SOLID-STATE THERMAL DESOLVATION AND STRUCTURAL STUDIES OF OXALIC ACID DIHYDRATE, ZINC ACETATE DIHYDRATE, COPPER (II) SULFATE PENTAHYDRATE AND NICKEL (II) SULFATE HEXAHYDRATE

BY

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DECLARATION

Declaration by the candidate

This thesis is my original work and has not been presented for a degree award in any other University. No part of this thesis may be reproduced without prior written permission of the author and/ or University of Eldoret.

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Dedicated to my wife Beatrice, and my children Ian, Nicole and Sonia.

ABSTRACT

For many years it has been widely accepted that crystal dehydration can be related to internal crystal structure. However, there is very little empirical data or experiments on this work. This work makes an attempt to use thermal studies to understand the internal structure of crystals. Three inorganic solvates (nickel (II) sulfate hexahydrate, copper (II) sulfate pentahydrate and zinc acetate dihydrate) and an organic solvate (oxalic acid dihydrate) were chosen and studied as model compounds. This was done through study of their crystallization habits, thermo chemical properties, dehydration kinetics and other related studies. The physiochemical properties of the known compounds were determined using DSC and TGA. Data mining was carried out in which crystallographic data of study materials were obtained from crystallographic data base. Using mined crystal data, modeling was carried out on the internal structures of the study materials. The observed internal structure obtained using modeling was then explained using thermal study observations. It was observed that the rate of dehydration is directly related to crystal packing. Compact molecular packing meant low rate of dehydration and vice versa. The numbers of hydrogen bonds were observed to also have impact on molecular packing and therefore thermal dehydration. The presence of tunnels within the crystal structure provided channels through which desolvated water left the crystal and hence increased rate of thermal dehydration. The nature of the DSC/TGA curves were used to compare rates of desolvation of the solvates in that the solvates whose curve has a sharper gradient has a higher rate of desolvation implying that its structure is less compact or more open facilitating easy escape of solvent. Copper (II) sulfate pentahydrate and zinc acetate dihydrate had lower energies of desolvation at 159.6 J/mole and 235.0 J/mole respectively. Oxalic acid dihydrate and nickel (II) sulfate hexahydrate had higher energies of desolvation at 503.6 J/mole and 241.8 J/mole respectively. Copper (II) sulfate pentahydrate and zinc acetate dihydrate salts had higher rates of desolvation and from modeling results their structures are more open compared to the structures of oxalic acid and nickel sulfate. These salts of oxalic acid dihydrate and nickel (II) sulfate hexahydrate had more packed structures due to the presence of many hydrogen bonds compared to salts of copper (II) sulfate pentahydrate and zinc acetate dihydrate. The presence of tunnels and the open nature of the crystals packing in various solvates facilitated escape of solvent.

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DSC –Differential thermal analysis

TGA –Thermogravimetric Analysis

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CHAPTER ONE

INTRODUCTION

1.1 Background Information

Many reactions that are of interest to the pharmaceutical scientists are concerned with substances that are at least solid. The kinetic characteristics of reaction occurring in crystalline materials are often different from those proceeding in a homogenous phase, such as a gas or liquid. Thus, kinetic analyses of solid state rate processes have topical interest and relevance to the pharmaceutical industry.

Many organic and inorganic compounds are known to crystallize with solvent molecules as an integral part of their structure. The phase stability of the multi-component solids is governed by temperature, pressure and concentration of the solvent in the system. However, even though the thermodynamics might indicate that a particular solvent is metastable under normal storage conditions, the conversion rate to the desolvated form could be relatively slow in pharmaceutical terms. Thus, knowledge of desolvation kinetics, behaviour and relative stability of crystalline organic and inorganic solvates are extremely relevant in the pharmaceutical industry with specific regard to drug formulation (Okoth, 1997; Pfiffer *et al*.,1920). This is because it has been established that physiochemical, processing, mechanical, compaction and bioavailability properties of solvated materials differ significantly from those of their desolvated yield products, the anhydrous form. Such differences have been ascribed to the existence of a different crystal structure in the solvates conferred by the presence of solvent molecules in the crystal lattice (Agbada, 1994; Brittian, 1988; Byrn, 1982). The differences in thermodynamic properties that are associated with crystalline modifications are believed to be the cause for the observed variation in the physical and chemical properties that include solubility and dissolution behaviour.

The most common groups of the solvates are the hydrates. Investigations have shown that the water of hydration can assume different roles in hydrates. Thus, in some pharmaceutical powders, the compression behaviour has indicated that water of hydration acts as an "in-built" binding agent to promote both plasticity and lubricity. The removal of this water through dehydration may therefore cause disruption of the

crystal structure thereby preventing tablet formation (Jaffe and Foss, 1959). In other situations, a rigid network of hydrogen bonding between water molecules and the parent compound is thought to inhibit inter planar slippage, a situation that results in the reduction in plasticity and bond strength in the hydrate (Beevers and Hansen, 1971). Thus, removal of such water molecules would affect all the above properties.

The knowledge obtained from the dehydration kinetics and mechanisms of solid drugs should help considerably in defining storage conditions and leads to a more rational approach to the best materials of stabilizing drugs. Thus, rate constants at labeled storage condition would be useful for estimating the expiration date of drugs.

Crystal behaviuor and temperature of dehydration are crystal characteristics that are known to be controlled by crystal packing, hydrogen bonding and any defects present within the crystal structure. In recent years, the kinetics of dehydration reactions of solid hydrates has been a subject of considerable study by solid - state chemists; however, most features of such reactions are yet to be completely elucidated. The role played by humidity, particle size and temperature in the solid- state reactions involving water- soluble drugs cannot be over emphasized (Yoshioka and Uchigama, 1986). The effect of such factors on individual reaction, however, may vary depending on reactants, the yield products and the nature of solid state reaction (Narten and Levy 1969). In this study, the kinetics and factors affecting dehydration in inorganic and organic solvates and direct comparison between them are covered. The thermal desolvation properties of crystals are related to their internal structure and this is believed to be directly related to the desolvation characteristics of the crystals.

1.2 Justification

During crystallization, solvent molecules can form or not form part of the crystal structure. When the solvent molecules are part of the structure and upon desolvation they are removed; it means that the internal structure of the crystal will be disrupted and this may lead to the eventual collapse of the crystal structure.

It is thus justified to understand macroscopic observations made on crystals in terms of microscopic molecular structure. Such relation can be made by linking physiochemical (for instance thermal) properties to a presolved crystal structure of a compound. Such an undertaking will lead to drawing a linkage between property and structure relationship, development of a small database of such relationship and their prediction.

Previous studies reported only on the desolvation properties of crystals without relating the properties to their internal structure. This particular study sought to provide a better understanding for the desolvation process of solvates through relating desolvation kinetics to the respective internal crystal structure. The physiochemical properties (thermal properties) used to understand the internal structure of the crystals, such that from the physiochemical properties of a given solvate one should be able to predict its internal structure and vice versa. It would also enable one to predict the behaviour of a particular crystal upon desolvation.

1.3 Objectives of the study

The general objective was to compare and relate thermal properties with internal structure of the solvates.

The specific objectives were to:

- Crystallize oxalic acid dihydrate, zinc acetate dihydrate, copper (II) sulfate pentahydrate and nickel (II) sulfate hexahydrate using solvent mixtures of water, ethanol, acetone and acetic acid.
- Investigate the thermal properties of the oxalic acid dihydrate, zinc acetate dihydrate, copper (II) sulfate pentahydrate and nickel (II) sulfate hexahydrate.
- Perform data mining on oxalic acid dihydrate, zinc acetate dihydrate, copper (II) sulfate pentahydrate and nickel (II) sulfate hexahydrate.
- Relate the macroscopic properties (thermal data) to microscopic properties (internal structure).
- Compare the various crystals in terms of their properties and internal structure.

CHAPTER TWO

LITERATURE REVIEW

2.1 Background Information

Desolvation of solids is a solid state reaction which is a broad topic in chemistry. Solid state reactions include areas of physical and industrial pharmacy that engulfs powder technology and formulation, stability of solids, kinetics and molecular details of such reactions. Molecular details of solid state reactions use crystal structure and other molecular information to provide explanations for the products and the rates of reactions in terms of the molecular changes that occur. This necessitates a deep understanding of crystallization process, crystal properties, forces holding crystals and the kinetics.

2.2 Crystallization

Crystallization is a technique for purification of solid. The compound is first dissolved in a minimum amount of hot solvent. If insoluble impurities are present, the hot solution is filtered off. The hot saturated solution is finally allowed to cool slowly so that the dissolved compound crystallizes at a moderate rate (Mendham *et al*., 2000). When the crystals are fully formed, they are isolated from the mother liquor (the solution) by filtration. If an extremely pure compound is required the filtered crystals may be subjected to recrystallization (Louis, 1968).

2.2.1 Solvents for Crystallization

The ideal solvent for crystallization of a particular compound is one that does not react with the compound and boils at a temperature that is below the compound melting point (Ralph and Joan, 1984). The solvent should also be able to dissolve a moderately large amount of compound when hot. It should be moderately volatile to enable crystals to dry readily, non toxic, non flammable and inexpensive (Bauman, 1979).

2.2.2 Selecting a solvent

A solvent must satisfy certain criteria in order to be used for recrystallization. The substance being purified must be insoluble or nearly insoluble in cold solvent. This solubility is often tested in at room temperature. The compound being purified should ideally be soluble in the hot solvent but insoluble or nearly so when cooled (Eric and

Dennis, 2006). The impurities must remain at least moderately soluble in the cold solvent, otherwise both the desired compounds and the impurities would recrystallize. This solubility property of the solvent with respect to the solubility of the solute and impurities is called the temperature coefficient of the solvent, and it must be favourable for a successful recrystallization. Another possibility is that the impurities are soluble in the hot solution, from which they may be filtered (Louis and Kenneth, 1987). The boiling point of the solvent should be lower than the melting point of the solid that is being purified. The solvent should not react chemically with the substance being purified.

Common recrystallization solvents have a wide range of polarity and the dielectric constants listed in Table 2.1 provide a measure of this property (Padungthon *et al*., 2011). Those solvents with dielectric constants in the range of 2-3 should be regarded as nonpolar and those with constants above 10 as polar. Solvents in the 3-10 range are of intermediate polarity.

Table 2.1: Common recrystallization solvents.

Solvent	**Boiling point (ºC)**	**Freezing point (°C)**	**Water soluble**	**Dielectric Const. (e)**	**Flammable**	**Specific gravity g/ml**
Water	100	0	_	78.54	No	1.000
95% ethanol	78	< 0	Yes	24.6	Yes	0.800
Diethyl ether	35	< 0	Slightly	4.34	Yes	0.714
Acetone	56	< 0	Yes	20.7	Yes	0.790
Acetic acid	118	17	Yes	6.15	Yes	1.050

Sometimes the organic chemist is unable to find a single pure solvent that is suitable for a particular recrystallization, so that it is necessary to use mixed solvents (Dana *et al*., 1986). This technique involves using a mixture of (two or more) solvents and is done as follows. One solvent is selected in which the compound is soluble when cold. The compound being purified is placed in the solvent in which it is insoluble when

cold. The compound being purified is placed in the solvent in which it is insoluble and then heated near the boiling point of the solvent. Then the second solvent is added in small portions until the solid dissolves. If crystals form on cooling, a suitable solvent mixture may have been found but trial and error with other solvent mixtures may be required before pure crystals are obtained (Kenneth, 1989).

A major requirement for using mixed solvents is that the solvents themselves be completely soluble (miscible) in one another. For example, carbon tetrachloride has a dielectric constant below 3 indicating that it is water-insoluble, so that a mixture of water and carbon tetrachloride could not be used. Some frequently used mixed-solvent pairs are ethanol- water, toluene-petroleum ether, acetic acid-water, diethyl ether-alcohol, and diethyl ether- petroleum ether. Mixtures of toluene- ethanol are infrequently used and then only with absolute ethanol, since the presence of water causes solvent separation, particularly on cooling (Dana *et al*., 1986).

2.2.3 Crystallization from solution

Crystal formation may be either spontaneous or induced. It consists of nucleation followed by crystal growth (Jasmine *et al*., 2012). Crystal growth is dependent on factors such as temperature, pressure, composition of the surrounding solution and availability of surface area.

Crystal growth involves deposition of solute particles onto the face of the crystal. Crystal growth is more of a chemical process than a physical process. For it to occur, the solute particles have to be transported onto the face of the crystal, the solute particles have to react with the surface and the reaction products which are not being utilized by the surface have to be removed. For the growth of good crystals, the temperature variation has to be quite minimal and slow and constant growth has to be ensured. The solute and solvent must have high degree of purity and agitation has to be ensured (Atkins, 1997).

2.2.4 Crystal structure/ form and crystal lattice

A well formed crystal is found to be completely bounded by flat surfaces. The planar surfaces are not confined to the exterior morphology but are also inherent in the interior structure of a crystal (Hook *et al*., 2010). The crystals of a given material tend

to be similar morphology which can either be needle or all plates (Lerner and Trigg 1991).

The flatness of crystal surface can then be attributed to the presence of regular layer of atoms in the structure and cleavage would correspond to the breaking of weaker links between particular layers of atoms.

A detailed study of crystal shows complete internal structure that is only seen to some extent on the outside. These details were discovered by the invention of the reflection goniometer and led to establishment of three laws of crystallography. The first law states that crystals are made up of constant interfacial angles i.e. angles between crystals are constant (Szczepanski, 2012). The second law states that crystals are made up of regular arrangement of points and the points are imaginary while the third law states that crystals are made up of many reflecting planes in all directions.

2.2.5 Forces within crystals

In crystal chemistry, the immediate neighbourhood of each atom and the forces that bind them to each other are important in explaining the overall geometry of the crystal. Crystals are held together by non covalent interactions that may be either hydrogen bonding or non covalent attractive forces (Peter *et al*., 2008). In both cases a regular arrangement of molecules in the crystals results. Whereas hydrogen bonding requires donor and acceptor functional groups, the non-covalent attractive interactions (also known as non-bonded interactions) depend on dipole moments, polarizability and electron distribution within molecules.

2.3 Solvates and hydrates

It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates (Brown *et al*, 1992). The water molecules, because of their small sizes, can easily fill structural voids and because of its multidirectional hydrogen bonding capability is also ideal for linking a majority of drug molecules into stable crystal structures. It is the activity of water in the medium that determines whether a given hydrate structure can form.

Solvates may be formed when a pure organic solvent or a mixture of solvent is used as the solvent for crystallizing the compound. Crystalline hydrates based on their

structure may be classified into three categories. The first category (class I) are the isolated site hydrates where water molecules are isolated from direct contact with other water molecules by interacting drug molecules, for instance cephradine dihydrate. The second category (class II) are channel hydrates where water molecules included in the lattice lie next to other water molecules and adjoining unit cells along an axis of the lattice, forming channels through the crystal for instance ampicilin trihydrate. It is subdivided into an expanded channel or non-stoichometric hydrates for instance cromyln sodium. The other one is planar hydrate which are channel hydrates in which water is localized in a two dimensional order or planar for instance sodium ibuprofen. The third (class III) category of crystalline hydrates are the ion associated hydrates, in which the metal ions are coordinated with water for instance culteridol calcium (Giron, 1999 and Corrigan, 1996). Stoichiometric hydrate forms pose a special challenge in dosage form development due to the unpredictability of water content in the crystal (Ford and wilson, 1999 and Elder, 1994).

2.3.1 States of Water in Hydrates

The water held in crystals may be stoichiometric (water of crystallization) or non-stoichiometric (Vippagunta *et al*., 2001). Many stoichiometric hydrates for instance hydrates of mercabtopurine, caffeine and theophyline exhibit different powder x-ray diffraction patterns upon dehydration. On the other hand dehydration of certain other hydrates does not change the crystal structure significantly, they yield very similar powder x-ray diffraction patterns upon dehydration. Among these are the hydrates of the cephalexin and cephaloglycins. When the water is present in non-stoichiometric proportions, the molecular water may form hydrogen bonded networks which as in ice are nearly tetrahedrally coordinated.

These networks contain cavities capable of accommodating other molecules for instance clathrates. Clathrates with water as the hosts exemplify this type of interaction. Sometimes the water molecules are not part of the crystal structure but are present as guests in a cage formed by molecules other than water. In this case the non stoichiometric water is present in cavities with sufficiently large spacing or windows between the cages that water can pass from one cavity to another and leave the lattice without affecting the overall structure. The non stoichiometric water could also be present as layers. Water can also be incorporated in the structure of crystalline hydrate

materials as ligands coordinated with metallic cations. For simple hydrates the coordinated water molecules appear to be more loosely held and easily removed in the presence of a desiccating agent at room temperature. The structural water found in organic crystals is more tightly held and requires higher temperatures for its removal. Incorporation of water molecules into the solid form influences the intermolecular interactions and crystalline disorder, thus altering the thermodynamic activity of the solid (Corrigan, 1996).

2.4 Thermal analysis

Thermal analysis is a branch of material science where the properties of materials are studied as they change with temperature. Thermal analysis measures physical or chemical changes in a material as a function of temperature. Two common complementary techniques of thermal analysis offered by the Thermal Analysis Service are Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). Thermal analysis Techniques such as DSC/TGA permit qualitative and quantitative studies on hydrates (Giron 1999; Ford 1999; Elder 1994). DSC used as a method to determine the water content on the pharmaceutical hydrates. This was based on the assumption that the enthalpy of binding of n moles of water molecules on the hydrate is the same as that of n moles of water molecules in liquid water (Han 2006). DSC provides information about physical and chemical changes that involve endothermic and exothermic processes, or changes in heat capacity, and is useful in material testing (for instance foods, plastics, and pharmaceuticals) while TGA is a technique for measuring changes in mass as function of temperature and is primarily used to determine the composition of substances.

2.4.1 Principle of thermal analysis

Differential scanning Calorimetry (DSC) measures heat flow to or from a sample as a function of temperature and time. A small portion of a sample is placed in an aluminium pan and heated and/ or cooled in a controlled manner. A reference material (usually an empty aluminium pan) simultaneously undergoes the same programmed time/temperature routine (Wunderlich, 1990). The heat flow (watts) and temperature of the sample are monitored in comparison to the reference material. The analysis is usually performed in an inert gas atmosphere, such as nitrogen. The amount of energy absorbed (endotherm) or evolved (exotherm) as the sample undergoes physical or

chemical changes (for instance melting, boiling, crystallization, curing) is measured in watts as a function of the temperature change. Any material reactions involving changes in heat capacity (for instance glass transition) are also measurable.

DSC experiments provide a graph of energy flow vs. temperature for thermal transitions in materials (Chang and Raymond, 2005). The transitions that can be measured include melting points, boiling points, glass transition temperatures, heat of reaction, thermal and oxidative stability, kinetic and energetic of some reactions.

Thermogravimetric analysis (TGA) continuously measures the weight of a sample as a function of temperature and time. The sample is placed on a small pan connected to a micro balance and heated in a controlled manner and /or held isothermally for a specified time. The atmosphere around the sample may consist of an inert gas, such as nitrogen, or a reactive gas, such as air or oxygen. The heating program may start in an inert atmosphere then be switched to air at a certain point to complete the analysis. Weight changes observed at specific temperature correlate to volatilization of sample components, decomposition, oxidation/reduction reactions, or other reactions or changes (Tao *et al*., 2009).

TGA provides a graph of mass versus temperature. This analytical technique is widely used in polymers science, inorganic chemistry, fuel science, and geology to measure the loss of volatile components or thermal stability of a sample. The experiments are usually run with a temperature ramp of 10 or 20 ºC/min and can be carried out in inert atmosphere, such as nitrogen, to study thermal stability or volatility, or in oxidizing atmospheres to study oxidative decomposition. The mass loss can be characteristic of a material and, where the losses are in discrete steps, the TGA experiments can offer quantitative data on the course of decomposition. The TGA also can be run in an isothermal mode, where the rate of weight loss at a fixed temperature is measured. This type of experiment can be used to predict loss rates of volatiles or decomposition rates for material.

The combined DSC/TGA is an analysis instrument capable of performing both DSC and TGA at the same time. It measures the heat flow and weight changes associated with transitions and reactions in materials over the temperature range ambient to 1500

ºC. The information provided differentiates endothermic and exothermic events which have no associated weight change (for instance melting and crystallization) from those which involve weight change (for instance degredation). Performing both DSC/TGA measurements at the same time on the same instrument and same sample offers greater productivity and removes experimental and sampling variables as factors in the analysis of data. The furnace is horizontal bifilar wound type whose temperature range ambient to 1500 ºC and a heating rate of 0.1 to 100 ºC. Other details include thermocouples: platinum/platinum rhodium, furnace cooling is forced air (1500 to 50 ºC in < 30 min) and sample capacity of 200 mg (350 mg including sample holder).

2.5 Desolvation

Desolvation refers to the removal of a solvent from the crystal structure. Desolvation of crystal solvate is a solid state process of the type below (Vlaer *et al*., 2004).

A (Solid) → B (Solid) + C (Gas)

Various equations and models describe the desolvation kinetics of such reactions by taking special features of their mechanism into account.

The desolvation endotherm in DSC includes such steps as breakage of solvate bonds and vaporization of solvent. Upon desolvation, the crystal structure may rearrange through the breakage and formation of intermolecular forces which include van der Waals interactions and / or hydrogen bonds in which case the rearrangement of the desolvated structure will also be included in the desolvation process. The area under the desolvation peaks in the DSC curve yields the heats (i.e. enthalpies) of the desolvation transition (Mitchel and Smith, 1977b).

Based on the vaporization and sublimation hypothesis (Equation 2.1), Rajendara *et al* ., 1992 formulated a method of calculating the number of moles of water per molecule of anhydrate (n), from the enthalpy of dehydration. It is assumed that each underlying endotherm in the DSC curve is a quantitative measure of water content corresponding to particular binding energy or location.

Based on vaporization hypothesis,

$$n = \frac{\Delta Hd.Ms}{(\Delta Hv - \Delta Hd).Mw} \quad (2.1)$$

ΔHd =specific enthalpy of dehydration (J/g of hydrate)

ΔHv = specific enthalpy vaporization of water (2261 J/g). (Stark and wallace, 1976)

Ms =molecular weight of the anhydrate

Mw =molecular weight of water

This equation is very useful in determining the water quantity from the DSC curve.

2.6 Dehydration and crystal structure

2.6.1 Background information

A major proportion and most widely found groups of solvates are hydrates (Galwey, 2000 and Wellace, 1976). Although the structure of many hydrates have been elucidated, very few dehydration reactions have compared the relationships between relativities and bonding order within sets of reactants.

The underlying factors that control bonding and hence crystal stability imply that chemically related hydrates adopt different packing arrangements in a manner that there is no obvious basis for classification of dehydration through common reactant lattices. Thus in most rate processes, the role of structure in dehydration is better considered individually for each reactant.

The constituent water in molecular hydrates is usually regarded as participating in extensive structural hydrogen bonding. These local linkages, among other factors for instance the role of non-volatile constituents of the reactant, are important in characterizing the initial step towards water release. Kinetic techniques applied to such systems do therefore analyze the interaction between the various species present therein (Alavi *et al*., 2009).

The stoichiometric amounts of water in crystal vary widely. Stepwise water loss is known in which hydrates containing progressively lesser stoichiometric water are

formed as reaction temperatures are elevated. All these depend on the structure of the compound.

As much as it is volatile, water loss in consecutive reaction is systematic. First to be lost are the most weakly held and those retained are already or become strongly bonded in the lower hydrate.

Elimination of water is accompanied by changes for instance density increase and overall increase in close packing due to increase in influence of chemical bonding. Loss of water during dehydration leads to a shrinkage in of the unit cell volume and is accompanied by an increase in molecular motion (Liu *et al*., 2001). Thus water escape would be more difficult in the more densely packed structures of the lower hydrates. Crystal structure is therefore very important in dehydration.

2.6.2 Packing Efficiency

According to Kitaigorodski's theory of crystal packing for organic molecules, the lowest energy structure is that which minimizes the void space in the lattice and maximizes the number of close contacts with neighbouring molecules (Fini *et al*., 1998). This theory was supported by Gavezzotti through his analysis of organic molecular structures (Gavezotti and philippini, 1995 and Mnyukh, 1979). The density rule states that the modification that has the lowest density is the least stable one at absolute zero. This theory is useful as an indicator of the relative stability of crystalline polymorphic forms (Fini *et al*., 1998 and Munn, 1978). However when chemical composition changes, for instance during desolvation, density comparisons are inappropriate and packing coefficient become a convenient means of comparing such structures. Thus in an effort to comprehend the thermodynamic instability imparted on the crystal lattice due to reduced packing efficiency, one may turn to Kitaigorodski's packing coefficient (C_k) as in Equation 2.2. It makes the assumption that molecular volume does not change from one crystal form to another.

$$C_K = ZV_M/V_C \qquad (2.2)$$

where Z is the number of molecules present in the unit cell, V_M is the volume occupied by the molecule and V_C is the volume of the unit cell of the crystal lattice.

2.6.3 Other factors influencing dehydration reactions

It is thought that dehydration occurs preferentially a long route of least hindrance, as in the case of anisotropic crystals where dehydration occurs along the direction of crystal voids. It follows obviously that the crystal packing of the structure is of utmost importance in the study of dehydration. The compactness of the crystal packing gives how tightly packed the molecules are. The more compact, usually due to number of hydrogen bonds, the more difficult it is for the solvent to escape. The ease of desolvation can also be determined by the tunnel size (cross-sectional area of the tunnel) and the number of tunnels per unit area since it is easier for solvents to escape from large bore tunnels than smaller ones (Galwey, 2000). The direction of the water chains in relation to the main plane of the crystal and also the straightness of the chain can affect dehydration rates.

Tunnels have been shown to have significant effects on dehydration mechanism facilitating migration of water molecules. In 5-nitroflurouracil hydrate and magnesium p-amino salicylate hydrate (Giron, 1999) where there is negligible tunnel area and reduced ease of dehydration (Bryn, 1982).

2.7 Kinetics of solid state reactions

2.7.1 Background information

Kinetics of solid-state desolvation reactions are very important especially in the pharmaceuticals where they are used to predict the shelf-life of hydrated drugs in order to arrive at expiry dates. However, the purpose of many kinetic studies is to gain insights into the controls and mechanisms of chemical changes that occur in selected reactants.

In order to determine the kinetics of a particular solid-state reaction in this particular work non-isothermal method was used owing to the fact it is a simpler method. This is an increasing temperature method that often involves the use of DSC and TGA to monitor heat and weight change, respectively with changing temperatures.

TGA experiments carried out on large single crystals, small single crystals and powdered crystals of copper (II) sulfate pentahydrate had been used to demonstrate

role that retained liquid water plays in maintaining crystal morphology during dehydration. Skeletal anhydrous crystals from large sized copper sulfate pentahydrate have the same morphology as the starting crystal on complete dehydration at controlled heating rates as long as solution phase is maintained with the crystal during decomposition. The dehydration of the copper sulfate pentahydrate is a three step process (Loic and Michele, 2011).

2.7.2 Fractional dehydration

The mass change is monitored with respect to temperature and is used to obtain fractional dehydration (α) data. The α-values are calculated as fractional decomposition of the original mass according to Equation 2.3.

$$\alpha = \frac{X_t - X_O}{X_f - X_O} \qquad (2.3)$$

where;

X_t is the mass of sample at a given temperature t, $X_o$is the initial sample mass at initial temperature and X_f is the final sample mass. Therefore 100% fractional dehydrated (α=1) corresponded to the loss of maximum amount of water during desolvation.

The shapes of α-time plots provide information about the solid-state reactions and have been studied. Typical examples are as shown in Figure 2.1a-d (Yoshioka and Uchigama ,1986)

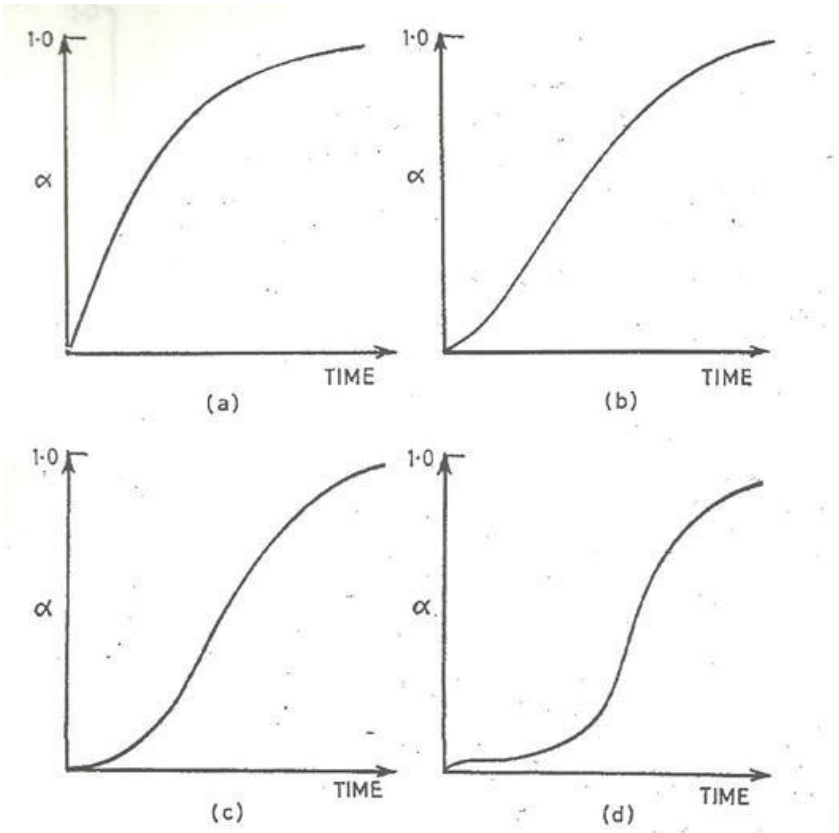

Figure 2.1: Typical fractional decomposition α-time curves for solid-state thermal decomposition reactions.

Figure 2.1a represents a reaction that is deceleratory throughout, in which the rate progressively decreases as the reactant is consumed. In Figure 2.1b there is a short initial acceleratory period, during which the reaction rate increases and there after the reaction is deceleratory. The reaction depicted in Figure 2.1c shows more pronounced acceleratory period that is followed by a more deceleratory period.

Figure 2.1d shows a complex reaction comprising of an initial deceleratory reaction giving rise to a small total yield product, possibly from a reaction limited to the surfaces of the reactant particles. This is followed by a sigmoid shaped α-time similar to that shown in Figure 2.1c.

The solid-state desolvation behaviours of hydrates are usually graphically expressed in terms of such fractional reaction α-time curves (Lyakhov and Boldyrev, 1972). The curves are usually sigmoid in shape but not always. Chemical rate processes that give sigmoid shaped α-time curves more often result from reactions that occur at the

reactant product interface. The interface is initially established at limited number of points on the surface of the reactant crystal (nuclei) by formation of micro-crystals of product.

The reaction at this point is very slow owing to the small area of such interface. For many solids there may be significant time-interval, the induction period between the times that reactant reaches the reaction temperature and the detection of significant product formation. Thereafter the reaction proceeds within the strained contact area of the reactant-product interface. There is then increase in the rate of product formation hence an acceleratory reaction.

.

Figure 2.2 is a typical sigmoid α-time curve. It illustrates three stages a, b, c, for a dehydration reaction. These stages can be explained as follows: stages ‘a’ represent the induction period relating to the formation of nuclei at localized points in the reactant, Stage ‘b’ corresponds to the acceleratory period relating to the growth of the reaction interface whereas stage ‘c’ stands for the deceleratory period where adjacent product islands overlap with one another thus reducing the reaction interface.

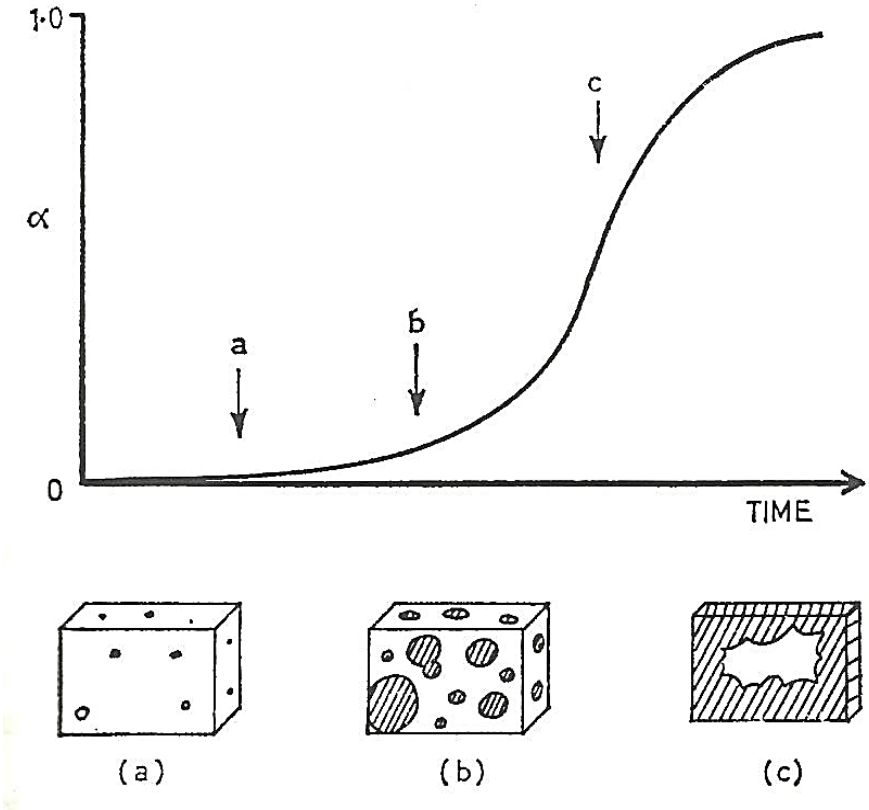

Figure 2.2: Interpretation of sigmoid fractional reaction curve for a single crystal desolvation .

The reactivity of solids is significantly influenced by certain factors that include particle size, nature, sample size, crystal imperfection, impurities and the damage to crystal surfaces. Thus, observed behaviour may therefore be sensitive to the method of reactant material preparation, length and conditions of storage and any sort of pre-treatment before decomposition (for instance crushing, abrasion, ageing and irradiation) (Brown *et al*., 1992).

2.8 Modeling

Molecular modeling is a powerful methodology for analyzing structures. It is an essential tool to medicinal chemist in drug design (Mandeep *et al*., 2012). It generally plays an important role in drug discovery process. This technique aims to introduce in a simple way the hierarchy of computational modeling methods used now days as standard tool by organic chemists for searching, rationalizing and predicting structure and reactivity of organic and bio- organic molecules.

In this particular work the numerous ways in which modeling can be used to interpret and rationalize experimental data were considered.

The overall aim of modeling methods is to try to relate experimental data to structure of compounds and it is mainly done using Mercury software. Mercury software offers a comprehensive range of tools for structure visualization and the exploration of crystal packing. Some key features of Mercury software include: - a full range of structure display, styles and the ability to measure and display distances, angles and torsion angles involving atoms, centroids and planes. It also has the ability to display unit cell axes, the contents of any number of unit cell in any direction, or a slice through a crystal in any direction. It can also show the location and display intermolecular and intramolecular hydrogen bonds, short non-bonded contacts, and user specified types of contacts. It has the ability to calculate, display and save the powder diffraction pattern for the structure on view and the ability to save displays. It has new graph set facility for displaying H-bonding patterns according to their Bernstein and Etter notation and it new labels toolbar provides easy control over atom labeling, giving the ability to label atoms, with many new properties.

2.9 Review of study materials

Four salts; oxalic acid dihydrate, zinc acetate dihydrate, copper (II) sulfate pentahydrate and nickel sulfate hexahydrate were selected as model compounds. This is because the crystal structures of these compounds are well known and could easily be mined from crystallographic database for purposes of modeling. Also the model compounds are simple, easy to crystallize, are easily available, and relatively cheap.

The choice of water as a solvent for this study was because in the production or transformation of drugs, attention is given to solvents that are used during the manufacturing process, especially when they are used in the last stage of the production. The presence of solvent molecules as residues of the precipitation from crystallizing can result in molecular adducts and modified crystal habits (Fini *et al*., 1998; Byrn *et al*., 1995). Crystal structures for solvates formation, too, get affected. Owing to the possible retention of organic solvent molecules, in the final step of production of a drug, the use of water is usually recommended.

2.9.1 Oxalic acid dihydrate

Oxalic acid is a compound with a chemical formula $H_2C_2O_4.2H_2O$. It is a colourless, crystalline, toxic organic compound belonging to the family of dicarboxyl acids; melting at 187 ºC, density 1.65 g/cm^3, soluble in water, alcohol and ether. Its solubility in water is 90 g/l(at 20 ºC) and it occurs in the form of its metal salts (usually calcium or potassium) in many plants. It is a symmetrical molecule with two delocalized carboxylic groups that make it a strongly polar molecule as well as very acidic and very soluble in water. Unlike other carboxylic acids, oxalic and formic acids are readily oxidized and combine with calcium, iron and sodium, magnesium or potassium to form less soluble salts called oxalates.

There are three known forms of oxalic acid whose structures have been solved. Oxalic acid dihydrate is very difficult to grow as large crystals from pure water. Commonly, the growth of large sized oxalic acid dihydrate is from a mixture of acetone and water (Toresen and Strassburger , 1964). The anhydrous oxalic acid is dimorphic with the α-oxalic acid form being orthorhombic and the β-oxalic acid is monoclinic. Thermal decomposition of oxalic acid has been widely reported, however, no such reports are available linking its thermal behaviour to its internal structure thus the need for current study.

2.9.2 Copper (II) sulfate pentahydrate

It is a chemical compound with formula $CuSO_4.5H_2O$. The salt exists as a series of compounds that differ in their degree of hydration. The anhydrous form is pale green or grey white powder, whereas the pentahydrate ($CuSO_4.5H_2O$) is bright blue with density of 2.284 g/cm^3 and soluble in water. Its solubility in water is 320 g/l (at 20 ºC). Previous studies have looked at thermal behaviour of the salt in that it decomposes before melting, losing two water molecules at 63 ºC, followed by two at 109ºC and the final water molecule at 200 ºC (Andrew *et al*., 1999; Egon *et al*., 2001). At 650 ºC it decomposes into copper (II) oxide (CuO) and sulfur trioxide (SO_3). Its blue colour is due to the water of hydration. When heated in an open flame the crystals are dehydrated and turn grayish white (Holleman and Wiberg , 2001).

2.9.3 Zinc acetate dihydrate

It is a compound with formula $(CH_3COO)_2Zn.2H_2O$. It is octahedral where both acetate groups are bidentate. It decomposes at 237 ºC and loses water at 100 ºC. It is soluble in alcohol and water. Its coordination geometry is octahedral and its molecular shape is tetrahedral. Its solubility in water is 430 g/l at (20 ºC).

It is normally used as a dietary supplement. It is also used to treat common cold, sold as a topical anti itch ointment, and in chewing gum it is a breadth freshener and plague inhibitor. In industry, it is used in wood preservation, manufacture of ethylene acetate as a dye mordant and as a precursor via a sol gel route to the transparent semiconductor zinc oxide.

2.9.4 Nickel (II) sulfate hexahydrate

It is a compound with chemical formula $NiSO_4.6H_2O$. The crystal structure is rhombohedral with density of 2.07 g/cm^3 and soluble in water. Its solubility is 650 g/l (at 20 ºC). It is normally obtained as a by-product of copper refining or dissolution of nickel metal or nickel oxide in sulfuric acid.

CHAPTER THREE

EXPERIMENTAL

3.1 Materials

Ethanol, acetic acid and acetone were purchased from Sigma Aldrich and were of analytical grade. Water used for crystallization purposes was de-ionized and double distilled.

Study materials; oxalic acid dihydrate, copper (II) sulfate pentahydrate, nickel (II) sulfate hexahydrate and zinc acetate dihydrate were also purchased from Sigma Aldrich and were of analytical grade.

3.2 Determination of solubility of the crystals in solvents of varying polarities

Solubility of the four salts in solvents of varying polarities was done so as to determine the best solvent/solvent pair for crystallizing the solvates.

About 0.10 g of copper (II) sulfate pentahydrate was placed in a series of test tubes and 1.00 ml of different solvents namely: distilled water, ethanol, acetic acid, and acetone were added. The sample was then stirred and its solubility at room temperature recorded. The test tubes were then placed in a beaker of boiling water and again their solubilities recorded. The test tubes were then allowed to cool to room temperature. Finally they were placed in an ice bath and observations recorded. The procedure was repeated for the three remaining salts namely: oxalic acid dihydrate, nickel (II) sulfate hexahydrate and zinc acetate dihydrate.

When a suitable single pure solvent could not be found for crystallizing a particular solvate, it became necessary to use mixed solvents. Two given solvents were then mixed in the ratio of 100:0, 75:25, 50:50, 25:75 and 0:100. The solvents were mixed in three major categories as follows:

Water: Acetone (100:0, 75:25, 50:50, 25:75 and 0:100)
Water: Ethanol (100:0, 75:25, 50:50, 25:75 and 0:100)
Water: Acetic acid (100:0, 75:25, 50:50, 25:75 and 0:100)

Each of the four solvates were then dissolved into each of the three categories of solvent mixtures in the indicated ratios when the mixture was cold and when hot and again the solubility of the solvate was noted in each case. The solubility results enabled one to determine the best solvent mixture for crystallizing a particular solvate.

3.3 Crystallization of the solvates

Once a suitable solvent mixture for crystallizing a particular solvate having been identified from the preceding procedure, it was then used to crystallize a particular solvate.

A given quantity of solvate was added to a flask after which the suitable solvent pair was added to it dropwise. The solution was then heated gently and as soon as boiling began the solvent pair was continuously added drop wise until the entire solid dissolved. The flask was then allowed to cool slowly undisturbed to room temperature during which time crystallization was observed. The mother liquor was then decanted off and the crystals scraped onto a filter paper using a stainless steel spatula and then squeezed between sheets of filter paper to remove traces of solvent.

The crystals were allowed to dry and some stored in a refrigerator awaiting thermal studies while the rest underwent melting point determination, shape and colour description. The procedure was repeated for the remaining three solvates against their suitable crystallization solvent pair.

3.4 Characterization

3.4.1 Visual properties

Here the four solvates were observed under a phase contrasting microscope (a.kruss optrovic model mbu 2100) integrated to a computer and the most important visual properties such as colour and morphology description of each solvate noted.

3.4.2 Melting point determination

Melting point was determined using Mel-Temp melting point apparatus. It consists of an electrically heated aluminum block that accommodates three capillaries. The sample was grind and then transferred to the capillaries. The sample was illuminated through the lower port and observed with a lens through the upper port. The temperature was noted when the sample just started melting and when the whole sample had melted.

3.4.3 Thermal studies

This was done using non isothermal method by Jupiter Netzsch STA 449C DSC / TGA machine. Sample weights of between 6.25 mg and 11.86 mg were used for thermal studies. The heating rate was 5 ^{o}C min^{-1}. Sample cell was an aluminium open cell. Data was collected using STA 449C program. Analysis of data was done using Netzschproteus program.

3.4.4 Data mining and Modeling

Data mining was carried out in which crystallographic data of study materials; oxalic acid dihydrate, zinc acetate dihydrate, nickel (II) sulfate hexahydrate and copper (II) sulfate pentahydrate were obtained from oxford crystallographic data base. Using mined crystal data modeling was carried out on internal structure of study materials using Mercury software.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Solubility studies

Solubility studies were carried out to determine the best solvent for crystallization of the respective solvates. The solvates were dissolved in solvents of varying polarities and the results were as provided in Table 4.1.

Table 4.1: Solubility of the salts.

Solvent		Oxalic acid dihydrate	Zinc acetate dihydrate	Copper (II) sulfate Pentahydrate	Nickel sulfate Hexahydrate
Distilled Water	Cold	√	√	√	√
	Hot	√	√	√	√
Ethanol	Cold	√	×	×	×
	Hot	√	×	×	×
Acetic acid	Cold	√	√	×	×
	Hot	√	√	×	×
Acetone	Cold	√	×	×	×
	Hot	√	×	×	×

√ - soluble × - insoluble

From the results, it was evident that all the solvates being polar dissolved in water since water is a polar solvent. The solvates were insoluble in ethanol apart from oxalic acid dihydrate. Acetic acid dissolved oxalic acid dihydrate and zinc acetate dihydrate. Acetone dissolved oxalic acid. An ideal solvent for crystallization is one that dissolves the solvate when hot and not when cold. From the results in Table 4.1 not a single solvent turned out to be suitable for a particular solvate recrystallization and so it became necessary to use mixed ratios of solvents. The Solvates were first dissolved in solvent systems of water and acetone in the ratios of water: acetone (100:0, 75:25, 50:50, 25:75 and 0:100). The solubilities of the hydrates were determined and recorded in Table 4.2.

Table 4.2: Solubility of solvates in solvent mixtures of water and acetone.

Solvate		Water: Acetone				
		100:0	**75:25**	**50:50**	**25:75**	**0:100**
Oxalic acid dihydrate	Cold	√	×	×	×	√
	Hot	√	√	√	√	√
Copper(II) sulfate pentahydrate	Cold	√	×	√	√	√
	Hot	√	×	√	√	√
Nickel sulfate hexahydrate	Cold	√	×	√	√	√
	Hot	√	√	√	√	√
Zinc acetate dihydrate	Cold	√	×	√	√	√
	Hot	√	√	√	√	√

Solvent mixtures of water and acetone turned out to be the best solvents for crystallizing salts of oxalic acid. This is possible because oxalic acid is a weak polar compound and acetone is non polar compound.

The solvates were again dissolved in solvent mixtures of water and ethanol in the ratios of water: ethanol (100:0, 75:25, 50:50, 25:75 and 0:100) and results recorded in Table 4.3.

Table 4.3: Solubility of solvates in solvent mixtures of water and ethanol

Solvate		Water: Ethanol				
		100:0	**75:25**	**50:50**	**25:75**	**0:100**
Oxalic acid dihydrate	Cold	√	√	√	√	√
	Hot	√	√	√	√	√
Copper(II) sulfate pentahydrate	Cold	√	×	×	×	×
	Hot	√	√	√	√	×
Nickel sulfate hexahydrate	Cold	√	√	×	√	√
	Hot	√	√	√	√	√
Zinc acetate dihydrate	Cold	√	×	×	×	√
	Hot	√	√	√	√	√

Solvent mixtures of water and ethanol were good for crystallizing salts of copper (II) sulfate pentahydrate and zinc acetate dihydrate.

The solvates were also dissolved in water and acetic acid solvent systems in the ratio water: acetic acid (100:0, 75:25, 50:50, 25:75 and 0:100) and their solubilities determined and recorded in Table 4.4.

Table 4.4: Solubility of solvates in solvent mixtures of water and acetic acid.

Solvate	**Water: Acetic acid**					
		100:0	**75:25**	**50:50**	**25:75**	**0:100**
Oxalic acid dehydrate	Cold	√	√	√	√	√
	Hot	√	√	√	√	√
Copper(II) sulfate pentahydrate	Cold	√	√	√	√	√
	Hot	√	√	√	√	√
Nickel sulfate hexahydrate	Cold	√	×	√	×	√
	Hot	√	√	√	√	√
Zinc acetate dehydrate	Cold	√	√	√	√	√
	Hot	√	√	√	√	√

Solvent mixture of water and acetic acid turned out to be good for crystallizing nickel (II) sulfate hexahydrate salt. Generally the inorganic solvates being polar were mainly crystallized using polar solvents of ethanol and acetic acid mixed with water.

4.2 Crystallization

The solvates were crystallized from a mixture of water and other solvents namely ethanol, acetic acid and acetone. Most salts of copper (II) sulfate pentahydrate and zinc acetate dihydrate were crystallized from water and ethanol mixtures in various ratios shown in Table 4.5. Nickel sulfate hexahydrate was crystallized from selected mixture of water and other solvents namely acetic acid, ethanol and acetone. Oxalic acid dihydrate was crystallized from a mixture of water and acetone in various ratios as shown in Table 4.5.

Table 4.5: Solvates crystallized from various solvent systems.

Solvate	Designation	Solvent systems
Oxalic acid dihydrate	D_1 D_2 D_3 D_4	Water: Acetone(25:75) Water: Acetone(50:50) Water: Acetone(75:25) Water: Acetone(100:0)
Copper(II) sulfate pentahydrate	A_1 A_2 A_3 A_4	Water: Ethanol(100:0) Water: Ethanol(75:25) Water: Ethanol (50:50) Water: Ethanol(25:75)
Nickel sulfate hexahydrate	C_1 C_2 C_3 C_4	Water: Acetic acid(75:25) Water: Acetic acid(25:75) Water: Acetone(75:25) Water: Ethanol(50:50)
Zinc acetate dihydrate	B_1 B_2 B_3 B_4	Water: Ethanol(75:25) Water: Ethanol(50:50) Water: Ethanol(25:75) Water: Acetone(75:25)

4.3 Oxalic acid

4.3.1 Physical properties

All salts of oxalic acid dihydrate were white in colour. Shapes of salts of oxalic acid crystallized from the various solvent systems were observed under a microscope and the ones crystallized from water: acetone (100:0) were needle-like shaped whereas the ones crystallized from water: acetone (75:25) were prismatic as shown in Figure 4.1. When crystallized from water: acetone (50:50), a few were needle-like shaped while majority were prismatic in shape. However, when crystallized from water: acetone (25:75) the crystals were prismatic in shape.

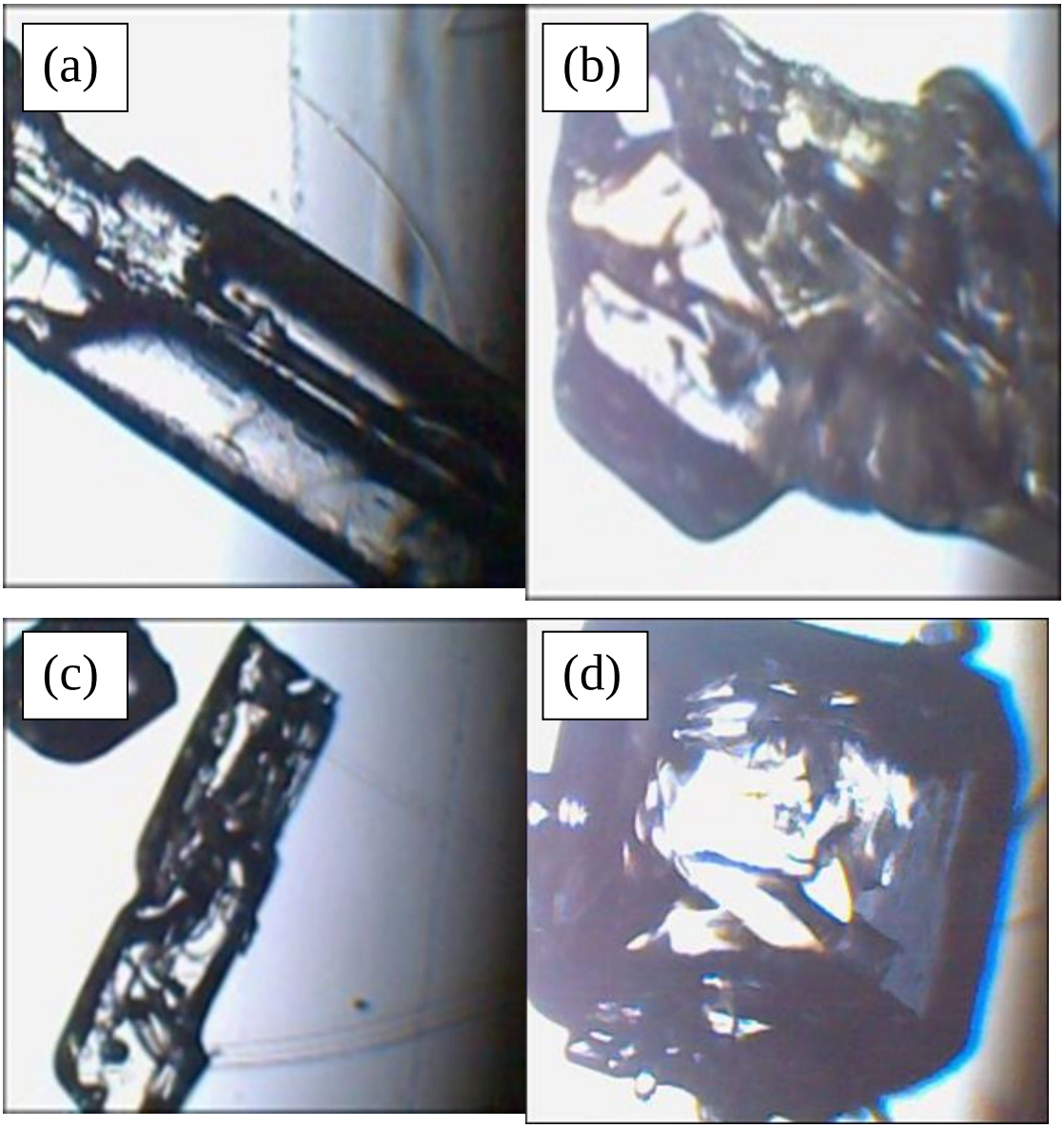

Figure 4.1: The microscopic images of various crystal forms of oxalic acid dihydrate crystallized from various solvent systems, water: acetone (a) (100:0) needle-like, (b) (75:25) prismatic, (c) (50:50) prismatic/needle-like, (d) (25:75) prismatic. (**Source: Author, 2008)**

4.3.2 Thermal studies

Non-isothermal methods were used for kinetic analysis. A non-isothermal method is a rising temperature method that involves the use of DSC and TGA to monitor heat and weight changes, respectively, with changing temperatures. Samples were analyzed and DSC/TGA curves produced. In TGA the weight loss corresponded to the dehydration endotherm of the hydrate as observed in the DSC measurements.

The DSC and TGA thermograms of oxalic acid were as shown in Figure 4.2. DSC curve showed a strong dip at 102 ºC which was basically due to loss of water molecules, and in TGA curve the weight loss corresponding to the endotherm was 15.63 %. This weight loss continued until it became constant just before 114 ºC. TGA/DSC graphs were rather broad showing that the solvate lost solvent slowly.

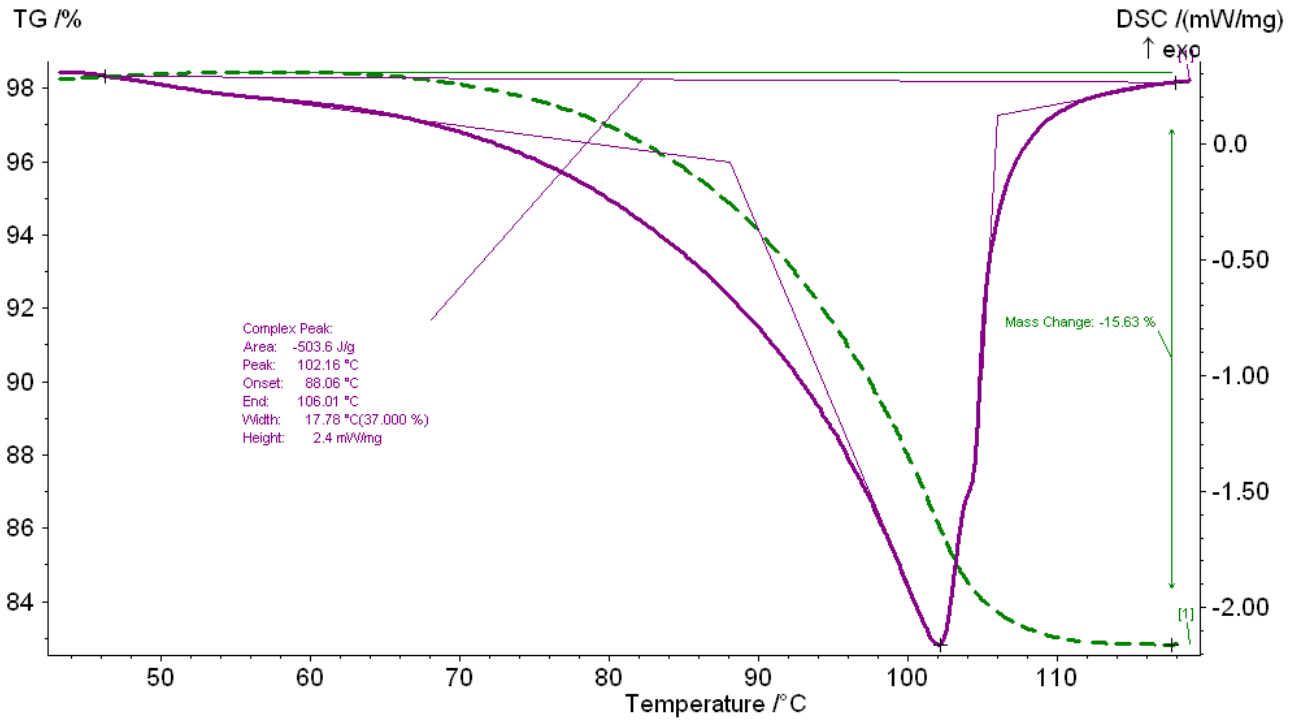

Figure 4.2: TGA and DSC profiles for oxalic acid dihydrate crystallized from solvent systems water: acetone (25:75) D_1.

From the DSC desolvation curve the enthalpy value of dehydration was used to calculate the number of molecules of water lost using Equation 2.1.

The enthalpy value of 504 J/g led to a stoichiometric value of n=1.0098 which is lower than the expected value of n=2. This was an indication that only one molecule of water was removed during desolvation process at 102 ºC. After the removal of the first water molecule the remaining water molecule was more bonded to the oxalic acid thus requiring more heat energy for its removal. From the curves the energy change involved during desolvation of each crystal was determined and recorded as indicated in Table 4.6. From this it was noted that there was no significant energy difference

during the desolvation within a particular crystal, thus solvent of crystallization did not influence significantly the way a particular crystal desolvated.

Table 4.6: Properties of oxalic acid dihydrate.

Solvent Systems	Energy change(J)	Mass change of solvent %	Expected mass change of solvent %	Molecules of Water lost	Temp (ºC) of onset of desolvation
H_2O: acetone (100:0) **D_4**	-2.612758	-54.38	-28.57	4	75
H_2O: Acetone(75:25) **D_3**	-6.995026	-60.46	-28.57	4	75
H_2O: acetone(50:50) **D_2**	-6.574568	-60.97	-28.57	4	75
H_2O: acetone(25:75) **D_1**	-3.182752	-15.63	-28.57	1	65

The percentage mass change was determined from the curve and compared with the actual expected mass change so as to determine the number of molecules of water lost or remaining after desolvation. The number of water molecules lost in this case was found to be one, which was in agreement with the value calculated using the vaporization hypothesis. This confirmed that during the dehydration of oxalic acid only one molecule of water was lost leaving the second one which was more tightly held.

4.3.3 Dehydration kinetic data treatment

The TGA curves were used to generate data for further kinetic studies. From the TGA curve in Figure 4.2, the weight of a crystal at a particular temperature was determined. The weight was then used to generate fractional dehydration data denoted by α. The α values were calculated as fractional decomposition of the original mass according to Equation 2.3.

Sigma plot version 11 spreadsheet software was used to generate α data for a particular crystal desolvation. α was plotted against temperature and the kinetic curves generated were sigmoid in shape. From the curves, the ease of desolvation of solvates

were compared as per the temperature at which the hydrates started dehydrating. Those that started at a lower temperature were easier to dehydrate than those which started at a higher temperature. Figure 4.3 shows the typical curves of the fractional dehydration against temperature for the four salts of oxalic acid.

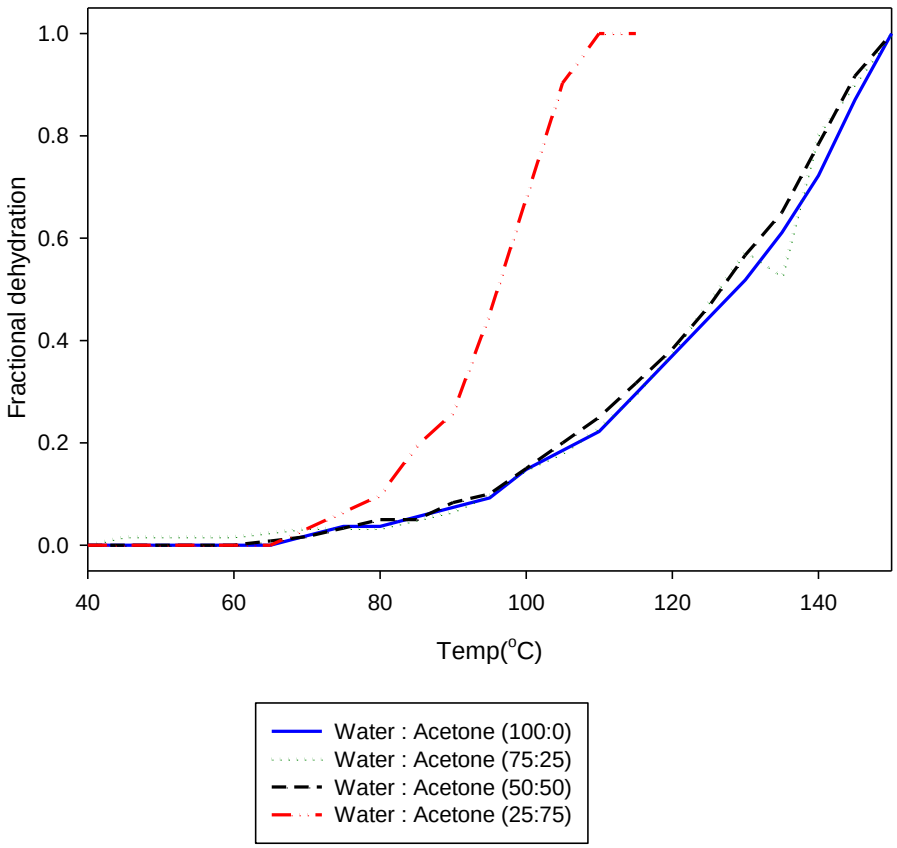

Figure 4.3: Fractional dehydration curves of the four salts of oxalic acid dehydrate.

Kinetic curves showed that, of the four salts of oxalic acid the one recrystallised from water: acetone (25:75) dehydrated faster than the rest which dehydrated almost at the same rate. The solvate desolvated more easily because the proportion of acetone was more than that of water. Acetone can only hydrogen bond with oxalic acid unlike water which can hydrogen bond with itself and also with oxalic acid. Thus, there were few hydrogen bonds in the structure making it more open enabling it to lose solvent more easily upon desolvation. The faster rate of desolvation of solvate crystallized from water: acetone (25:75) as is evident from Figure 4.3 is supported by the results in Table 4.6 where it had a relatively low heat of desolvation.

4.3.4 Modeling

Molecular packing plays a very important role in explaining rates of desolvation in solvates. The more closely packed a crystal the harder it will be for solvent molecules to escape. Thus, the compactness of the packing which is a ratio of the molecules in the unit cell to the volume of the unit cell might be expected to play a role in hindering the escape of solvent molecules particularly in cases where some solvent molecules do not escape out the tunnel direction.

Using mined data of oxalic acid from Oxford crystallographic database modeling was done on its internal structure to show packing and alignment within crystal.

The Mercury program (version 2.3) was used for modeling and the space fill model was used to show the packing within the unit cell of the solvate. When rotated to give the best conformation, four tunnels/spaces were seen as can be seen in Figure 4.4. Generally the numbers of tunnel/spaces were few suggesting that the structure was more packed thus it may have lost solvent with difficulty.

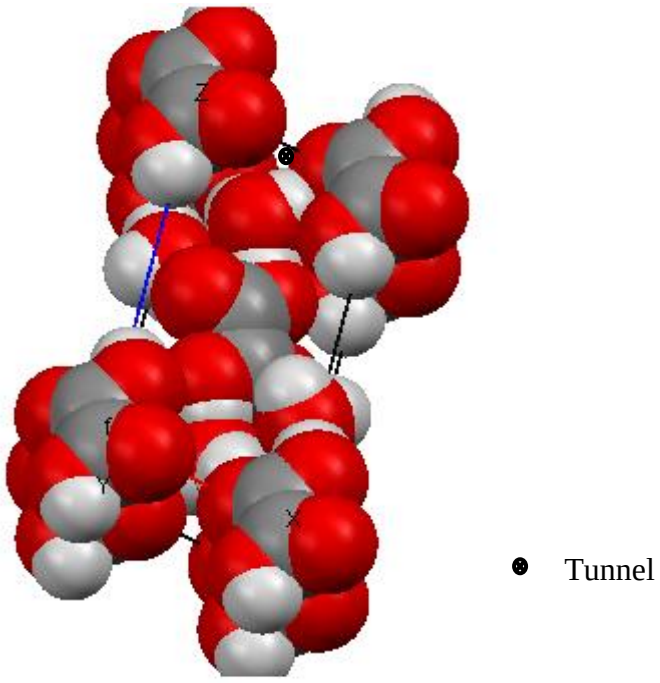

Figure 4.4: Space filling model showing the molecular packing within oxalic acid dihydrate solvate.

Hydrogen bonding of water to the host organic molecules in the crystal lattice may play an important role in desolvation of solvates. In general it would be expected that the stronger the hydrogen bond (or the shorter the hydrogen bond distance or the higher the number of hydrogen bonds) the higher the threshold temperature for desolvation. The number of hydrogen bonds within the unit cell of oxalic acid was determined by way of counting as shown in Figure 4.5. When rotated to give the best conformation the numbers of hydrogen bonds were thirty seven. The numbers of hydrogen bonds were on average many meaning that the structure was more compact and the rate of desolvation was rather low.

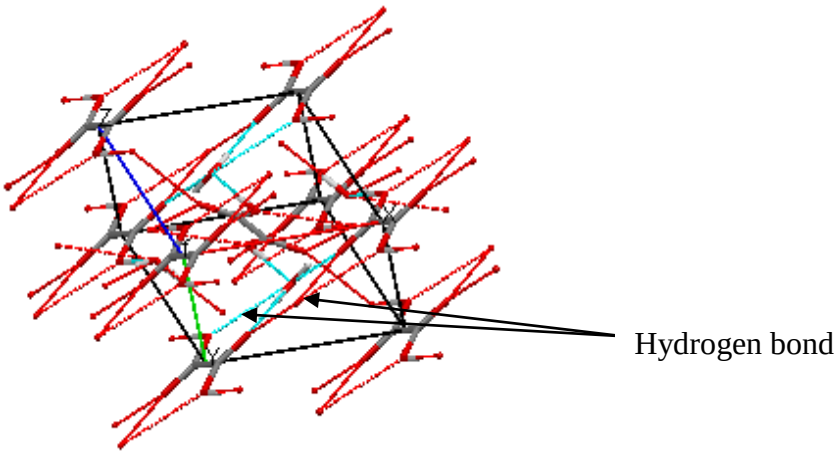

Figure 4.5: Crystal packing showing hydrogen bonds within oxalic acid dihydrate.

4.4 Zinc acetate dihydrate

4.4.1 Physical properties

Crystals of zinc acetate dihydrate were also white in colour as expected of all zinc compounds. The shapes of all the salts crystallized from the various solvent systems when viewed under microscope were plate-like in form as shown in Figure 4.6.

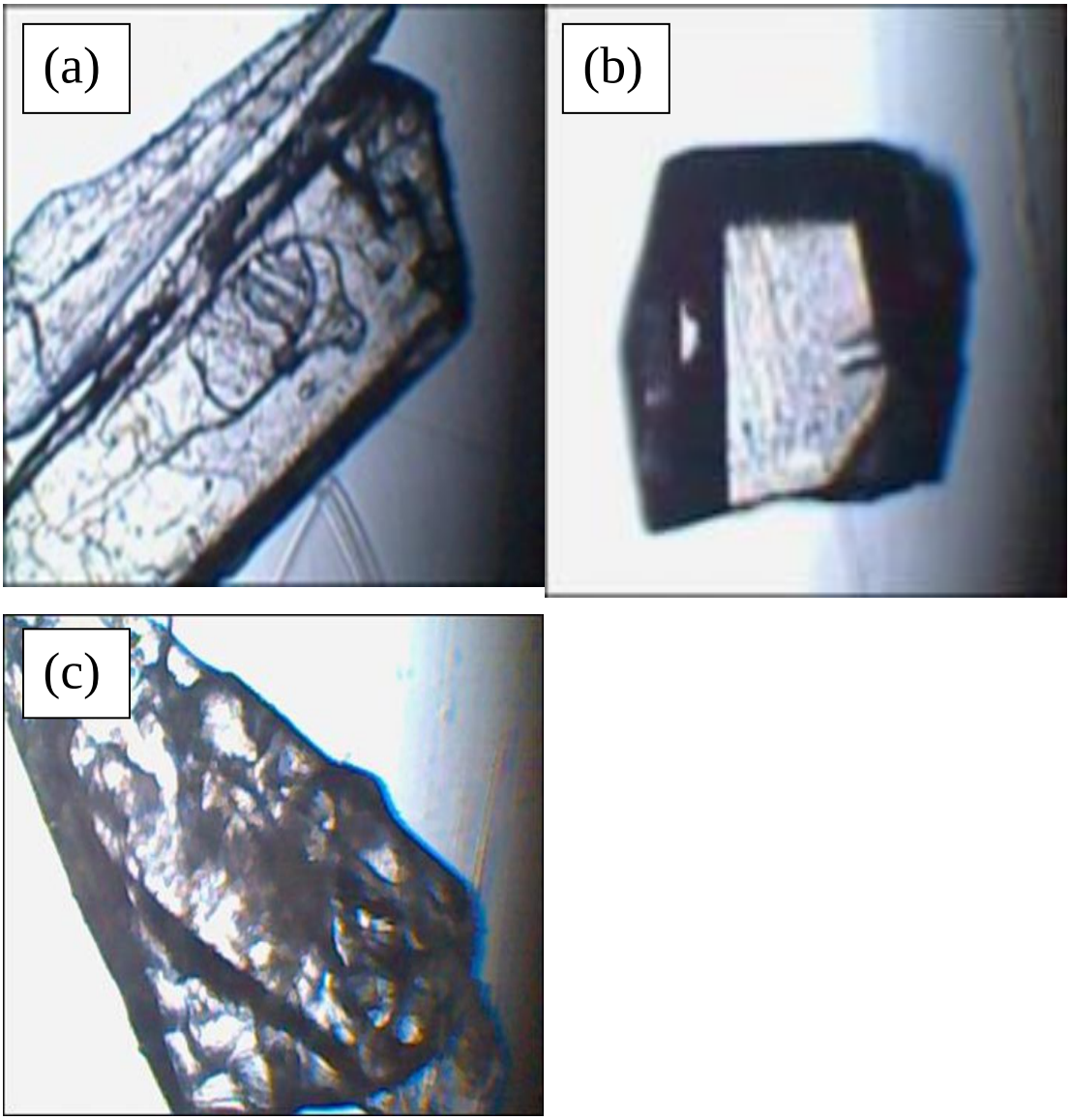

Figure 4.6: The microscopic images of various crystal forms of zinc acetate dihydrate from solvent systems, water: ethanol (a) (75:25) plate-like, (b) (50:50) plate-like, (c) (25:75) plate-like. (Source: Author, 2008)

4.4.2 Thermal studies

The DSC/TGA thermograms of zinc acetate dihydrate were as shown in Figure 4.7 below. DSC showed strong dips at 106 ºC and 111 ºC. The endotherm at 106 ºC was possibly due to loss of most loosely held first water molecule while the endotherm at 111 ºC was possibly due to the loss of the second water molecule. The TGA showed a weight loss of 16.11 % at these temperatures. The weight loss continued until it became constant just before 140 ºC.

DSC/TGA curves were narrow indicating that the solvate lost solvent rather fast.

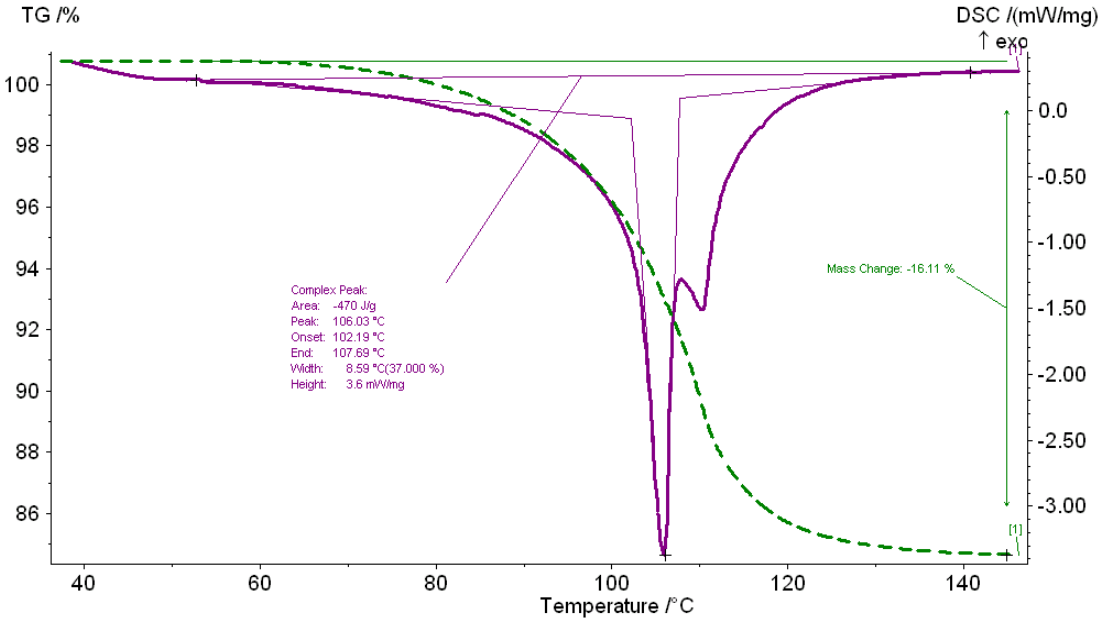

Figure 4.7: DSC/TGA profiles of zinc acetate dihydrate crystallized from water: ethanol (25:75) B_3.

From the DSC desolvation curve, the number of molecules of water lost *n* during dehydration was calculated using Equation 2.1. The enthalpy value of 470 J/g gave a stoichiometric value of *n*=2.1485 which was close to the expected value of 2. Here all the water molecules were lost as opposed to the case of oxalic acid, an indication that it was easier for it to loose water compared to oxalic acid for reasons that has been looked at section 4.3.2.

From the curves, the energy change during a particular desolvation were determined and recorded in Table 4.7. The energy change during desolvation of the various crystals did not show any significant difference. The number of water molecules lost as per Table 4.7 was very much comparable to the one calculated using the vaporization hypothesis equation (i.e. Equation 2.1) thus confirming that the two water molecules were lost in two steps during the desolvation process.

4.4.3 Dehydration kinetic data treatment

Like in the case of oxalic acid TGA curves were used to generate data for further kinetic studies. Fractional dehydration values were calculated and plotted against

temperature for the four salts of zinc acetate. The four salts started desolvating at different temperatures as can be seen in Figure 4.8.

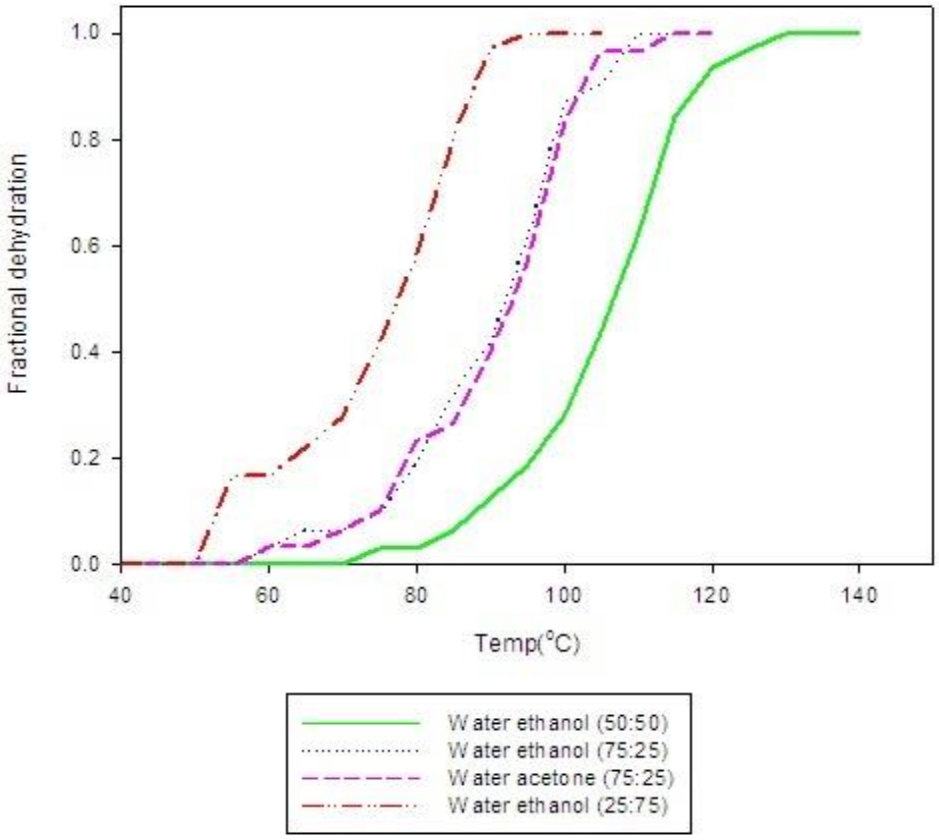

Figure 4.8: Fractional dehydration curves of the four salts of zinc acetate dehydrate.

The salt recrystallised from water: ethanol (25:75) started to desolvate at a much lower temperature (45 ºC). The proportion of ethanol is more than water hence it formed fewer hydrogen bonds than the solvate that was crystallized from water: ethanol (50:50). The solvate crystallized from water: ethanol (25:75) having fewer hydrogen bonds had a more open structure making it lose solvent easily. The ease of desolvation of the solvate is further supported by the results in Table 4.7 which shows that it required lower amount of heat energy to lose solvent.

Table 4.7: Properties of zinc acetate dihydrate.

Solvent Systems	Energy change(j)	mass change of solvent %	expected mass change of solvent %	molecules of water lost	Temp (ºC) of onset of desolvation
H_2O: Acetone(75:25) B_4	-4.006497	-14.80	-16.44	2	55
H_2O: ethanol(25:75) B_3	-3.274920	-15.89	-16.44	2	45
H_2O: ethanol(50:50) B_2	-3.750600	-16.11	-16.44	2	70
H_2O: ethanol(75:25) B_1	-3.975114	-15.83	-16.44	2	55

4.4.4 Modeling

Zinc acetate dihydrate was analyzed using the same method as oxalic acid. Space fill model was used and when rotated the best conformation indicated ten tunnels/spaces as shown in Figure 4.9. Generally this particular solvate had more tunnels and the packing was less compact making it lose solvent more easily.

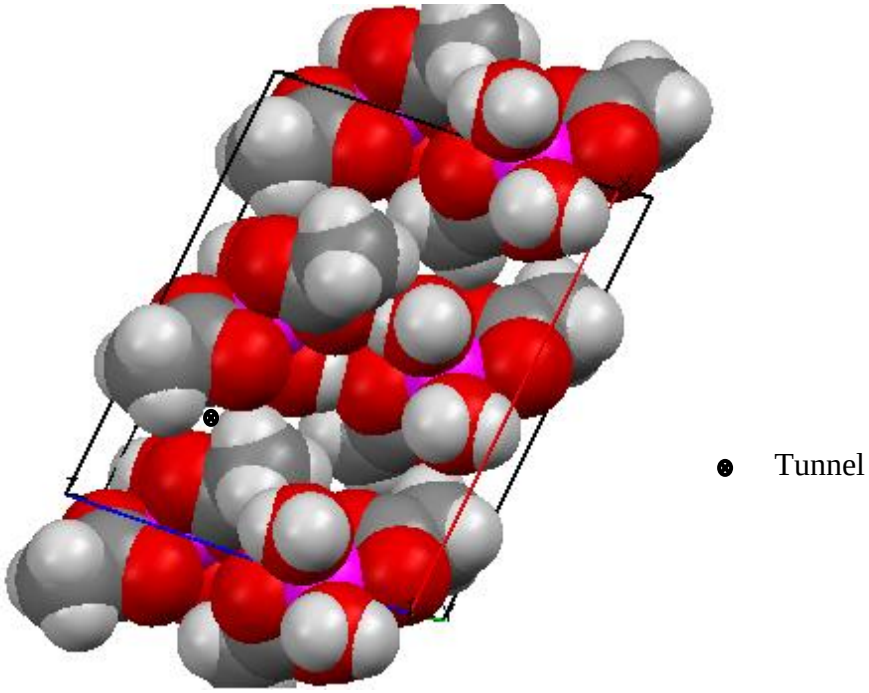

Figure 4.9: Space fill model showing the molecular packing within zinc acetate dihydrate.

The number of hydrogen bonds per unit cell was determined. When rotated the best conformation gave the numbers of hydrogen bonds as thirty and is shown in Fig 4.10.

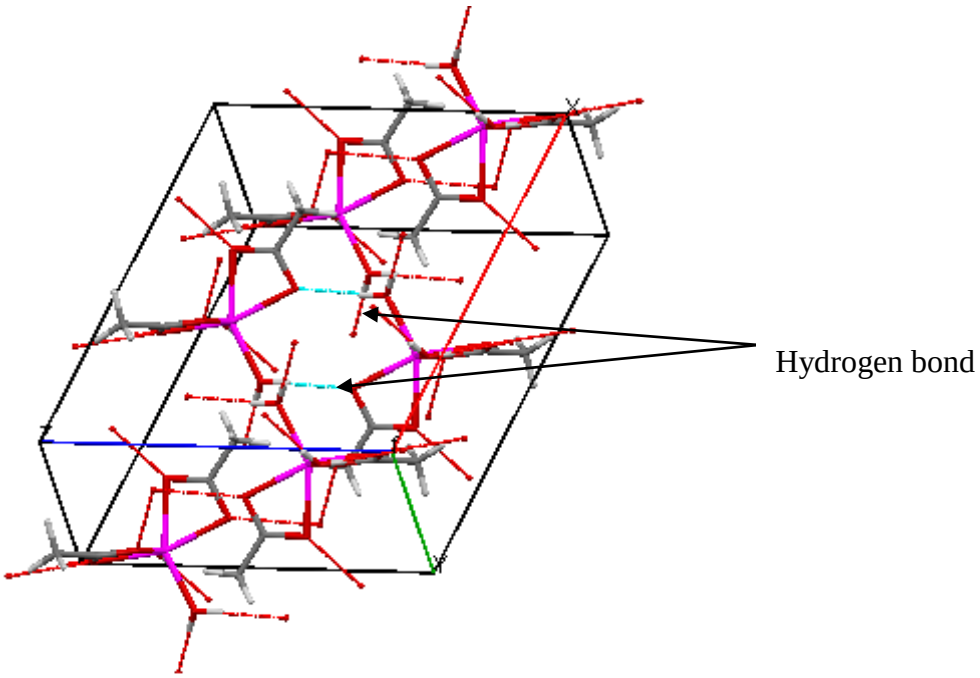

Figure 4.10: Crystal packing showing the number of hydrogen bonds in zinc acetate dehydrate.

The numbers of hydrogen bonds were generally fewer than in oxalic acid explaining why the structure was more open enabling it to lose solvent more easily.

4.5 Copper (II) sulfate pentahydrate

4.5.1 Physical properties

All the salts were blue and their shapes were plate like (Figure 4.11) apart from the one crystallized from water: ethanol (75:25) solvent system, which turned out to be needle like.

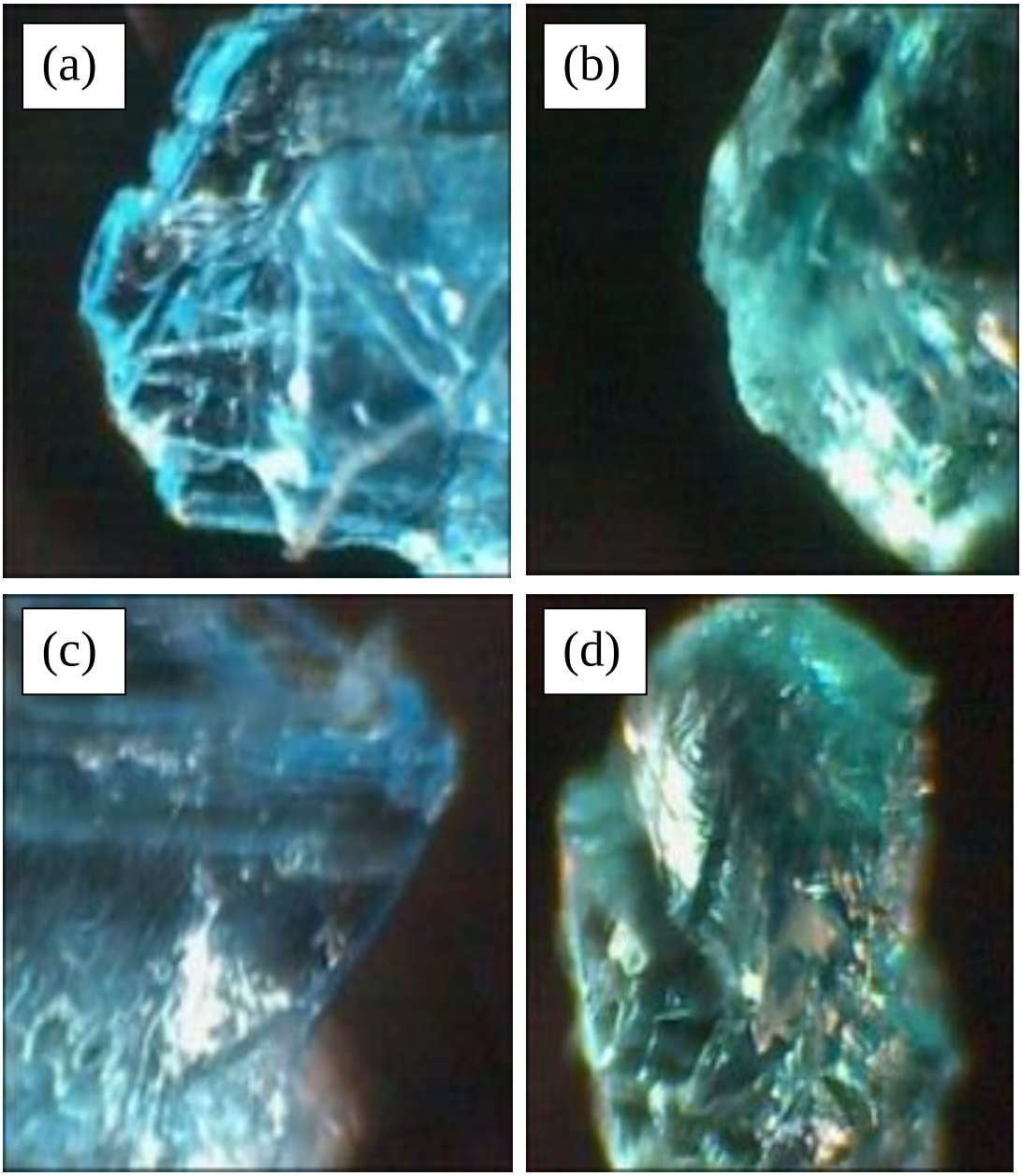

Figure 4.11: The microscopic images of various crystal forms of copper (II) sulfate pentahydrate from solvent systems, water: ethanol (a) (100:0) plate-like, (b) (75:25) plate-like, (c) (50:50) plate-like, (d) (25:75) needle-like.

(Source: Author, 2008)

4.5.2 Thermal studies

The DSC/TGA thermograms of copper sulfate were as shown in Figure 4.12. DSC curve showed strong dips at 102 ºC, 120 ºC and 140 ºC and a weak dip at 96 ºC. The peaks were basically due to loss of water molecules which were more loosely held. In TGA analyses the weight loss that corresponded to the endotherm at (96 ºC, 102 ºC and 120 ºC) was 12.82 % and at 140 ºC was 14.11 %. Four water molecules were lost

at temperatures of 96 ºC, 102 ºC, 120 ºC and 140 ºC leaving the fifth molecule. The weight loss continued until it became constant just after 140 ºC.

TGA curves were narrow and this implied that the solvate lost solvent relatively faster.

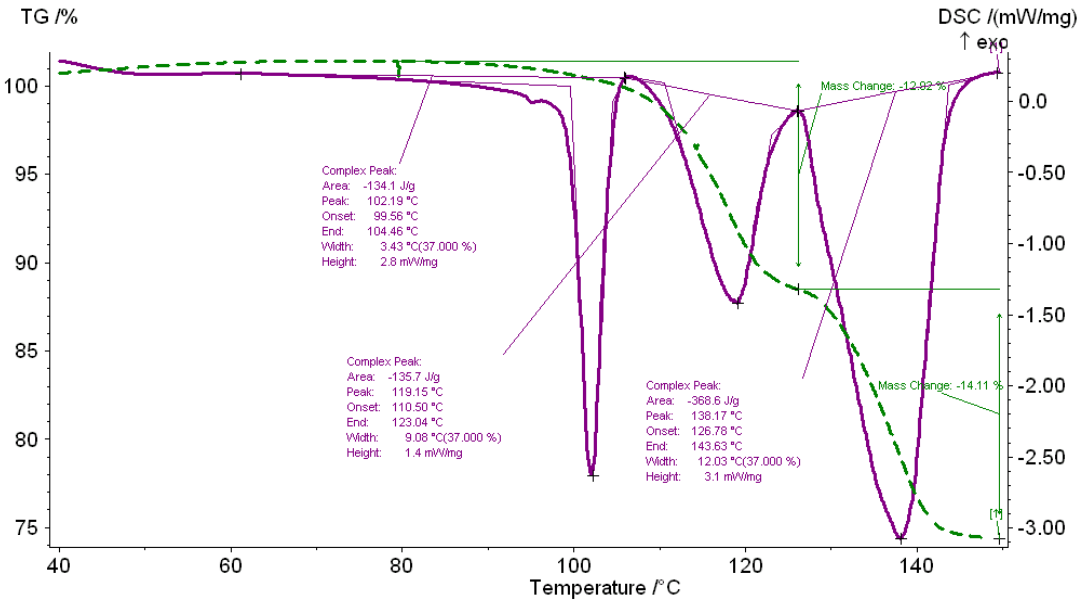

Figure 4.12: **DSC and TGA curves of copper (II) sulfate pentahydrate solvate crystallized from water: ethanol (75:25) A_2.**

From the DSC curve the number of water molecules lost was calculated using Equation 2.1. The enthalpy value of 134.1 J/g, 135.7 J/g and 368.6 J/g led to stoichiometric values of *n* as 1, 1 and 2, respectively. The *n* values were totaling to 4 which was very much comparable to the total number of water molecules lost by the solvate as per Table 4.8. The water molecules were removed in four steps during the desolvation process.

4.5.3 Dehydration kinetic data treatment

The TGA curves were used to generate data for further kinetic studies. Like in the previous cases of other solvates, the curves were used to generate fractional dehydration data. Sigma plot version 11 was then used to plot the curves of fractional dehydration against temperature and like the case of oxalic acid and zinc acetate the graphs were sigmoid in shape. The kinetic curves of the four solvates of copper sulfate were as shown in Figure 4.13.

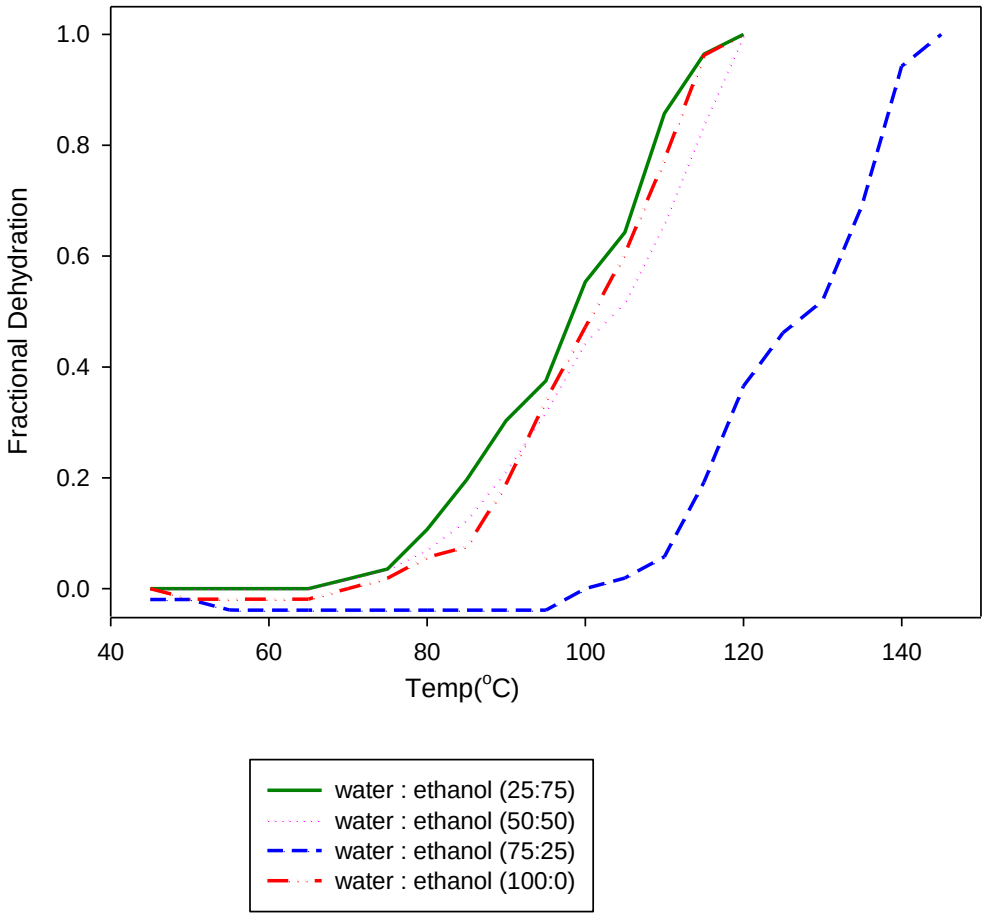

Figure 4.13: **Fractional dehydration curves of the four salts of copper (II) sulfate pentahydrate.**

The ease of desolvation of the four salts of copper (II) sulfate was compared based on the onset temperature of desolvation. Three solvates crystallized from water: ethanol (25:75), water: ethanol (50:50) and water: ethanol (100:0) had almost the same onset temperature (65 ºC) of desolvation while the one that was recrystallised from water: ethanol (75:25) started to desolvate at a significantly higher temperature (95 ºC). This was because there were many hydrogen bonds in its structure making it more compact thus difficult to desolvate compared to the rest.

Table 4.8: Properties of copper (II) sulfate pentahydrate.

Solvent Combination	energy change(j)	Mass change of solvent(%)	expected mass change of solvent(%)	Molecules of Water lost	Temp (°C) onset of desolvation
H_2O:ethanol (25:75) A_4	-6.934389	-26.09	-36.00	4	65
H_2O: ethanol(50:50) A_3	-8.504000	-28.00	-36.00	4	65
H_2O: ethanol(75:25) A_2	-6.647446	-26.76	-36.00	4	95
H_2O: ethanol(100:0) A_1	-5.193:25	-27.31	-36.00	4	65

4.5.4 Modeling

Like in the case of oxalic acid, mercury programme was used for analysis. The space fill model was used. When rotated the best conformation gave the total number of spaces/tunnels are seven as shown Figure 4.14. The structure had relatively many large tunnels making it more open thus it lost solvent molecules easily.

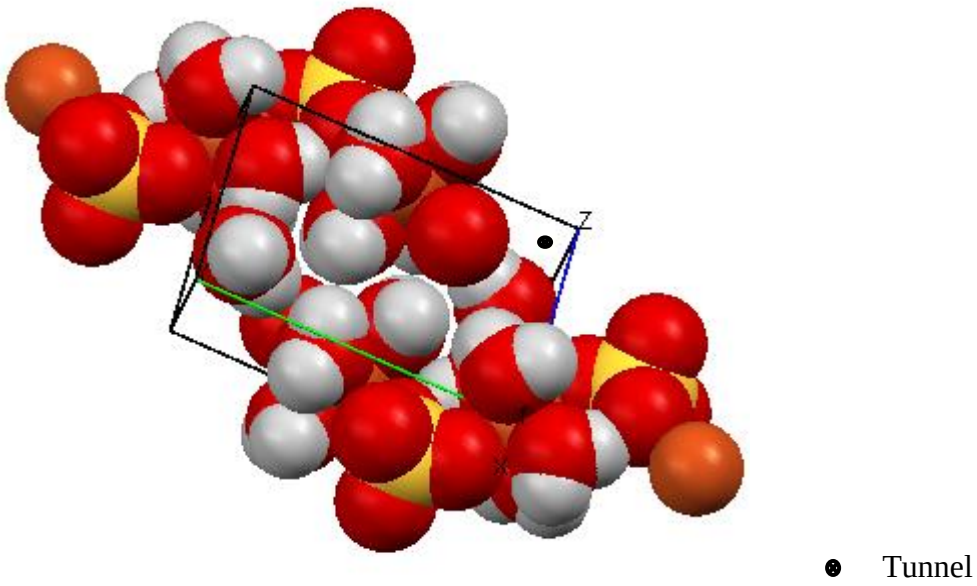

Figure 4.14: **Space fill model showing molecular packing within copper (II) sulfate pentahydrate solvate.**

The number of hydrogen bonds per unit cell was also determined as can be seen in Figure 4.15. When rotated along a, b and c axes to give the best conformation the number of hydrogen bonds were twenty. The numbers of hydrogen bonds were few implying that it had a more open structure enabling it lose solvent easily.

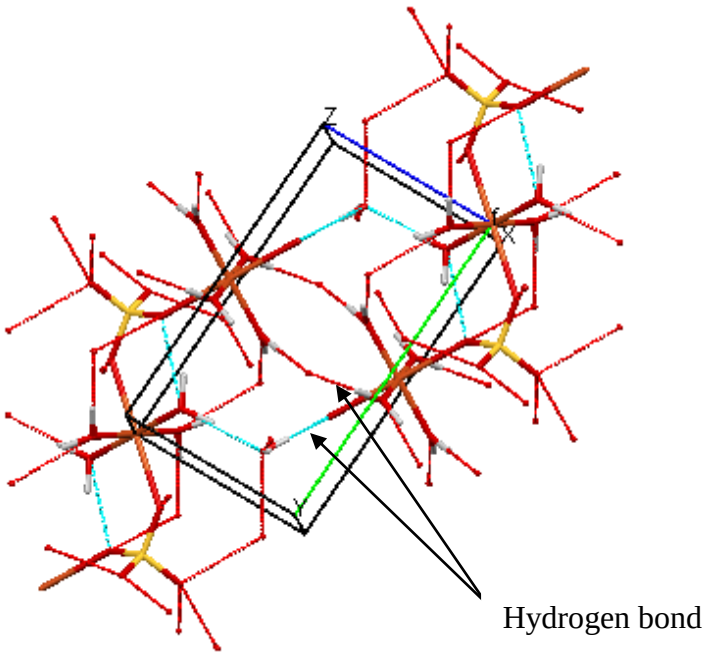

Figure 4.15: Crystal packing showing hydrogen bonds in copper (II) sulfate pentahydrate solvate.

4.6 Nickel sulfate hexahydrate

4.6.1 Physical properties

The crystals of this hydrate were green and all their shapes when viewed under microscope were needle-like as shown in Figure 4.16.

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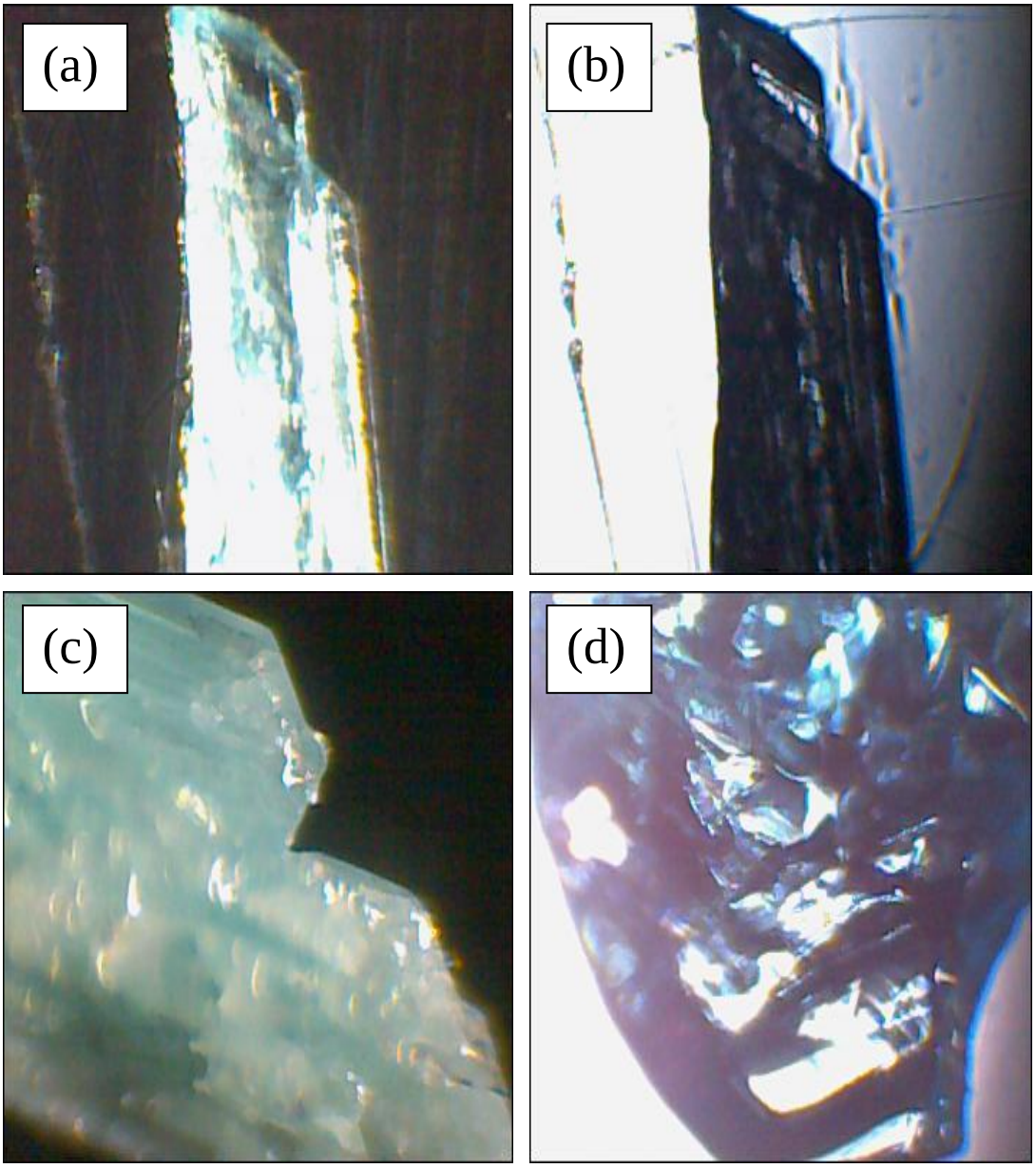

Figure 4.16: The microscopic images of various crystal forms of nickel (II) sulfate hexahydrate from different solvent systems; (a) From water: acetic acid (75:25) needle-like, (b) From water: acetic acid (25:75) needle-like, (c) From water: acetone (75:25) needle-like, (d) From water: ethanol (50:50) needle-like.
(Source: Author, 2008)

4.6.2 Thermal studies

The DSC thermograms of nickel (II) sulfate hexahydrate showed strong peaks at 105 ºC and 140 ºC as shown in Figure 4.17 due to loss of water molecules. The TGA

confirmed weight losses at these temperatures. TGA curves were rather broad an indication that the solvate lost solvent slowly.

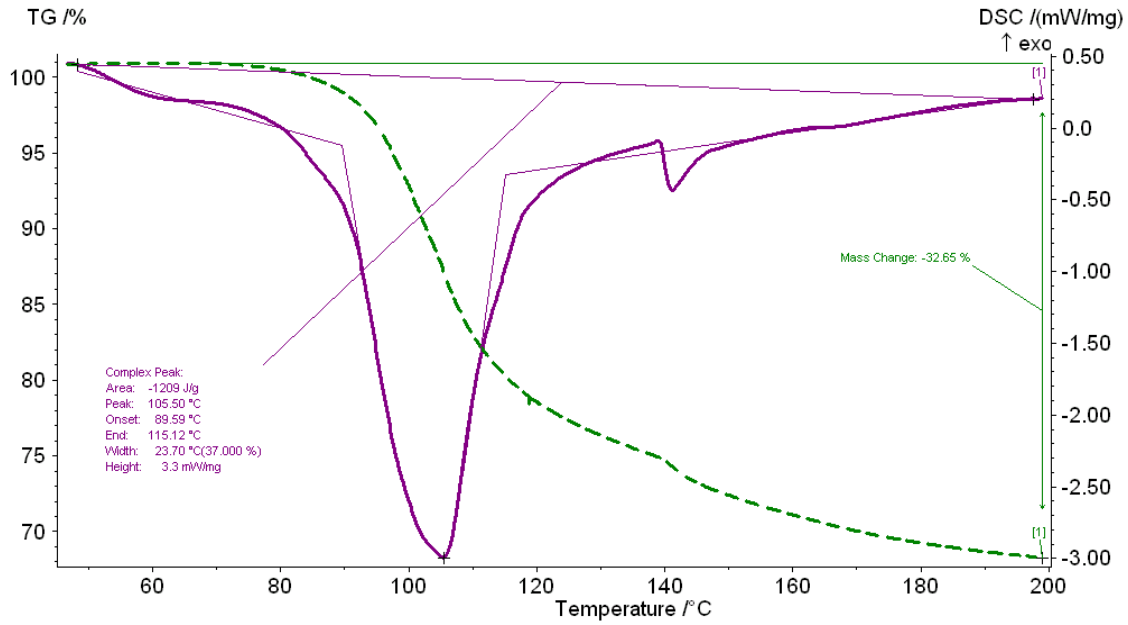

Figure 4.17: DSC and TGA curves of nickel sulfate hexahydrate solvate crystallized from water: ethanol (50:50) C4.

From the DSC desolvation curve the number of water molecules lost were calculated using Equation 2.1 as in the previous curves. The enthalpy value of 57.63 J/g and 457.6 J/g gave stoichiometric value of *n*=5. This value was in agreement with the one in Table 4.9. During desolvation of nickel sulfate not all the water of crystallization were removed. Out of the six water molecules one remained which required more energy to remove.

Table 4.9: Properties of nickel sulfate hexahydrate.

Solvent Combination	Energy change(j)	Mass change of solvent(%)	Expected mass change of solvent (%)	Molecules of water lost	Temp (° C) Onset of desolvation
H_2O: Ethanol (50:50) C_4	-9.48690	-31.37	- 41.06	5	100
H_2O: Acetone (75:25) C_3	-10.542480	-32.65	-41.06	5	70
H_2O: CH_3COOH (75:25) C_2	-7.755002	-30.23	-41.06	4	100
H_2O: CH_3COOH (75:25) C_1	-8.372500	-31.25	-41.06	5	100

4.6.3 Desolvation kinetic data treatment

TGA curves were used to generate fractional dehydration data which was plotted against temperature for the four salts of nickel sulfate shown in Figure 4.18.

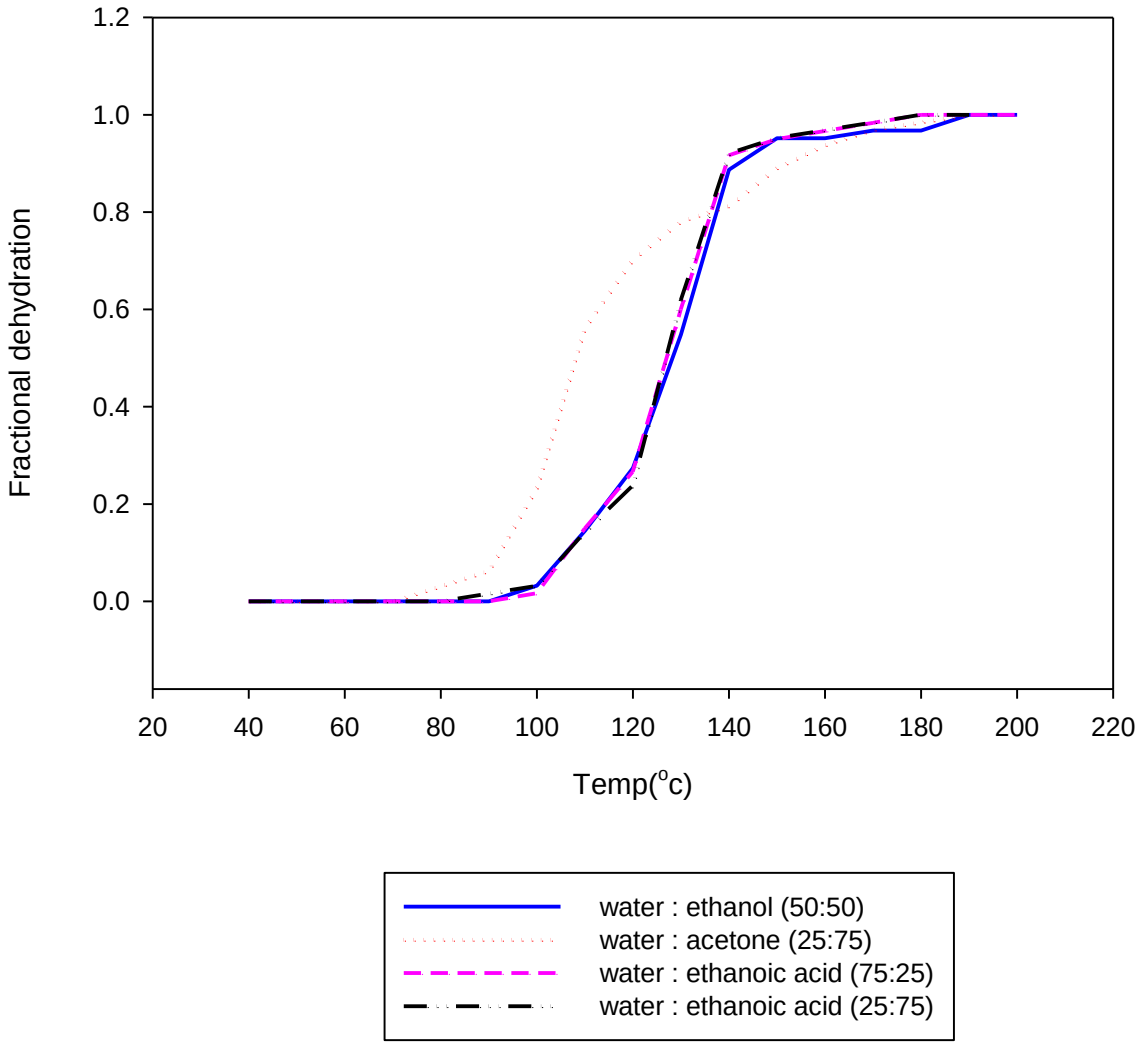

Figure 4.18: Fractional dehydration curves versus temperature for salts of nickel sulfate hexahydrate.

The rates of desolvation of the four salts were compared. The salt recrystallised from water: acetone (75:25), C_3 dehydrated more easily compared to the rest, C_1, C_2, and C_4 whose onset temperature of dehydration were almost the same. C_3 dehydrated more easily because more of the volatile solvent (acetone) got into the structure than water thus the acetone was easily desolvated. The other reason could have been that C_3 dehydrated much faster because the number of hydrogen bonds per unit cell were fewer hence the solvate had a more open packing making it lose solvent molecules more easily.

4.6.4 Modeling

Like in the previous cases the space fill model was used. When rotated to give the best conformation three tunnels/ spaces were observed as shown in Figure 4.19. The number of tunnels per unit cell was generally few suggesting that the structure was more compact making it hard to lose solvent molecules.

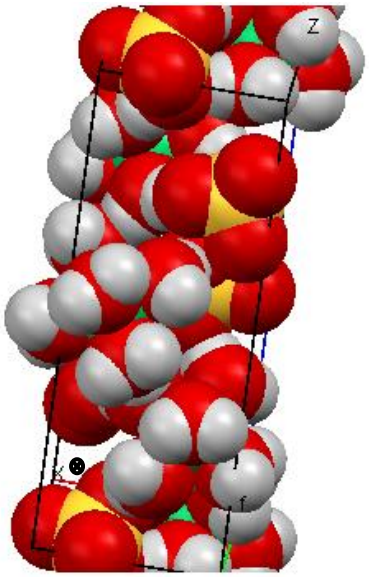

Figure 4.19: Space fill model showing molecular packing within nickel sulfate hexahydrate solvate.

Number of hydrogen bonds within the molecules was also determined as can be seen in Figure 4.20. When rotated to give the best conformation the numbers of hydrogen bonds were thirty seven. The numbers of hydrogen bonds were generally many making the structure very compact thus, it lost solvent with a lot of difficulty.

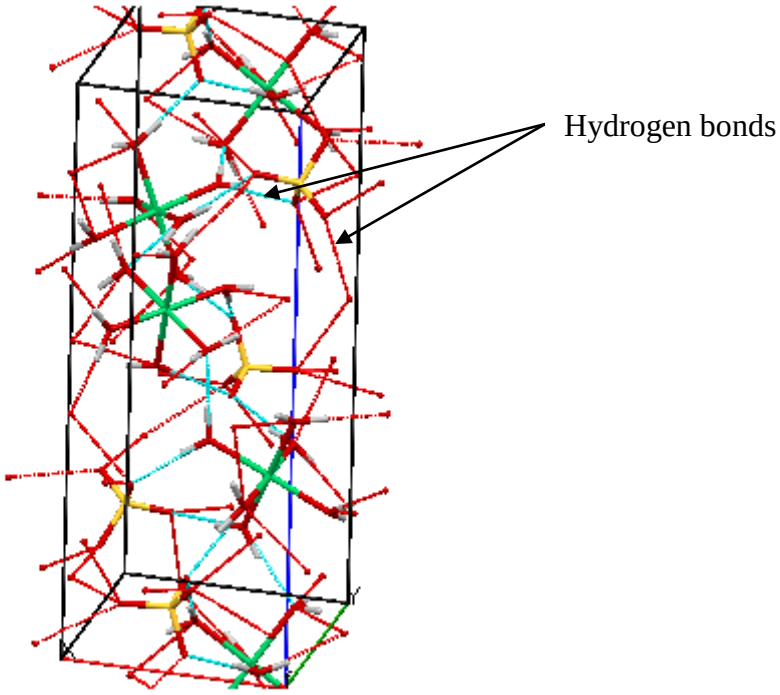

Figure 4.20: Crystal packing showing hydrogen bonds in nickel sulfate.

4.7 Comparative study

During this study it was noted that all the hydrates desolvated with increase in temperature. The heats of dehydration of copper (II) sulfate pentahydrate, zinc acetate dihydrate, nickel sulfate hexahydrate and oxalic acid dihydrate were determined and found to be 159.6 J/mole, 235.0 J/mole, 241.8 J/mole and 503.6 J/mole, respectively. These energy values indicate that it was easier for copper sulfate pentahydrate to dehydrate compared to the other hydrates and this was because the structure was more open thus there was minimal hindrance to escape of water as shown in Figure 4.22. The copper (II) sulfate was capable of forming only two hydrogen bonds per molecule of the compound as compared to oxalic acid which was able to form six as depicted by Figure 4.21. Modeling also revealed that the structure of copper sulfate was more open because of it forming fewer hydrogen bonds compared to the rest as shown in Figure 4.23. On the same note it was relatively difficult for oxalic acid to dehydrate compared to the rest and this was due to the compact nature of the structure. It was more compact due to the high number of hydrogen bonds that were present within the structure.

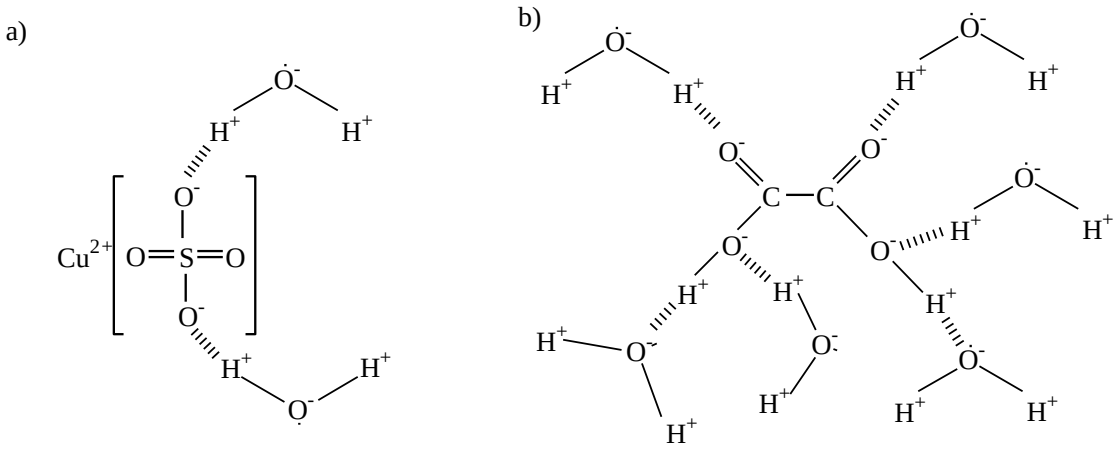

Figure 4.21: Hydrogen bonding within a molecule of: (a) Copper sulfate, (b) Oxalic acid.

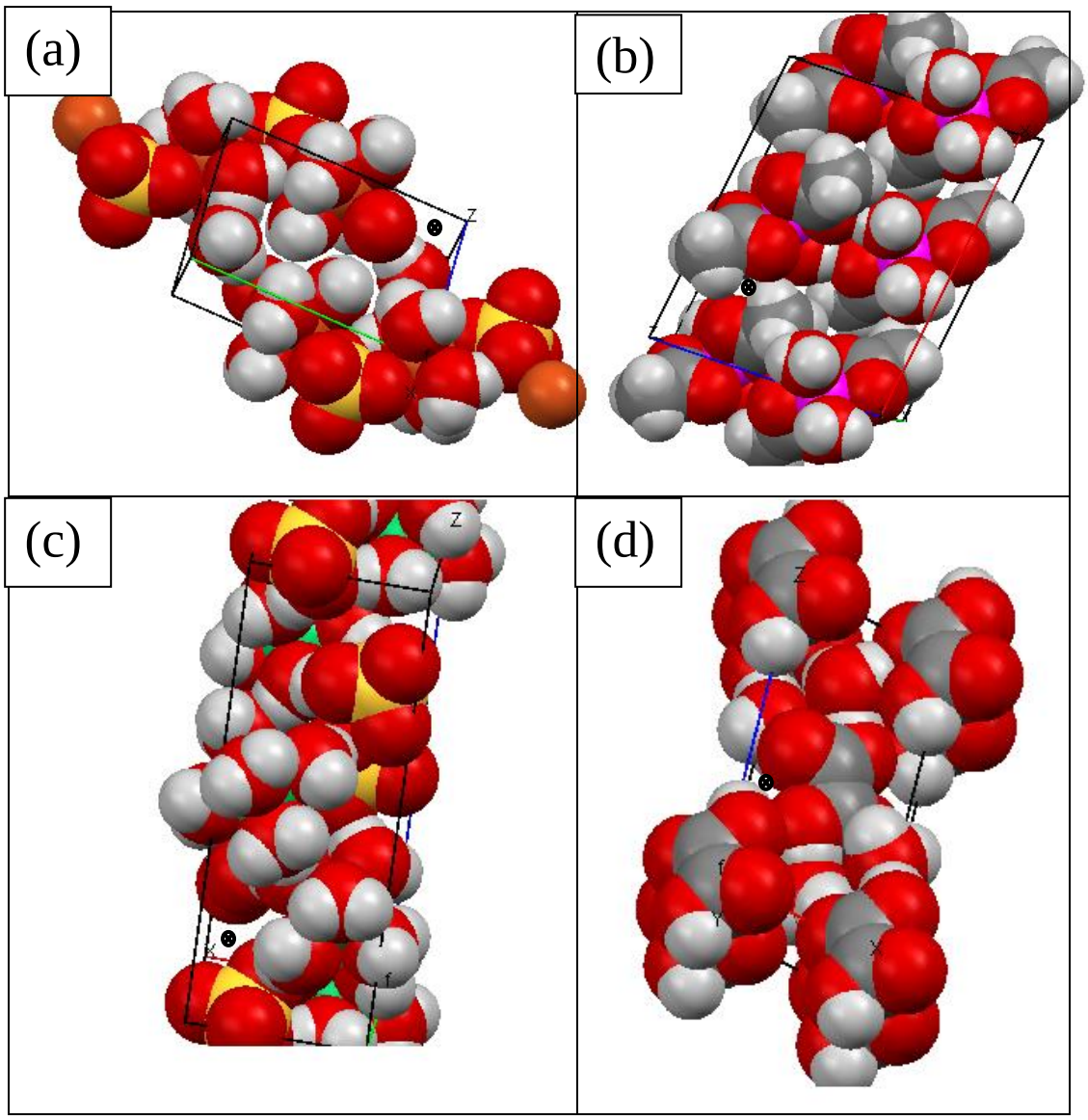

Figure 4.22: Space fill models showing molecular packing within (a) Copper sulfate pentahydrate (b) Zinc acetate dihydrate (c) Nickel sulfate hexahydrate and (d) Oxalic acid dihydrate.

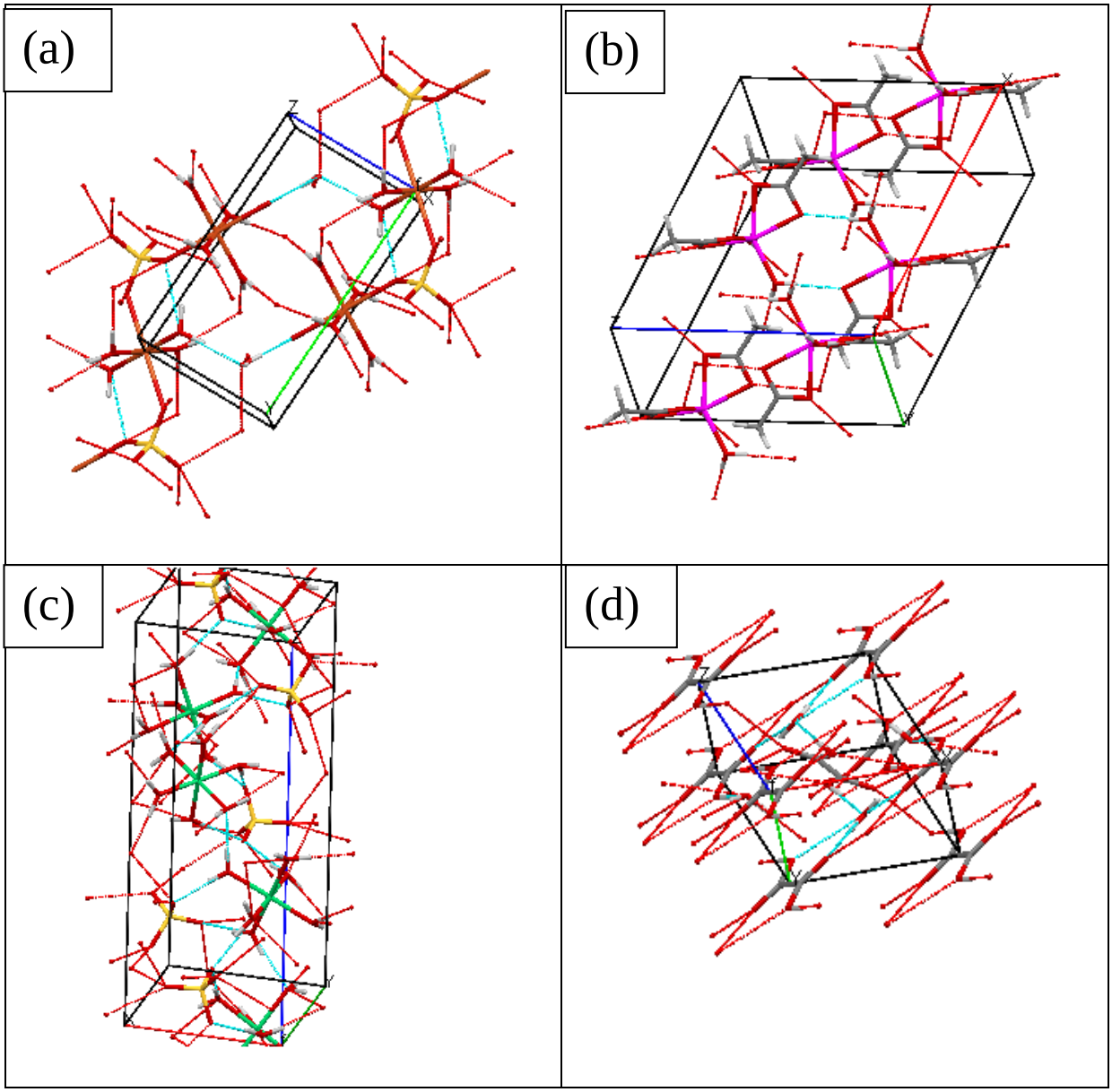

Figure 4.23: Crystal packing showing hydrogen bonds in (a) Copper sulfate pentahydrate (b) Zinc acetate dihydrate(c) Nickel sulfate hexahydrate and (d) Oxalic acid dihydrate.

Fractional dehydration data of a crystal of each of the four salts were determined and plotted against their respective temperatures on the same axes as can be seen in Figure 4.24.

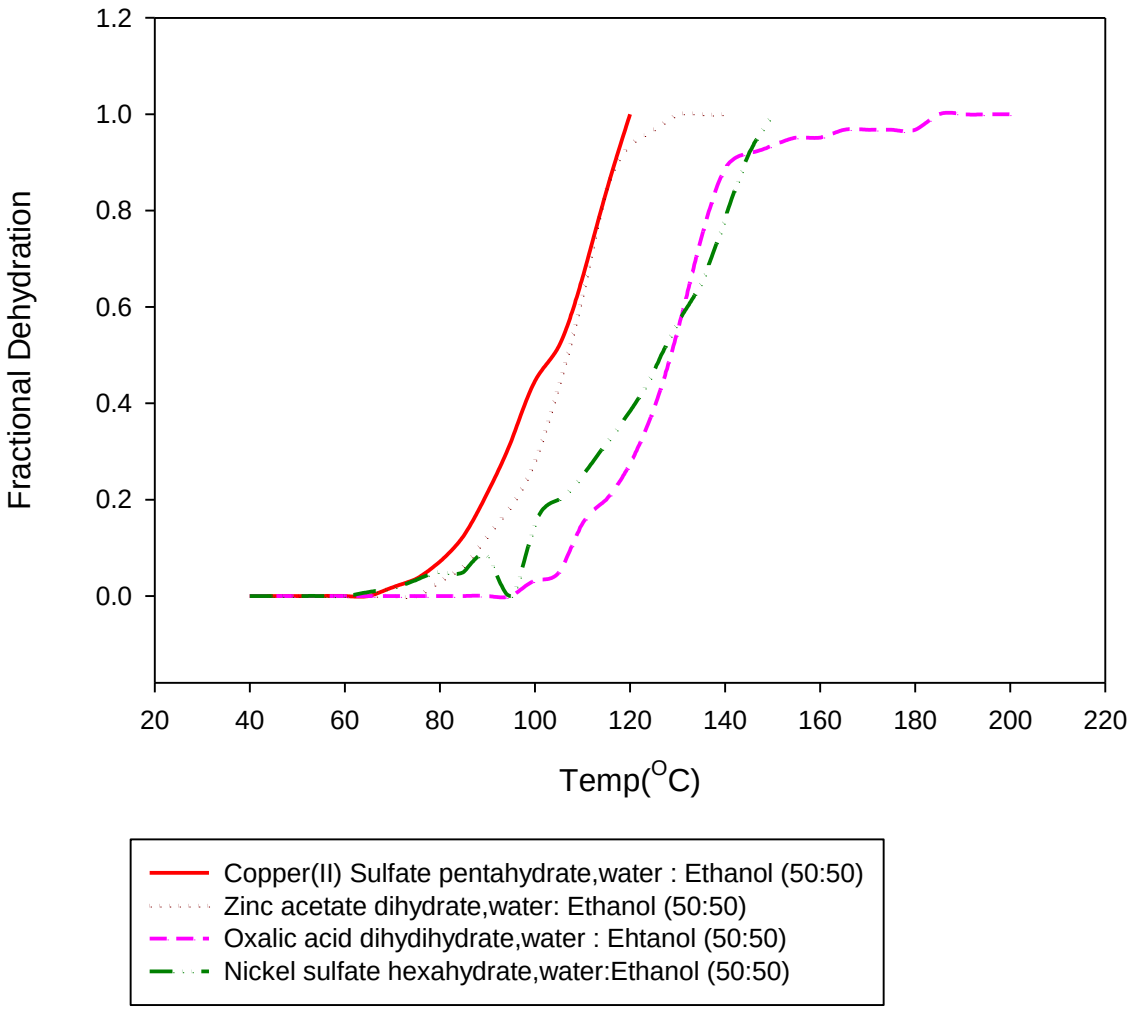

Figure 4.24: Fractional dehydration curves of the four selected studied compounds.

It was evident from Figure 4.24 that copper (II) sulfate pentahydrate and zinc acetate dihydrate desolvated much faster compared to nickel sulfate hexahydrate and oxalic acid dihydrate because the gradients of the curves were sharper and their onset temperature of dehydration were much lower. These observations were in agreement with the previous discussions on molecular packing. The relative ease with which the solvent was removed by desolvation suggested the presence of spaces in terms of loose packing or channels that served as paths (sinks) for the solvent. The two salts had the highest number of spaces/tunnels and the least number of hydrogen bonds per

unit cell (Table 4.10) making them more open indicating very minimal hindrance to the removal of solvent upon desolvation hence the smooth curve.

Table 4.10: Table of comparative studies of the solvates.

Compound	Energy of dehydration in J/mole of water	Packing factor(no. of spaces/tunnels)	Number of Hydrogen bonds
Copper(II) sulfate Pentahydrate	159.6	**7**	**20**
Zinc acetate dehydrate	235.0	**6**	**30**
Nickel sulfate hexahydrate	241.8	**4**	**37**
Oxalic acid dehydrate	503.6	**4**	**37**

Salts of oxalic acid dihydrate and nickel sulfate hexahydrate had low rates of desolvation because their molecular packing were more compact.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATION

5.1 Conclusion

It was not possible to crystallize the various organic and inorganic crystals from single solvent and thus it was necessary to use mixed solvents. All the solvates were crystallized easily from mixed solvents. Oxalic acid (organic solvate) was mainly crystallized from solvent mixtures of water and acetone. The rest i.e Inorganic solvates were mainly crystallized from solvent mixtures of water and ethanol. Crystals of oxalic acid dihydrate were white and their shapes were mainly prismatic in habit. Those of zinc acetate dihydrate were also white but their shapes were plate like. Crystals of copper (II) sulfate pentahydrate were clear blue and their shapes were also plate like whereas those of nickel sulfate hexahydrate were green with shapes that were needle like.

Kinetics of a particular solid-state reaction was done non-isothermally involving the use of DSC and TGA to monitor heat and weight change, respectively with changing temperature. All the hydrates dehydrated with increase in temperature. DSC and TGA profiles of the hydrates indicated that in TGA the weight loss corresponded to the dehydration endotherm of the hydrate as observed in the DSC measurements. The DSC curves showed strong peaks indicating the loss of one or more molecules of water. Oxalic acid dihydrate had the highest heat of dehydration of 503.6 J/mole followed by the inorganic hydrates in the order of nickel sulfate hexahydrate (241.8 J/mole), zinc acetate dihydrate (235.0 J/mole) and lastly copper (II) sulfate pentahydrate (159.6 J/mole). These energy values clearly indicated that it was much difficult for oxalic acid dihydrate to dehydrate compared to the rest of the hydrates possibly due to the compact nature of its structure which prohibited free escape of solvent molecules compared to the rest of the solvates whose heats of dehydration were significantly low.

The solid state dehydration behaviour of the hydrates was graphically expressed in terms of fractional reaction α-temperature curves. From the curves the temperature of the onset of dehydration for oxalic acid dihydrate was much higher (105 ºC) than the

rest of the hydrates whose onsets were in the order nickel (II) sulfate hexahydrate (90 ºC), zinc acetate dihydrate (70 ºC) and copper (II) sulfate pentahydrate (60 ºC). From these results it was evident that it was much harder to dehydrate salts of oxalic acid compared to the rest of the hydrates.

Modeling of the hydrates was done using mined data of the hydrates from Oxford crystallographic data base. From modeling results it became evident that oxalic acid had a more packed structure compared to the rest of the inorganic hydrates thus explaining why it was much more difficult to dehydrate. This compact nature of oxalic acid was as a result of the presence of the many hydrogen bonds that were present within the structure. The structures of the other inorganic hydrates were less compact and had fewer hydrogen bonds explaining the open nature of the structures that facilitated the escape of solvent molecules.

It was thus evident that thermal properties had a very close relationship with the packing factor within the unit cell of a crystal. In this study it was noted that the amount of heat energy required to dehydrate a particular solvate/hydrate had a linear relationship with the packing factor and the number of hydrogen bonds present there in. Those solvates that had a higher packing factor (i.e close packing) had the highest number of hydrogen bonds within the unit cell and their heat of dehydration tended to be also high. Thus it was much more difficult to dehydrate an organic hydrate compared to inorganic hydrate.

5.2 Recommendation

Knowledge of desolvation kinetics of crystalline organic and inorganic solvates are extremely relevant to the pharmaceutical industry, with specific regard to drug formulation. Further studies should be done on dehydration of solvates by isothermal means with an aim of determining activation energy which is an important dehydration parameter. Activation energy can then be used to explain the internal structure of the solvates.

Variable X-ray can also be done on the solvates to monitor changes in internal structures as temperature varies.

REFERENCES

Agbada, C. O. and York, P. (1994). Int. J. Pharm., 106, 33-40.

Alavi, S. Susilor, R. Ripuseester, J.A. (2009). J. Chemical physics, 130(17)

Andrew, K.G. Michael, E .Brown, W. (1999). Thermal decomposition of Ionic solids. Elsevier. 228-229.

Atkins, P.W. (1997). Physical chemistry,W.H Freeman and co., new York.

Bauman, J.B. (1979). Solvent selection for crystallization. J. Chem. Ed, 56(1), 64.

Beevers, C.A. and Hansen, H.A. (1971). Acta crystallogr B27, 1323-1325.

Brittain, H.G. (1988). Drug dev. Ind. Pharm, 14, 2029-2046.

Brown, M.E.; Galwey, A.K.and Wan Po, L.A. (1992). Thermochin.Acta, 203, 221-240.

Byrn, S. R.; Pfeiffer, R.; Ganey, M; Holberg, C. and Poochinian, G. (1995). Pharm. Res; 12, 945-954.

Bryn,S. (1982). Solid state Chemistry of Drugs ; Academic press: London ,: 8-9,149-188.

Chang, T. and Raymond, Y. (2005). Physical chemistry for the Biosciences, New York : University science.

Corrigan, W. (1996). Physicochemical characterization of Diclofenac N-(2-hydroxyethyl)pyrrolidine: Anhydrate and Dihydrate crystalline Forms. J Pharm. Sci., No.1.

Dana, W. Mayo, Ronald M. Pike and Samuel S. Butcher (1986). Microscale organic laboratory. John Wiley and sons, inc. 78-79.

Egon, W. Nils W, Arnold F. H (2001). Inorganic Chemistry Academic press.1263.

Elder, J.P. (1994) ThermochonicaActa 234,153-169.

Eric, V. Ansyln; Dennis, A. Dougherity (2006). Modern physical organic chemistry-University science books (41) 978-985.

Fini, A. Sanahez-Soto, P. J. Fernandez-Hervas, M. J. and Holgado, M. A. (1998). Int. J. Pharm; 156 , 79-85.

Ford, J.L, Wilson, R, (1999). Handbook for Thermal Analysis and Calorimetry (4) 923-1016.

Galwey, A.K. (2000).Thermochim.Acta,355,181-238.

Gavezotti, A. and Philippini,G.,J.Am.Chem.Soc.,117,(1995),12299-12305.

Giron, D. (1999). J thermal analysis and Calorimetry 56 1285-1304.

Holleman, A.F.; Wiberg, E. (2001).Inorganic chemistry .San Diego: Academic press.

Hook, J.R. Hall, H.E. (2010). Manchester physics series, John Wiley and sons, Solid state physics (2nd Edition).

Jaffe, J. and Foss, N.E. (1959). J. Am-Pharm. Assoc. Sci. Ed., 48, 26-29.

Jasmine, A. J, Sebastein, S. Alexandre, D. Mehran, M. and Jacqueline, B. (2012) Crytal growth and design.12: 5980-5985.

Jun, H. (2006). Advances in characterization of pharmaceutical hydrates.J Trends in Bio/pharmaceutical industry /3.

Kenneth, L.W .(1989). Macroscale and microscale organic experiments,D.C. heath and Company 39-40.

Kitiagorodski, A.I., (1973) MolecularCrystals and Molecules,Volume 29 of Physical Chemistry series A of monographs, Loebl ,E.M.ed.,Academic Press,New York.

Lerner, R.G. Trigg, G.L. (1991). VHC publishers, Encyclopaedia of physics (2nd Edition).

Liu, W. Hou, Y. Zhu, Y. Chang, D. Ma, D. (2001). Journal of thermal analysis and Calorimetry, 63,233-566.

Loic, F. Michele, P. (2011). Thermochimica Acta 521,155-160.

Louis, F. F. (1968). Organic experiments, Raytheon education company 2nd edition 41-49.

Louis, F. F. Kenneth, L. W. (1987). Organic experiments, D.c. heath and company 6th edition 42-44.

Lyakhov, N.Z, Boldyrev, V.V. (1972). Russ. Chem. Rev, 41, 919.

Mandeep, K. Arshdeep, K. Ramninder, K. Komalpreet, K. (2012). 1: 244 molecular modeling. Internal journal for natural product science.

Mark,T. Ledwidge, Silvia, M. Draper, Deborah, J.Wilcock, Owen, l.Corrigan (1996).Physicochemical characterization of Diclofenac N-(2-hydroxyethyl)pyrrolidine: Anhydrate and Dihydrate crystalline Forms .J Pharm. Sci., vol.85,No.1.

Mendham, J. Denney, R.C. Barnes, J.D. Thomas, M.J. (2000). Text book of quantitative chemical analysis. Pearson education 6th edition 212-213.

Mitchell, J.Jr. and Smith, D.M.(1977b). Aquametry Part 1,2ended.,Wiley,New York, 210.

Mnyukh, Yu.V.(1979). Mol.Cryst.Liq.Cryst.,52, 163.

Munn, R.W. (1978). Chem.Brit., 14, 231.

Narten, A.H. Levy, H.A. (1969). Science,165, 447-454.

Okoth, M. O. (1997). Mphil. Thesis, University of Strathclyde, Scotland, UK.

Peter, A.Wallace, T.C. and Holl, Z.N. (2008): Chemical principles: The Quest for Insight. University of Florida Innovative Teaching laboratory: The forces between molecules.

Pfiffer, R.R.; Yang, K.S. and Tucker, M. A. (1920). J. Pharm. Sci., 59, 1809.

Padungthon, S. Greenleaf, J.E. Sengupta, A.K. (2011). Chemical engineering and design, 89, 2613-2619.

Ralph, J. Fessenden and Joan, S. Fessenden (1984). Organic laboratory techniques. Brooks/ Cole company 20-29.

Rajendra,K.K.;Devalina,L. and Grant,D.J. (1992). Int.j.Pharm.,82, 117-127.

Stark, J.G, Wallace, H.G. (1976). Chemistry Data. Book,SIed.,JohnMurray,London, 122.

Szczepanski, A. (2012). Geometry of crystallographic groups. World scientific publishing.

Tao, Z. Jin, J. Yang, S. Hu, D. Li, G. Jiang, J. (2009). J. Molecular science, part B,48, 1114-1124.

Toresen, J.l. Strassburger,J. (1964). science, 146, 53.

Vippagunta, SR et al. (2001) Cystalline solids Adv Drug Deliv Rev; 48: 13-19.

Vlaer, L.T. Nikolova M. M,Gospodinov, Georgi,G. (2004). Non-isothermal kinetics of dehydration of some selenite hexahydrates (J).Journal of solid state chemistry, 177 (8): 2663-2669.

Wunderlich, B. (1990). Thermal Analysis. New York : Academic press, 137- 140.

Yoshioka, S.and Uchigama. M. (1986); J. Pharm. Sci; 75, No 1, 92-96.