CHAPTER 2

THE CRYSTALLINE STATE

2.1 INTRODUCTION

The solid-state is the phase of matter most commonly encountered by pharmaceutical scientists. Most pharmaceutical materials, such as active pharmaceutical ingredients (API's) and excipients, and dosage forms like tablets and capsules are solids (Cui, 2007:5). Based on the order of molecular packing, the solid-state can be split into two main subphases; the crystalline state, with long-range molecular order and the amorphous state, with short-range order (the latter will be discussed in detail in the next chapter). Crystalline solids can be divided further into polymorphs, solvates, hydrates and co-crystals (Cui, 2007:6). In the pharmaceutical environment, these crystalline subphases consist of (at least) two different molecules, one is the API and the other is an organic solvent (in the case of a solvate), water (a hydrate) or another crystal (a co-crystal). In this chapter we will focus on the crystalline state and its importance to the pharmaceutical scientist.

2.2 CRYSTALS AND POLYMORPHISM

Crystals are solids in which atoms are arranged in a three-dimensional, periodic repeating pattern, called a crystal lattice. The crystalline state is the naturally favoured state of solids because it is the state with the lowest free energy. Molecules will always try to arrange themselves in a periodic structure when taken to a low temperature. However, noncrystalline solids (or amorphous solids) can be formed when the atoms are unable to arrange themselves periodically, due to rapid cooling or high viscosity (Myerson, 1999:55). Because molecules in crystalline solids have lower potential energy than in amorphous or other disordered states, there is a higher natural occurrence of the crystalline state. The reason for the low potential energy of a crystalline system lies in the order of molecular packing. By arranging in an orderly fashion, the molecules can pack more tightly and more efficiently, thereby reducing the specific volume (Cui, 2007:6). This reduction in specific volume lowers the energy of the system. Additionally, in the crystalline state, molecules have directional specific intermolecular interactions, such as hydrogen or covalent bonding, further stabilising the system and increasing the order.

Polymorphism is defined by Myerson (1999:75) as the ability of a chemical species to crystallise into more than one distinct structure, akin to allotropism in elements. These polymorphs can display significantly different physical and chemical properties. A good example is carbon, which can crystallise as graphite (hexagonal) or as diamond (cubic). For these two solids, properties such as hardness, density, vapour pressure, dissolution rate and electrical conductivity differ greatly. Physical differences such as these are not limited to the polymorphs of carbon and can occur in all materials that display polymorphism.

Probably the best way to visualise polymorphism of a system consisting of one type of molecule is by using the energy landscape (which will be discussed in detail in the next chapter), where the lowest dips represent different crystalline forms (or polymorphs). The molecules in these energy minima all have the necessary molecular coordinations to pack tightly enough for the molecules to propagate in three directions, forming a unit cell (Cui, 2007:9). Depending on the molecular order, which is a function of the molecular coordinations, some of the energy minima will be lower than the rest, even if they are all crystalline. It is a known that for any system there is only one global energy minima, with all the other dips and basins merely representing local energy minima. This can also be seen in polymorphism where only one polymorph, existing at a given set of conditions, will be the thermodynamically stable form. The other polymorphs present will eventually transform into the most stable form. For example, when heating or cooling a crystalline solid with more than one polymorphic form, the material will change with temperature to the polymorph which is the most stable at the specific temperature region. The rate at which these polymorphic transitions occur can range from very slow to rapid. In solution, the transition between polymorphs can be hastened due to solvent mediation of the transitions. Because polymorphs have different degrees of solubility at different temperatures, with the less stable form having the highest solubility, the less stable polymorph will dissolve, leaving the more stable polymorph will grow (Myerson, 1999:77).

In the case of organic crystals, the metastable phase often appears first and then transforms into the stable form. This observation is known as the *Law of Successive Reactions*, or Ostwald's step rule, which states that, in any process, the state that is initially obtained is not the most stable state, but the least stable state that is closest in terms of free-energy to the original state. Although Ostwald's rule has been observed in a wide variety of systems, it is most likely to be seen in organic molecular crystals (Myerson, 1999:78). A recent example can be found in the work of Aree *et al.* (2008:2457) who studied two different polymorphs of β-cyclodextrin-benzoic acid complex. Both crystal forms were obtained from a 50% aqueous ethanol mixture, however form I (triclinic, $P1$) formed within a week while form II (monoclinic,

C2) only formed after 1.5 years. In both forms, the *β*-cyclodextrin structures were isostructural and the included benzoic acid geometries were also similar, with preferred orientation. The benzoic acid was situated at an inclination of 52° with respect to the O-4 plane of the cyclodextrin, pointing their COOH groups to the O-6 side of the cyclodextrin and was mainly held in position by hydrogen bonding with surrounding water molecules. Both forms of *β*-cyclodextrin-benzoic acid complexes formed dimers as a structural motif of packing, and it is here where the difference between the two polymorphs can be seen. Form II forms a screw-channel type lattice, while form I forms an intermediate-tetrad type lattice. This increases the lateral displacement of neighbouring dimeric layers for form II, with the distance for form II being 6.49 Å and 2.55 Å for form I (figure 2.1). The increased distance between neighbouring dimers of form II increases its symmetry (monoclinic, *C2*) and stabilises this polymorph. Form II displayed slower assembly kinetics with increased stability, in accordance with Ostwald's rule. Crystal lattices will be described in more detail later on in this chapter.

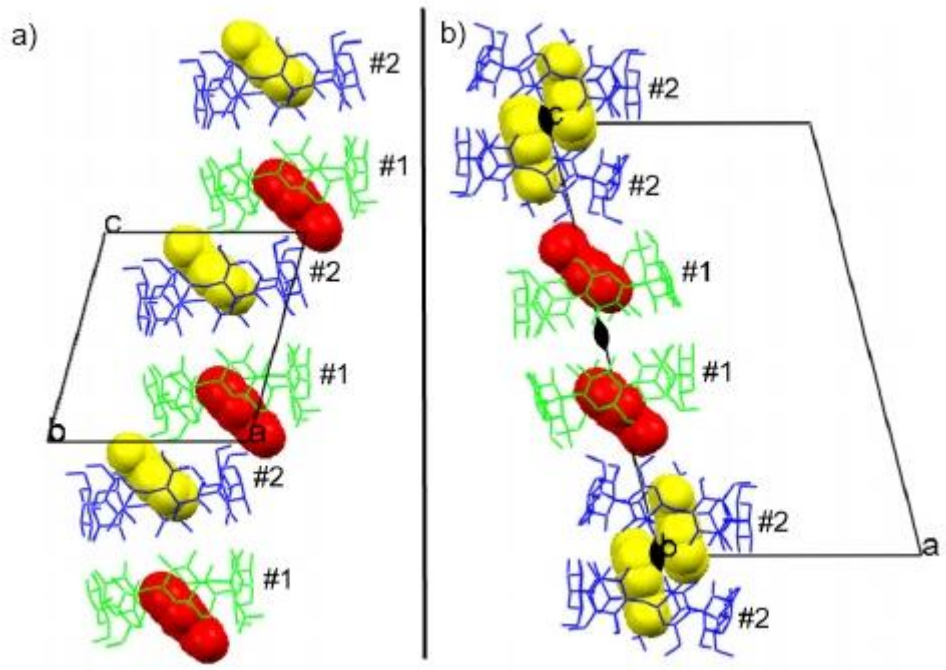

Figure 2.1: Distinction of crystal packing in the *β*-cyclodextrin-benzoic acid complexes from form I (a) and form II (b), water molecules are omitted for clarity and the view is down the *b*-axes (Aree *et al.*, 2008:2457).

To the pharmaceutical scientist, this interconversion of one polymorph to the next is of significant importance. According to Arrhenius law, the conversion rate is determined by the

magnitude of activation energy (Cui, 2007:9). The activation energy in this case is essentially an energy barrier between two polymorphs. The API polymorph with the highest activation energy can be stored longer at room temperature than the other polymorphs of the same API. However, factors such as seeding, impurities, crystal defects and particle size can drastically lower this energy barrier and lead to the formation of metastable polymorphs. Giron (2005:32) published a review article about the different factors that can contribute to instability in polymorphic systems. In this work he emphasises the need for the pharmaceutical scientist to obtain adequate knowledge regarding the thermodynamic properties of the polymorphs used in context of drying, granulation and storage under atmospheric conditions. These considerations are of great importance when deciding which processes to use for formulation of the API.

Other types of crystals the pharmaceutical scientist might encounter include hydrates and solvates, where water or organic solvents respectively are trapped or incorporated into the crystal structure. The probability of working with such crystals is quite high, since it has been reported that approximately one-third of all API's are capable of forming hydrates (Vippagunta *et al*., 2001:15). Because solvates differ in crystal packing (and therefore lattice energy and entropy) from pure crystals, they also display significant differences in physical chemical properties relative to other polymorphs of the same substance. Of particular interest to the pharmaceutical scientist are the hardness, tabletability, solubility and dissolution rate of solvates and hydrates. The amount of literature on this subject is quite extensive and date back to work done by Higuchi *et al*. (1963:150) and Haleblain and McCrone (1969:911). Because hydrates and solvates have foreign molecules in their crystal lattice, they may exist in higher energy states than the pure crystal, leading to enhanced thermodynamic properties (Khankari & Grant, 1995:61). The pharmaceutical behaviour in terms of solubility, bioavailability and processibility of API's in the solvated or hydrated forms can therefore be improved. Another important consideration is the possible changes that can occur during storage, transport and processing of solvates or hydrates. Hüttenrauch (1978:55) investigated the influence of pharmaceutical processing stresses (such as drying, granulation, milling and compression) on crystals. These stresses caused defects in the crystal lattice, leading to lattice disorder and eventually affecting the physical properties of the crystals. Upon dehydration, some hydrates may become amorphous, while other cases have been reported where hydrates converted to a higher state of hydration, thereby reducing its solubility (Vippagunta *et al*., 2001:17). Contrary to hydrates, solvates can also pose serious health concerns, depending on the solvent entrapped in the crystal. Many organic solvents are toxic in concentrations usually found in solvates, with the exception of ethanol, leading to serious regulatory concerns (Griesser, 2006:211). Therefore, solvates

need to be carefully evaluated, and the formation of solvates is usually avoided during the discovery process (Cui, 2007:10).

Organic crystals also have another interesting feature, in its ability to have different molecular conformations of the same species in two different polymorphs. When the molecules present are in different conformations, it is called conformational polymorphism (Myerson, 1999:79). Conformational polymorphism (figure 2.2) is a much neglected field in polymorphism studies, however its importance, not only to the pharmaceutical scientist but to any scientist working on the solid state, cannot be denied.

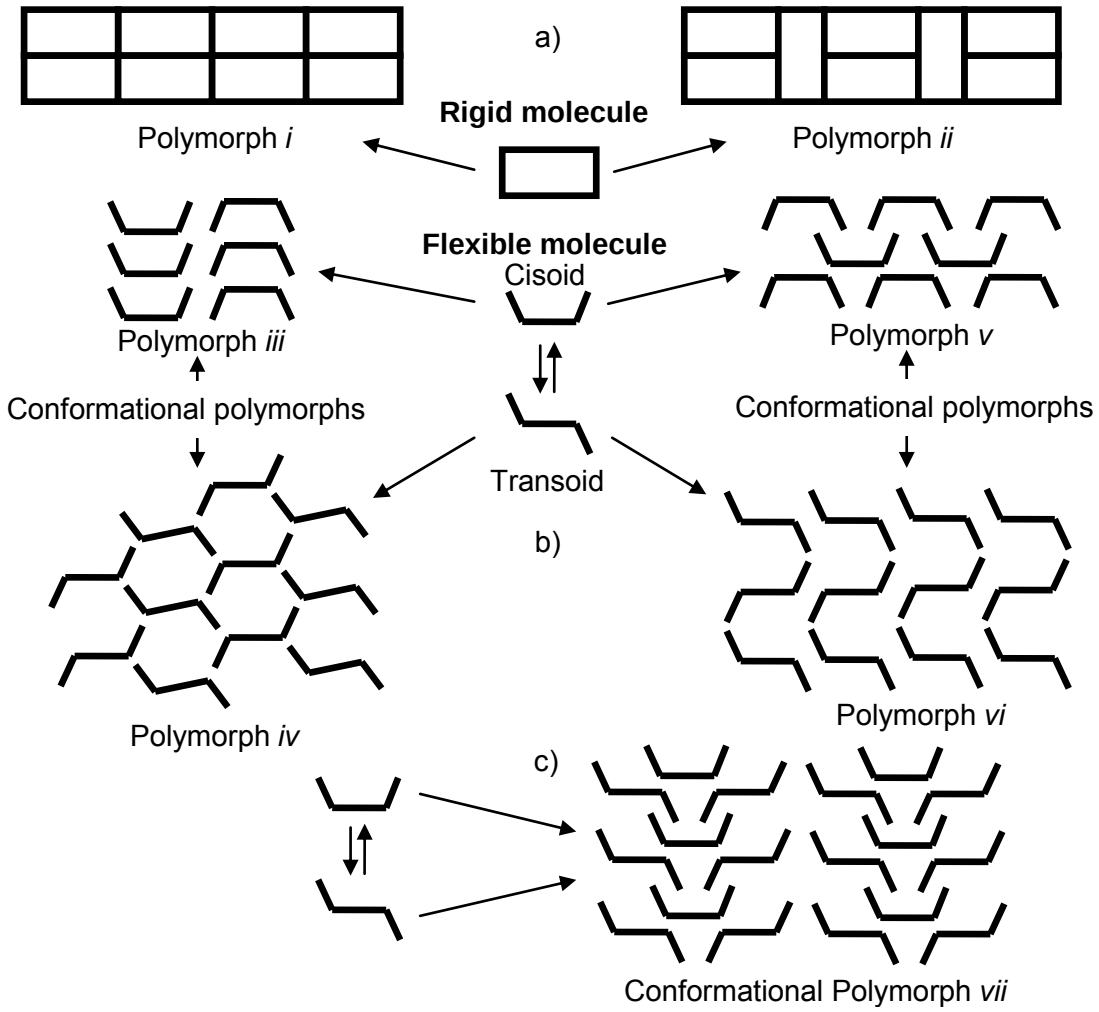

Figure 2.2: Schematic representation of polymorphs for a rigid molecule (a), a conformationally flexible molecule (b) and two symmetry-independent molecules in a conformational isomorph (c), adapted from Nangia (2008:596).

Most API's are organic molecules, with chiral points about which single bonds can rotate. The energy needed for these rotations is relatively low, usually around 1 – 3 kcal mol^{-1}, with the highest values around 8 kcal mol^{-1} for molecules that are sterically hindered, and it should be noted here that the energy needed for these intramolecular torsion rotations (0.5 – 10 kcal mol^{-1}) lie in the same range as nonbonded intermolecular interactions. Changes in the molecular conformation directly influence the stability of the polymorphs that contain these different conformations. It is possible for crystals to be entirely comprised of metastable conformations of organic molecules. This infers an automatic instability in the solid, despite it being crystalline. In typical cases, the higher energy of slightly disfavoured torsion angles are compensated for by C-H···O or van der Waals interactions. Alternatively, crystals can be comprised of molecules with extremely disfavoured torsion angles, bound tightly together by strong hydrogen bonds (Nangia, 2008:596).

A classic example can be found in the work of Almenningengen *et al*. (1985:59) who studied the conformations of *ortho*-H biphenyl molecules in the crystalline and gas phases. The lowest energy conformation of *ortho*-H biphenyl has an inter-ring twist angle of 44°, however, in crystals *ortho*-H biphenyl occurs in the flat conformation, with an energy value of about 1.5 kcal mol^{-1} higher. The molecules are packed in a herringbone T-motif which stabilises this metastable conformation.

Macroscopic observations of conformational polymorphism include colour changes upon heating (Etter and Siedle, 1983:641) and the thermosalient phenomenon ("jumping crystals"). These "jumps" can range from very subtle to heights of up to several times the crystal's size (Skoko *et al*., 2010:14192). It should be noted here that these observations are not the rule, and some conformational polymorphs do not exhibit either upon heating, as these events are dependent not only on the conformation of the molecules but also the dimensions of the unit cell. With this in mind, let us first revisit the basic concepts of the crystal lattice.

2.3 CRYSTAL LATTICES

A lattice can be thought of as a three-dimensional repeating pattern and is essential to the understanding of crystal structure. A lattice is a set of points arranged so that each point has identical surroundings (figure 2.3). In addition, a lattice has three special dimensions: *a*, *b* and *c*, and three angles: *α*, *β* and *γ*. These dimensions and angles are known as lattice parameters. The smallest three-dimensional unit of the lattice that contains all the

information necessary to replicate the lattice to any size is called the unit cell (Myerson, 1999:56).

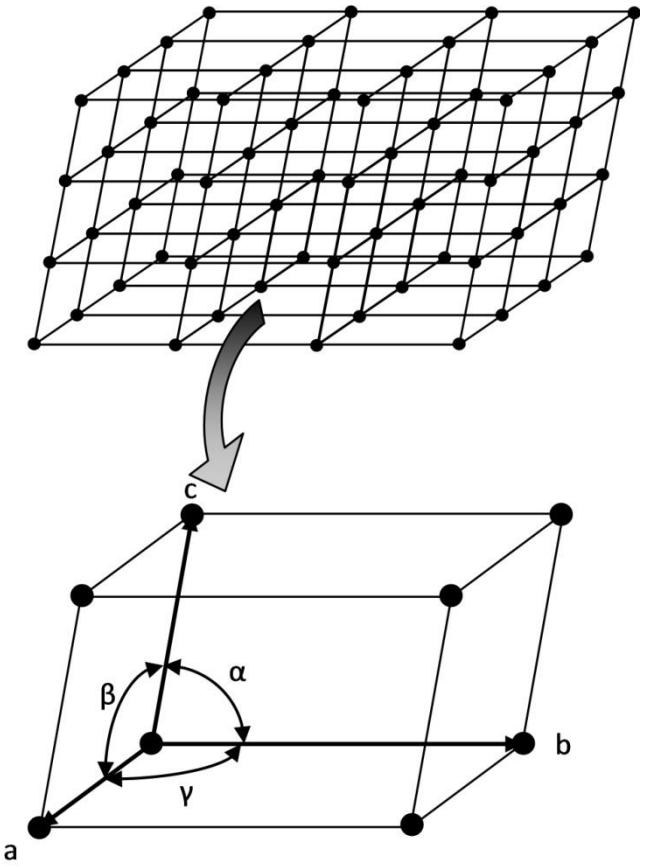

Figure 2.3: The periodic three-dimensional arrangement of atoms, represented by points, in a crystal lattice, with the unit cell underneath illustrating the lattice parameters, adapted from Myerson (1999:56).

In 1845 a French physicist, Auguste Bravais, found that there are only fourteen possible point lattices, known as Bravais lattice. All crystals have a three-dimensional structure that is categorised by one of the Bravais lattices, which are in turn categorised according to the lattice parameters. This division of the lattices results in seven categories, known as crystal systems (table 2.1). In each of the systems, the simplest unit cell is called the primitive (*P*) lattice. These primitive lattices have points in only the corners of the lattice and therefore have only one lattice point per unit cell. Every crystal system has a *P* lattice. For instance, the *P* lattice of a trigonal system is a rhombohedron, normally referred to as an *R* lattice. There are also face-centred (*F*), body-centred (*I*) and base-centred (*C*) lattice types. The *F* lattice has points on the corners and in the centre of each face and is found in the cubic and orthorhombic systems. The *I* lattice has points on the corners and in the centre of the unit

cell and is found in cubic, tetragonal and orthorhombic systems. The *C* lattice has points in the corners and in the centre of one set of parallel faces and is found in orthorhombic and monoclinic systems (Myerson, 1999:58).

Table 2.1: Crystal systems and Bravais lattices (Myerson, 1999:58)

System	Axial lengths and angles	Bravais lattices
Cubic	Three equal axes at right angles $a = b = c,\ \alpha = \beta = \gamma = 90^o$	Simple Body-centred Face-centred
Tetragonal	Three axes at right angles, two equal $a = b \neq c,\ \alpha = \beta = \gamma = 90^o$	Simple Body-centred
Orthorhombic	Three unequal axes at right angles $a \neq b \neq c,\ \alpha = \beta = \gamma = 90^o$	Simple Body-centred Base-centred Face-centred
Rhombohedral (Trigonal)	Three equal axes, equally inclined $a = b = c,\ \alpha = \beta = \gamma = 90^o$	Simple
Hexagonal	Two equal coplanar axes at 120º, third axis at right angles $a = b \neq c,\ \alpha = \beta = 90^o,\ \gamma = 120^o$	Simple
Monoclinic	Three unequal axes, one pair not at right angles $a \neq b \neq c,\ \alpha = \gamma = 90^o \neq \beta$	Simple Base-centred
Triclinic	Three unequal axes, unequally inclined and none at right angles $a \neq b \neq c,\ \alpha \neq \beta \neq \gamma \neq 90^o$	Simple

As mentioned earlier, thermosalient crystals “jump” when heated or cooled. This “jump” is the result of a sudden, anisotropic change in unit cell volume. The change in unit cell volume is a direct result of a conformational change in the molecules inside the cell. This phenomenon was studied by Skoko *et al*. (2010:14195) on the anticholinergic API, oxitropium bromide. Oxitropium bromide crystals show a sharp phase transition at 293 K, and single crystal x-ray diffraction data was collected below 290 K and at 300 K. The results showed two distinct conformers, each specific to a crystal phase. The stick-type overlays of

the conformers, as well as the changes they bring on in the unit cell's dimensions, are illustrated in figure 2.4.

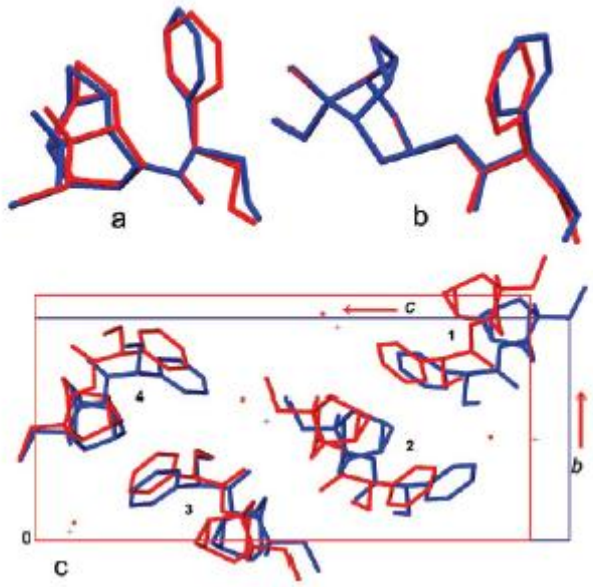

Figure 2.4: Molecular overlay of oxitropium in phase A (blue) and phase B (red). In (a) the overlays are anchored at the three bridging atoms, in (b) at the tricyclic moiety and (c) illustrates the changes in unit cell dimensions with a change in molecular conformation (Skoko *et al*., 2010:14196).

The geometry of the epoxy-aza-tricyclic-nonyl portion of the molecules remains essentially constant, with flexibility in the ester bridge resulting in different orientations of the phenyl ring and hydroxyl moiety. Fabrication of efficient actuators (mechanical devices which convert thermal or light energy into motion or mechanical work on a macroscopic level) have renewed the interest in thermosalient solids, as well as the need to understand the mechanism behind it (Skoko *et al*., 2010:14192).

2.4 CRYSTALLISATION

Crystallisation is a phase change that results in the formation of a crystalline solid. Crystallisation can occur from solution, from vapour and from melt. The most common type of crystallisation is from solution, in which crystallisation is induced by changing the state of the system in some way that reduces the solubility of the crystallising species (Myerson, 1999:87).

The goal of crystallisation is not only to produce pure crystals, but also to obtain other desired properties, such as a certain particle size distribution, a certain shape, a desired strength as well as other physical chemical properties (Myerson, 1999:86).

2.4.1 SOLUBILITY AND SUPERSATURATION

Solutions are made up of two or more components, known as the solvent and the solute(s). At a given temperature there is a maximum amount of solute that can dissolve in a given amount of solvent. When this occurs, the solution is said to be saturated. The amount of solute required to make a saturated solution at a given temperature is called its solubility. A saturated solution is in thermodynamic equilibrium. For crystallisation to occur, the state system must be shifted to the non-equilibrium state in which the concentration of the solute exceeds its equilibrium concentration at the given solution conditions. Solutions that are in this non-equilibrium state are said to be supersaturated. The five main methods of creating a supersaturated solution are temperature change, solvent evaporation, chemical reaction, changes in pH and alteration in solvent composition. Of these, temperature change is by far the most common method employed, since solubility usually decreases with cooling (Myerson, 1999:87).

Supersaturation is the fundamental driving force for crystallisation and can be expressed in dimensionless form in equation 2.1:

$$\mu - \mu^*/RT = \ln a/a^* = \ln(\gamma c/\gamma^* c^*) \qquad (2.1)$$

Where μ is the chemical potential, c is the concentration, a is the activity, γ is the activity coefficient and * represents the property at supersaturation (Myerson, 1999:88). Supersaturation is present in every equation used to describe crystal growth from solution. Lui *et al*. (2004:241) included various properties of supersaturation in their mathematical model (equation 2.2) to calculate the growth rate of ciprofloxacin crystals.

$$\frac{\quad(\quad)\quad(\quad(\quad)\qquad(\quad))\quad\frac{\quad(\quad)}{}}{\Sigma\quad\frac{}{(\qquad)}} \qquad (2.2)$$

Where G is the growth rate, $C(t)$ is the solution concentration at time (t), Mt is the suspension density and V is the solid free solution volume. To determine these variables small samples were pumped out of the batch every 15 minutes, filtered and dried at 368.15 K under vacuum. L_i is the concentration of crystals of ith size, as determined by a laser diffraction granulometer (Malvern Mastersizer), where L_1 would be the smallest crystal size that appears in the crystal size distribution. Crystal size distribution is a convenient way of

measuring crystal growth, as the concentration of small crystals will decrease with time and the concentration of larger crystals will increase. This method was developed specifically for crystallisation from solution and does not involve crystal shape factors, making it convenient and widely applicable, since crystallisation from solution is the most commonly used method of creating polymorphs.

2.4.2 NUCLEATION AND CRYSTAL GROWTH

Crystallisation from solution involves two distinct steps, nucleation and crystal growth. Nucleation is the birth of new crystals and crystal growth is the growth of existing crystals to larger sizes. These two properties and their relationship to each other are responsible for the properties of the crystals obtained, such as shape and size distribution. Classical nucleation theory says that, when a solution enters the non-equilibrium supersaturated regions, the molecules of the solute begin to form aggregates, or clusters (Myerson, 1999:89). If assumed that the aggregates are spherical, an equation (2.3) can be written that gives the change in Gibbs free energy required to for a cluster of a given radius:

$$\Delta F = 4\pi r^2\sigma - (4\pi r^3/3V_m)RT\ln(1 + S) \qquad (2.3)$$

Where r is the cluster radius, σ is the solid liquid interfacial tension, V_m is the specific volume of a solute molecule, and S is the supersaturation ratio. The first term in equation (2.3) is the change in Gibbs free energy for forming the surface of a cluster, while the second term is the change in Gibbs free energy for forming the cluster volume (Myerson, 1999:89). A plot of G as ‘n function of cluster size (figure 2.5) shows that at smaller cluster size the slope of the free-energy curve is positive. This means that the growth of a cluster requires a positive change in Gibbs free-energy. Since all spontaneous processes require a negative change in Gibbs free-energy, this cluster will be likely to dissolve. For larger clusters we see that the slope of the curve is negative, indicating that thermodynamically the clusters will want to grow. The point on the curve where the slope is horizontal is known as the critical size. Nucleation requires that a cluster of critical size forms in the solution. An equation for the critical size can be obtained from equation (2.3) by setting the derivative of r equal to zero, since the derivation is zero at critical size (Myerson, 1999:89), thereby yielding equation 2.4.

$$r_c = 3V_m\sigma/RT\ln(1 + S) \qquad (2.4)$$

Equation (2.4) shows that the critical size decreases as the supersaturation increases, thereby increasing the likelihood that nucleation will occur. It was mentioned in the previous section that Lui *et al*. (2004:241) developed a mathematical model to calculate the growth rate of crystallisation from solution.

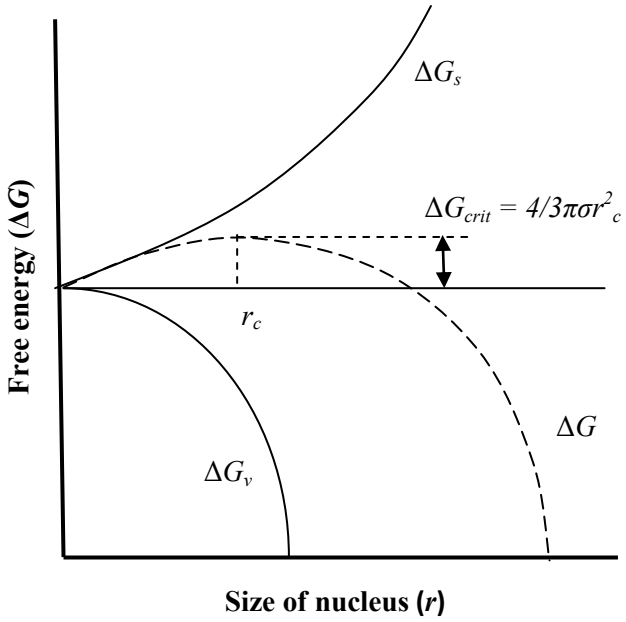

Figure 2.5: Change in Gibbs free energy plotted against cluster radius (Myerson, 1999:90).

They extended their model further, to also encompass nucleation rate, as it is absolutely essential for the simulation of any crystallisation process. Traditionally, the nucleation rate was estimated using equation 2.5.

$$B^0 = n^0 G \tag{2.5}$$

Where n^0 is the population density at zero crystal size and G is the crystal growth rate determined from equation 2.2. The value of n^0 is always obtained from extrapolation. However, since n^0 has little physical meaning, and cannot truly be measured by any instrument, Lui *et al.* (2004:241) changed equation 2.5 to equation 2.6.

$$B^* = n(L_1,t) \times G \tag{2.6}$$

Where B^* is the nucleation rate, n is the population density of the smallest crystals, L_1 is the concentration of the smallest crystals, determined with a Malvern Mastersizer, and G is the crystal growth rate. By using this new mathematical model, the nucleation rate can be more readily and truly calculated from experimental data.

When a nucleus is formed, it is the smallest crystalline entity that can exist under a given set of conditions. Immediately after the formation of the nuclei, solute molecules attach to its surface and the crystal lattice, leading to crystal growth. Crystal growth can be described in a macroscopic way, by looking at the overall change in some dimension of the crystal. Although this type of description gives no information about the mechanics of crystal growth,

it is useful in describing the kinetics of the process and for the development of models to predict the crystal size distribution. Crystal growth involves the incorporation of growth units, molecules, atoms or ions depending on the type of crystal, into the crystal lattice. This growth unit must find its way to an appropriate site on the crystal surface where it can be incorporated into the crystal. Figure 2.6 shows the three types of sites at which the growth unit can be incorporated into the crystal. The first type is a flat surface which is atomically smooth, shown as site A. If a growth units attempts to become incorporated at this site, it can bind in only one place. Site B, known as a step, provides two places for the growth unit to bind to the crystal, while site C, which is known as a kink provides three places in which the growth unit can bond. From an energetic point of view, site C is the most favourable site, followed by site B and then A. This translates to a crystal growth mechanism by which molecules are absorbed on the surface and then diffuse along the surface until they are incorporated into the lattice at a step or kink site. The incorporation pattern indicates that the crystals grow by the spreading of steps. This model, however, provides no information on the origin of these steps, or the rate-controlling factor in the growth process (Myerson, 1999:94).

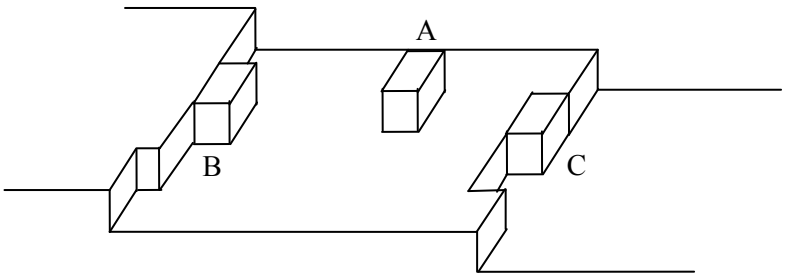

Figure 2.6: The surface structure of a growing crystal (Myerson, 1999:94).

Crystal growth theory attempts to provide this information, and will be discussed in the next paragraph. Chernov *et al*. (2005:10) used an atomic force microscope (AFM) to investigate the stages in crystal growth from solution. Figure 2.7 shows the straight steps on the (101) face of a lysozyme crystal. The kinks present on the steps can clearly be seen, and were found to be roughly 490 nm apart, translating to 75 lattice spacing along the b-axis. The crystals were grown from solution, with a supersaturation ratio of 1.78. These steps grew around screw dislocation outcrops (figure 2.9) on the (101) face of a monoclinic lysozyme crystal. Before we continue this discussion, let's first investigate the theory behind the origin of screw dislocations.

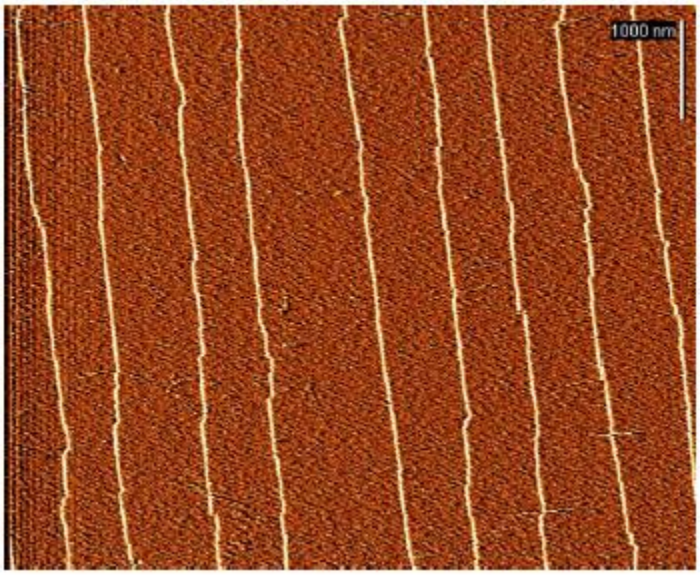

Figure 2.7: Straight steps on the (101) face of a monoclinic lysozyme crystal parallel to the b-axis, adapted from Chernov *et al.* (2005:10).

In 1949, a British theoretical physicist, Frederick Charles Frank, put forward the idea that dislocations in crystals could be the source of new steps. Molecules can be absorbed on the crystal surface and diffuse to the top step of the screw dislocation, as seen in figure 2.8. The surface then becomes a self-perpetuating spiral staircase, allowing crystals to grow continuously (Myerson, 1999:94).

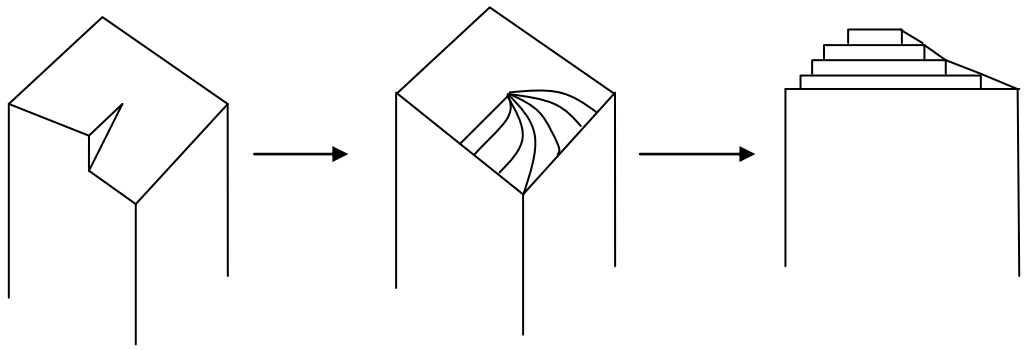

Figure 2.8: The origin of a growth spiral from a screw dislocation, adapted from Myerson (1999:97).

Chernov *et al*. (2005:8) found four different rectangular spiral steps developing from screw dislocation outcrops (figure 2.9).

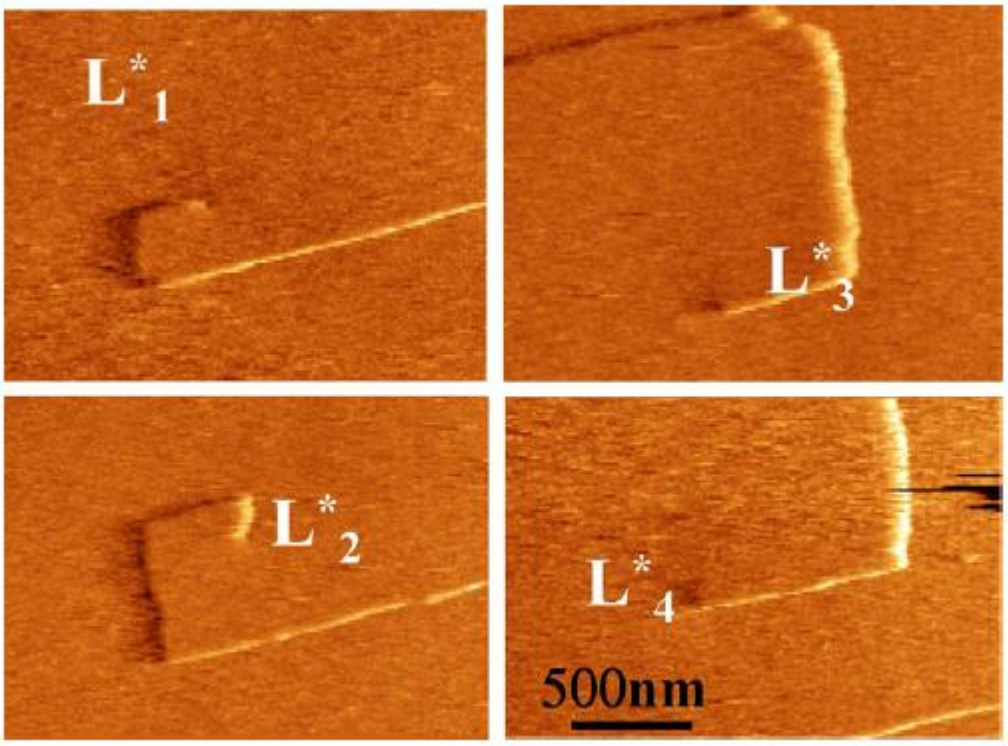

Figure 2.9: Rectangular spirals steps developing around a screw dislocation on the (101) face of a monoclinic lysozyme crystal (Chernov *et al*., 2005:8).

The steps differed in lengths ($L^*_{1,2,3,4}$) and were the first segments pinned by propagation normal to itself (in other words, these steps were only one lattice spacing high (2.5 nm) and had just started to grow). Because of the differences in length, nucleation rate will also be different for each of the steps. It was hypothesised by Chernov *et al*. (2005:8) that the variations in step length is a direct result of the random nature of kink nucleation, since step length is a function of the interkink distance. This is mostly of academic importance only to the pharmaceutical scientist, since instruments such as an AFM is not readily accessible. However, it gives us good insight into the mechanism behind crystal growth and methods of changing and/or controlling its outcome.

2.5 CRYSTAL STRUCTURE AND HABIT

The faces, along with their relative areas on the grown crystal, determine the overall form of the crystal. This overall form is called the crystal habit, structure or morphology. Crystals of the same substance can have the same faces, but different habits, because of differences in the relative areas of their faces. Crystals can also exhibit the same habit, but consist of different combinations of faces (Myerson, 1999:98).

The crystal habit is known to be a function of the crystal growth rate, solvent used and impurities in the system. Gypsum, for example, displays drastic changes in habit with different growth rates (figure 2.10).

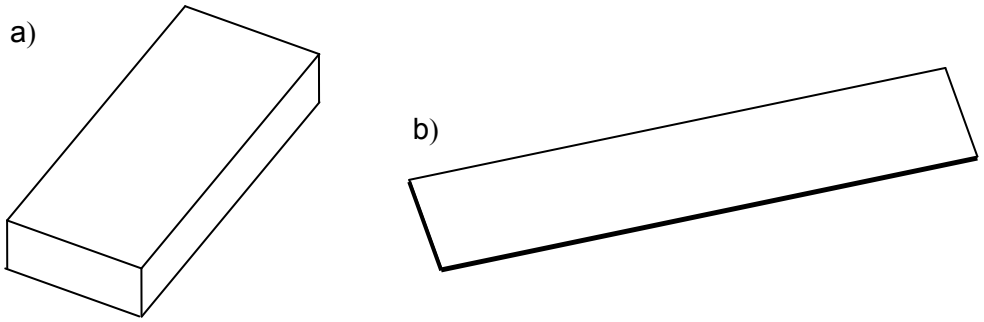

Figure 2.10: Changes in crystal habit between gypsum grown slowly (a) and rapidly (b), adapted from Myerson (1999:101).

The explanation for these differences in habit arises from the fact that smaller faces grow faster that large faces. We know from the *Bravais-Friedel-Donnay-Harker Law* (BFDH) that the growth rate of a face is inversely proportional to the interplanar spacing of that face, meaning that if the fast growing faces are allowed to grow too rapidly, they would effectively disappear on the crystal (Myerson, 1999:101). This presents macroscopically as a decrease in relative area of the smallest faces. Solvents can have a similar effect on the crystal habit, by retarding growth of certain faces. Different solvents will have different solvent-solute interactions, which will change the specific absorption on crystal faces.

Zipp and Rodriguez-Hornedo (1993:48B) studied the growth kinetics of phenytoin crystals in phosphate buffer as a function of pH, supersaturation and temperature. A prediction of phenytoin crystal morphology was made using both the BFDH model and attachment energy calculations. The results from both of these predictions corresponded well with the experimentally observed morphology. However, the 200 face was determined by the above mentioned models to be morphologically important but were only observed for crystals grown from low supersaturation ($\sigma \leq 0.4$), indicating that growth of phenytoin crystals along the *a* crystallographic axis was more dependent on supersaturation than growth along the *c* axis. The proposed reason for this inconsistency between predicted and experimental data was solvent-solvent interaction at the growing crystal faces and the types of intermolecular bonds that formed in the crystal.

The implications for the pharmaceutical scientist are obvious. The solubility of a solid increases with an increase in the effective surface area of the solid. We now know that the effective surface area of a crystal is a function of the crystal habit, which is in turn a function of the crystal faces and therefore, different crystal faces will dissolve at different rates. Other pharmaceutically relevant factors which are influenced by the crystal habit include, the bulk density (the volume mass that the crystals take up when packed randomly), the flow properties of the solid and the rheological properties of a crystal-liquid suspension (Myerson, 1999:100). Shell (1963:100) studied the effect of crystal habit on tabletting behaviour. He found that habits which exhibited the highest anisotropy of cohesion also exhibited the best tabletting behaviour, while the crystal habits that were physically harder, were also more difficult to tablet.

2.6 CONCLUDING REMARKS

The solid-state is the state of matter that is most commonly encountered by pharmaceutical scientists. In this chapter we discussed the crystalline state, its origins, appeal and some practical pharmaceutical implications. The various considerations for the pharmaceutical scientist with regards to manipulation of the crystalline state to yield desired polymorphs were described. In the next chapter we will discuss the amorphous state, which is of significant importance to the pharmaceutical scientist, since all polymers and numerous small molecule API's exist (albeit partially) as amorphous systems. The thermodynamic properties of the amorphous state are of particular interest, not only with regard to enhanced solubility and bioavailability, but also to pharmaceutical formulations in general.

REFERENCES

ALMENNINGENGEN, A., BASTIANSEN, O., FERNHOLT, L., CYVIN, N. N., CYVIN, S. J. & SAMDAL, S. 1985. Structure and barrier of internal rotation of biphenyl derivatives in the gaseous state: Part 1. The molecular structure and normal coordinate analysis of normal biphenyl and perdeuterated biphenyl. *Journal of molecular structure*, 128(1-3):59-76, Apr.

AREE, T., CHAICHIT, N. & ENGKAKUL, C. 2008. Polymorphism in b-cyclodextrin–benzoic acid inclusion complex: a kinetically controlled crystal growth according to the Ostwald's rule. *Carbohydrate research*, 343:2451-2458, Jul.

CHERNOV, A.A., RASHKOVICH, L.N. & VEKILOV, P.G. 2005. Steps in solution growth: dynamics of kinks, bunching and turbulence. *Journal of crystal growth*, 275(1-2):1-18, Feb.

CUI, Y. 2007. A material science perspective of pharmaceutical solids. *International journal of pharmaceutics*, 339:3-18, Apr.

ETTER, M.C. & SIEDLE, A.R. 1983. Solid-state rearrangement of (phenylazophenyl) palladium hexafluoroacetylacetonate. *Journal of the American Chemical Society*, 105(3):641-643, Feb.

GIRON, D. 2005. Polymorphs: thermodynamic and kinetic factors to be considered in chemical development. Part 1. *American pharmaceutical review*, 8:32-37, Jul/Aug.

GRIESSER, U.J. 2006. The importance of solvates. (*In* Hilfiker, R., *ed*. Polymorphism in the pharmaceutical industry. Weinheim: Wiley-VCH. p. 211-257.)

HALEBLAIN, J.K. & McCRONE, W.C. 1969. Pharmaceutical applications of polymorphism. *Journal of pharmaceutical sciences*, 58(8):911-929, Aug.

HIGUCHI, W.I., LAU, P.K., HIGUCHI, T. & SHELL, J.W. 1963. Polymorphism and drug availability. Solubility relationships in the methylprednisolone system. *Journal of pharmaceutical sciences*. 52(2):150-153, Feb.

HÜTTENRAUCH, R. 1978. Molecular pharmaceutics as a basis of modern pharmaceutical technology. *Acta pharmaceutica technologica*. *Supplement*, 6:55-127.

KHANKARI, R.K. & GRANT, D.J.W. 1995. Pharmaceutical hydrates. *Thermochimica acta*, 248:61-79, Jan.

LUI, Y., WANG, J. & WEI, H.Y. 2004. Determination of crystallization kinetics in solution. *Journal of crystal growth*, 271(1-2):238-244, Oct.

MYERSON, A.S. 1999. Crystallization basics. (*In* Myerson, A.S., *ed*. Molecular modelling applications in crystallization. Cambridge, New York: Cambridge University Press. p. 55-105.)

NANGIA, A. 2008. Conformational polymorphism in organic crystals. *Accounts of chemical research*, 41(5):595-604, May.

SHELL, J.W. 1963. X-ray and crystallographic applications in pharmaceutical research III. Crystal habit quantitation. *Journal of pharmaceutical sciences*, 52(1):100-101, Jan.

SKOKO, Z., ZAMIR, S., NAUMOV, P & BERNSTEIN, J. 2010. The thermosalient phenomenon. "Jumping crystals" and crystal chemistry of the anticholinergic agent oxitropium bromide. *Journal of the American Chemical Society*, 132(40):14191-14202, Sep.

VIPPAGUNTA, S.R., BRITTAIN, H.G. & GRANT, D.J.W. 2001. Crystalline solids. *Advanced drug delivery reviews*, 48(1):3-26, May.

ZIPP, G.L. & RODRIGUEZ-HORNEDO, N. 1993. Growth mechanism and morphology of phenytoin and their relationship with crystallographic structure. *Journal of physics D: Applied physics*, 26(8B):48-55, Aug.