only true down to a temperature at which glass forms (T_g) (Ymén, 2011).

From here if cooling continues, the rate at which the viscosity rises increases with a unit drop in temperature. With the rise in viscosity the liquid will transform into a syrup-like substance, then into a viscoelastic state and eventually into a brittle state.

This brittle state is termed a glass. A glass can therefore be defined as a liquid with an exceptionally high viscosity ($\pm 10^{14}$ Pa . s) (Guillory, 1999).

The reason for this is that the molecular movements become hindered by the molecules having come too close together (i.e. the viscosity has increased by a high enough order), thus hindering the gradual change and here the formation of a glass takes place on further cooling (Ymén, 2011).

The reason for saying that large amplitude motions appear to have ceased, is because they still take place, but at a rate much slower than in the liquid form. This means that they have a molecular structure somewhat similar to that of a liquid, but appear to be solid and behave more like solids when examined on experimental time scales (Cui, 2007). Glasses can be considered solids when looking at it mechanically, though structurally it is clearly not (Guillory, 1999). Because the large amplitude motions still take place in glasses, the coordinations of molecules can reach an energy level high enough to be transformed to a more stable form (i.e. overcome the activation energy to reach the energy minima shown in Figure.1.2 and is explained in section 1.2.4). This process is known as “structural relaxation” (Angell *et al.*, 2000).

Few solids when tested will be perfectly crystalline and most will therefore contain certain areas that are less crystalline or have some disorder. If, however, most of the substance being tested consists of the disordered content, its form will be classified as amorphous. When this amorphous form exists below the glass transition temperature it is defined as a glass (Saunders & Gabbott, 2011).

It is possible for a substance to be of a nature that is only partially crystalline and can be detected by means of X-ray powder diffractometry. As mentioned earlier these diffraction patterns will display a broadened peak or increased background level when compared to the purely crystalline substance (as is displayed in Figure 2.8). Either the one or two-phase models can be used to describe this occurrence. The substance being analysed can have disorder in a crystalline substance that will be described by the one-phase model or consist of two separate phases, one entirely crystalline and the other entirely amorphous, the latter being best described by the two-phase model (Ymén, 2011).

If one looks at an amorphous substance from the perspective of energy, one will find that the different coordinations of the molecules will have different energy levels and an average is usually found when analysing samples. In crystalline solids on the other hand, as mentioned earlier, the energy levels will be very uniform. This was explained in section 1.2.3 and can be seen in the deep dips for crystalline solids and the wider basins for amorphous solids in Figure 1.2 (Shamblin *et al.*, 2000).

Since most APIs in a solid phase will have some aspect making it less than 100% crystalline it is important to investigate the possible disordered states of these substances and how they could influence properties like stability or functionality (Petit & Coquerel, 2006).

It is found that the percentage of crystallinity from 100% crystalline (i.e. seamless long-range order) to 100% amorphous (i.e. complete lack of long-range order) in solids exists as a continuum in most pharmaceutical substances (see Figure 1.17) (Hancock & Zografi, 1997).

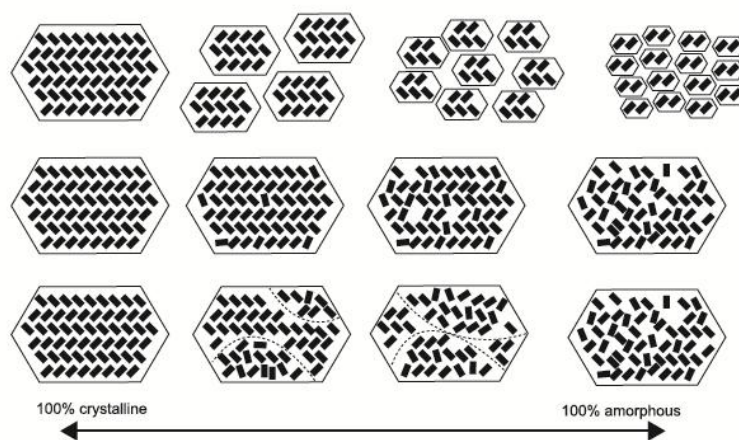


Figure 1.17 Graphic depiction of the continuity between 100% crystalline and 100% amorphous solids (Adapted from Petit & Coquerel, 2006).

For this reason it is often found to be quite difficult to classify the various phases found and, therefore, several families of intermediate solid phases can be defined according to the various states of disorder found in solids (Threlfall, 1995). The general term used for these intermediate phases of partial crystallinity is mesophases (Petit & Coquerel, 2006).

If one is to make a pharmaceutical product of one of these amorphous substances, the heterogeneity in potential energy of these amorphous solids will lead to worse-than-average physical- and chemical stability results. This is because the molecules in the product with the worst stability will be used as the determining factor for specification of stability (Cui, 2007). This can make it quite difficult for an amorphous solid to be accepted as an API. However, it is not impossible as can be seen in countless examples of amorphous drugs found on the market today.

1.4.2.2 Stability of glasses

If a glass transition does occur in a substance, it is important to know at what temperature it takes place in order to keep the product at conditions wherein no transition will occur or at least be sluggish enough for the product to be stable long enough to have an acceptable shelf-life. This concept can be clarified by considering what happens chemically and physically in a glass. As was explained in the previous section, the molecules in a glass are not completely fixed in a location but are in motion, even though this motion is so slow that it will not be observed in the time-scale of *in situ* experiments at the temperature where the product is termed a glass. At this temperature spontaneous crystallization is less likely to occur. Craig (2007) explains that an increase in temperature to or near the glass transition temperature will increase the mobility of the molecules in the glass to an extent that will supply the activation energy needed for structural relaxation to occur. It makes sense, therefore, to store the product at a temperature far enough below the glass transition temperature for the risk of physical instability to be a minimum (Craig, 2007).

1.4.2.3 Thermodynamics and kinetics of amorphous solids

The higher Gibbs free energy found in amorphous phases when compared to crystalline solids cause them to be thermodynamically out of equilibrium. They are thus energetically driven to crystallisation or structural relaxation to reduce their free energy levels. The quantification of excess enthalpy, entropy and free energy is theoretically possible by means of calculating the heat capacities of the crystalline and amorphous phases over the same temperature range (Petit & Coquerel, 2006).

1.4.2.4 Glass transition

Petit and Coquerel (2006) explain glass transition as being driven by kinetics though thermodynamically it is necessary to inhibit amorphous/glassy solids from having lower enthalpies than crystalline solids. This occurrence is termed the Kauzmann paradox.

The glass transition temperature differs from the melting point in this respect. This means that the T_g can be influenced by the sample history and contamination with for instance water (Griesser & Stowell, 2003).

Kinetic factors like heating and cooling rates affect the glass transition because slower rates give molecules more time for molecular motions to cause relaxations (i.e. pack more efficiently with lower free energy (as can be seen in Fig. 1.2 as the dots moving from the basins to the deeper dips near the glass transition temperature)) (Ymén, 2011).

1.5 Physical vapour deposition

Sublimation

The term sublimation is used for the phenomenon of phase change in a material from solid directly into the vapour phase, without first going through the liquid phase (Guillory, 1999).

Gases and vapours

If the atoms (e.g. helium) / molecules (e.g. hydrogen gas) that the material in question is made up of tends to fill the whole volume of the container it is in, it is termed a gas. If the gaseous material in question (e.g. water vapour) tends to condense and adsorb to surfaces, it is termed a vapour. Vapour molecules are usually larger (i.e. have a larger molecular diameter) than gas molecules (Mattox, 2010).

1.5.1 Principles of physical vapour deposition

Vapourised molecules moving through air collide with the various gases and molecules air is comprised of and follow the laws of conservation of energy and the conservation of momentum to be “thermalised” to the ambient energy (i.e. the energy

of the ambient molecules in the container). The energy transferred in these collisions can be written as the following equation:

$$\frac{E_t}{E_i} = 4M_t M_i \cos^2 \theta / (M_i + M_t)^2$$

(Equation 1.15)

Where E is energy, M is mass, θ is the angle of the collision, t is target sphere and i is the incident sphere (Mattox, 2010).

1.5.1.1 The ideal gas law

In circumstances where the ambient pressure is low enough for molecular interactions to be of little consequence, one can make use of the ideal gas law to explain gas pressure and volume as a function of temperature. It can be written as the following equation:

$$\frac{PV}{T} = R$$

(Equation 1.16)

Where P is the pressure, V is the volume, T is the temperature and R is a constant (Martin, 1993).

This law can be related to the amount of molecules occupying a certain volume at a certain temperature and pressure by making use of Avogadro's number (the number of molecules per mole (6.023×10^{23})). One mole of a gas takes up a volume of 22.4 litres under "standard temperature and pressure" (0°C and 760 Torr). A standard cubic centimetre of a gas contains 2.69×10^{19} molecules under these conditions (Mattox, 2010).

From this one can see that the factors influencing the thermalisation of the vapourised molecules is the amount of collisions, the energies and masses of the molecules involved, the gas pressure and the gas temperature (Mattox, 2010).

The average distance that a vapourised molecule can move between collisions is termed the mean free path and is proportional to the temperature and the pressure of the environment (Mattox, 2010). The frequency of collisions in a gas is

proportional to the pressure divided by the molecular weight times the Kelvin temperature (Mattox, 2010).

1.5.1.2 Vacuum deposition

Vacuum deposition/vacuum evaporation is a vapour deposition method that is used to reduce the collisions between the vapourised molecules themselves and between the vapourised molecules and other gas molecules in the path it moves from the evaporation source to the substrate. The environment is termed a “good” vacuum environment if the path between the vapourisation source and the substrate onto which deposition should occur is long and without collisions (Mattox, 2010).

If a volume of space exists under a pressure lower than that of the ambient pressure it is termed a vacuum. The volume will contain less gaseous molecules than the ambient environment if it contains the same gaseous species and is at the same temperature (Mattox, 2010).

“A “rough” vacuum ($>10^{-3}$ Torr) is one having a pressure about 10^{-6} of that of the atmosphere or about 10^{13} molecules/cm³. In a very ultrahigh vacuum (VUHV) (10^{-12} Torr) there are about 10^4 molecules per cubic centimeter” (Mattox, 2010).

Heating and cooling at ambient pressures can be accomplished by means of conduction, convection and radiation. In a “good” vacuum hardly any convection takes place and heating and cooling occur solely by conduction and radiation. The distance that the substrate is placed from the evaporation source should thus be far enough for radiant heating from the heat source to be insignificant (Mattox, 2010).

1.5.1.2.1 Vapour pressure and condensation

If a material in a closed container reaches a partial pressure higher than the equilibrium pressure (i.e. the pressure at which the same amount of molecules are leaving the surface as are returning to the surface), condensation will take place (Mattox, 2010).

The vapourised molecules could be reflected from or re-evaporate from the substrate and do not always condense. The contact/residence time of non-reactive gas atoms or molecules is much shorter than that of vapours. The residence time is dependent

on the interaction between the molecules and the surface as well as the temperature of the surface (Mattox, 2010).

The vapourised molecules can become physisorbed to the substrate surface by means of weak chemical interactions and a “heat of condensation” is released on adsorption. The energy released from the condensing of thermally vapourised molecules is the heat of vapourisation/sublimation (the change in enthalpy between the material in solid/liquid form and that of the vapour) and the energy needed to be cooled to the ambient energy (this is dependent on the heat capacity of the material (see section 1.2.4)). The heat released when condensation takes place can influence the substrate temperature considerably if the rate of vapour deposition is high (Mattox, 2010).

1.5.1.2.2 Creation of amorphous forms by physical vapour deposition

Creating amorphous forms by vapour deposition can be done by sublimation and deposition of materials that are glassy/amorphous by nature or using a vacuum to lower the pressure and therefore create an environment in which the sublimation and deposition can occur at lower temperatures, reducing the mobility of impinging molecules in order to inhibit the molecules from packing in a crystalline manner. This will result in the formation of a solid without a crystalline structure. This method is called quenching and is similar to the method of quench cooling from a melt (see section 1.6) (Mattox, 2010).

The form and size of the crystals formed by this method are dependent on both the temperature of sublimation and the distance of the surface on which the crystals are collected from the material undergoing sublimation. Differences in temperature of sublimation can alter the modification of polymorphs. With lower temperatures having the effect of leading to the formation of less stable forms and at higher temperatures, more stable forms tend to be created (Guillory, 1999).

In order to capture the molecules in a frozen disordered state from the vapour form, the surface on which the molecules are to be deposited should be kept at a temperature much lower than the hypothetical T_g . This is done to sufficiently remove the kinetic energy from the molecules and make it possible for them to be “caught” without moving to preferred crystalline coordinations (see section 1.2.3) (Suga, 2011).

This removal of kinetic energy was also observed experimentally by Suga (2011) and the conclusion was made that lower substrate temperatures cause higher residual entropy S_0 . This means that faster removal of the kinetic energy will result in more disorder in the formed frozen-in solid.

When using the physical vapour deposition method one can regularly find that crystals form on surfaces near the liquid phase i.e. the melt of organic molecules, if it so happens that no crystals were formed below the melting point of the material used (Guillory, 1999).

1.5.1.2.3 The relevance of pressure in polymorphism

When considering the phase rule (equation 1.1) in a system where two solid polymorphic forms are present and the temperature and pressure are variable factors, the variance is a value of unity. If either of these factors is fixed the variance will be zero.

Pressure versus temperature phase diagrams (Figure 1.18) show the various curves representing equilibria between phases. The conditions at which solid-solid, solid-liquid or solid-vapour transitions will take place are thus made visible by these plots. The plots can be representative of monotropy or enantiotropy in the case of polymorphism (Giron, 1995).

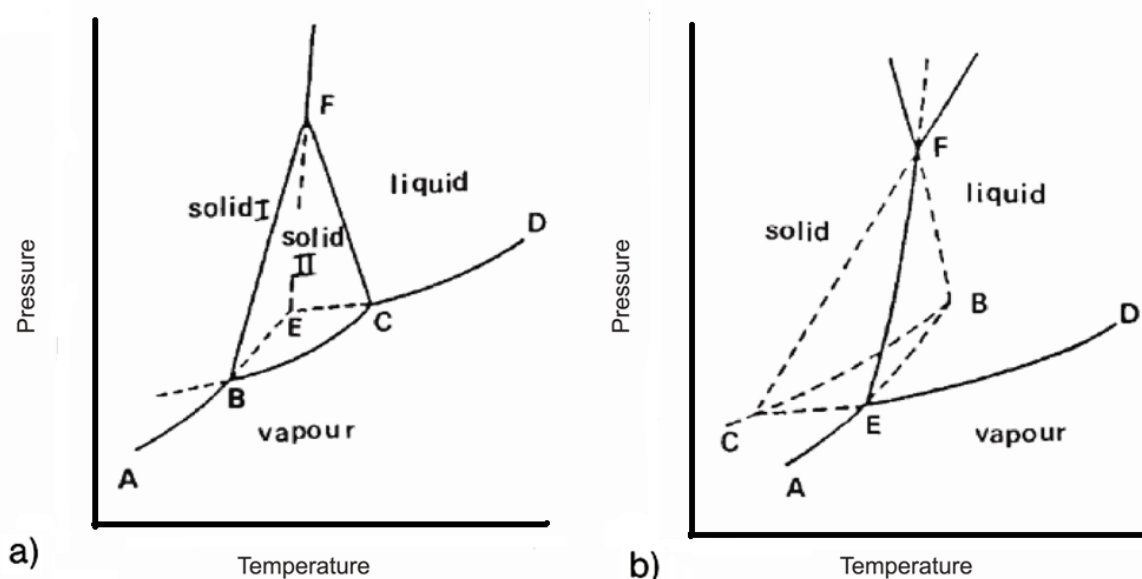


Figure 1.18 Phase diagram showing the influence of pressure and temperature on (a) enantiotropic and (b) monotropic polymorphs (Adapted from Giron, 1995).

In the case of enantiotropy (Figure 1.18 (a)) the liquid-vapour curve (CD) intersects the solid-vapour curves (AB for solid I and BC for solid II) before intersecting the solid-solid equilibrium curve, there will be a reversible solid I \leftrightarrow solid II transition point present at a certain pressure. There will thus be an equilibrium curve between the two solid forms (FB) (Giron, 1995).

In the case of monotropy (Figure 1.18 (b)) the transition is irreversible because thermodynamically metastable forms exist (the equilibria of which are represented by the dashed lines). The equilibrium curve between solid I and vapour is represented by AE, the solid-liquid equilibrium is represented by FE and the liquid-vapour line is represented by ED.

1.6 Quench cooling from melt / vitrification

Quench cooling/vitrification is a method that is used to cool a molten phase of a material (i.e. the temperature before quenching is higher than the melting temperature of the material) to a temperature below its hypothetical glass transition temperature at a rate high enough to prevent crystallisation (inhibit the molecular coordinations to reach the energy minima on the energy landscape (see section 1.2.3) (Giordano *et al.*, 2003). In order to create a glass it is thus necessary to skip the crystallisation step (Suga, 2011).

Guillory (1999) describes this as integrating the free energy into the solid. A vital requirement is that the material does not decompose upon melting. This problem can, however, be limited or prevented by instantly cooling the melt with nitrogen after melting has occurred (Giordano *et al.*, 2003). The main factor influencing the cooling rate needed to prepare a glassy/amorphous solid is the inclination of the material in question to crystallise spontaneously. This is influenced by the conformational variety present in the molten state and the nucleation capacity of the melt (Petit & Coquerel, 2006). One can then produce solids with varying potential energies by altering the quenching rate. This can be represented by the various possible coordinations on the energy landscape (see section 1.2.3) (Cui, 2007).

1.7 Pharmaceutical relevance of polymorphic forms

As was mentioned in previous sections one can find different properties of the various possible forms that include, but are not limited to kinetic, thermodynamic,

spectroscopic, interfacial and mechanical properties. The different chemical and physical properties of these forms have a large impact on the ease with which one can process the material and manufacture products. It also has a direct effect on stability, dissolution and bioavailability which then has a major influence on the quality as well as effectiveness of drug products (Yu *et al.*, 2003).

Finding the most stable form of an API to be used in the manufacturing of products is usually the preferred approach, because it is the form that would be stable and usable for the longest duration of time and will, therefore, have the longest shelf-life and the smallest possibility of changes taking place in the chemical composition of products. This form is usually more crystalline. As was explained in section 1.4, crystalline states possess lower levels of potential energy than amorphous or other disordered states and are more thermodynamically stable because of this (Cui, 2007).

This approach, however, is not always the way to create the form with the most wanted pharmacokinetic properties, seeing as though the increased stability of the active often leads to poor solubility and wettability. This in turn leads to a smaller amount or decreased rate of the drug dissolving in biological fluids and this can cause higher amounts of the drug needed for the same pharmacological effect, consequently increasing the cost to produce drug products with the desired effect (Blagden *et al.*, 2007).

Hancock and Parks (2000) state that by making use of different polymorphic forms, one can obtain solubility improvements of up to two fold. In their literature study they also found noteworthy solubility improvements of amorphous drug forms like a 1.4 fold improvement for indomethacin (Imaizumi, 1980), a 2 fold improvement for cefalexin (Egawa *et al.*, 1992), a 2.5 fold improvement for tetracycline (Miyazaki *et al.*, 1975) and an improvement of roughly 10 fold for a macrolide antibiotic (Sato *et al.*, 1981) and novobiocin acid (Mullins & Macek, 1960).

If the dissolution rate is the rate limiting step in the absorption of a drug, the metastable states of this drug could be considered as possible drug forms (Guillory, 1999).

1.8 Aims and objectives of this study

1.8.1 Motivation and background

The approximate number of global deaths in HIV-negative cases of TB according to the World Health Organisation 2011 global tuberculosis control report in 2010 was 1.1 million (range 0.9-1.2 million), with an added 0.35 million (range, 0.32-0.39 million) deaths involving HIV-positive people. 8.8 million (Range, 8.5-9.2 million) incident cases of TB were estimated during this period. An estimated 1.1 million of the 8.8 million (13%) incident cases of TB were co-infected with HIV, of which 82% were of the African Region (WHO, 2012).

The approximate number of deaths in the African Region during 2010 was 254 000 (range, 227 000–282 000) and the number of incident cases was 2.3 million (range, 2.1 million–2.5 million) (WHO, 2012).

The figures for tuberculosis in South Africa in 2010 are as follows:

In a population of roughly 50 million people the mortality estimates (excluding cases of HIV-positive patients) were 25 000 (16 000-38 000), that is roughly 50 (31-75) per 100 000 population. The incidence was 490 000 (400 000-590 000). This number places South Africa in the top 5 of countries with the highest incidence. South Africa had a reported number of confirmed multi-drug resistant tuberculosis (MDRTB) cases during 2010 of 7386 (WHO, 2012).

The global numbers of confirmed cases of MDRTB are slowly declining, but are rising in the African Region greatly resulting from coinfections with HIV in this region.

The estimated cost of controlling TB in the 22 countries termed high-burden countries (accounting for 80% of global TB cases) in 2012 is US\$3.3 billion (WHO, 2012).

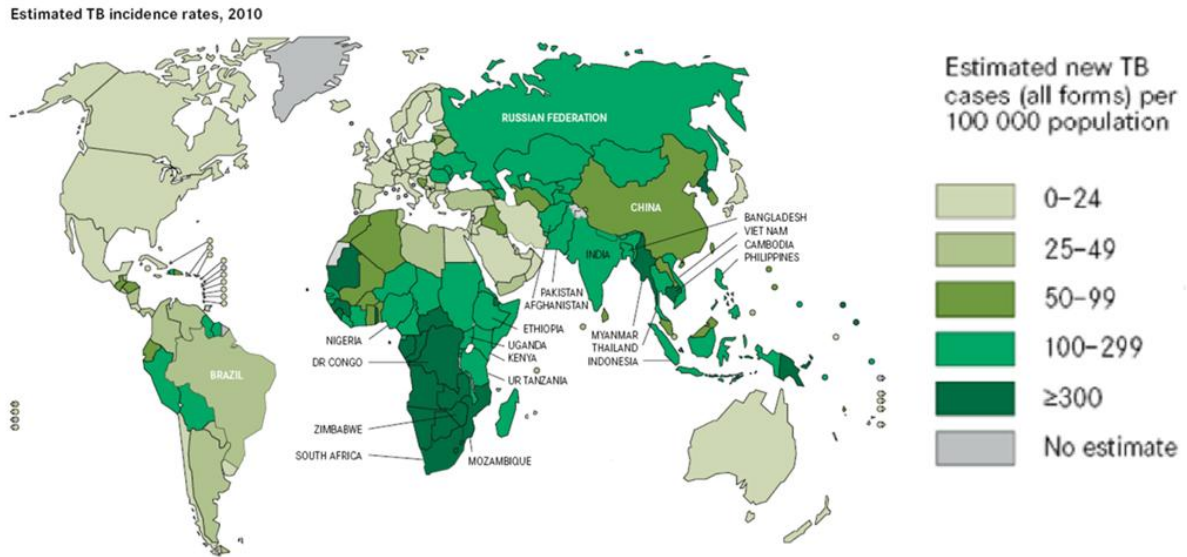


Figure 1.19 Estimated rates of TB incidence during 2010 (adapted from WHO, 2012).

According to Kumar *et al.* (2011), ethionamide is one of the most successful and commonly used second line drugs used for the treatment of MDR-TB. Ethionamide in the commercially available raw material form found today is very poorly water soluble, practically insoluble (USP, 2012) which leads to difficulty in creating cheap and effective dosage forms for the drug. This increases the cost of medication and limits the range of possible dosage forms available for use. Currently the only form of this drug on the market is conventional release tablets that need to be taken daily at doses of 0.5 to 1 g (Zhu *et al.*, 2002).

A common problem in the treatment of tuberculosis or any other ailment requiring prolonged treatment is patient compliance. In the case of tuberculosis though, non-compliance can eventually result in the ineffectiveness of the treatment and this can lead to the development of multi-drug resistant tuberculosis (MDR TB) or extensively drug resistant tuberculosis (XDR TB).

Gastrointestinal intolerance is a problem associated with the use of this drug and can reduce patient compliance (Bass *et al.*, 1994).

At this stage the amount of evidence to indicate the lowest effective levels of dosage is lacking, but with the aim of minimising the possibility of resistance developing, the maximum tolerated dose when considering gastrointestinal disturbances is given as standard. According to Gibbon (2010), this is determined to be about 1 gram of the

currently available form of the drug per day. Patients can experience undesirable effects like gastrointestinal disturbances when given 1 gram of the drug as a single dose. These effects can be decreased or avoided by lowering the dosage.

Amorphous forms of drugs are generally accepted to be more soluble but having the disadvantage of being chemically less stable than crystalline forms as a result of having greater molecular mobility, higher free volume and absence of a crystalline lattice in its molecular structure among other reasons (Singhal & Curatolo, 2004). The amorphous form will also tend to be thermodynamically less stable (Kokshenev, 2011). Conversion from an amorphous to a more stable form in the gastro-intestinal tract (GIT) can also cause the greater solubility of the drugs to be reversed (Blagden *et al.*, 2007). This causes the problem of not having a form of ethionamide that has good solubility traits but is stable enough to be used in pharmaceutical production of drug products.

1.8.2 Aim and objective

Creating new forms of this API by means of a range of methods and techniques and determining the physico-chemical properties of these forms in order to find useful solid-state forms. With the problem being the poor solubility of the drug and the general instability of amorphous forms, the main objective would therefore be to produce a form of the drug that is more readily soluble in water but still stable enough to be of practical use and has significance as a more cost effective alternative to be used in the manufacturing of new dosage forms for this drug.