

CHAPTER 3

THE AMORPHOUS STATE

3.1 INTRODUCTION

The amorphous field of study is in a constant state of flux. Many of the old concepts have been revised and a lot of old theories on the subject have changed. It is now known that slow cooling of a liquid at constant pressure does not always yield the same configurational ground state (Mishima *et al.*, 1984:393; 1985:76) and that polymorphism can be present in inorganic amorphous systems, a phenomenon known as polyamorphism. The amorphous state is now recognised as “the most significant unsolved problem in condensed matter physics” (Angell, 1995:6675) and Anderson (1995:1615) called it the “deepest and most interesting unsolved problem in solid state theory”. In this chapter we will explore the amorphous state, the theory behind it and its implications for the pharmaceutical scientist.

3.2 THE AMORPHOUS STATE

Before starting off on the ubiquitous question of “what is the amorphous state?” lets first revisit the term, phases. A phase is the term used to describe a physical state of matter with a homogenous (uniform) macroscopic appearance. It is an aggregate of either a single type of molecule or a mixture thereof. The thermodynamic energy of the molecules determines the phase in which it is macroscopically observed and the most important aspect consideration is the size or scale of the observation, since the homogeneity of the system is influenced by the scale of the observation (Cui, 2007:4). For example, a system which macroscopically may present itself as crystalline could, upon closer inspection, contain amorphous material and vice versa. A liquid could contain pockets of lower density within itself and a gas could contain areas with more frequent collisions between molecules. This all constitutes a phase which is build up of heterogeneous parts to form a well-defined interface which we observe as a homogeneous macroscopic system. This heterogeneity, and its impact on molecular motion, is essential in our understanding of the ambiguous phase of matter known as the amorphous state.

Although a great deal of effort is placed in obtaining a drug with a high degree of crystallinity and assessing the different possible polymorphic and/or solvated forms of the drug, it is also

possible to obtain a fully or partially amorphous state of the same drug. Various final stages of the synthesis and/or formulation of new drugs can induce this amorphous character into the solid (Roy, 1970:33). The four most common methods of inducing this amorphous character are: vapour condensation, supercooling of the melt, mechanical activation of a crystalline mass (for example, during milling) and rapid precipitation from a solution (Hancock & Zografi, 1997:1). A broader representation of the different methods to prepare amorphous material can be seen from figure 3.1. Here the relative energies of the initial states are indicated, as well as the energies of the final amorphous material, as plotted on a temperature (T) against pressure (P) diagram. The relative positions of the final amorphous products with regard to temperature, pressure and the glass transition temperature (T_g) is also shown (Angell, 1995:6676).

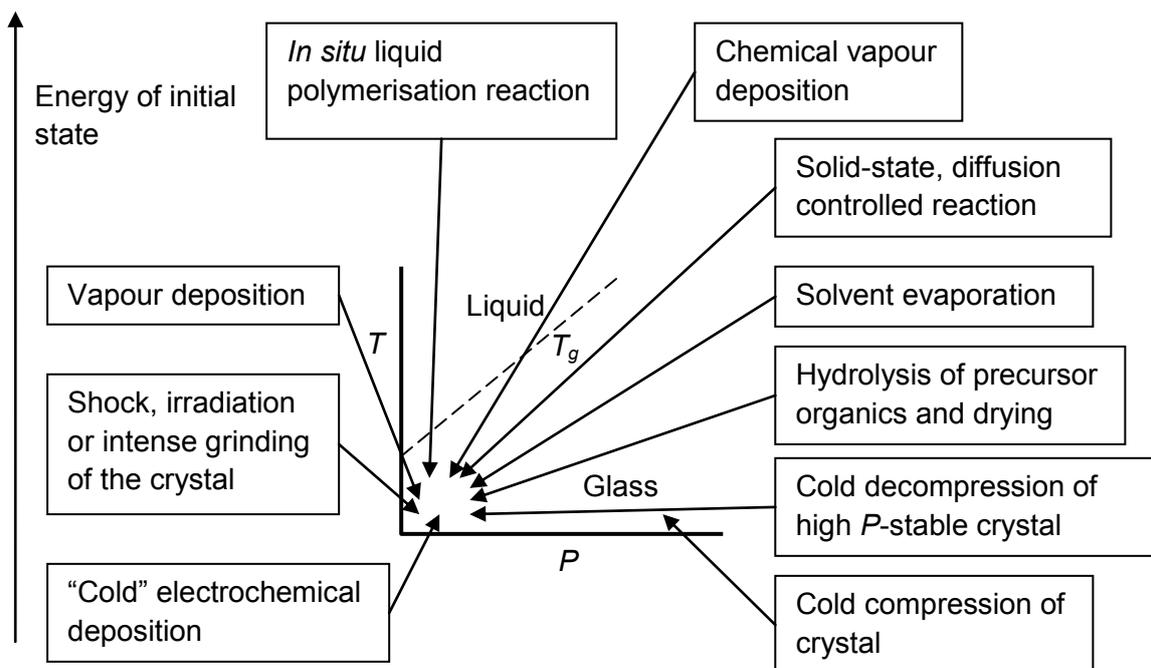


Figure 3.1: Schematic representation of the different routes to the amorphous state, adapted from Angell (1995:1926).

Since polymeric molecules (like excipients), large peptides, proteins as well as small organic and inorganic molecules can be amorphous, it is possible for a multi component pharmaceutical formulation to form an amorphous solid-state solution, analogous to a liquid solution. This can have severe consequences for the thermodynamic properties of the

formulation (Hancock & Zografi, 1997:1), including changes in physical and chemical stability, half life and dissolution rates.

One of the easiest ways of presenting the energy states of condensed matter is the energy landscape, which was described in great detail by Stillinger (1995:1937) and is illustrated in figure 3.2. As we know the potential energy of a phase is determined by several factors, including intermolecular distance and order of molecular packing. The energy landscape diagram takes this into account by plotting potential energy against molecular coordinates, consisting of the different positions, orientations and conformations the molecules in the system can adopt. For example, intermolecular distance can be expressed in terms of molecular positions, while molecular packing orders can be expressed in terms of molecular coordinations (Cui, 2007:7). In the liquid phase, the molecules are close together and intermolecular interactions are strong. This is represented as small fluctuations in the potential energy state upon changing molecular coordinations. As the temperature further decreases, the intermolecular distances are reduced further and the intermolecular interactions also strengthen further. This causes an even further fluctuation in energy with molecular coordination, because the molecules now need to overcome more hindrance in order to change their molecular coordinations. In the supercooled liquid region the liquid starts to show structural heterogeneity, where certain molecular coordinations have lower potential energy than others and will be “preferred” by natural laws. It is believed that this initial heterogeneity is the result of some sort of local order, resulting from directional intermolecular interactions. Upon further cooling the system nears T_g and the heterogeneity becomes even more apparent. At this point, the energy fluctuations in the supercooled liquid may generate spots with higher local energy than the bulk liquid, and these molecules will create tiny stable crystals (or nuclei). The reason these high local energy spots are the origins of nuclei, is because nucleation requires high kinetic energy to overcome the energy barrier generated by the interfacial energy of newly formed nuclei. Crystals are illustrated in figure 3.2 as sharp dips because all crystals exhibit highly ordered molecular packing. Only particular “crystal-forming” coordinations can form and exist in crystals. The crystalline states will also always exhibit lower potential energy than disordered states (Cui, 2007:8).

The energy landscape offers us a powerful tool with which to visualise the reasons crystallisation might sometimes be difficult, through the dynamic redistribution of molecular coordinations (represented by dots in figure 3.2). In the supercooled liquid phase, the first signs of structural heterogeneity appear as molecules change their coordinations to the preferred lower potential energy conformations. However, in this phase there is only a small

energy difference between the crystallisation coordinations and the other energy basins, increasing the probability that the molecules will distribute into one of the wide energy basins, rather than the narrow crystal-forming basins. As the temperature is cooled further, and the liquid nears T_g , the energy difference between the crystal-forming coordinations and the other energy basins increase, due to the fact that only crystals can propagate in three dimensions, thereby significantly lowering their potential energy.

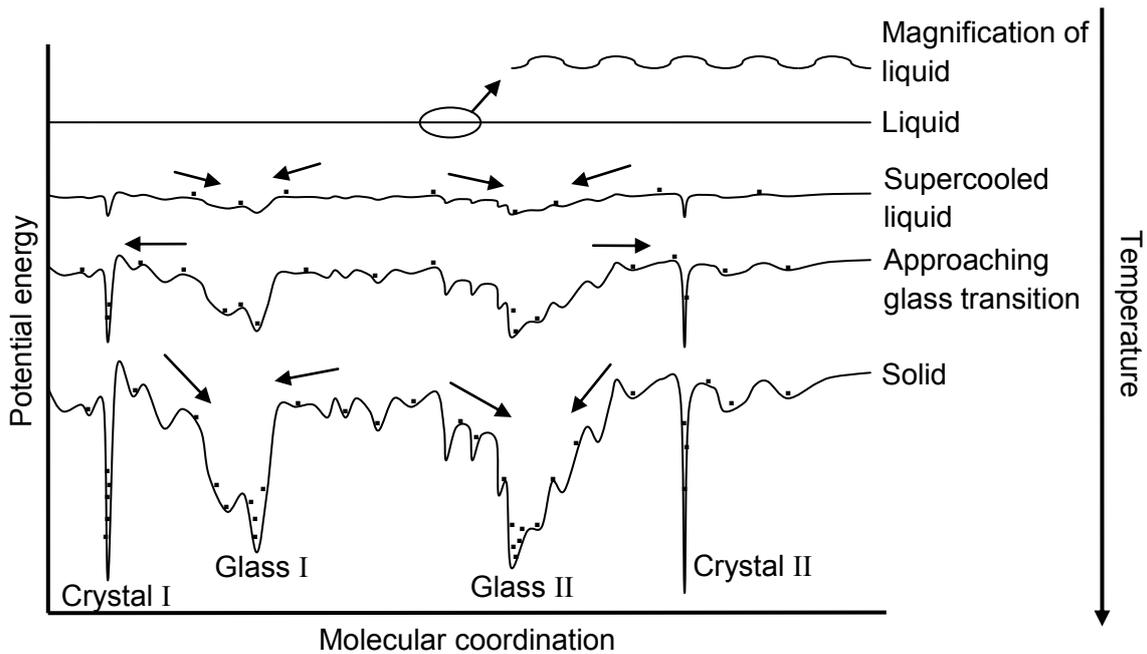


Figure 3.2: The energy landscape of liquid and solid phases, adapted from Cui (2007:7).

Amorphous materials have higher energy levels due to the structural frustration experienced as a result of its inability to grow three dimensionally over long ranges of order. This short range order of amorphous materials play a crucial role in our understanding of the amorphous state and will be described in more detail in the next paragraph. If the molecules have sufficient molecular mobility, and hence kinetic energy, they could roll from the wider, but shallower, energy basins to the deeper narrow basins with lower potential energy. The kinetic energy would allow the molecules to “climb” over energy barriers and fall into crystal-forming coordinations. It is a well known fact that all amorphous material will eventually return to its (lowest energy) crystalline state, however, the rate at which this transition occurs can vary greatly. The reason being that as the temperature decreases, and the viscosity increases, the molecules lose kinetic energy and their movements become sluggish. This increases the time it takes for an amorphous material to crystallise, depending on the positions of the molecular coordinations in question relative to a crystal-forming coordination

(Cui, 2007:8). The energy landscape is also a valuable visualisation tool for the influence of the thermal history on the sample. If the temperature is reduced slowly molecules can have sufficient time adopt the preferred coordinations and arrange themselves in one of the global energy minima, leading to crystallisation. On the other hand, if the temperature is rapidly decreased, the molecules lose their kinetic energy too quickly and become “frozen” in one or more of the wide energy basins, and the system forms a glass. With these two temperature changes as extremes, it is only reasonable to assume that different cooling rates between them could give a mixture of crystalline and glassy states depending on the amount of molecular coordinations the system can adopt. It was mentioned earlier that different polymorphs exist in the amorphous state, illustrated in figure 3.2 by the two wide energy basins as glasses I and II, and although this is true for water (Mishima *et al.*, 1984:393) and a few inorganic materials (Poole *et al.*, 1997:322) it is yet to be conclusively proven for small organic molecules (Cui, 2007:13). The reason being, that it is nearly impossible to conclusively discern between two organic glasses. Techniques used for the elucidation of crystals, such as x-ray powder diffraction and single crystal x-ray diffraction, do not apply to amorphous material. It can only be used to confirm the existence of an amorphous state, but not to differentiate between them, because of the diffuse “halo” effect. Furthermore, even though glasses show structural heterogeneity, it is only on a molecular scale, not a macroscopic scale. In other words, they are not two separate phases.

As mentioned in the previous paragraph, amorphous solids have short range order, usually only over a few molecular dimensions, and their physical properties differ from their corresponding crystalline states. This decrease in the order range of amorphous materials causes it to occupy a larger specific volume than the corresponding crystal, almost akin to the liquid state, although the positions of the molecules relative to each other are also more random than in a liquid. Plotting the enthalpy (H) or specific volume (V) of a solid as a function of its temperature (figure 3.3), illustrates the origin and need of the glass transition in an amorphous solid. As the temperature rises, the volume and enthalpy of the crystal increase slightly. This increase is governed by the heat capacity (C_p) and thermal expansion coefficient (α) of the specific crystal. At the melting temperature (T_m), there is a sharp discontinuity in the volume and enthalpy as the crystal undergoes a first-order phase transition to the liquid state. Upon rapid cooling of the melt (usually with liquid nitrogen) the values of H and V follow the equilibrium line (slope) of the liquid beyond the melting temperature into the “supercooled liquid” region. This decrease in H and V continues on further cooling, until the slope changes at a characteristic temperature, known as the glass transition temperature (T_g). Below T_g the glassy material has a higher H and V than the

supercooled liquid and the original crystalline state, giving rise to enhanced thermodynamic properties (for example solubility) and greater molecular mobility (Hancock & Zografi, 1997:2).

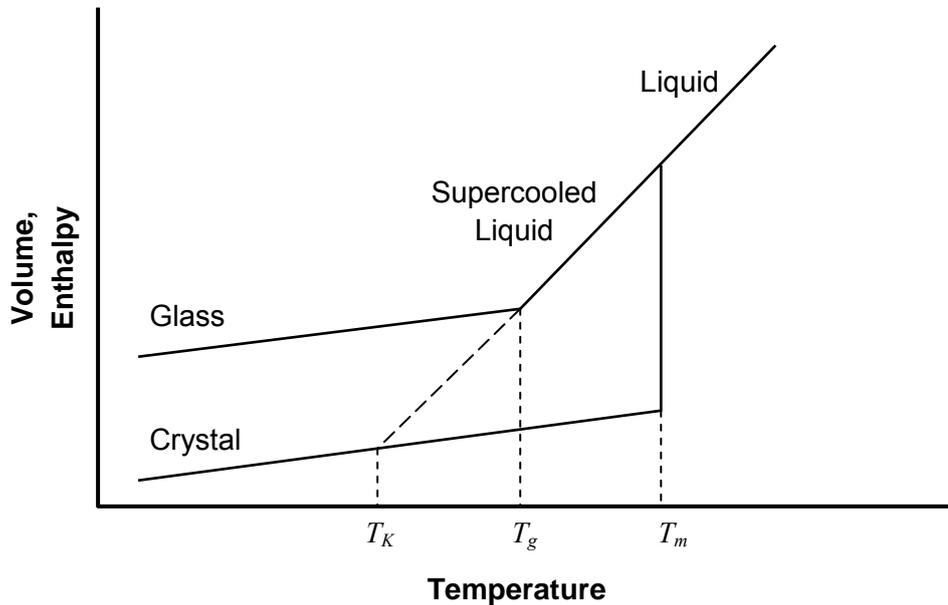


Figure 3.3: Schematic depiction of the variation in volume or enthalpy with temperature (Hancock & Zografi, 1997:2).

From a physical point of view the glass transition is incredibly important because it prevents the Kauzmann Paradox and entropy catastrophe. Rao *et al.* (2001:4), while discussing the fragility of glassy systems, reported that above T_m the entropy of the melt is largely configurational, arising out of the numerous energetically equivalent arrangements in which the system can be realised. As the melt is cooled towards T_g , the configurational entropy is gradually lost, but never completely. This means that as the temperature nears T_g , fewer and fewer configurational states become available. At and below T_g the different configurational states have become so few that the remaining ones can only be accessed through highly cooperative rearrangements, causing a rapid increase in viscosity and freezing the system into a state corresponding to one of the many local free energy minima. This freezing of the system is also associated with an abrupt decrease in C_p , giving the glassy system a C_p which is only slightly higher than that of the crystal, compared to the much higher C_p of the supercooled liquid. Upon cooling from T_m the supercooled liquid loses more entropy than the crystal, but it can afford this entropy loss because it had acquired configurational entropy at T_m in the form of equation 3.1:

$$= \text{---} \quad (3.1)$$

If the system was to lose all of the acquired configurational entropy, it would reach the Kauzmann temperature (T_K), subject to the constraint (equation 3.2):

$$= \int_T^T \quad (3.2)$$

Where ΔH_m is the melting enthalpy, ΔS_m is the melting entropy (from equation 3.1) $\Delta C_p = C_p(\text{melt}) - C_p(\text{crystal})$. The temperature T_K can never be attained, because at $T_g > T_K$ the melt becomes so viscous that configurational changes cannot occur on ordinary time scales. If the glass transition did not occur, and the melt could be cooled to below T_K , there would be a paradoxical situation where the supercooled liquid would have lower entropy than the parent crystal. A thermodynamic absurdity known as the Kauzmann Paradox (figure 3.4). The glass transition and its role in determining the thermodynamics of an amorphous system will be discussed in more detail later. For now, let us focus on the pharmaceutical implications of amorphous systems.

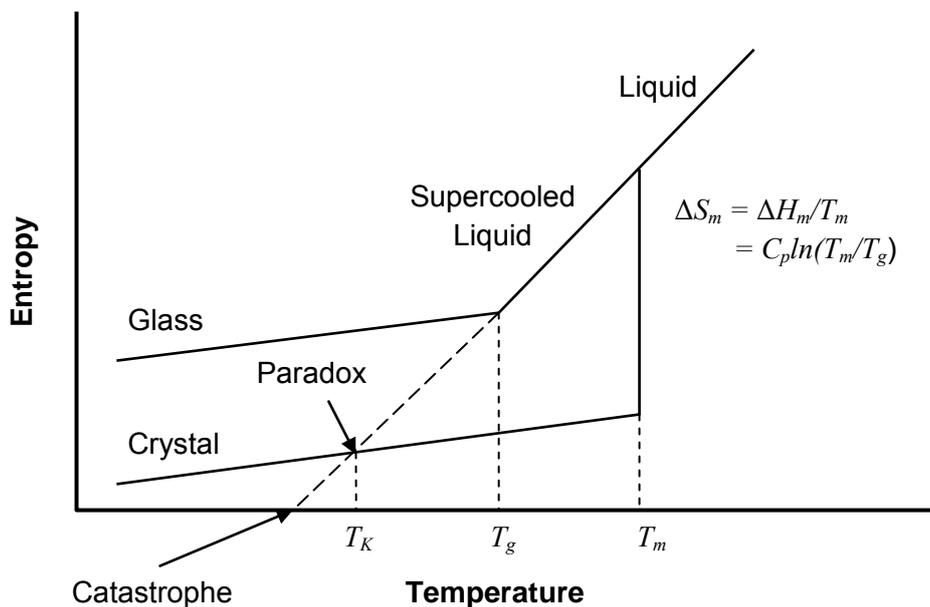


Figure 3.4: Schematic depiction of the Kauzmann paradox and entropy catastrophe (Rao *et al.*, 2001:5).

From a pharmaceutical perspective the amorphous state leaves us in an interesting situation. Although the high internal energy and specific volume of the amorphous system may lead to enhanced dissolution and bioavailability (Hüttenrauch, 1978:55), it may also convert back to the crystalline state during processing or storage (Yoshioka *et al.*, 1994:1700). For example the recrystallisation following powder compression described by Mitchell and Down (1984:337) while studying the compacts of various active pharmaceutical ingredients (API's) and other materials prepared on a single punch tablet press using both unlubricated and lubricated dies. The crystal growth rates after compression varied from within 60 minutes for aspirin, anhydrous calcium gluceptate and metoclopramide hydrochloride to about 12 weeks for sucrose and hydrous iron sulphate. Although the tablets punched with the lubricated die exhibited a slower onset of crystallisation, these tablets also eventually showed considerable structural reorganisation after about eight days, until no significant difference remained between those tables punched with and without lubrication. This recrystallisation after powder compaction, also known as post compression hardening, will be discussed in more detail in the section on molecular mobility.

There are two main considerations for a pharmaceutical scientist when dealing with a compound that is in the amorphous state. In the first case, a material may be intrinsically amorphous (for example microcrystalline cellulose, starch, poly(vinylpyrrolidone) and many other excipients) or rendered amorphous on purpose, in order to take advantage of the enhanced thermodynamic properties. In the second case, a material in the crystalline state may have been inadvertently rendered amorphous by some process (for example milling, lyophilisation, granulating and drying). Knowing the difference is very important when considering how to deal with the formulation of the material, since, in the latter case efforts should be made to convert the amorphous portions back to the crystalline state, where as if the material was intended to be amorphous efforts should be made to prevent it from crystallising (Hancock & Zografi, 1997:2).

3.3 MOLECULAR MOBILITY

At the core of the amorphous state's unique physical chemical properties, is its existence in a higher potential energy state than the corresponding crystal. This high energy state gives the molecules in an amorphous system a higher degree of freedom, which manifests as rotational and translational motions. As described in the previous section, the glassy state is a highly viscous state of the supercooled liquid which freezes the system into one of many

possible local free energy minima, with a corresponding loss of configurational entropy and C_p . The molecules are not packed into lattices, as is the case with crystals, leaving them more room to move. The implication of this enhanced molecular mobility, for a pharmaceutical scientist, is that special care needs to be taken when studying the physical chemical properties of the amorphous system.

Rotational and translational motions can greatly complicate studies of the glass transition. The scale and types of these motions are influenced by temperature and these motions can also work cooperatively or even couple, further complicating these studies. This temperature dependence of molecular motions directly determines many important physical properties of amorphous materials, such as the location of the glass transition temperature and the ease of glass formation (Hancock & Zografi, 1997:2). One can only say for certain that at T_g the mean molecular relaxation time (τ) associated with the predominant molecular motions is about 100 s and that T_g can be expected to vary with experimental heating and cooling rates, sample mass (Koike, 1995:1183), sample history, sample geometry (Mayes, 1994:3114; Keddie *et al.*, 1994:219) and sample purity (Her *et al.*, 1994:219). The different types and rates of these molecular motions have a profound influence on the choice of technique used to study the glass transition temperature (Hancock & Zografi, 1997:2).

The temperature dependence of molecular motions is most frequently described using the empirical Vogel-Tammann-Fulcher (VTF) equation 3.3 (Angell, 1995:1924; 1995:6677):

$$\tau = \tau_0 \exp(DT_0/T - T_0) \quad (3.3)$$

Where τ is the mean molecular relaxation time, T is the temperature and τ_0 , D , and T_0 are constants. The value of T_0 in the VTF equation is believed to correspond to the theoretical T_K and τ_0 can be related to the relaxation time constant of the unrestricted material. When T_0 is 0, the familiar Arrhenius equation is obtained and D is directly proportional to the activation energy for molecular motion. When T_0 is greater than 0, there is a temperature dependent apparent activation energy. In almost all cases molecular relaxations in amorphous systems follow a nonexponential function. This nonexponentiality appears to be the result heterogeneous microstructure within glasses which leads to a distribution of types and rates of molecular motion under any given temperature conditions (Hodge, 1995:1945). The empirical Kohlrausch-Williams-Watts (KWW) stretched exponential function (equation 3.4) is most often used to describe the distribution of molecular motions (Hancock & Zografi, 1997:4):

$$\Phi(t) = \exp\{-(t/\tau)^\beta\} \quad (3.4)$$

Where $\Phi(t)$ is the extent of relaxation at time t , and β is a constant. A β value of unity corresponds to a single relaxation time with exponential behaviour and therefore the smaller the value of β , the more the distribution of molecular motions deviates from a single exponential. A general means of ranking glasses in terms of the temperature dependence of molecular motions, similar to Angell's strong/fragile classification system (which will be discussed later), would be of great use to pharmaceutical scientists but has not yet been developed because of the greater complexities of the glassy state (Hancock & Zografi, 1997:4).

Another method of evaluating the molecular motions is by describing them in terms of the temperature dependence of viscosity (η) above T_g . This is done by using the Williams-Landel-Ferry (WLF) equation (3.5), first used to describe the η in polymers above T_g :

$$\eta = \eta_g \exp\{C_1(T - T_g)/(C_2 + (T - T_g))\} \quad (3.5)$$

Where η_g is the mean viscosity at T_g and C_1 and C_2 are constants. The constants C_1 and C_2 are found to be quite universal for a range of polymers and are equivalent to $DT_0/(T_g - T_0)$ and $(T_g - T_0)$ respectively in the VTF equation (Williams *et al.*, 1955:3701). Although the WLF model was first introduced to study polymers, it has also been shown to fit the viscosity data for several small organic molecules using the universal constants (Ollett & Parker, 1990:355; Soesanto & Williams, 1981:3338). It should be noted that, as with any model, there are limitations and in some cases the values cannot be assumed to be accurate.

Angell (1995:1924; 1995:6677) stated that it is possible to classify amorphous systems as "strong" or "fragile", depending on the magnitude and temperature dependence of the apparent activation energy for molecular motions near and above T_g (figure 3.5). A strong amorphous system exhibits Arrhenius-like changes in its molecular mobility with temperature and a relatively small change in C_p at T_g . The opposite is true for a fragile amorphous system, which has a stronger temperature dependence of molecular mobility and a large change in C_p at T_g . Examples of these fragile amorphous systems are molecules that are nondirectionally and noncovalently bonded. The constant D (known as the strength parameter) in the VTF equation is an indicator of the fragility, with low values (<10) corresponding to fragile glass formers and high values (>100) being indicative of strong glass formers.

The conditions under which a glass was formed determine the extent to which the glass's properties deviate from equilibrium. We can therefore expect multiple metastable glasses to exist below T_g (Pikal *et al.*, 1978:767; Roy, 1970:33), and even polyamorphic glasses that convert via first-order transitions (Hachisuka *et al.*, 1991:2382; Matsuda *et al.*, 1992:627; Tsukushi *et al.*, 1994:187). The cooling rate of the supercooled liquid not only determines the polyamorph formed, but also the types and scales of the molecular motions below T_g . The consequences of different thermal histories on amorphous systems have been widely reported and are too numerous to be described in detail, but some examples include the works of Angell (1995:1924; 1995:6677), Guo *et al.* (1991:1500), Byron & Dalby (1987:65), Ahlneck & Zografis (1990:87), and all of the previously quoted works in this paragraph, to name but a few.

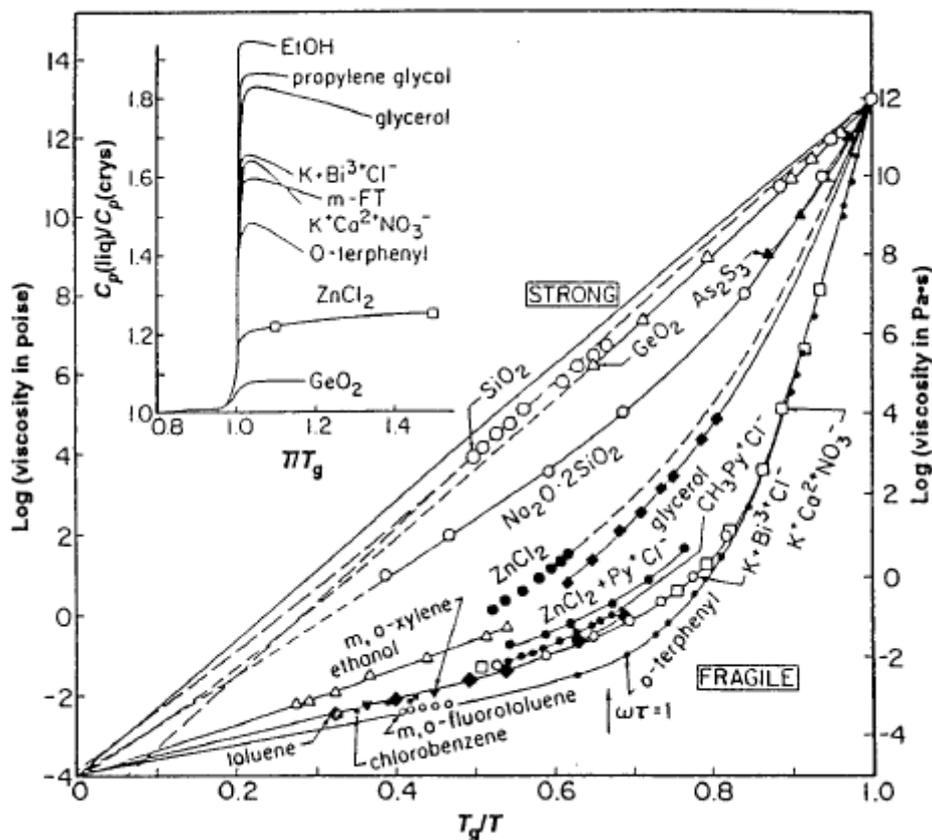


Figure 3.5: Molecular mobility (expressed as viscosity) of amorphous materials as a function of normalised temperature above T_g . Figure adapted from Angell (1995:1924).

A good visual representation can also be found in the work of Aasland and McMillan (1994:634), who photographed the microstructure of a quenched $Y_2O_3-Al_2O_3$ melt (figure 3.6). The photo shows droplets of one glass phase embedded in a matrix of another glass phase. Both of these glass phases are of identical composition ($Y_2O_3-Al_2O_3$), the only difference being the densities. The droplets are the low density and low entropy phase, while the matrix constitutes the high density phase. During cooling of the melt, the low density droplets started to form via nucleation from the high density liquid, but its progress was abruptly halted by the rapid increase in viscosity associated with the ultra fast cooling. It is reasonable to assume then, that if the melt was allowed to cool slowly (for example at room temperature), the droplet phase could have continued to grow from the matrix, further increasing the heterogeneity of the system. This is but one example, not only of the influence of thermal history in the amorphous system, but also of how the same glassy system can have points of varying density, directly influencing local molecular mobility.

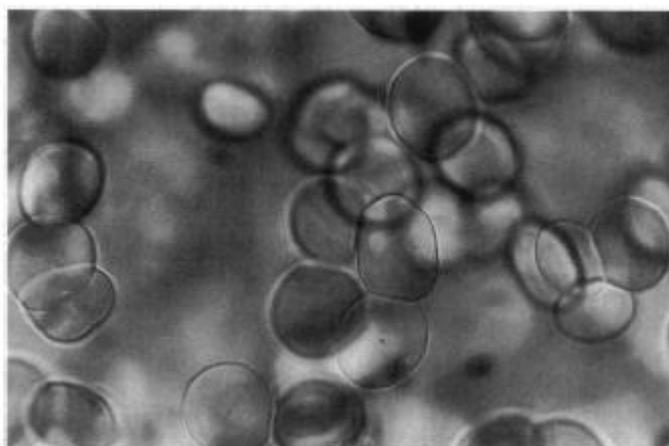


Figure 3.6: Microstructure of a quench cooled $Y_2O_3-Al_2O_3$ melt, showing the two glassy phases of identical composition, adapted from Aasland and McMillan (1994:634).

The rate at which molecules in the solid state undergo rotational and translational motions is a critical factor for a pharmaceutical scientist to consider when dealing with the solid-state properties of pharmaceuticals, especially those in the amorphous state. Hancock and Zografi (1997:8) examined this important consideration by looking at its impact on three broad areas: crystallisation, chemical degradation and mechanical responses to stress.

3.3.1 CRYSTALLISATION

It is a known fact that molecules in the amorphous state are thermodynamically metastable relative to the crystalline state. This means that the potential for crystallisation during handling and storage is always present. This crystallisation is responsible for phenomena such as postcompression hardening of tablets (Elamin *et al.*, 1994:213; Lordi & Shiromani, 1984:729; Mitchell & Down, 1984:337), lyophilised cake collapse (Levine & Slade, 1988:2619) and particle aggregation in dry powder inhalers (Ward & Schultz, 1995:773). In all of these cases the amorphous systems were rendered crystalline by some process and it is the work of the pharmaceutical scientist to study the mechanisms behind the change and attempt to counter act it.

Since crystallisation from the amorphous state is primarily governed by the same factors that determine crystallisation from the melt (Turnbull & Fisher, 1949:71), we can illustrate the important factors to consider by using the equation for heterogeneous nucleation (equation 3.6) from the melt. The rate of nucleation (I) is expressed as:

$$I = A \exp(-(\Delta G_a + \Delta G^*)/kT) \quad (3.6)$$

Where ΔG_a is the activation energy for transport across the nucleus-amorphous matrix interface, ΔG^* is the free energy change for nucleation with a critical nucleus of radius r , A is a constant, k is the Boltzmann constant and T is the temperature. Assuming the nucleus is a sphere, then ΔG^* can be expressed as equation 3.7:

$$\Delta G^* = 16\pi\Delta g^3/3\Delta G_v^3 \quad (3.7)$$

Where ΔG_v is the difference in free energy per unit volume between the crystalline and amorphous forms, $G_c - G_L$, and Δg is the interfacial free energy per unit area at the nucleus-amorphous matrix interface. Further, it can be shown that:

$$\Delta G_v = (G_c - G_L) \approx -(\Delta H_f)(\Delta T_r) \quad (3.8)$$

Where ΔH_f is the heat of fusion, $\Delta T_r = (T_m - T_c/T_m)$ is the degree of supercooling, T_m is the melting temperature and T_c is the crystallisation temperature.

What the equations above tell us is that for any amorphous system, the optimal temperature for nucleation (and hence crystallisation), will depend on the degree of supercooling below T_m and where the temperature lies relative to T_g . The molecular mobility decreases as the temperature nears T_g . The influence of the proximity of T_m to T_g and its impact on molecular

mobility and nucleation was probably best illustrated by Jolley (1970:173) and illustrated here in figure 3.7.

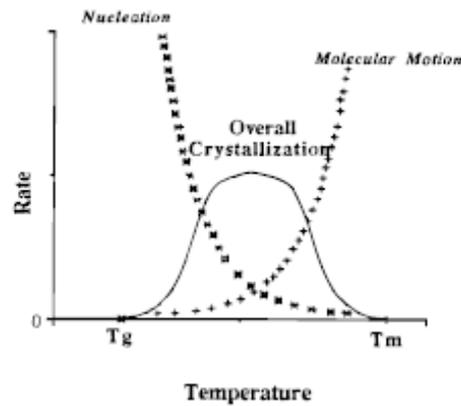


Figure 3.7: The parameters controlling crystallisation from the amorphous state. Adapted from Jolley (1970:173).

The increase in viscosity (where molecules are moving closer together but still possess sufficient kinetic energy to exhibit liquid-like behaviour) that accompanies cooling from T_m should give rise to a maximal crystallisation rate somewhere between T_g and T_m . Such a crystallisation can be seen in the work of Saleki-Gerhardt *et al.* (1994:237) while studying the disorder in crystalline solids. They found a crystallisation exotherm between T_g and T_m on a non-isothermal DSC scan of amorphous sucrose (figure 3.8).

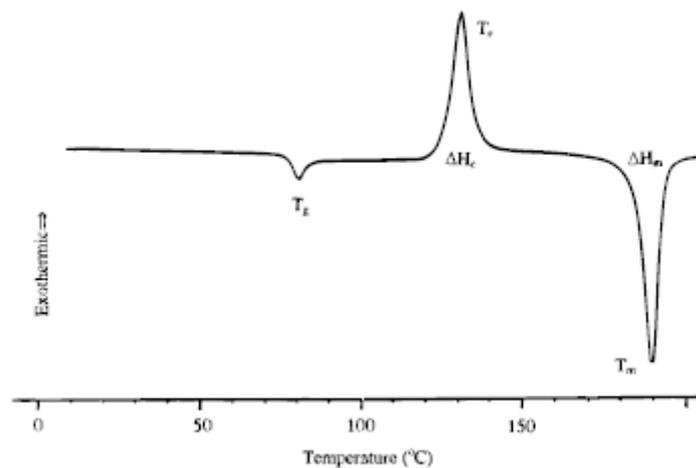


Figure 3.8: Non-isothermal DSC scan of amorphous sucrose, showing the T_g , T_m , heat of crystallisation (ΔH_c), T_m and heat of melting (ΔH_m). Adapted from Saleki-Gerhardt *et al.* (1994:239).

Much attention has been given to the T_g and its role in the stability of active pharmaceutical ingredients. However, there are many reported cases where crystallisation of amorphous pharmaceuticals have occurred at temperatures far below T_g (in some cases even as low as $T_g - 50\text{K}$) and in much less time than the typical pharmaceutical shelf-life of two years (Alig *et al.*, 1997:261; Bhugra *et al.*, 2007:455; Vyazovkin & Dranca, 2005:18637; 2007:7283).

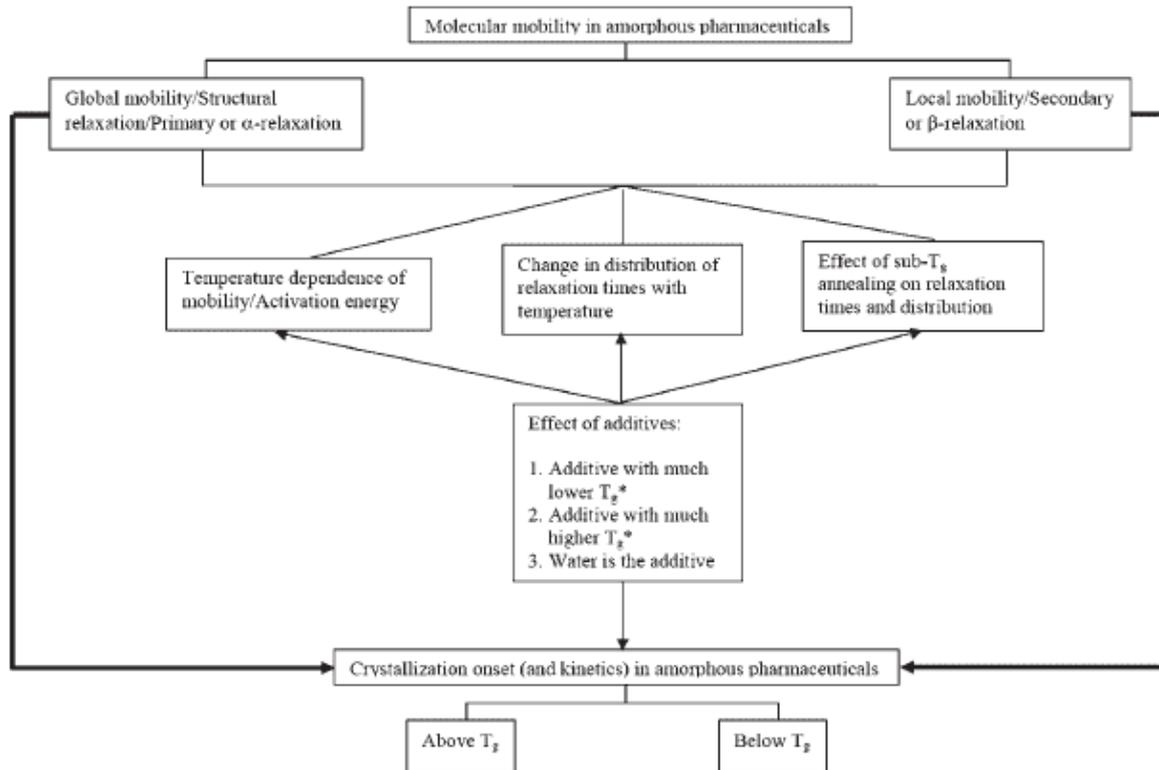


Figure 3.9: The types of molecular mobility in amorphous systems and the effect of additives. Scheme adapted from Bhattacharya and Suryanarayanan (2009:2937).

It was also discovered that the addition of small molecules to unstable therapeutic macromolecules (with a tendency to aggregate), substantially improved their stability. This increase in stability was credited to the inhibition of local molecular motions, brought on by the small molecules (Yoshioka *et al.*, 2006:961; 2007:1660). The recent studies by Vyazovkin and Dranca (2005:18637; 2007:7283) have shown that even if local molecular mobility is not directly responsible for instability in an amorphous system, it facilitates the global mobility (manifesting as the T_g) which destabilises the system. The relationship between local and global mobility has been well described by Ngai (2003:S1107) and from

that work it can be argued that local molecular motions are the precursors to glass transitions. Bhattacharya and Suryanarayanan (2009:2937) provided a schematic representation (figure 3.9) of the relationship between local and global mobility, mobility and crystallisation and the effects of additives on mobility and crystallisation. The α - and β -relaxations will be discussed in more detail later.

3.3.2 CHEMICAL REACTIVITY

One would expect the molecules in an amorphous system to have sufficient free volume and molecular mobility to react more readily than molecules in a crystal. Although this has been proven to be the case in several experiments (Carstensen & Morris, 1993:657; Oberholtzer & Brenner, 1979:863), the opposite is also true. In some cases the chemical reaction requires a certain amount of positional specificity between the reacting molecules, and in these cases the reaction occurs more readily in the highly ordered crystalline state (Sukenik *et al.*, 1975:5290; 1977:851). In cases such as these, preparation of the product/formulation in the amorphous state will actually increase the chemical stability of the system. This should give the pharmaceutical scientist more incentive to investigate the reasons behind the instability, assuming there is any, and offers a powerful tool with which to address the issue of chemical instability.

3.3.3 MECHANICAL PROPERTIES

The product manufacturability, stability and performance of a solid pharmaceutical are critically dependant on its rheological or mechanical properties. Most crystalline materials exhibit high levels of brittleness and/or elasticity upon exposure to external stresses. On the other hand, molecules in amorphous systems exhibit varying degrees of viscoelasticity, depending on their temperature relative to T_g (Hancock & Zografi, 1997:10). This viscoelastic behaviour allows an amorphous solid to flow under conditions of external stress, and is important for its function as an excipient, for example the creation of tablet bonds after powder compression (Sebhatu *et al.*, 1994:1233) and the prevention of fracture of the polymeric film coats of tablets. Care should therefore be taken when handling or storing an amorphous excipient for use in a specific purpose, as water absorption can plasticise the excipient, increasing molecular mobility and leading to crystallisation. Beyond a certain percentage crystalline content the excipient may lose its viscoelastic properties and will not be able to perform its role, such as the formation of tablet bonds mentioned above, thereby compromising the stability of the pharmaceutical formulation. An example is microcrystalline cellulose, which should contain about 30% amorphous content, used as a direct

compression tableting excipient. The threshold of water content in microcrystalline cellulose is between four and six percent, any concentration higher than that and the microcrystalline cellulose starts to lose its viscoelastic properties until all direct compact properties are eventually lost (Amidon & Houghton, 1995:923).

3.4 BETA RELAXATIONS

The local mobility in glassy systems originates from entire molecular motions or intramolecular motions, in the form of intramolecular reorientations (Sixou *et al.*, 2001:1845), these relaxations are noncooperative and occur much faster than α -relaxations (Paluch *et al.*, 2005:224205) with typical relaxation times of $<10^{-1}$ s. These noncooperative β -relaxations were shown to be universally present glasses from small organic molecules by Johari and Goldstein (1970:2372) and have since come to be known as Johari-Goldstein (JG) relaxations. It should be noted at this point that only relaxations involving motions of the entire molecule are classified as JG relaxations. Although some consider these motions to be spatially uniform (Wagner & Richert, 1998:19; Vogel & Rossler, 2000:4285; 2001:5802), Johari (2002:317) argues that these motions are confined to isolated regions in the glass.

Ngai (2003:S1107) presented an extended coupling model to explain the origin of these β -relaxations, in which the molecular dynamics of supercooled liquids involve three time regimes: short, intermediate and long. To better visualise this model, it is better to first return to the Kohlrausch-Williams-Watts (KWW) stretched exponential function model (equation 3.4) and review its underlying concepts. In Ngai's model, the short time regime is described as "caged" relaxations with only vibrational motions and a negligible change in $\exp(-t/\tau)$. The intermediate-time regime is characterised by noncooperative independent relaxations, the β -relaxations. These noncooperative β -relaxations also show an exponential decay in relaxation time, accompanied by a gradual increase in cooperative motions due to mutual interactions between neighbouring relaxing units. The long-time regime consists of slower, cooperative α -relaxations, resulting in the T_g . In Ngai's extended coupling model the independent β -relaxations are related to the cooperative α -relaxations by the concept of a segment of time, called the crossover time (τ_c), which is independent of temperature. Earlier work by Ngai (1998:6982) demonstrated that the same value of τ_c , about 2 ps as determined for glass-forming polymers, was also valid for small molecule organic glass formers. The relaxation time of the noncooperative motions was expressed in equation 3.9:

$$\tau_0 = \tau_\alpha^{\beta_{KWW}} \times \tau_c^{(1-\beta_{KWW})} \quad (3.9)$$

Where τ_0 is the independent relaxation time at T_g , τ_α is the α -relaxation time and τ_c is the crossover time. Ngai and Paluch (2004:857) then went on to show a close correlation between calculated noncooperative τ_0 and JG relaxations times in many class formers. This was yet another indication that that these β -relaxations are precursors to the cooperative α -relaxations.

When a supercooled melt nears the T_g , the relaxation time of the molecules covers a wide spectrum, leading to dynamic heterogeneity in the molecular motions (Sillescu, 1999:81). There are also regions of slow and fast relaxing molecules, due to varying degrees of local density or free volume, leading to spatial heterogeneity (Ediger, 2000:99). Aasland and McMillan (1994:634) have also proven that there can be regions of varying densities within the same glassy system (figure 3.6). This means that relaxation times in glasses (below T_g) are much more heterogeneous than in supercooled liquids (above T_g), implying that β -relaxation times are much more heterogeneous than α -relaxation times. Consequently, a pharmaceutical scientist will have to plan carefully when attempting to study these relaxations. Another important consideration for a pharmaceutical scientist, studying β -relaxations, is the fact that the activation energies of α -relaxations are much higher than those of β -relaxations (Johari, 1973:1766). The difference stems from the mechanism underlying these relaxations, namely cooperativity and noncooperativity respectively. β -relaxations have also been identified with a transition temperature characterised by a change in C_p , although this change is extremely weak compared to that of the T_g (Kishimoto *et al.*, 1973:3026). In the potential energy hyperspace of an α -relaxation (figure 3.10), the β -relaxations present as local energy minima, corresponding to a particular configuration obtained by molecular reorientation and restricted translational motion. Aging of the sample decreases the energy and entropy of the system, increasing the barrier of the global minimum for α -relaxation and subsequently decreasing the number of local minima (Johari, 2002:317). It is therefore imperative for the pharmaceutical scientist to take care when annealing an amorphous sample for the study of β -relaxations, as annealing for too long or at too high a temperature would decrease the number of β -relaxations and give an inaccurate assessment of the system's secondary relaxations.

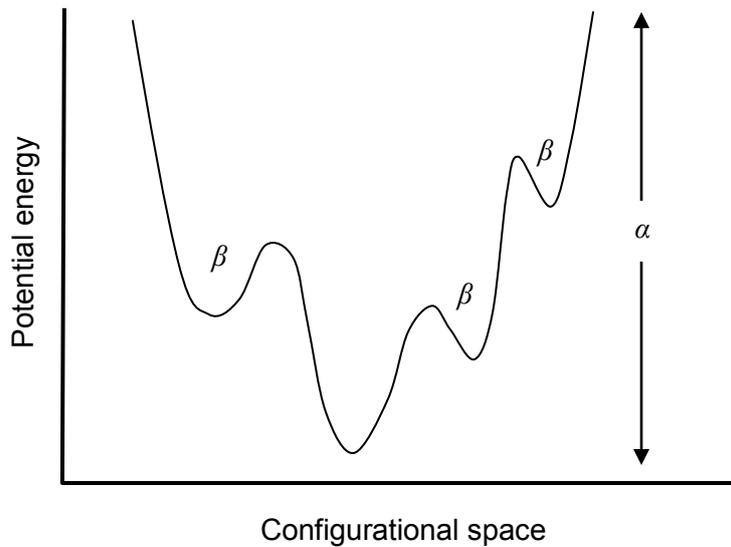


Figure 3.10: Schematic representation of the potential energy landscape of α - and β -relaxations. Adapted from Johari (1985:279).

3.5 ALPHA RELAXATIONS (GLASS-TRANSITIONS)

Contrary to β -relaxations, α -relaxations require more cooperation between neighbouring molecules in order to change in their relative positions. These relaxations are responsible for the glass transition. The name was given because these relaxations appear at a lower frequency in a dielectric relaxation profile. Because of the highly cooperative nature of these molecular motions, it is also sometimes referred to as “global mobility” (Bhattacharya & Suryanarayanan, 2009:2937).

These cooperative molecular motions lead to non-Arrhenius behaviour near the T_g of fragile amorphous material. The size of cooperatively rearranging regions can be defined using configurational entropy (S_c) via the Adam-Gibbs equation (3.10):

$$\tau = \tau_0 \exp(C/TS_c) \quad (3.10)$$

Where C is a constant. The importance of this equation is its ability to link supercooled liquid dynamics with the thermodynamic function S_c , which changes with temperature according to equation 3.11:

$$S = \int_T^T \left(\frac{C_p}{T} \right) \quad (3.11)$$

Where C_p^{conf} is the configurational heat capacity, the difference in C_p between the liquid and crystalline states (figure 3.11) and T_2 is the temperature at which S_c reaches zero (Crowley & Zografi, 2001:82).

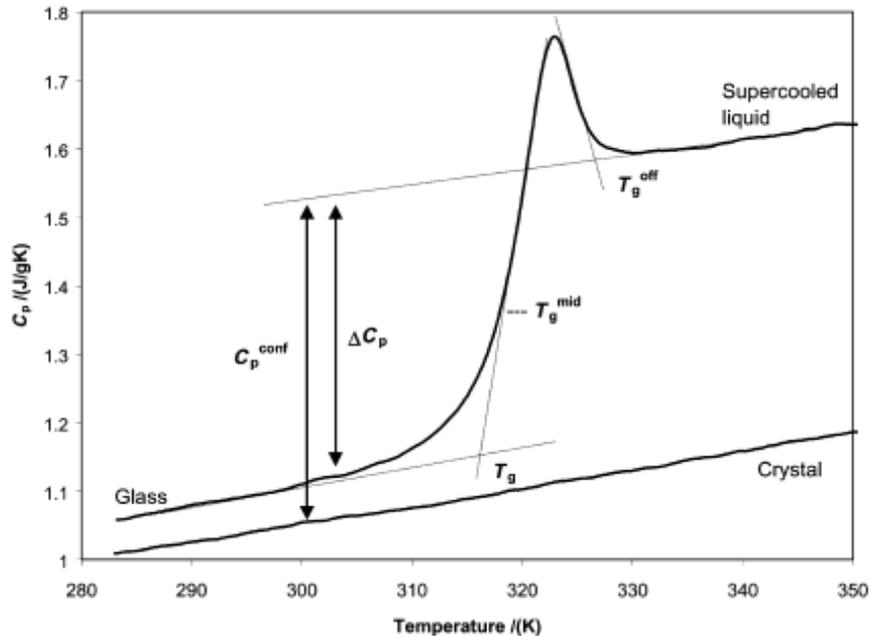


Figure 3.11: A glass transition of amorphous indomethacin, showing the T_g , T_g^{mid} , T_g^{off} , ΔC_p and C_p^{conf} , adapted from Crowley and Zografi (2001:84).

Although the T_g and its importance to a pharmaceutical scientist have been described earlier, in the section about molecular mobility, it should be noted that determination of the activation energy of α -relaxations offers a valuable tool with which to probe physical properties of a glassy system, such as the fragility parameter (m) and the strength parameter (D). Knowledge of these properties can be very valuable when considering which dosage form to choose for formulation, as well as long term stability of the amorphous system.

3.6 LIQUID CRYSTALS

We have now seen that cooling of the melt, either by supercooling or viscous slowdown, can lead to amorphous-, metastable semi-crystalline- and even crystalline forms of the compound in question. However, depending on the chemical structure of the compound, liquid crystals (LC) can also be formed. These LC's are liquids that possess a certain level of

orientational order, manifesting in the LC molecules pointing in a certain direction. Of course, for these molecules to point in a direction a certain degree of freedom is needed, found in translational (positional) freedom. Translational freedom is essential for LC behaviour and therefore LC's can be categorised into two classes: thermotropic and lyotropic. Thermotropic LC's are formed by temperature variations, and are usually one compound systems, while lyotropic LC's are formed by dissolving the compound in certain solvents and therefore consist of multiple compounds (solvent and solute). Both of these processes increase the molecular mobility of the compound, thereby giving it sufficient translational freedom to reorient into a LC (Cui, 2007:14). The LC phase can also consist of multiple subphases, of which nematic and smectic are the most common. The nematic phase consists of molecules pointing in only one direction, and therefore exhibit only linear orientational order. Smectic phases consist of molecules assembled into layers and exhibit two-dimensional order.

Thermotropic LC's are formed by temperature changes, such as the cooling of a melt or heating of a solid, for example above the T_m the system is isotropic and stable. Because of the high kinetic energy of the system the molecules cannot align themselves in only one direction. Cooling of the system decreases the kinetic energy as well as the molecular mobility. At a certain point above T_m the molecules begin to stabilise and point in a certain direction. This marks the beginning of LC behaviour in the system. Upon further cooling, now below T_m , the molecular mobility decreases to such an extent that translational movement is no longer possible, and the LC crystallises into an ordered crystal or "freezes" into a glassy state (Wunderlich & Grebowicz, 1984:23). As mentioned above, the structure (or more specifically the molecular geometry) plays a vital role in LC behaviour. The molecules must be able to align in order for the system to display directionality. Molecular shapes that allow this sort of alignment are either rod- or disc-like. As a general rule, thermotropic LC formers have a rigid core with flexible outer groups, thereby increasing the activation energy needed for rotational reorientation. This allows the molecules to maintain certain orientations while keeping fluidity and translational mobility. Alternatively, lyotropic LC formers are often elongated amphiphilic (surface active) molecules which align themselves in such a manner that the part of the molecules with the highest affinity for the surrounding media will form an outer layer, hiding the rest of the molecule and forming anti-parallel double layers and smectic LC phases (Cui, 2007:15). In addition to molecular geometry, molecular interactions such as dipole-dipole interactions and steric effects also influence LC behaviour. Larger organic molecules with multiple chiral points can, upon heating, absorb enough energy for rotational reorientations to occur. Rather than pointing in one direction like normal nematic

phases, chiral LC formers orient in a helical fashion because of steric effects. These nematic phases are called “chiral nematic” phases.

It is important for the pharmaceutical scientist to consider that any pure phase, including ordered crystals, amorphous solids and isotropic melts, might exhibit LC behaviour under conditions of temperature change and dissolution (in water or organic solvents). These LCs cause multiple phase transitions, depending on the amount of energy added to the system, as it moves from the solid- or semi-solid- to LC- to isotropic liquid phases and potentially back again if the energy is removed. LC systems have low temperature thresholds for these phase transitions, meaning that the energy needed to induce them can accidentally be exceeded by some formulation process. These phase changes have a considerable impact on the integrity of a pharmaceutical formulation, and screening of the drug and excipients (such as hydroxypropylcellulose, ethylcellulose and cellulose acetate) for LC behaviour should be a priority. Furthermore, certain lyotropic LC formers in liquid pharmaceutical formulations have been proven to cause haemolysis and opalescence (Cui, 2007:17), making them a serious regulatory concern.

3.7. CONCLUDING REMARKS

The amorphous field of study is dynamic and exciting, with broad implications for the pharmaceutical scientist. The nature of pharmaceuticals lends itself greatly to amorphous systems, in terms of excipients, API's and formulation processes, and the need to manipulate these systems in order to achieve certain formulation goals. In this chapter, we discussed the theories behind the amorphous system in order to gain a better understanding of its underlying mechanisms. Only through understanding of these mechanisms, can we attempt to study and manipulate the amorphous state. In the coming chapter, we will discuss the instruments and methods used to investigate the different polymorphic and amorphous forms obtained in this study.

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