CHAPTER 1
SOLID STATE OF PHARMACEUTICAL COMPOUNDS

1.1 Introduction

Of the most important challenges in the pharmaceutical industry are the discovery of new active pharmaceutical ingredients (API's) and the improvement of existing ones through continuous research. Polymorphism is a phenomenon that relates to the existence of two or more crystal forms of a single compound in its solid state (Cui, 2007:9; Yu *et al*., 1998:118). The pharmaceutical industry is dominated by solid state materials, whether APIs or excipients (Cui, 2007:5). The solid phase can be characterised as crystalline or non-crystalline, depending on the packing of the molecules within the crystal lattice (Cui, 2007:6; Stephenson *et al*., 2001:67; Yu *et al*., 1998:118). The importance of polymorphism in the search for new and improved APIs must be emphasised. Polymorphic forms of a drug may present with different physico-chemical properties (Stephenson *et al*., 2001:67; Yu *et al*., 1998:118). The characterisation of the physico-chemical properties of new polymorphic forms is of utmost importance in the discovery of new and improved drugs (Yu *et al*., 1998:118). Through characterisation of the different polymorphs of a solid, the opportunity arises to study and optimise certain characteristics of the solid form. These properties, among others, include solubility, stability, dissolution rate, bioavailability and hygroscopicity of the crystalline or non-crystalline form (Kratochvíl, 2011:129).

1.2 Polymorphism

1.2.1 Defining polymorphism

Different crystal structures, containing only one molecular species, were discovered by Mitscherlich in 1822-1823, which led to the first crystallographic use of the term "polymorphism" (Bernstein, 2002:2). The term polymorphism can be divided into two Greek words, i.e. "poly", meaning many and "morph", relating to the form. Therefore, the simplest definition of polymorphism is the existence of the many/different forms of a compound in its solid state. In the context of solid state, the term polymorphism can be

described as the existence of two or more crystal forms of a compound in its solid state (Bernstein, 2002:2; Yu *et al*., 1998:118).

According to McCrone's definition (1965:725), "the polymorphism of any element or compound is its ability to crystallise as more than one distinct crystal species" (Hilfiker *et al*., 2006:1). By definition, some authors include the existence of hydrates, solvates and amorphous forms in the term polymorph. Yu *et al*. (1998:118) state in an extended definition, as supported by various authors, that all solid forms, derived from the same molecular species with unchanged vapour, liquid or solution phases, are included in the definition of polymorphism.

1.2.2 Importance of polymorphism

As the definitions of polymorphism describe, most pharmaceutical compounds can exist as more than one crystal form. Through thorough research and characterisation, the thermodynamically most stable, crystal forms of active pharmaceutical compounds are determined. In most pharmaceutical products these stable, solid forms are utilised to ensure product stability and long shelf-life. Although most of these solid forms are generally stable, they are also known to be the forms that have less free energy and therefore they are less soluble and allow for a slow dissolution rate (Snider *et al*., 2004:394). Ultimately, poor bioavailability is the consequence of poor pharmacokinetic properties of the solid forms. Poor bioavailability must therefore be improved through proper formulation strategies in order to reach an acceptable amount of drug compound in the system and to ensure pharmacological drug efficacy (Snider *et al*., 2004:394). In effect, where an active drug compound with poor pharmacokinetic properties is used to develop a pharmaceutical product, the processes of development and formulation become much more complicated, time-consuming and costly (Chen *et al*., 2006:E402; Florence & Attwood, 2009:18; Singhal & Curatolo, 2004:336; Wu *et al*., 2010:3).

As mentioned, the main objectives of pharmaceutical research are to either improve existing APIs, or to develop new ones. Polymorphism studies of pharmaceutical compounds reveal the existence of different crystal forms for each compound. Active characterisation of the different crystal forms is of importance, since the existence of resulting forms cannot be predicted and neither can their physical and chemical properties. Such different crystal forms have different levels of free energy within their structures that may result in differences in their physical and chemical properties. This implies that the

solubility, dissolution rate and bioavailability could be improved by studying and characterising the phenomenon of polymorphism on active pharmaceutical compounds, to hence enable selecting the polymorph that remains most stable in the preferred dosage form for the relevant route of administration (Florence & Attwood, 2009:18; Raw *et al*., 2004:400; Singhal & Curatolo, 2004:336; Wu *et al*., 2010:4).

Knowledge of the physico-chemical properties of different solid forms of a pharmaceutical active compound can be utilised to optimise various aspects in manufacturing and the quality control of the pharmaceutical product. Factors, such as powder flow and compressibility are influenced by differences in crystal forms. The conditions for storage can, for example, be determined in order to ensure that the product remains stable for the longest time possible and to avoid chemical and structural instability, due to phase transformations and degradation of the active compound. Instability, due to phase transitions, can influence the concentration of active within the product. Therefore it is essential that these factors are dealt with during the product development phase and the research of the solid state properties of an active ingredient (Florence & Attwood, 2009:17; Raw *et al*., 2004:400; Snider *et al*., 2004:394).

1.3 Solid state

The physical state of matter in which a pharmaceutical compound may exist is a solid, a liquid, or a gas (Aulton, 2002:16; Cui, 2007:5). The most common state for the use of pharmaceutical compounds is the solid state (Cui, 2007:4; Vippagunta *et al*., 2001:4; Wu *et al*., 2010:3). Solid state materials are characterised through their inability to change the shape and volume of their structures. A solid doesn't expand or flow to fill a certain unoccupied space, as they consist of atoms, molecules, or ions that are bound in such tight manner that it stay in the solid phase under a specified set of conditions. The arrangement of molecules within a solid can be in an organised and repeating fashion (crystalline), or in an unorganised way (amorphous).

The study of the solid state properties of AP'Is directly impact on all aspects of the pharmaceutical industry. The lack in ability to predict the possible crystallisation outcomes of a solid form poses a tremendous challenge to solid state researchers (Braga *et al*., 2009:26). Therefore, it is important that the molecular structure of a solid phase is well understood in terms of its thermodynamic and kinetic properties. This understanding will

ultimately improve the control and design of APIs in their solid state and therefore optimise the performance of the solid drug form. The ultimate goal of solid state research is the optimisation of a drug in its solid form for a specified application (Byrn *et al*., 1994:1148).

The following aspects tend to cause a certain level of difficulty in solid state reactions:

- Nucleation of the molecules during the reaction to form a solid product.
- The amount of amorphous content present.
- Possibility of crystal structure disorder.
- Possible variety of forms produced from the reaction (Byrn *et al*., 1994:1149).

As these aspects complicate solid state reactions, the prediction of the stability of a solid form is very difficult under these circumstances. Predicting the stability of multiple solid forms of a compound, or even in a product formulation, is yet an even bigger challenge (Byrn *et al*., 1994:1149).

1.3.1 Classification of solid forms

A compound in a solid state can be described as one of three different groups of solid forms, i.e. as crystalline, amorphous, or a pseudopolymorph (Lee *et al*., 2008:580).

However, there is a discrepancy involving the true classification of solid forms. Cui (2007:6) states that an API in the solid phase can be classified as either a crystalline- or an amorphous form and that the use of the term pseudopolymorphism should be avoided, due to the fact that a solvate can also turn out being a polymorph. Accordingly, a solid should thus be classified as either a crystalline, or an amorphous solid. The crystalline forms (Figure 1.1) of a pharmaceutical drug is therefore characterised as a polymorph, a solvate (including hydrate), or a co-crystal (Cui, 2007:6; Vippagunta *et al*., 2001:3).

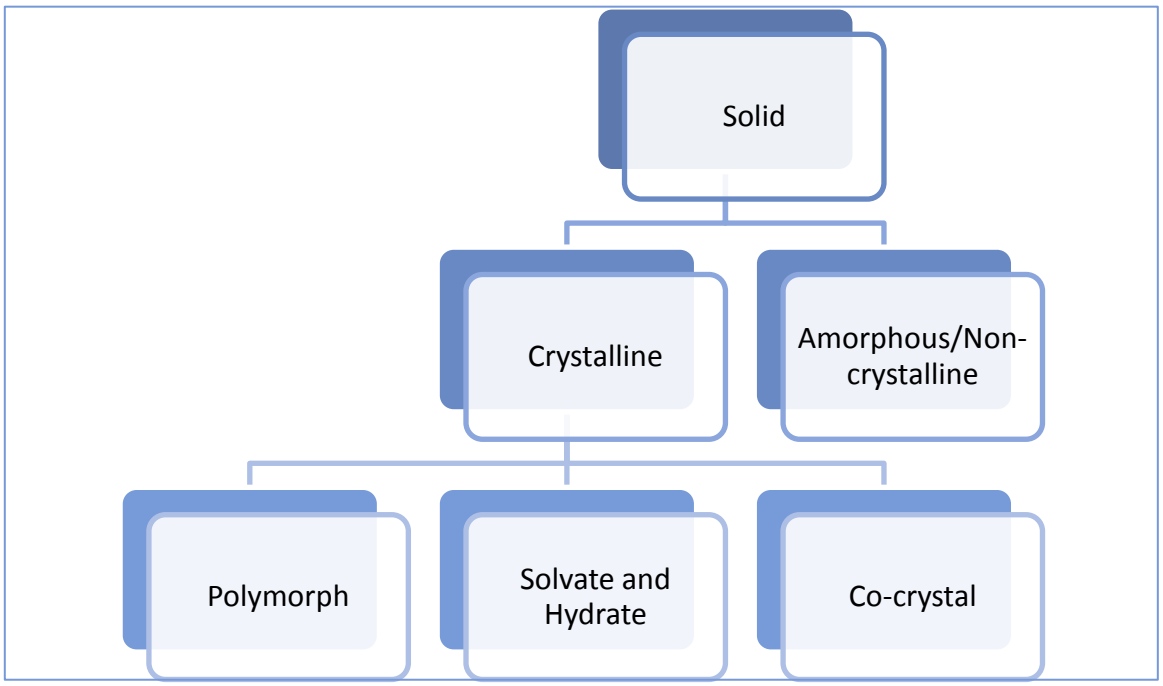

Figure 1.1 Diagrammatic representation of the classification of solid state forms, according to Cui (2007:5).

1.4 Crystalline solid

"…crystalline, implies an ideal crystal in which the structural units, termed unit cells, are repeated regularly and indefinitely in three dimensions in space" (Vippagunta *et al*., 2001:4).

The crystalline phase of a solid implies that the molecules within the crystal lattice are arranged in different orders. The molecules of a crystalline solid are packed in both short- and long-range orders. The organisation of molecules that lie next to each other are referred to as the short-range order. The regular and periodic existence of molecules that aggregate together is called long-range order (Brown, 2001:13; Cui, 2007:5).

Most pharmaceutical compounds are used in the solid phase. The majority of these compounds exist in a crystalline state. The advantage that most crystalline solids hold over their amorphous counterparts is that they usually are more stable and therefore impose fewer problems with handling and storage (Stephenson *et al*., 2001:67; Vippagunta *et al*., 2001:4).

Crystal forms that consist of the same drug molecules and other molecular compounds (i.e. solvent or co-crystal) have recently been included in the definition of crystal

polymorphism. This implies that crystalline solids can therefore be either polymorphs, solvates (including hydrates), or co-crystals (Braga *et al*., 2009:27).

1.4.1 Polymorphs

Polymorphs show identical chemical compositions. However, their crystal structures within the crystal lattice differ, resulting in differences in properties with regards to their chemical and physical natures. Polymorphs may hence exhibit different solubility and dissolution profiles, due to their differences in crystal structures. Polymorphs of a single compound can all be characterised as unstable, except for one, i.e. the stable polymorph being the one with the lowest free energy. The stable polymorph, however, is the least soluble in all solvents, has a slow dissolution rate and is not as reactive as the unstable polymorphs with higher free energy. Nevertheless, the stable polymorph is regarded as the safe route for product development, due to the lower risk of phase transformations during manufacturing, than the less stable ones (Kratochvíl, 2011:131; Vippagunta *et al*., 2001:4).

Polymorphs and hydrates display the following differences and similarities:

- Polymorphs consist of crystal structures that differ in their molecular packing and hence the molecules are of the same drug substance.
- Hydrates are crystals that consist of one species of drug molecules with the inclusion of water molecules.
- The crystal structures of each solid form are different and hence exhibit differences in terms of aqueous solubility, dissolution rates, hygroscopicity and stability.
- Temperature, relative moisture, or pressure can initiate phase transformation from one polymorph into another, or from a polymorph into a hydrate, or even from a hydrate into a polymorph. This implies that reversible transformation can occur during manufacturing, processing, storage and stability testing. A change in structure may also occur as a result of solution mediated transformation.
- The level of hydration depends on the activity of the water present in the system.

Alterations in water vapour pressure influence polymorphs. In the event that the molecular mobility is changed by the sorption of water, the molecules of the polymorphic structure

can rearrange to form a new or different polymorph. This structural change, due to water sorption, is referred to as solution mediated transformation (Morris, 1999:132).

1.4.2 Solvates

A crystal solvate forms during the process when a compound is crystallised with the inclusion of a solvent (Vippagunta *et al*., 2001:4). Solvates can be divided into two groups, according to the binding position of the solvent, i.e. polymorphic- and pseudopolymorphic solvates (Bernstein, 2002:5; Florence & Attwood, 2009:19).

The order of molecular packing may contribute to the ability of the crystal to include solvent molecules to facilitate a stable, crystal structure. When a crystal is formed with the solvent being an integral part of the crystal structure, it is called a polymorphic solvate. The solvent holds the structure of the crystal intact. Desolvation of a polymorphic solvate is normally more difficult, because the solvent is tightly bound to the compound molecules within the crystal structure. When the crystal actually manages to lose the solvent molecules, the crystal will consequently fall apart. This collapse of crystal structure leads to the formation of a new crystal form by means of recrystallisation. Polymorphic solvates tend to have superior stability (Bernstein, 2002:5; Florence & Attwood, 2009:19).

Pseudopolymorphic solvates can be described as crystallised solids within which the solvent fills structural voids in the crystal. The solvent is not tightly bound and is therefore not included in the crystal bonding within the crystal lattice. This type of solvate is known for its ability to freely lose the solvent molecules, without demolishing the crystal lattice during the desolvation process. After desolvation, analysis will show that the crystal is in an unsolvated state, which can be confusing, since the chemical structure of the crystal remains that of the initial solvate. This type of solvate is not as ordered as polymorphic solvates, therefore characterisation of pseudopolymorphic solvates is not very easy (Bernstein, 2002:5; Florence & Attwood, 2009:19; Vippagunta *et al*., 2001:4).

1.4.2.1 Method for preparing solvates

Solvates are generally attained through crystallisation from either a single solvent, or a mixture of solvents. The vapour diffusion process can also be utilised. The crystallisation process to produce solvates is in accordance with the methods using solvents to obtain crystal polymorphs (Guillory, 1999:207).

1.4.3 Hydrates

Crystalline hydrates account for almost a third of all active pharmaceutical solids (Vippagunta *et al*., 2001:15). Most pharmaceutical formulations consist of anhydrates and salts (Kratochvíl, 2011:133). As already mentioned, a crystal structure that contains/includes a solvent molecule is called a solvate. In the case of the solvent being water, the crystallised solid is then referred to as a crystal hydrate. Hydrates are known to consist of two-component systems, expressed by factors such as temperature, pressure and water activity. Anhydrous crystals are described as one-component systems. The level of potential free energy is expressed through pressure and temperature. As water molecules are very small, voids found within the structure of a crystal can easily be occupied by them. Apart from this, water also acts as a link between the compound molecules from which a crystal structure, that is very stable, is formed.

It can thus be concluded that water within the hydrated crystal structure, can bind to nearby water molecules or functional groups. The structure of crystal hydrates is held together by the hydrogen bonding capabilities of water. A change in volume of the unit cell occurs when water is added, or removed from the hydrated system. This volume change is generally equivalent to the volume of the water molecule(s) being added or removed from the hydrate structure. One of the main concerns regarding hydrates is the variation of water activity that can occur at any time during the existence of the drug substance. It is hence important to gather all the required knowledge of active compounds and excipients when exposed to water (Byrn *et al*., 1999:236; Florence & Attwood, 2009:19; Kratochvíl, 2011:133; Morris, 1999:133).

1.4.3.1 Classification of hydrates based on their crystal structure

Classification of hydrates is critical in establishing a level of confidence in predicting and reproducing hydrate behaviour within certain limits (Morris, 1999:160). Because water molecules are very small, they can easily fill the structural voids created in the crystal structure when the large drug molecules pack together. Two aspects can be considered when classifying hydrates, i.e. the crystal structure, or the crystal energy. Classification based on the structure of the hydrate is mainly used within the pharmaceutical industry. The structure of crystalline hydrates can be used for classification in three distinct groups:

Class I is also referred to as isolated site (lattice) hydrates. This implies that water molecules are kept apart from each other and can therefore not come into direct contact

with each other. Dehydration of isolated site hydrates is very slow, even with the addition of heat in approaching the actual temperature of dehydration (Morris, 1999:142, 162; Vippagunta *et al*., 2001:15).

Class II, or channel hydrates (also referred to as lattice channels), are hydrates within which water molecules are included in the crystal structure. These water molecules can be neighbouring molecules within the crystal lattice. The adjacent positions of these water molecules result in the formation of channels that spread throughout the crystal lattice. The removal of water molecules through dehydration has no altering effect on the crystal structure. With channel hydrates, dehydration commences early, when exposed to conditions of increasing temperatures. At a specific temperature the hydrate system will have an adequate amount of free energy for the water molecule on the surface of the channel to be removed first. After the removal of the first water molecule, the channel is exposed, whilst a thermodynamic gradient furthermore exists in the direction of the water being removed from the channel. Dehydration may ultimately result in a structural change that will result in the solid becoming amorphous (Morris, 1999:145, 162; Vippagunta *et al*., 2001:15).

Channel hydrates can be divided into expanded channel (non-stoichiometric) hydrates, planar hydrates (lattice planes) and dehydrated hydrates. The non-stoichiometric hydrates have the tendency to take up extra moisture in the formed crystal channels, due to exposure to high relative humidity (Kratochvíl, 2011:133). Absorbed moisture may cause the crystal to expand, introducing additional strain on the crystal lattice, which can favour the formation of the amorphous modification. Planar hydrates can be described as channel hydrates where water is included in a localised, two-dimensional manner. Dehydrated hydrates are described as crystals that dehydrate, despite exposure to high vapour pressures, i.e. the hydrate will almost indefinitely dehydrate when removed from the solution in which it was prepared. The resulting anhydrous structure (dehydrated hydrate) is comparable to the structure of the initial hydrated form. The dehydrated hydrate (anhydrous form) has a lower density than the hydrated form. This type of hydrate can be classified as a polymorph in the event that a similar anhydrous crystalline form exists (Morris, 1999:149-154; Vippagunta *et al*., 2001:15).

Class III is specifically described as ion-associated hydrates. This type of hydrate is characterised based upon the co-ordination of water and metal ions. The interaction of the metal ions and water may result in a structural altering effect on crystal hydrates.

Dehydration will only commence at very high temperatures, because of the strong interaction between the water and the metal ions (Morris, 1999:155; Vippagunta *et al*., 2001:15).

1.4.3.2 Conditions for hydrate formation

The energy needed for the hydrate structure to allow water molecules to bind to it, is unique to each hydrate. It is not a rule of thumb that a hydrate will form when water is present. Even water soluble compounds may still be unable to form hydrates when exposed to water. A hydrate is only formed if the water activity is sufficient enough to allow hydration. The capacity to take up water will be challenged, until the specific hydrated form is no longer able to take up any water molecules. A critical value will be reached, due to the increase in relative humidity, in the event where excess water is added to the system. When this critical value is achieved, hydration to the next possible hydration state commences. If such hydration continues, the hydrate will eventually deliquesce, i.e. the adsorption of atmospheric water can result in the hydrate being transformed from its solid crystal state into a liquid state. The free energy that is able to break the crystal structure of a hydrate is less than the free energy available to break an anhydrate crystal when exposed to a solvent. This is due to the interaction between the hydrate and the solvent (water) that has already occurred (Byrn *et al*., 1999:236-243; Florence & Attwood, 2009:19-22; Morris, 1999:130-132).

1.4.3.3 Method for preparing hydrates

The basic method for preparing hydrates is by dissolving a drug compound in an aqueous solvent. This aqueous solution must then be cooled, or evaporated to establish the opportunity for crystal hydrate formation. Variable temperatures used for the evaporation process will ultimately result in different crystal hydrates. Alternatively, the concept of supersaturation can be used. With supersaturation, crystal hydrates form rapidly after the initial step of nucleation is completed (Byrn *et al*., 1999:236-243).

According to Florence and Attwood (2009:20), hydration of an anhydrous crystal exposed to water can be explained by the following reaction:

$$A_{(c)} + x.H_2O \rightleftharpoons A \bullet x.H_2O_{(c)}$$

Where: $A_{(c)}$ is the anhydrous crystal that reacts with water, x represents the amount of water molecules that participated in the formation of the resulting hydrate ($A \bullet x.H_2O_{(c)}$).

Water molecules serve the following purposes in crystal hydrates: (1) Structural voids are filled with water, (2) Hydrogen bonds supplied by the water molecules allow binding to nearby water molecules and functional groups and (3) Cations (sodium and other cations) are co-ordinated by water (Byrn *et al*., 1999:238).

1.4.3.4 Stability of hydrates

Instabilities of hydrates increase at elevated temperatures causing dehydration during the drying process (Kratochvíl, 2011:134). The stability of the anhydrous form, or a lower hydrated state, is dependent on the relative humidity, water activity in its vapour phase, as well as the partial vapour pressure. The stability of hydrates in conditions where the relative humidity can constantly change is important. This feature of hydrates is essential in the quality control of a hydrate, since the conditions for handling and storage depend upon the reaction of the hydrate to a change in relative humidity. Hydrates may be susceptible to recrystallization when the hydration level changes with changes in relative humidity. Consequently, the hydrate can convert into a different form, thus being a new or pharmaceutically undesirable form. The absorption of atmospheric water can result in the hydrate being transformed from its solid crystal state to a liquid state, i.e. deliquescence. When the crystal hydrate loses all of its water to transform into a powder, it is called efflorescence. Both these processes are dependent on the relative humidity (higher or lower than a specified relative humidity) at a fixed temperature. Recrystallisation, due to its unstable nature, can provide quantitative difficulties when the active drug, in its hydrated form, is utilised during an analysis that is mass dependant. Moisture uptake, or moisture loss can be quantitatively measured with Karl Fischer titration (KFT), or by thermogravimetric analysis (TGA) (Byrn *et al*., 1999:241-243; Florence & Attwood, 2009:19-22; Morris, 1999:130).

1.4.3.5 Instability of hydrates due to phase transformations

The processes of hydration and dehydration are ever present in crystal hydrates. Many pharmaceutical compounds tend to undergo phase transformations during processing, which may be as a result of one of the following scenarios:

The hydrate crystal (or in some cases an amorphous solid) may go through the process of structural relaxation to transform from its initial metastable form into a more stable form (Morris, 1999:167-168). The resulting stable form can be either a polymorph, or a crystal hydrate that relates to a different state of hydration. A change in temperature or pressure may cause solid state transformation, whereas the hydrate system is shifted over the phase boundary to produce a different hydrate, or in some cases a polymorph. The structural relaxation of a solid is generally a kinetically controlled process that can even occur during storage of the formulated product (Morris, 1999:167-168).

A metastable form can be kinetically trapped within the dosage form during manufacturing of the final product. Kinetic trapping is much easier to achieve in solids, than in other forms, such as liquids. In order to accomplish kinetic trapping of a certain phase, the molecular mobility of the drug compound must be confined to a minimum. The resulting metastable phase may exhibit reasonable stability, but the solubility and dissolution rate of the metastable form can prove to be much better. Consequently, the bioavailability should improve to a large extent. When the phase that is formed is not the expected phase, the storage and stability of the product will cause a great deal of concern. The two processes that will often result in kinetic trapping of a metastable phase are tableting and wet granulation. Polymorphic and pseudopolymorphic transformations may occur, due to the heat and pressure that are generated during the tableting process. Wet granulation is used with high success in achieving kinetic trapping of a metastable phase. The solid that is produced through the wet granulation process may have one of the following characteristics:

- No altering effect on the composition of the solid form.
- The solid consists of a mixture of different forms.
- The solid consists of crystalline forms in its metastable phase.
- The solid consists of a metastable, amorphous form (Morris, 1999:168-170).

A stable form may exist that remains stable only whilst present in the formulation matrix. *In situ* transformations become a real possibility after production of the final product. These transformations are a result of the forced transformation, due to the metastable form, or surrounding conditions. Transitions can be attributed to hydration or dehydration processes, polymorphic phase changes, or the transformation from amorphous to crystalline form. During product development, specifically during accelerated stability studies, the temperature at which dehydration (or polymorphic phase transformation) commences can be reached or even surpassed. The stability testing conditions could lead to a higher molecular mobility, which will result in quicker structural relaxation of the metastable phase. Finally, the relative humidity of the stability testing conditions may initiate hydration, or dehydration, which may lead to the occurrence of pseudopolymorphic phase transformations. Phase transformations that are revealed during stability studies may even occur while the product is handled or stored. A common exception is the crystallisation of an amorphous solid into a crystalline form, when the glass transition temperature (T_g) of the amorphous solid is exceeded. Therefore, the temperature for processing, storage and handling of an amorphous or metastable crystal form should be kept well below the critical temperature at which phase transformations could occur (Morris, 1999:173-175).

Even active compounds that are already formulated into their final products can undergo phase transformation, due to the influence of external factors. The most important external factors that must be considered include relative humidity, temperature and pressure. When hydrates are exposed to these factors, the molecular mobility of the crystal structures are influenced to such an extent that the phase transformation occurs at an increased rate. Transformation of a hydrate into an anhydrous form is the result of dehydration and in some cases, this anhydrous form can be characterised as an amorphous form. The dehydration rate for the different hydrate classes can be predicted for an approximate room temperature and a relative humidity above its critical value. The dehydration rate is somewhat dependent on the particle size, i.e. smaller particles relate to quicker dehydration because of the larger exposed surface area. An exception to this rule is when very small crystallites (particle size smaller than 20 µm) agglomerate; the dehydration rate depends upon the size of the agglomerate and not on the size of the small individual particles. The presence of crystal defects may also lead to a more rapid dehydration (Morris, 1999:163-164).

Dehydration of a hydrate to a lower hydrated form (or anhydrous form) will increase the solubility of the hydrate, but at the cost of reduced stability. Some hydrates with a low level of hydration may be transformed through the hydration process into the status of higher hydrates, being thermodynamically more stable, but less soluble. Generally, the thermodynamically stable form will be less soluble than the thermodynamically less stable hydrates (Byrn *et al*., 1994:1149; Vippagunta *et al*., 2001:17).

During the process of determining the physical and chemical properties of hydrates, the crystal forms are exposed to water. Different levels of water exposure are achieved through solubility determinations, dissolution rate, accelerated stability, as well as during wet granulation in the development of a solid dosage form. When transformation occurs due to exposure to moisture or water, it is referred to as solution mediated transformation. The transformation depends on the level of mobility that the solution phase provides. High mobility of the solution will facilitate the molecular rearrangement to transform from the current hydrated form into the thermodynamically most stable, hydrated form. It is accepted that solution mediated transformations occur more rapidly than solid-solid transformations. Ultimately, the solution rate mediated transformation will correlate with the solubility of the drug compound (Vippagunta *et al*., 2001:17).

1.5 Non-crystalline / amorphous solids

1.5.1 Definition of the amorphous state

Amorphous solids are the existence of a solid form that consists of short-range, molecular packing within its structure. These solids illustrate no molecules in a reiterated, long-range conformation and are therefore not in a crystalline state (Braga *et al*., 2009:26; Byrn *et al*., 1999:22; Craig *et al*., 1999:179). Different amorphous solids, as a result of solid state research, have become an important focus in the pharmaceutical industry. The necessity to overcome poor physical and chemical properties of crystalline forms has become a significant driving force in the discovery and development of amorphous forms with improved pharmaceutical properties (Threlfall, 1995:2452).

1.5.2 Structural aspects of amorphous solids

As mentioned in Section 1.5.1, amorphous solids display arranged, molecular packing in the short-range order, but are ultimately distinguished from crystalline solids by the

absence of long-range, molecular packing. Therefore, an amorphous form of a solid/API cannot be characterised as a crystal, hence the term non-crystalline (Yu, 2001:30). Literature refers to amorphous solids as liquid-like, because they are structurally identical to liquids, whilst exhibiting the properties of a solid (Brown, 2001:13; Threlfall, 1995:2452). The more varied intermolecular distances between the molecules in the structure of amorphous solids are longer than those found between the molecules of crystalline solids. Molecules in amorphous solid structures are energetic, more mobile and are spread in varying and unstructured conformations throughout the solid form (Byrn *et al*., 1999:22; Cui, 2007:11).

Solids that exist and present as non-crystalline structures are solids that don't relate to either polymorphs, nor to crystal habits. Therefore, they are classified as amorphous solids. These solids are known to be isotropic; hence the properties of the solid depend on the direction of the dimensions of molecular packing. The physical and chemical properties of amorphous solids are substantially different from those of the crystalline forms containing the same drug compound. The structural and chemical stability of amorphous solids are usually their biggest weakness, since they are most of the time not as thermodynamically stable as their crystalline equivalents. The nature of the molecular mobility of amorphous solids normally results in the improvement of the dissolution profile of the pharmaceutical compound, and consequently an improved bioavailability after oral administration (Brittain, 1999:240; Byrn *et al*., 1999:22; Kratochvíl, 2011:137; Lee *et al*., 2008:580; Wu *et al*., 2010:4).

1.5.3 Amorphous solids

Amorphous solids, morphologically presenting as a glass, has proven to have a significant role within the pharmaceutical industry. The formation of a glass is dependent on the kinetics of the said molecules. The most common method for preparing an amorphous solid is through rapid cooling of the melt, with the cooling being so fast that no crystallisation is induced. However, this rapid cooling doesn't necessarily produce an amorphous solid. A specific temperature, referred to as the glass transition temperature (T_g), indicates the transformation from the equilibrated supercooled liquid state into a non-equilibrated glassy state. For the melt to crystallise, sufficient time is needed to overcome the thermodynamic barrier that manages the nucleation process. This implies that a high level of kinetic energy is required for the crystallisation process to commence. Allowing sufficient time will result in a high kinetic energy, due to the fluctuation of energy levels and

as a result will create the opportunity for nucleation and inevitably crystallisation of the solid (Cui, 2007:11; Willart & Descamps, 2008:905).

When the melt is cooled too slowly, sufficient time is allowed for the molecules to rearrange into energy minima, allowing for nucleation and crystal growth processes to a thermodynamically more stable, solid form. Ideally, the melt must be cooled rapidly to minimise the time allowed for the molecules to form nuclei and to rearrange into energy minima. More stable glasses (less viable to crystallisation) are formed through rapid cooling of the melt. Structural relaxation may comprise instability as a consequence of the rapid cooling process. This way the melt gets "frozen" in its liquid state to produce a solid glass form. The term "frozen" does not imply that no molecular movement exists, but that the molecular movement is substantially slower. The amorphous form will exist for a longer period of time if the molecular mobility is at its slowest, or even absent. However, according to Cui (2007:11), the molecules in the amorphous system are always moving due to different molecular energy levels and ongoing structural changes during which the molecules move to their energy minima. Despite the fact that a glass is structurally more liquid-like, the behaviour of a glass relates to that of a solid (Byrn *et al*., 1999:22; Cui, 2007:11; Willart & Descamps, 2008:905-907; Wunderlich, 2011:94; Yu, 2001:34).

1.5.4 Methods for preparing amorphous solids

Different methods for preparing amorphous solids from one pharmaceutical compound may result in the origin of different amorphous solids for that active compound (Threlfall, 1995:2452). The general methods for preparing amorphous solids are through rapid cooling (quench cooling) of a glass forming liquid, grinding of the crystalline solid form to convert into the amorphous form, compression, rapid solvent evaporation and lyophilisation, or spray-drying of the original crystalline form. According to Hancock and Zografi (1997:1), the methods that are most frequently used to prepare amorphous solids are vapour condensation, supercooling of the melt, mechanical stress and precipitation from a solution (Buckton, 2002:145-148; Byrn *et al*., 1999:22; Cui, 2007:11; Hancock & Zografi, 1997:1; Threlfall, 1995:2452-2453; Vippagunta *et al*., 2001:3-26; Willart & Descamps, 2008:905-907; Wu *et al*., 2010:4-5).

1.5.5 Properties of an amorphous glass

An amorphous solid has no typical melting point (T_m), but rather a glass transition temperature (T_g). To become an amorphous solid, the molecules must transform from the

liquid phase (melt) into a more rubbery state *via* constant structural change, when reaching the glass transition temperature upon cooling. This transition temperature, a kinetic factor, depends on both the heating- and the cooling rates; hence the T_g is not a predetermined temperature. This specific temperature (T_g) indicates the transformation from the equilibrated supercooled liquid state into a non-equilibrated glassy state with increased structural energy, during which the molecular mobility within the glass state changes (Hancock & Zografi, 1997:2). In other words, the T_g describes the setting point for the melt, along with the change in its listed pharmaceutical properties. The less mobile the molecules are, the more stable the glass and therefore the longer the solid would possibly exist in its amorphous state. The molecular mobility below T_g is in fact not zero and hence can provide adequate mobility for changes in the physical and chemical properties. It is, however, important to understand that the molecules within the amorphous state are in constant movement. Degradation, as well as structural relaxation, both requires molecular mobility to occur (Hancock & Zografi, 1997:3; Liu *et al*., 2002:1854; Yu *et al*., 1998:125).

The most important properties of an amorphous glass are discussed next with reference to the following: (1) High potential energy, (2) Structural heterogeneity and (3) Structural relaxation.

1.5.5.1 High potential energy

The presence of high potential energy in amorphous solids is a unique property relative to their crystalline counterparts. The absence of long-range order, together with an insufficient packing of molecules, account for the high potential energy levels within the amorphous glass.

High potential energy is relevant to the pharmaceutical sciences for the following reasons:

- Amorphous forms with high potential energy are thermodynamically unstable and would therefore tend to revert to the thermodynamically more stable form. The rate at which the conversion happens is controlled by the kinetics of the solid. An amorphous solid may be used to produce a pharmaceutical product, if the conversion to the thermodynamically stable form is delayed, due to slower kinetics (Buckton, 2002:145; Byrn *et al*., 1999:22; Cui, 2007:11).
- Amorphous forms present with higher molecular mobility, which makes them chemically more reactive. The degradation rate of amorphous solids is faster, due

to the higher molecular mobility. This degradation reaction rate depends on the energy levels present in the glass, as well as on the mobility of the molecules that form part of the degradation reaction (Byrn *et al*., 1999:22; Cui, 2007:11; Wu *et al*., 2010:4).

- Improved solubility is often the essential consequence of an amorphous solid with high potential energy. This hold significance for drug compounds with characteristic low aqueous solubility. An enhanced solubility has the advantage of improving the bioavailability for such compounds. Careful consideration is required, since the improved solubility of an amorphous solid, due to higher potential energy, is usually overshadowed by its chemical instability and the time dependent transformation into the thermodynamically, more stable, crystalline form (Cui, 2007:11; Vippagunta *et al*., 2001:3; Wu *et al*., 2010:4).

1.5.5.2 Structural heterogeneity

As mentioned in previous paragraphs, the absence of long-range, molecular order is unique to amorphous solids. During the formation of a glass *via* rapid cooling of the supercooled liquid, the molecules move to a different molecular co-ordination within the glass. This co-ordination is representative of molecules frozen in the glassy state. The heterogeneity of the co-ordination within an amorphous solid is a distinctive characteristic, when compared to the homogeneous, molecular co-ordination of crystalline forms (Byrn *et al*., 1999:22; Cui, 2007:11).

Structural heterogeneity affects the potential energy levels of amorphous solids directly. More specifically, potential energy levels of the molecules may vary with different molecular co-ordination, i.e. the potential energy of each amorphous system is different and depends on the unique molecular co-ordination of the respective molecules within amorphous states. Despite the allocation of energy to all molecules, the potential molecular energy in the amorphous system may be higher for some molecules, than for others (Cui, 2007:11).

When a supercooled liquid is cooled at a slow rate, the molecules are given sufficient time to rearrange into the molecular co-ordinations that they favour at their energy minima. Consequently, the potential energy level of the amorphous system will be lower. Contrary, when the supercooled liquid is quenched at a fast rate, the molecules will have insufficient time to rearrange into the favourable energy minima. As a result, a glass is produced,

which exhibits a high potential energy state. Therefore, it can be concluded that the high potential energy and the structural heterogeneity are closely associated to the process used to prepare an amorphous solid. Different amorphous preparation methods will result in different properties of the achieved amorphous states (Buckton, 2002:145; Cui, 2007:11; Willart & Descamps, 2008:905).

1.5.5.3 Structural relaxation

As mentioned before, potential energy is distributed among all molecules in the amorphous system. However, some molecules still exist at higher potential energy levels than other molecules in the amorphous system. Despite the solid glassy appearance of an amorphous glass, there is still a constant movement of the large-amplitude molecules in the amorphous system. Structural relaxation can be described as the process during which molecules that exist at high potential energy levels, rearrange their molecular co-ordination, by slowly moving into their state of energy minima, i.e. the solid progressively shifts to a more relaxing state of equilibrium. During the progressive movement towards equilibrium, the high potential energy and the free volume decrease, whilst the molecular order increases to a more arranged, molecular packing. The excess energy from the initially high potential energy, amorphous solid is released as heat during structural relaxation, yielding the enthalpy relaxation process. Through the structural relaxation process, the energy levels are progressively decreased, which will ultimately result in the amorphous system becoming the ideal glass at a state of equilibrium. Together with the energy levels decreasing, the molecular mobility of the amorphous system slows down as well. Ultimately, the molecules in the amorphous system are arranged to such an extent that the molecules appear to be more uniformly packed, although they will in no way be uniformly arranged as in crystalline forms. The phenomenon of structural relaxation is therefore a unique and significant aspect of amorphous solids (Cui, 2007:11; Liu *et al*., 2002:1854; Willart & Descamps, 2008:905).

The fact that the molecules move, emphasises the occurrence of constant change in structure and also the levels of energy present in the amorphous solid state. Factors that are influenced by the changing energy levels are solubility, bioavailability and the physical and chemical stability of the amorphous solid (Buckton, 2002:145; Byrn *et al*., 1999:22; Cui, 2007:13; Hancock & Zografi, 1997:2; Threlfall, 1995:2452; Vippagunta *et al*., 2001:3; Willart & Descamps, 2008:905).

1.5.6 Stability of amorphous solids

Technically, an amorphous solid is referred to as a metastable solid, relative to crystalline solids. Metastable best describes the physical state of an amorphous solid, because most amorphous forms are thermodynamically unstable (physically and chemically) and if allowed sufficient time at favourable conditions, they will transform into the thermodynamically more stable, crystalline form *via* nucleation and crystal growth. The nucleation process is optimal if the temperature is below the T_g. Optimum crystal growth is achieved at temperatures between the T_g and the melting point (T_m) of the crystalline state (Craig *et al*., 1999:194; Hancock & Zografi, 1997:8; Yu, 2001:33).

Heat and relative humidity (RH) are two environmental factors responsible for the crystallisation of amorphous solids during storage.

1.5.6.1 Effect of temperature on stability

Storage of an amorphous solid at a temperature of 50˚C below the T_g is desirable, although it is not to say that the solid would indeed remain stable in an amorphous state (Craig *et al*., 1999:194; Kratochvíl, 2011:138). At lower temperatures glasses tend to have slower existing molecular mobility and hence recrystallisation of the amorphous form is inhibited. As soon as the storage temperature rises above the T_g the molecular mobility of the amorphous state will increase. The amorphous solid can become a melt and will consequently flow, if the temperature is increased to above the glass transition temperature. The flow is a result of the increased molecular mobility which is enabled by the increase in free volume. In most cases this leads to the crystallisation of the solid into the more stable, crystalline form. Ultimately, the changes in molecular mobility determine the extent of changes with regards to the physical and chemical properties. Temperatures below T_g may have the effect of modifying the relaxation time of the glass, and hence will affect the stability of the glass (Willart & Descamps, 2008:906).

1.5.6.2 Effect of moisture on stability

The presence of moisture (water) could have a plasticising effect, which will subsequently cause an increase in molecular mobility, which in turn will result in lowering the T_g of the amorphous solid. The degree of crystallisation may be dependent on the molecular mobility, as well as the structural relaxation of the solid (Buckton, 2002:145; Byrn *et al*., 1999:22; Craig *et al*., 1999:194; Hancock & Zografi, 1997:8).

Amorphous solids have the tendency to exhibit a higher degree of hygroscopicity, which occurs when a solid absorbs water vapour from the atmosphere. Therefore, the hygroscopic nature of an amorphous solid is dependent on the atmospheric relative humidity (RH). At a high RH, most solids will take on water. When a solid absorbs atmospheric moisture at a low RH, the solid is very hygroscopic (Byrn *et al*., 1999:22). The following levels of hygroscopicity are described in the European Pharmacopoeia (EP, 2005:565) for pharmaceutical solids:

- Deliquescent – a liquid is formed, due to sufficient water uptake from the moisture in the atmosphere.
- Very hygroscopic – a mass increase of 15 % (w/w) or more due to water uptake.
- Hygroscopic – a mass increase between 2 % (w/w) and 15 % (w/w) due to water uptake.
- Slightly hygroscopic – a mass increase of 0.2 % (w/w) or more, but less than 2 % (w/w).

The degree of hygroscopicity of pharmaceuticals is based on water content measurements of samples stored at 25ºC/80 % RH for a period of 24 hours (EP, 2005:565).

Apart from being thermodynamically less stable, amorphous solids are usually more hygroscopic than crystalline solids. The hygroscopicity of a solid is to an extent controlled by its particle size. The reduction in particle size results in the exposure of larger surface areas. Therefore, the opportunity for water uptake is increased, because of the presence of more active sites that are available for the water molecules to bind to. Atmospheric moisture raises concerns regarding the influence it may have on the chemical and structural stability of hygroscopic solids. Hygroscopicity is partly responsible for amorphous solids to transform into the more stable, crystalline state (Byrn *et al*., 1999:22; Kratochvíl, 2011:138; Lee *et al*., 2008:578).

Free water molecules will most likely have an altering effect on the stability of the amorphous, solid form. Such instability could ultimately result in a phase transformation, induced by the plasticising effect of moisture. In some instances, water is not absorbed to react with the molecules of the amorphous solid, but instead is adsorbed, only to be concentrated on the surface of the amorphous solid. When water is added to an amorphous solid as a plasticiser, the resulting effect is an increased molecular mobility

(Kratochvíl, 2011:138). Consequently, in the case of amorphous solids, a transformation into the more stable, crystalline form could occur. The crystallisation of a solid can be identified when plotting sample weight against % RH. The amorphous solid will absorb moisture and the mass will increase with an increase in % RH. The mass increase will only last until the crystallisation process occurs, whereafter the crystallised solid will stabilise and lose weight again (Buckton, 2002:145; Kratochvíl, 2011:138; Lee *et al*., 2008:578).

Such transformation has a direct altering effect on the solubility of the solid drug. Factors, such as powder flow and compressibility can change, due to the impact of water on hygroscopic solids. This poses immense complications during the manufacturing of pharmaceutical products. To determine the best possible storage conditions for a product containing a hygroscopic drug compound, the precise hygroscopic nature must be known. The chemical reactivity of a hygroscopic solid is increased by the presence of free water molecules. Chemical degradation becomes a real possibility when free water reacts with the solid drug compound in the presence of excipients (Buckton, 2002:145; Byrn *et al*., 1999:22; Lee *et al*., 2008:578).

1.5.7 Solubility of amorphous solids

The individual molecules that ultimately form a solid may be in different energy states at a given time, and may therefore exist as a disordered mixture of different crystalline and/or non-crystalline phases in one solid (Grant & Brittain, 1995:323). The difference in solubility can result in the inter-conversion from a metastable form to the more stable, polymorphic/solvate form. This conversion may cause difficulty in determining the true solubility of a metastable solid, because of the presence of the stable form in solution. The measured solubility will then tend to correlate with that of the stable form at the intended temperature. Solids with larger amounts of lattice free energy (i.e. less stable or metastable forms) will have much more free energy to release, which will result in the solid particles dissolving quicker than expected. The solubility of the solid will increase, due to the high amount of lattice free energy and will play its part as a source of power to optimise the dissolution process (Brittain & Grant, 1999:281).

However, different forms of the same pharmaceutical active will not differ once they are in solution, as they are then thermodynamically equivalent. This being said, it is important to

note that the differences in dissolution rates for the various forms of a pharmaceutical active solid will ultimately cause variations in the bioavailability of the solid.

In conclusion, it is evident that the solubility of a solid in a given solvent is of high importance in the pharmaceutical industry. Together with the solubility, the dissolution rate at which the solid transfers into solution also plays a very significant role in the optimisation and improvement of the bioavailability of the pharmaceutical active solid (Brittain & Grant, 1999:281).

1.5.7.1 Equilibrium (intrinsic) solubility *versus* metastable solubility

The free energy of molecules within a solid ultimately determines the solubility of the solid. The intrinsic solubility of a solid refers to the solubility of the solid, where the form of the drug in solution is identical to the form of the initial drug. Contrary, metastable solubility refers to the solubility of a less stable, polymorphic/amorphous form of the drug, where the drug in solution is not necessarily the same as the initial drug form (Grant & Brittain, 1995:321; Larsson, 2010:10).

In the event where equilibrium is reached between the solute and the solvent ($A\text{-}A_{(solid)} \leftrightarrow A\text{-}A_{(aq)}$), the change in free energy (ΔG) can be relayed to the condition of equilibrium described by the equilibrium constant (K). Therefore,

$$\Delta G = -RT\ln(K)$$

Where: R is the gas constant, and T the temperature of experimental conditions.

The more acceptable equation with respect to amorphous solids is

$$\Delta G = \Delta H - T\Delta S$$

Where: ΔH is the change in enthalpy, ΔS the change in entropy, and T the temperature at which the dissolution process occurs. Both equations illustrate the importance of the temperature during the solubility process. By using these equations, the differences in solubility between crystalline and amorphous forms can be illustrated (Aulton, 2002:18; Hancock & Parks, 2000:397).

Amorphous solids are almost always more soluble than their crystalline counterparts. When comparing solubility data in the literature, it can be concluded that the expected improvement in solubility (i.e. metastable solubility) will be at least two-fold. The amorphous form of a solid drug compound is said to be the state with the most free energy available. As a result of the free energy, the solubility and ultimately the bioavailability of the solid form will be affected (Hancock & Parks, 2000:397). However, it must be emphasised that the experimental determination of the metastable solubility of a thermodynamically unstable, amorphous solid is very complex. The complexity of determining the solubility is caused by the thermodynamic properties of the amorphous form, which displays the need to transform into the more stable, crystalline form when exposed to solvents or solubility media. The potential energy in crystalline solids is lower than in amorphous solids (glasses), making the crystalline state the thermodynamically favoured solid form of existence (Cui, 2007:11). The improved solubility supports the objective of achieving faster dissolution rates, i.e. better pharmaceutical properties and ultimately higher oral bioavailability (Byrn *et al*., 1994:1148; Byrn *et al*., 1999:22; Hancock & Parks, 2000:397; Kratochvíl, 2011:138).

1.5.8 Effect of amorphism on the dissolution rate

For drug molecules to be absorbed and bioavailable, they must first dissolve. When a powder or tablet is placed in an aqueous medium, the molecules move from their current solid state into solution. This transfer of molecules or ions is called dissolution. Dissolution can generally be defined by the Noyes-Whitney equation, which stipulates the dissolution rate in the event that the dissolution process is controlled by diffusion. The Noyes-Whitney equation is defined as (York, 2002:8):

$$dC/dt = DA(C_s - C) / h$$

Where: dC/dt represents the dissolution rate at steady state, D is the diffusion coefficient of the drug in solution, A is the surface area of the drug particles in contact with the solvent, C_s is the saturation solubility of the drug, C is the concentration of the drug in the gastro-intestinal fluid and h is the thickness of the diffusion layer around the drug particles (Ashford, 2002:236; Brittain & Grant, 1999:308; Wong & Collins, 2008:478).

The dissolution profile of an active drug compound reveals important information about the release of the drug from a solid dosage form. The cumulative concentration of drug that moves from the solid dosage form into solution is given as a function of time. As a result,

the dissolution rate can also be determined. The dissolution rate may be influenced by the following factors (Brittain & Grant, 1999:310; Wong & Collins, 2008:510):

- Solubility of a solid in specific conditions related to a specific temperature (normally 37˚C) and pH value.
- Concentration of the drug in a bulk solution.
- Volume of the relevant dissolution medium (or in some exceptions the volume flow rate).
- Exposed surface area that is wetted during the dissolution process.

Among the above factors that affect dissolution rates, the most important factor is the solubility of the molecules/particles in the dissolution medium. If the drug is poorly soluble in the dissolution medium, the dissolution rate will be slow and consequently influence its bioavailability in a negative way. The dissolution rate is generally proportional to the solubility of the polymorphic form. This means that the slowest dissolution rate will be achieved by the most stable, polymorphic form and that the more soluble metastable form will exhibit a faster dissolution rate. The dissolution rate may also influence the rate at which the API is absorbed. Therefore, the correct polymorphic form, formulated in a suitable dosage form, can ultimately affect bioavailability due to a faster absorption rate. However, the use of the more soluble metastable form may result in fluctuations in dosages, due to the instability of the metastable form to transform into the most stable, polymorphic form (Ashford, 2002:237; Brittain & Grant, 1999:317; Wong & Collins, 2008:511).

1.6 Conclusion

Materials exist in either a solid, liquid or gaseous state. Most pharmaceutical materials exist in the solid state. The solid state of pharmaceutical compounds can be categorised according to its molecular packing. The phenomenon of a single compound existing in different forms is called polymorphism. The study of these different forms of a single drug has become a significant focus point to pharmaceutical researchers. To characterise these different forms and determine their pharmaceutical properties (physical and chemical properties) hold immense value in the field of drug research and development in the pharmaceutical industry. Different forms of a drug compound will exhibit different

physical and chemical properties, due to differences in molecular packing and the amount of potential free energy of the molecules. The most important pharmaceutical properties that researchers strive to improve are solubility, stability (chemical, structural, and formulated within a dosage form), rate and extent of dissolution, absorption and ultimately the bioavailability of the active drug (Chieng *et al*., 2011:618).

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