SOLID FORMS OF SOME ACTIVE PHARMACEUTICAL INGREDIENTS (API)

A Thesis
Submitted for the Degree of
Doctor of Philosophy

By
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To
My Family

STATEMENT

I hereby declare that the matter embodied in this thesis entitled **"Solid Forms of Some Active Pharmaceutical Ingredients (API)"** is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad under the supervision of **Prof. Gautam R. Desiraju**.

In keeping with the general practice of reporting scientific observations due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad
April 2008

Prashant M. Bhatt

CERTIFICATE

Certified that the work **"Solid Forms of Some Active Pharmaceutical Ingredients (API)"** has been carried out by **Prashant M. Bhatt** under my supervision and that the same has not been submitted elsewhere for a degree.

Dean
School of Chemistry

Prof. Gautam R. Desiraju
Thesis Supervisor

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PREFACE

An understanding of the solid state properties of crystalline and amorphous forms of an active pharmaceutical ingredient (API) are extremely important in the development of a new drug. Accordingly there has been a tremendous impetus to identify novel polymorphs, solvates (pseudopolymorphs), salts and co-crystals of APIs. These variations amount to extensions of pharmaceutical space and have both scientific and legal importance.

Chapter 2 of the thesis describes less explored saccharinate salts of APIs and their favourable properties establishing saccharin as a salt former worth trying during salt selection studies of APIs by forming the saccharinate salts of quinine, haloperidol, mirtazapine, pseudoephedrine, lamivudine, risperidone, sertraline, venlafaxine, zolpidem and amlodipine. These salts have been characterized with single crystal X-ray methods. These saccharinates are generally very water soluble when compared to the free base. Additionally, aqueous solutions of these API saccharinates are of moderate pH. Both these properties may be advantageous in the pharmaceutical industry.

In the Chapter 3, two stable amorphous modifications of desloratadine saccharinate are reported as their normal and acid salts along with the desloratadine and desloratadine hydrochloride as crystalline modifications of desloratadine. The amorphous desloratadine saccharinates have higher solubilities than their marketed crystalline counterparts and they are also fairly stable in the dry condition. Amorphous des sac also shows promise to be used for drug delivery by inhalation route as a spray or powder formulation, and this has many advantages over the conventional oral route. The pH 5.8 of the saturated solution of des sac is ideal for its use for inhalation formulations.

Chapter 4 focuses on little known type of polymorphs namely *tautomeric polymorphism* by taking the example of anti-ulcer drug Omeprazole. Omeprazole was crystallized in five different forms containing different compositions of 5-methoxy and 6-methoxy tautomers. Crystals containing 0%, 8%, 10%, 12% and 15% 5-methoxy tautomer were prepared by different methods. Simulated PXRD patterns of the crystals showed that the forms reported in patents as A, B and C correspond to crystals **III**, **V** and

IV respectively. Structurally speaking, forms A, B and C occur in a structural continuum that begins with a pure 6-methoxy tautomer crystal and ends with an 85:15 mixture of 6-methoxy and 5-methoxy tautomers. This raises a series of questions regarding definition of polymorphism.

Co-crystals of the anti HIV drugs lamivudine and zidovudine are discussed in Chapter 5. Co-crystallisation of lamivudine with 4-quinolinone and lamivudine with 3,5-dinitrosalicylicacid result in co-crystals. Zidovudine forms a co-crystal with 2,4,6-triaminopyrimidine. These co-crystals are characterized by crystallographic and thermal methods.

Chapter 6 exemplifies a new strategy for the determination of absolute configuration using anomalous scattering by co-crystal formation with the co-crystal former containing a heavy atom. Co-crystal formation could be an alternate method for such compounds to introduce a heavy atom in the structure and consequently for the determination of absolute configuration. Co-crystallisation experiments with pregnenolone and cholesterol results in co-crystals with 4-iodophenol and 2,4,6-trichlorophenol. Determination of absolute configuration using the Flack parameter showed that the determined absolute configuration matches with the reported absolute configuration of pregnenolone and cholesterol with high accuracy.

Chapter 7 outlines a summary of significant results presented in this thesis and some implications for further studies.

Salient crystallographic details of the crystal structures discussed in this thesis are listed in Appendix. A full list of atomic coordinates has been deposited with University of Hyderabad and can be obtained from Prof. Gautam R. Desiraju (gautam_desiraju@yahoo.com).

Prashant M. Bhatt

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CHAPTER ONE

SOLID-STATE CHEMISTRY OF PHARMACEUTICALS

1.1 Overview

Solid dosage forms of a drug are desirable because of ease of handling, and lower production and storage costs.[1] However, it is difficult to deal with solid sample during the development stage. Accordingly, an understanding of the solid state properties of crystalline and amorphous forms of an active pharmaceutical ingredient (API) are very important in the development of a new drug.[2] There are two common viewpoints of concern for solid dosage forms of APIs- that of the regulator and that of the marketer or the developer.[1a] The regulator viewpoint deals with safety and efficiency. It states –"I do not care how it works; it just has to be safe, therapeutical and efficacious, and it has to work every time and in the same way." Regulators have issued series of guidelines to help developers in this regard, developers are advised to determine several characteristics of materials they are working with. The guidance most commonly referred in the field of solid state characterization is the ICH (International Conference of Harmonization) guidance Q6A.[3] The second viewpoint of developer deals with "know-how" and varies for innovator and generic companies. For the innovator company safety and efficiency are also important factors. The innovator would generate all the possible solid forms of a particular API and characterize them to the extent the possible and select a form with desirable properties for further studies. It would also patent some of these forms to stop generic companies from entering in the business. On the other hand generic companies would try to generate all the possible solid forms of API still under patent protection, especially the forms missed by the innovator company. Subsequently they can characterize the forms and patent them. Accordingly there has been a tremendous impetus to identify novel polymorphs, solvates (pseudopolymorphs), salts and co-crystals of APIs.[2] Figure 1 pictorially represents importance of solid state technology in various disciplines of the pharmaceutical industry.

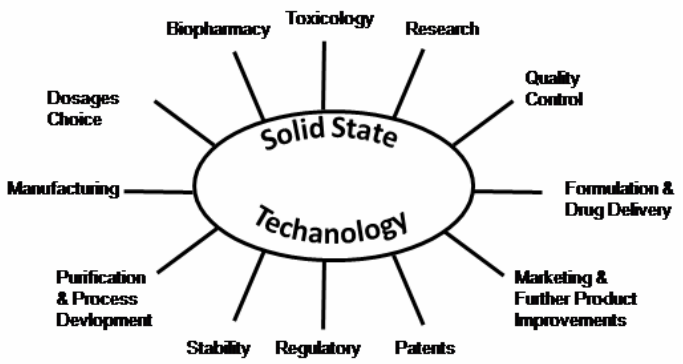


Figure 1. Importance of solid state chemistry in the pharmaceutical industry. The diagram is adapted from reference 1c.

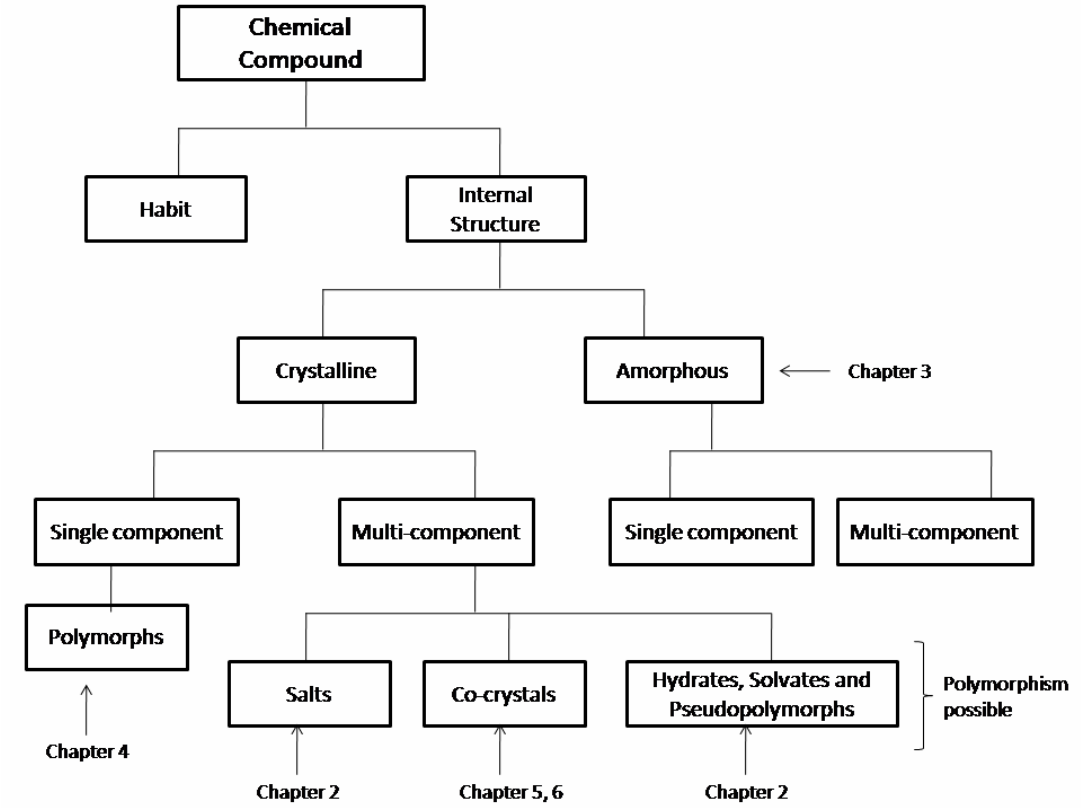


Figure 2. Schematic diagram showing classification of chemical compounds in various solid state categories.

Solids can be broadly classified into two categories, crystalline and amorphous. Crystalline forms are defined by the presence of long range order while amorphous forms are defined by lack of long range order. These crystalline and amorphous forms can be further classified into various types as given in Figure 2.

1.2 Crystalline state

Crystalline forms of API are very important since most of the drugs are marketed as crystalline forms. Crystals are made up of molecules arranged in a periodic fashion; this periodic arrangement of molecules determines the physical properties of the drug and in turn it can affect its performance.[1,2] The infinite periodic arrangement of a crystal can be defined in terms of the smallest repeating unit which is called the unit cell, which contains all the structural features and the symmetry elements. Repetition of the unit cell in three dimensions generates the entire crystal. Symmetry considerations show 230 unique arrangements of points in space, termed as space groups. These 230 space groups describe all the possible ways in which molecules can pack in the crystal lattice.[4] However only a few space groups are frequently observed in practice.[5] According to the Cambridge Structural Database (CSD), ~75% of all organic and organometallic compounds crystallize in only five space groups -$P2_1/c$, $P2_12_12_1$, $P\bar{1}$, $P2_1$ and $C2/c$ - and ~90% of all organic and organometallic crystal structures belong to 17 common space groups.[6]

1.2.1 Forces responsible for crystal packing

Interionic interactions: These interactions are generally observed in ionic crystals and are of magnitude around 30 kcal mol^{-1}.

Hydrogen bonds: The hydrogen bond is defined in the standard formulation as an X–H…A interaction, where both X and A are electronegative atoms.[7] O–H…O, N–H…O, O–H…N and N–H…N are some well-studied and commonly observed strong hydrogen bonds.[8] The binding energies of strong hydrogen bonds are normally greater than 5 kcal mol^{-1} and the distance between the proton and the acceptor atom (H…A) is significantly shorter than the sum of their respective van der Waals radii. For unusually activated

donors and acceptors, say as in the case of the inorganic fluoride ion F–H…F^-, and the charged O–H…O^-, N^+–H…N or O^+–H…O, O^+–H…N^- systems, the hydrogen bonds are very strong and show similarities to covalent bonds.[9] For systems in which X and/or A are of moderate to low electronegativity the hydrogen bond energy drops significantly, and such bonds are termed weak hydrogen bonds.[10] Weak hydrogen bonds can be classified in the following three categories based on the hydrogen bond donor-acceptor strengths: a) weak donors and strong acceptors, for example, C–H…N/O/S,[11] (b) strong donors and weak acceptors, such as O/N–H…Cl/F–C, O/N–H…π[12] and (c) weak donors and weak acceptors, such as C–H…Cl–C, C–H…F–C and C–H…π interactions.[13]

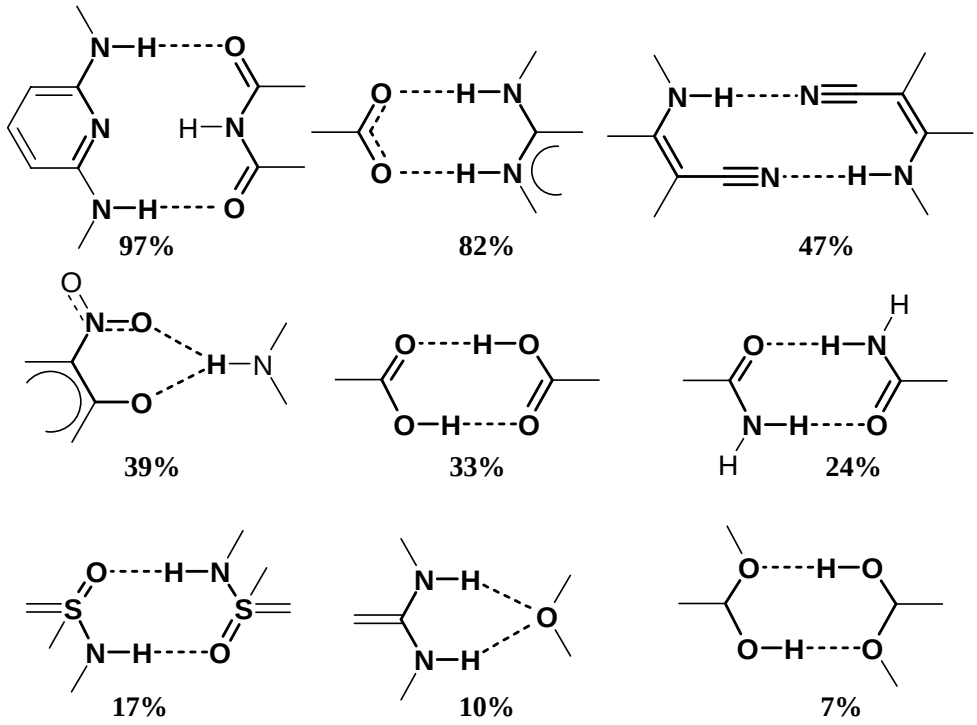


Figure 3. Examples of some supramolecular synthons with their occurrence frequencies.

These interactions can be combined by the designed placement of functional groups in the molecular skeleton to generate supramolecular synthons. The supramolecular synthon was defined by Desiraju as "*a structural unit within supermolecules, which can be formed and/or assembled by known or conceivable*

synthetic operations involving intermolecular interactions".[14] Supramolecular synthons are designed combinations of interactions and not individual interactions. Synthons are ranked according to their frequency of occurrence and according to their probabilities of formation. Some examples of supramolecular synthons and their probabilities of formation are shown in Figure 3.

Van der Waals interactions: These forces are generally weak interactions between uncharged atoms and molecules and are isotropic in nature. These forces constitute a major proportion of the crystal energy because all the portions of the molecule are involved in them. The structure of organic compound in which the van der Waals forces operate are characterised by close packing.[15] They are very weak in magnitude but very numerous. Therefore, their overall importance may also be high.

1.2.2 Mechanism of crystallisation

Even after extensive research the exact mechanism of crystallisation is not known till the date. However, a plausible mechanism is supported partly by some experimental evidence.[16] Crystallisation can be termed as a supramolecular reaction. On the one side, there is the solution, which is an entropy-dominated situation. On the other, there is the crystal, which is the largely enthalpically determined outcome of the reaction. Between these must lie the crystal nucleus, which is possibly the highest energy point in the reaction coordinate. The simplified mechanism can be visualised as following.

In solution, the solute is dissolved in a solvent. In solution various clusters involving both solute molecules and solvent molecules are formed using various intermolecular interactions. This brings elements of short range order in solution. These clusters are continuously breaking, forming and rearranging. At supersaturation these clusters become larger in size and more short range order enters in the system. At this stage nucleation occurs due to variety of reasons like foreign particle, physical disturbance, scratched surface of vessel etc. and solvent molecules from solute-solvent clusters exit into the bulk solvent simultaneously forming the crystal, which is

characterised by long range order.[17] The next step is crystal growth, and solute molecules from solution then help the crystal to grow into some size by adding to nucleated crystal.

1.3 Polymorph

The crystalline state can be classified in various categories as shown in Figure 2. Polymorphism is possible in all these categories. The literal meaning of polymorphism in Greek is "many forms" (poly = many and morph = form) and it also used in many disciplines other than crystallography. The first use of the polymorphism term in crystallography was by Mitscherlich in 1822.[18] He recognized different crystal structures of the same chemical compound in many arsenate and phosphate salts. One must also appreciate the landmark work of Groth, who summarized a great deal of information on crystalline materials including polymorphism using optical goniometry and other techniques. This work was published between 1906 and 1919 in the form of a five volume compendium covering over 10,000 compounds.[19] MacCrone defined polymorphism as "a solid crystalline phase of a given compound resulting from possibility of at least two different arrangements of the molecules of the compound in a solid state".[20] However, this definition does not include polymorphs involving different molecular conformations and dynamic isomers like tautomers.[21] A safe criterion for polymorphism would be if the crystal structures are different but lead to identical liquid and vapour states. This definition also has many complications[22] and has been discussed in detail in chapter 4. In general, for normal and uncomplicated cases MacCrone's definition still works well and is the most commonly used by structural chemists all over the world.

The different molecular arrangements can impart to polymorphs different physical properties like melting point, solubility, dissolution rate, stability etc.[23] These different properties make understanding, characterisation and control of polymorphs very important. Table 1 lists various properties which can be different for polymorphs.

Table 1. Properties that can be different for polymorphs. Adapted from reference 1d.

Packing properties	**Thermodynamic properties**
• Molar volume and density	• Melting and sublimation temperatures
• Refractive index, optical properties	• Internal energy
• Conductivity,electrical and thermal	• Enthalpy
• Hygroscopicity	• Heat capacity
Kinetic properties	• Entropy
• Dissolution rate	• Free energy and chemical potential
• Rates of solid state reactions	• Thermodynamic activity
• Stability	• Vapour pressure
Surface properties	• Solubility
• Surface free energy	**Spectroscopic properties**
• Interfacial tensions	• Electronic transitions, ultraviolet-visible spectra
• Habit	
Mechanical properties	• Vibrational transitions, infrared and Raman spectra
• Hardness	
• Tensile strength	• Rotational transitions
• Compactibility, tabletability	• Nuclear magnetic resonance chemical shifts
• Handling, flow and blending	

1.3.1 Basis of polymorphism – kinetic Vs thermodynamic polymorph

The Curtin–Hammett principle can be applied to the crystallisation reaction in the same way as it is to chemical reactions and is shown in Figure 4. According to it the route to the kinetically favoured crystal would be the fastest, because the activation energy (G) barrier to that state is lower ($\Delta G^{\neq}_{\text{kinetic}}$). The thermodynamically favoured crystal would take longer to form because the activation barrier is much higher ($\Delta G^{\neq}_{\text{thermodynamic}}$), but it would be more stable because the final energy state is the lowest. If the same crystalline form is both kinetically and thermodynamically favoured, polymorphism is highly unlikely.[24]

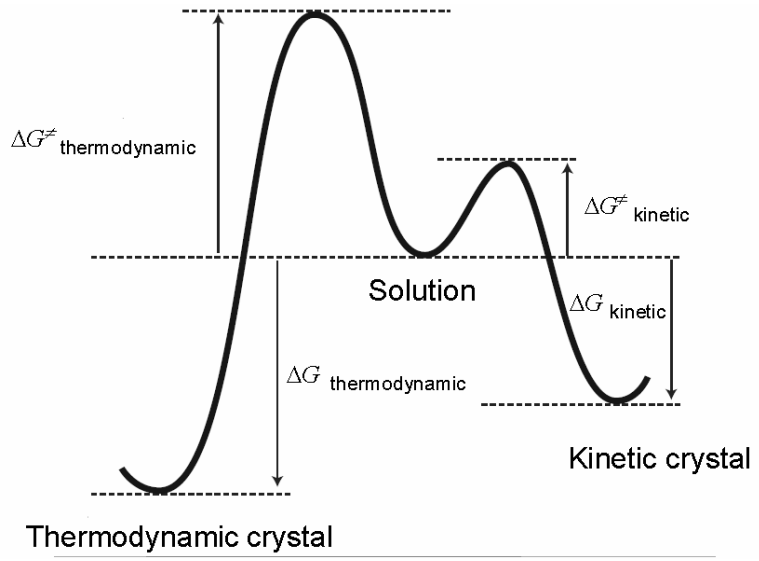


Figure 4. Kinetic and thermodynamic outcome of crystallization reaction. Adapted from reference 24.

Qualitatively this can be viewed as following. There are two main and often competing factors which govern the crystallisation reaction, 1) directional intermolecular interactions like hydrogen bonds 2) close packing. Generally, the energy contribution from close packing is more than that of the intermolecular interactions. This would tend to favour the thermodynamic crystal. Conversely, solute-solvent clusters present in solution, which in turn give birth to crystal nucleus, are stabilized by intermolecular interactions. Therefore, intermolecular interactions generally favour kinetic crystals. It is highly unlikely to observe polymorphism in crystal systems where the best interactions are accompanied by the best packing. Examples like benzoic acids, naphthalene and D-glucose almost surely belongs to this monomorphic category.[24] However, crystallisation is a mostly kinetically driven process and it is no surprise that thermodynamic polymorphs of very old and simple compounds like maleic acid[25] and trinitrobenzene [26] are only recently beginning to be found. It requires considerable effort sometimes to isolate the thermodynamic polymorphs. Recently observed polymorphism in compounds like aspirin[27] and benzamide[28] also indicate complexity involved in the polymorphism phenomenon.

1.3.2 Classification of polymorphic pairs

Polymorphic pairs are classified in various categories depending upon different considerations like thermodynamic, structural, molecular and many more.

1.3.2.1 Enantiotropic and monotropic polymorphic pairs

From thermodynamic consideration polymorphic pairs can be divided into the above two categories. Monotropic systems are defined as systems where a single form is more stable regardless of temperature. Enantiotropic systems are defined as systems where the relative stabilities of the two forms invert at some transition temperature. In other words, if the free energy curves of two forms cross below the melting point of the lower melting polymorph, they are said to be enantiotropically related and if the free energy curves do not cross below the lower melting polymorph, they are said to be monotropically related.

1.3.2.2 Synthon and packing polymorphs

From the structural aspect a polymorphic pair can be divided as synthon or packing polymorphic pairs. When two polymorphs differ in terms of different synthons present in their respective structure, they could be called synthon polymorphs. If the polymorphs differ by just the packing arrangements of molecules in the crystal then they could be called packing polymorphs.

1.3.2.3 Conformational and configurational polymorphism

This deals with the polymorphism involving flexible and dynamic molecules. When molecules adopt significant different conformations in different crystal polymorphs, these polymorphs are called as conformational polymorphs. Configurational polymorphism exists when different configurations of molecules (cis-trans isomers or tautomer) crystallize in different crystalline forms. Polymorphs involving different tautomers are also referred as tautomeric polymorphs (see chapter 4).

1.3.3 Importance of polymorphs in pharmaceutical industries

As seen in the Table 1, API polymorphs can have different physical properties that can affect drug performance drastically. Dissolution rate and solubility properties are the most crucial for API polymorphs.[29] In the physiological absorption of a drug, the dissolution of the drug is often the rate determining step and it may affect the bioavailability of the drug. The rate and extent of physiological absorption determines the overall efficacy of a drug. Bioavailability may vary for polymorphic forms and this is an important scientific and regulatory issue.[30,31] There are many examples where the bioavailability of polymorphs varies significantly, Phenobarbital,[32] indomethacin[33] and mercaptopurine[34] are a few from the list. Hence a polymorph having higher dissolution rate, solubility and/or bioavailability may be considered for formulation. Generally, metastable forms have better solubility properties than most stable polymorphs but they may have stability issues.[1c] These metastable forms might be chemically less stable and/or may have a tendency to convert into a stable polymorph. Such forms should be avoided in the formulation. For example in ritonavir,[35] the more soluble polymorph converted to a new and less soluble polymorph, leading to recall of the product. Mostly, it is a choice between better stability and better solubility and polymorphs fulfilling both these criteria are well sought after.

As the performance of a drug should be constant for all the marketed batches, only a particular polymorph or polymorphic composition should be used for formulation and it should remain constant over the period of time while marketing. Hence control of polymorphism is very important in quality control. Moreover, different structures and properties make polymorphs patentable. Ranitidine hydrochloride, cefadroxil, terazosin hydrochloride and aspartame are the few well known examples of the patent cases regarding polymorphism.[23a]

1.4 Salt of API

Among various solid modifications of drugs, salts are the most common and have been used for years. An estimated half of all drug molecules used in medicine are administered as salts. Salts of drugs are primarily made to make the drug water

soluble as most of the drugs are neutral organic molecules and have limited water solubility.[36] This increased solubility may sometimes result in better bioavailability. In addition to this, salt formation also influences many other properties like melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties.[37] Hence it is important to select a salt with desirable properties among all the possible salts. Salt selection is a very important and essential part of the drug development process and many companies are using high-throughput techniques for this purpose. It is easier to select a salt forming agent by knowing the pKa value of each ionisable group present in API. According to what is referred to as the 'rule of three', there should be a minimum difference of about 3 units between the p*K*a value of the group and counter ion for the formation of a stable salt.

Although the choice of salt former is largely limited by the acidity or basicity of the ionisable group of API, factors like safety of the counterion, route of administration and the intended dosage form must be also taken into account as well. Many inorganic and organic acids like HCl, HBr, H_2SO_4, benzoic acid and acetic acid are used as salt formers (Table 2). For weakly basic drug substances, salts of an inorganic acid (e.g., hydrochloride, sulphate, or phosphate), a sulphonic acid (mesylate or isethionate), a carboxylic acid (acetate, maleate or fumarate), a hydroxyacid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered. Hydrochloride salts have often been the first choice for weakly basic drugs, since as a consequence of the low counterion p*K*a, salts can nearly always be formed, and recrystallisation from organic solvents is normally straightforward. However, the potential disadvantages of hydrochloride salts may include unacceptably high acidity in formulations, the risk of corrosion, less than optimal solubility due to the risk of salting out and the potential for poor stability if the drug is acid labile and hygroscopic.[38] Occasionally, salts may be also prepared to decrease drug substance solubility for use in suspension formulations where very low solubility is necessary for taste-masking, or to prepare an extended release product.

Table 2. Classification of common pharmaceutical salts. Adapted from reference 36b.

	Anions
Inorganic acids	hydrochloride, hydrobromide, sulfate, nitrate, phosphate
Sulfonic acids	mesylate, esylate, isethionate, tosylate, napsylate, besylate
Carboxylic acids	acetate, propionate, maleate, benzoate, salicylate, fumarate
Anionic amino acids	glutamate, aspartate
Hydroxyacids	citrate, lactate, succinate, tartrate, glycollate
Fatty acids	hexanoate, octanoate, decanoate, oleate, stearate
Insoluble salts	paemoate (embonate), polystyrene sulfonate (resinate)
	Cations
Organic amines	triethylamine, ethanolamine, triethanolamine, meglumine, ethylenediamine, choline
Insoluble salts	procaine, benzathine
Metallic	sodium, potassium, calcium, magnesium, zinc
Cationic amino acids	arginine, lysine, histidine

One of the negative aspects of salt formation is that the percentage active content decreases markedly as higher molecular weight counterions are used. If the parent API is of moderate or low activity then the amount of API salt required may be too large for a single capsule or tablet and can affect patient compliance. The other problem which is frequently encountered during salt formation is an increased tendency of hydrate formation, which may be problematic at the formulation stage.

1.5 Co-crystal

Co-crystal is defined as material which contains two or more discrete molecular entities in the crystal lattice. Co-crystal is also often referred as molecular complex. Sometime back Desiraju[39] and Dunitz[40] had interesting debate over the appropriateness of the term ‘co-crystal’. Although term ‘co-crystal’ has many drawbacks, it is so heavily used in a literature for years that it is difficult to replace it.

Co-crystals are generally formed by evaporation of a solution containing stoichiometric moles of the components, although sublimation and growth from the melt are also used. They can also be prepared by solvent-drop grinding. A series of papers by Motherwell and co-workers suggest solvent-drop grinding as an efficient and eco-friendly way for co-crystal formation.[41]

Co-crystals of many compounds are known for years in solid state chemistry however, it is only recently that pharmaceutical co-crystals have generated much commercial and academic interest.[42-46] Pharmaceutical co-crystals are important because they can improve many properties of the parent API like solubility, dissolution rate, stability, crystallinity and many more. This is particularly important for the APIs, which do not have acidic or basic group to form salts. Pharmaceutical co-crystals increase the chemical space of an API and co-crystals with favourable properties can be patented also. Moreover if the co-crystal former is a GRAS (Generally Regarded As Safe) compound, then the co-crystal may not need exhaustive and separate clinical trials, barring perhaps toxicological studies.

Zaworotko and Almarsson advocated the synthon theory for the rational design of co-crystals.[43,44] They provided a number of examples where pharmaceutical co-crystals are formed using acid-amide and acid-pyridine heterosynthons (Figure 5). However, there are number of examples of compounds which do not form co-crystals despite having favourable complementary functional groups. This could be because of kinetic and solubility factors. There are also examples of co-crystals which do not have the expected synthon which was predicted from the synthon based design of the co-crystal. In short, there is no guaranty for co-crystal formation based on synthon theory but it can definitely help to choose possible co-crystal formers among the large number of compounds that are available for the cocrystallisation experiments.

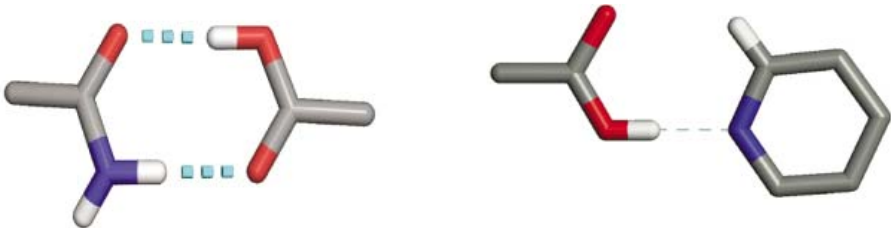


Figure 5. Acid-amide and acid-pyridine heterosynthons.

In recent years many pharmaceutical co-crystals with favourable properties have been claimed. Co-crystals of itraconazole[45] and carbamezapine[44] are early and important examples. Itraconazole is an extremely water insoluble antifungal drug. Its solubility and dissolution properties have been improved by co-crystal formation with succinic acid and some other diacids (Figure 6). Childs and coworkers reported co-crystals of fluoxetine hydrochloride (API salt) with benzoic acid and some other organic acids and showed them to exhibit interesting solubility properties.[46]

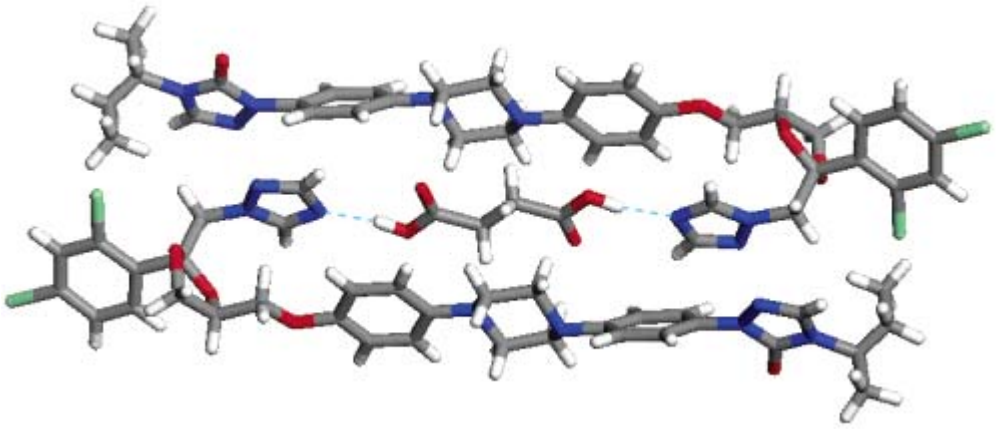


Figure 6. Molecular arrangement in co-crystal of itraconazole and succinic acid. Adapted from reference 45.

1.6 Solvates, hydrates and pseudopolymorphs

Solvates are defined as crystalline forms of a compound that include solvent molecules in the crystal lattice. When solvent included is water they are called hydrates. Solvates can be classified into two categories: (a) *host–guest compounds*, *clathrates*, or, more generally *inclusion compounds*, in which the main function of the guest molecule is

cavity filling, with or without additional weak hydrogen bonding, in a host molecule and;[47] (b) *pseudopolymorphs* wherein different solvated crystal structures of a particular compound have the same/different solute to solvent ratio.[48] The physical property changes during solvate formation are similar to those related to polymorphism and therefore solvates are often referred to as pseudopolymorphs to distinguish them from true polymorphs. Seddon,[49] Desiraju,[50] Bernstein[51] and Nangia[52] had an interesting discussion over the use of the term pseudopolymorph sometimes back.

Solvates, hydrates and pseudopolymorphs are of great importance in the pharmaceutical industry.[53] The drug development process exposes active pharmaceutical ingredients (APIs) to organic and aqueous solvents during crystallization, wet granulation, storage and dissolution and can lead to the formation of solvated crystals by design or by accident. Crystalline forms of APIs with included solvent molecules differ in pharmaceutical performance like mechanical behaviour, stability, dissolution and often bioavailability.[23a,23e] The choice of development of solvated or unsolvated forms will depend on its pharmaceutical properties like stability under different conditions, shelf life etc.

The most important point is that some APIs form solvates while others do not. The propensity of an API molecule to form solvates has been related to molecular structural features, hydrogen bond patterns, and crystal packing. It is surprising that about one third of the entries for solvates are hydrates although water is not a good solvent for crystallisation for many compounds, and other solvents are commonly used for crystallisation. Hydrated forms of pharmaceutical solids are more common than other solvates due to the abundance of water in the atmosphere. Its small size and its ability to act as both hydrogen bond donor and hydrogen bond acceptor facilitate hydrate formation.[54]

Some important drugs which are marketed as solvates or hydrates are indinavir (ethanol), paroxetine (hydrate) and cephadrine dihydrate.

1.7 Amorphous solids

Amorphous forms are defined by lack of long range order and metastable character. Literally "amorphous" means having no definite form.[55] It is difficult to make a distinction between truly amorphous solids and nanocrystalline solids in which the size of the crystals is very small (less than two nanometer). Even amorphous materials have some short-range order among the atomic positions (over length scales of about one nanometer). Furthermore, in very small crystals a large fraction of the atoms are located at or near the surface of the crystal; relaxation of the surface and interfacial effects distort the atomic positions, decreasing the structural order. In short it is not always possible to make a clear distinction between nanocrystalline and amorphous solids.[55a]

It is difficult to study the short range order of amorphous materials. Spectroscopic methods like IR and Raman spectroscopy can sometimes provide information regarding molecular assembly and hydrogen bonding patterns and X-ray, neutron and to some extent electron scattering can give some information about average separation of molecular species in amorphous materials.[55] The structure of amorphous materials needs statistical descriptions and can be defined by the correlation function **g(r)**. This function gives the average number of atoms lying between a distance **r** and **r+d(r)** with reference to the origin.

An amorphous material is also characterized by its glass transition temperature (*Tg*). At *T*g the properties of the glassy materials deviate from those of the equilibrium supercooled liquid to give a nonequilibrium state having even higher *H* and *V* than the supercooled liquid (Figure 7). Below *T*g the material is "kinetically frozen" into a thermodynamically unstable glassy state with respect to both the equilibrium liquid and the crystalline phase, and any further reduction in temperature has only a small effect upon its structure. Molecular motions in glasses typically occur over a period in excess of 100 s, and viscosities are usually greater than 10^{12} Pa·s.[56]

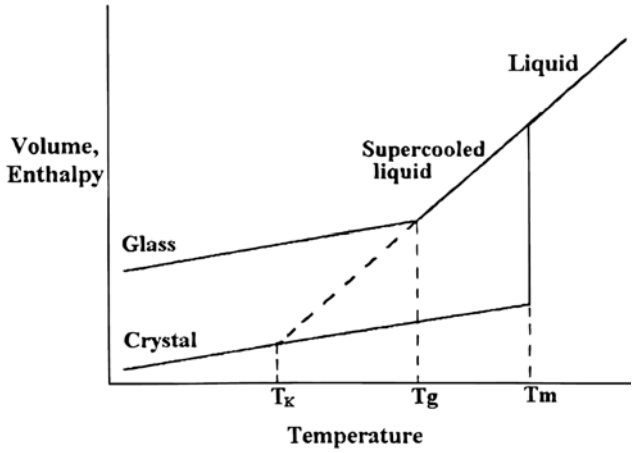


Figure 7. Schematic representation of the variation of enthalpy (or volume) with temperature. Where *Tg* and *Tm* are glass transition temperature and melting point respectively. Adapted from reference 55a.

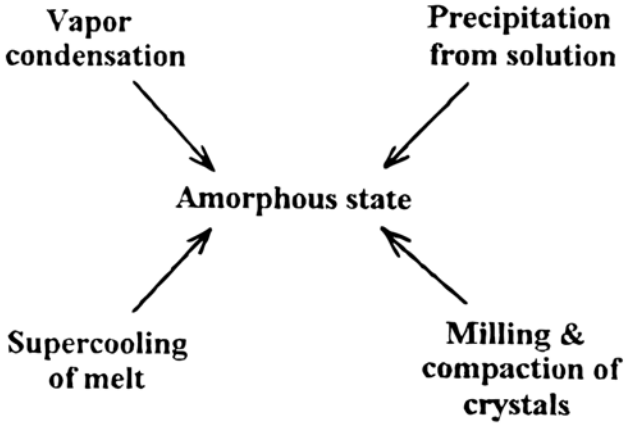


Figure 8. Common ways of preparation of amorphous material. Adapted from reference 55a.

Amorphous materials can be prepared by many methods like supercooling of melt, freeze drying, milling of crystals etc. as shown in Figure 8. Lack of long-range order and metastable character of amorphous material is used for several applications like magnetic application, structural application, consumer electronics and also in pharmaceutical industry.[55] Amorphous forms of an API are of high interest in drug

delivery. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability.[55a,55d,55e,55f,55i] However, it can also create the possibility that during processing or storage the amorphous state may spontaneously convert back to the crystalline state and this is the case most of the time. The metastable character of amorphous forms and their tendency to crystallize in stable crystalline forms is a serious problem for the use of amorphous forms in formulation and marketing. This is one of the strong reasons why not many drugs are sold in an amorphous form despite other favourable properties for drug delivery. Generally the problem of recrystallisation is overcome by the addition of some polymers as stabilizer. In recent years some APIs have been marketed in amorphous forms including Accolate (zafirlukast), Ceftin (cefuroxime axetil), Accupril (quinapril hydrochloride), and Rezulin (troglitazone).

1.8 References and notes

1. (a) *Solid state characterization of pharmaceuticals*, eds. A. Zakrzewski and M. Zakrzewski, Assa international Inc., Danbury, Connecticut, USA, **2006**. (b) *Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences*, ed. H. G. Brittain, Marcel Dekker, New York, **1999**, vol. 95. (c) S. R. Byrn, R. R. Pfeiffer and J. G. Stowell, *Solid-State Chemistry of Drugs*, 2nd edn., SSCI, West Lafayette, Indiana, **1999**. (d) S. Dutta and D. J. W. Grant, *Nat. Rev. Drug Discovery*, **2004**, *3*, 42.

2. (a) K. R. Morris and N. Rodriguez-Hornedo, *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, New York, **1993**. (b) S. L. Morissette, Ö. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A.V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, *Adv. Drug Deliv. Rev.* **2004**, *56*, 275. (c) C. R. Gardner, C. T. Walsh and Ö. Almarsson, *Nat. Rev. Drug Discovery*, **2004**, *3*, 926. (d) B. Rodríguez-Spong, C. P. Price, A. Jayasankar, A. J. Matzger and N. Rodríguez-Hornedo, *Adv. Drug Deliv. Rev.* **2004**, *56*, 241.
3. ICH Q6A. Federal Register, **2000**, vol. 65, 83041.

4. M. J. Buerger in *Elementary Crystallography* Wiley Interscience, New York, **1963**, 253–273.
5. P. M. Zorky, *J. Mol. Struct.*, **1996**, *374*, 9.
6. Cambridge Crystallographic Data Centre, Cambridge Structural Database, University Chemical Laboratory, Cambridge, UK, **1999**.
7. (a) G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer: Berlin, **1991**. (b) D. Hadzi, *Theoretical Treatments of Hydrogen Bonding*, Wiley: Chichester, **1997**. (c) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press: Oxford, **1997**. (d) G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press: Oxford, **1999**. (e) T. Steiner, *Angew. Chem. Int. Ed. Engl.*, **2002**, *41*, 48. (f) J. Martz, E. Graf, A. D. Cian and M. W. Hosseini, in *Crystal Design and Function, Perspectives in Supramolecular Chemistry*, vol. 7, G. R. Desiraju, Ed.; Wiley: Chichester, **2003**, pp. 177-209.
8. (a) R. E. Meléndez and A. D. Hamilton, *Topics in Current Chemistry*, "*Design of Organic Solids*", vol. 198, E. Weber, Ed.; **1998**, pp 97-130. (b) G. T. R. Palmore and J. C. MacDonald, *The Amide Linkage*: *Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*, A. Greenberg, C. M. Breneman and J. F. Liebman, Eds.; Wiley: New York, **2000**. (c) J. N. Moorthy, R. Natarajan, P. Mal and P. Venugopalan, *J. Am. Chem. Soc.*, **2002**, *124*, 6530. (d) P. W. Baures, J. R. Rush, A. V. Wiznycia, J. Desper, B. A. Helfrich and A. M. Beatty, *Cryst. Growth Des.*, **2002**, *2*, 653. (e) P. Gilli, V. Bertolasi, L. Pretto, A. Lyćka and G. Gilli, *J. Am. Chem. Soc.*, **2002**, *124*, 13554. (f) V. S. S. Kumar, A. Nangia, M. T. Kirchner and R. Boese, *New J. Chem.*, **2003**, *27*, 224. (g) J. -H. Fournier, T. Maris, J. D. Wuest, W. Guo and E. Galoppini, *J. Am. Chem. Soc.*, **2003**, *125*, 1002. (h) A. D. Bond, *New J. Chem.*, **2004**, *28*, 104. (i) S. Perruchas, K. Boubekeur and P. Batail, *Cryst. Growth Des.*, **2005**, *5*, 1585. (j) B. K. Saha, A. Nangia and M. Jaskólski, *CrystEngComm*, **2005**, *7*, 355. (k) V. R. Vangala, R. Mondal, C. K. Broder, J. A. K. Howard and G. R. Desiraju, *Cryst. Growth Des.*, **2005**, *5*, 99.

9. (a) P. Gilli, V. Ferretti, V. Bertolasi and G. Gilli, *J. Am. Chem. Soc*., **1994**, *116*, 909. (b) T. Steiner and W. Saenger, *Acta Crystallogr*., **1994**, *B50*, 348. (c) C. Flensburg, S. Larsen and R. F. Stewart, *J. Phys. Chem*., **1995**, *99*, 10130. (d) P. R. Mallinson, K. Woźniak, G. T. Smith and K. L. McCormack, *J. Am. Chem. Soc*., **1997**, *119*, 11502. (e) T. Steiner, *J. Phys. Chem. A*, **1998**, *102*, 7041. (f) P. Gilli, V. Bertolasi, V. Ferretti and G. Gilli, *J. Am. Chem. Soc*., **2000**, *122*, 10405. (g) P. Vishweshwar, N. J. Babu, A. Nangia, S. A. Mason, H. Puschmann, R. Mondal and J. A. K. Howard, *J. Phys. Chem. A*, **2004**, *108*, 9406. (h) M. D. Ward, *Chem. Commun*., **2005**, 5838.

10. (a) P. W. Baures, A. M. Beatty, M. Dhanasekaran, B. A. Helfrich, W. Pe´rez-Segarra and J. Desper, *J. Am. Chem. Soc*., **2002**, *124*, 11315. (b) Y. Nishiyama, J. Sugiyama, H. Chanzy and P. Langan, *J. Am. Chem. Soc*., **2003**, *125*, 14300. (c) M. Jarvis, *Nature*, **2003**, *426*, 611. (d) R. Boese, M. T. Kirchner, W. E. Billups and L. R. Norman, *Angew. Chem. Int. Ed*., **2003**, *42*, 1961. (e) D. Das, R. K. R. Jetti, R. Boese and G. R. Desiraju, *Cryst. Growth Des*., **2003**, *3*, 675. (f) A. D. Santis, A. Forni, R. Liantonio, P. Metrangolo, T. Pilati and G. Resnati, *Chem. Eur. J*., **2003**, *9*, 3974. (g) K. J. Wallace, W. J. Belcher, D. R. Turner, K. F. Syed and J. W. Steed, *J. Am. Chem. Soc*., **2003**, *125*, 9699. (h) E. A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem., Int. Ed.*, **2003**, *42*, 1210. (i) M. Fourmigué and P. Batail, *Chem. Rev*., **2004,** *104*, 5379.

11. (a) R. D. Green, *Hydrogen Bonding by C-H Groups*, McMillan: London, **1974**. (b) R. Taylor and O. Kennard, *J. Am. Chem. Soc*., **1982**, *104*, 5063. (c) G. R. Desiraju, *Acc. Chem. Res*., **1996**, *29*, 441. (d) T. Steiner, *Chem. Commun*., **1997**, 727. (e) G. R. Desiraju, *Chem. Commun*., **2005**, 2995.

12. (a) M. F. Richardson, Q. -C. Yang, E. N. Bregger and J. D. Dunitz, *Acta Crystallogr*., **1990**, *B46*, 653. (b) J. A. K. Howard, V. J. Hoy, D. O'Hagan and G. T. Smith, *Tetrahedron*, **1996,** *52*, 12613. (c) V. R. Thalladi, H. -C. Weiss, D. Bläser, R. Boese, A. Nangia and G. R. Desiraju, *J. Am. Chem. Soc*., **1998**, *120*, 8702. (d) W. Caminati, S. Melandri, P. Moreschini and P. G. Favero, *Angew. Chem. Int. Ed*., **1999**, *38*, 2924. (e) Y. Tatamitani, B. Liu, J. Shimada, T. Ogata,

P. Ottaviani, A. Maris, W. Caminati and J. L. Alonso, *J. Am. Chem. Soc*., **2002**, *124*, 2739. (f) J. L. Alonso, S. AntolLnez, S. Blanco, A. Lesarri, J. C. Lipez and W. Caminati, *J. Am. Chem. Soc*., **2004**, *126*, 3244.

13. (a) P. K. Thallapally and A. Nangia, *CrystEngComm*, **2001**, *27*, 1. (b) L. Brammer, E. A. Bruton and P. Sherwood, *Cryst. Growth Des*., **2001**, *1*, 277. (c) F. Zordan, L. Brammer and P. Sherwood, *J. Am. Chem. Soc*., **2005**, *127*, 5979. (d) F. Zordan, S. L. Purver, H. Adams and L. Brammer, *CrystEngComm*, **2005**, *7*, 350. (e) K. Reichenbächer, H. I. Süss and J. Hulliger, *Chem. Soc. Rev*., **2005**, *34*, 22.
14. (a) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl*., **1995**, *34*, 2311. (b) C. B. Aakeröy, *Acta Crystallogr*., **1997**, *B53*, 569. (c) G. R. Desiraju, *Chem. Commun*., **1997**, 1475. (d) A. Nangia and G. R. Desiraju, *Top. Curr. Chem*., **1998**, *198*, 57. (e) A. Nangia and G. R. Desiraju, *Acta Crystallogr*., **1998**, *A54*, 934. (f) W. D. S. Motherwell, G. P. Shields and F. H. Allen, *Acta Crystallogr*., **1999**, *B55*, 1044. (g) G. R. Desiraju, *Stimulating Concepts in Chemistry*; F. Vögtle, J. F. Stoddart and M. Shibasaki, Eds.; Wiley-VCH: **2000**, pp 293–308. (h) M. J. Zaworotko, *Chem. Commun*., **2001**, 1. (i) A. F. Williams, *Supramolecular Synthons*: *Encyclopedia of Supramolecular Chemistry*, J. L. Atwood and J. Steed, Eds.; **2004**. (j) T. Gelbrich and M. B. Hursthouse, *CrystEngComm*, **2005**, *53*, 324.
15. A. I. Kitaigorodsky, *Molecular crystals and molecules*, Academic press, New York, **1973**.
16. (a) A. S. Myerson and P. Y. Lo, *J. Cryst. Growth*, **1990**, *99*, 1048. (b) A. S. Myerson and P. Y. Lo, *J. Cryst. Growth*, **1991**, *110*, 26. (c) R. M. Ginde and A. S. Myerson, *J. Cryst. Growth*, **1992**, *116*, 41. (d) A. S. Myerson and R. M. Ginde, *Handbook of Industrial Crystallization*, A. S. Myerson, Ed.; Butterworth-Heinemann: Stoneham, MA, **1992**. (e) S. Martini, M. L. Herrera and R. W. Hartel, *J. Agric. Food Chem.*, **2001**, *49*, 3223. (f) L. G. M. Beekmans, R. Vallee and G. J. Vancso, *Macromolecules*, **2002**, *35*, 9383. (g) S. Datta and D. J. W. Grant, *Cryst. Growth Des*., **2003**, *3*, 1351. (h) S. Devarakonda, J. M. B. Evans

and A. S. Myerson, *Cryst. Growth Des*., **2003**, *3*, 741. (i) S. Ueno, R. I. Ristic, K. Higaki and K. Sato, *J. Phys. Chem. B*., **2003**, *107,* 4927. (j) I. Weissbuch, M. Lahav and L. Leiserowitz, *Cryst. Growth Des.* **2003**, *3*, 125. (k) I. Weissbuch, V. Y. Torbeev, L. Leiserowitz and M. Lahav, *Angew. Chem. Int. Ed*., **2005**, *44*, 3226. (l) S. Chattopadhyay, D. Erdemir, J. M. B. Evans, J. Ilavsky, H. Amenitsch, C. U. Segre and A. S. Myerson, *Cryst. Growth Des.*, **2005**, *5*, 523. (m) R. J. Davey, G. Dent, R. K. Mughal and S. Parveen, *Cryst. Growth Des.* **2006**, *6*, 1788.

17. (a) W. Ostwald, *Z. Phys. Chem*., **1897**, *22*, 289. (b) M. Volmer, *Kinetic der Phasenbildung*, Steinkopf: Leipzig, **1939**. (c) A. C. Zettlemoyer, *Nucleation*, Dekker: New York, **1969**. (d) B. Lewis, *Nucleation and Growth Theory*: *Crystal Growth*, Ed.; B. R., Pamplin, Pergamon: Oxford, **1980**. (e) R. J. Davey and J. Garside, *From Molecules to Crystallizers*, Oxford University Press: Oxford, U.K., **2000**. (f) R. J. Davey, N. Blagden, S. Righini, H. Alison, M. J. Quayle and S. Fuller, *Cryst. Growth Des*., **2001**, *1*, 59. (g) H. Groen and K. J. Roberts, *J. Phys. Chem. B*, **2001**, *105*, 10723. (h) R. J. Davey, N. Blagden, S. Righini, H. Alison and E. S. Ferrari, *J. Phys. Chem. B*., **2002**, *106*, 1954. (i) R. J. Davey, W. Liu, M. J. Quayle, and G. J. T. Tiddy, *Cryst. Growth Des.*, **2002**, *4*, 269. (j) N. Blagden and R. J. Davey, *Cryst. Growth Des*., **2003**, *3*, 873. (k) J. H. ter Horst, H. J. M. Kramer and P. J. Jansens, *Cryst. Growth Des*., **2002**, *2*, 351. (l) J. Drenth, K. Dijkstra, C. Haas, J. Leppert and O. Ohlenschlager, *J. Phys. Chem. B*, **2003**, *107,* 4203. (m) C. S. Towler, R. J. Davey, R. W. Lancaster, and C. J. Price, *J. Am. Chem. Soc*., **2004**, *126*, 13347. (n) R. Banerjee, P. M. Bhatt, M. T. Kirchner and G. R. Desiraju, *Angew. Chem. Int. Ed*., **2005**, *44*, 2515. (o) G. R. Desiraju, *Angew. Chem. Int. Ed*., **2007**, *46*, 8342.
18. E. Mitscherlich, *Ann. Chim. Phys*., **1822**, *19*, 350.
19. P. H. R. Groth, *Chemische kristallographie*, W. Engelemann, Leipzig, vol. 1-5, **1906**, **1908**, **1910**, **1917**, **1919**.

20. W. C. McCrone, *Polymorphism in Physics and Chemistry of the Organic Solid State*; eds. D. Fox, M. M. Labes and A. Weisemberg, Interscience, New York, **1965**, 726.
21. (a) P. Corradini, *Chem. Ind. (Milan)*, **1973**, *55*, 122. (b) N. C. Panagiotopoulos, G. A. Jeffrey, S. J. LaPlaca and W. C. Hamilton, *Acta Crystallogr.*, *Sect. B*, **1974**, *30*, 1421. (c) J. Bernstein and A. T. Hagler, *J. Am. Chem. Soc.*, **1978**, *100*, 673. (d) J. Bernstein, *Conformational Polymorphism. In Organic Solid State Chemistry*, vol 32, Studies in organic chemistry, ed. G. R. Desiraju, Elsevier, Amsterdam, **1987**.
22. J. D. Dunitz, *Acta Crystallogr.*, *Sect. B*, **1995**, *51*, 619.
23. (a) J. Bernstein, *Polymorphism in Molecular Crystals*, Clarendon Press, Oxford, **2002**. (b) C. P. Price, A. L. Grzesiak and A. J. Matzger, *J. Am. Chem. Soc.*, **2005**, *127*, 5512. (c) A. T. Hulme, S. L. Price and D. A. Tocher, *J. Am. Chem. Soc.*, **2005**, *127*, 1116. (d) A. V. Trask, N. Shan, W. D. Motherwell, W. Jones, S. Feng, R. B. Tan and K. J. Carpenter, *Chem Commun.*, **2005**, 880. (e) D. J. W. Grant and S. R. Byrn, *Adv. Drug Deliv. Rev.*, **2004**, *56*, 237. (f) S. Coste, J.-M. Schneider, M.-N. Petit and G. Coquerel, *Cryst. Growth Des.*, **2004**, *4*, 1237. (g) A. V .Trask, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2004**, 890. (h) P. A. Bonnet, J. van de Streek, A. V. Trask, W. D. S. Motherwell and W. Jones, *CrystEngComm*, **2004**, *6*, 535. (i) M. R. Caira, S. A. Bourne, W. T. Mhlongo and P. M. Dean, *Chem. Commun.*, **2004**, 2216. (j) A. L. Grzesiak, M. Lang, K. Kim and A. J. Matzger, *J. Pharm. Sci.*, **2003**, *92*, 2260. (k) W. I. Cross, N. Blagden, R. J. Davey, R. G. Pritchard, M. A. Neumann, R. J. Roberts and R. C. Rowe, *Cryst. Growth Des.*, **2003**, *3*, 151. (l) R. J. Davey, *Chem. Commun.*, **2003**, 1463. (m) M. L. Peterson, S. L. Morissette, C. McNulty, A. Goldsweig, P. Shaw, M. LeQuesne, J. Monagle, N. Encina, J. Marchionna, A. Johnson, M. J. Cima and Ö. Almarsson, *J. Am. Chem. Soc.*, **2002**, *124*, 10958. (n) Ö. Suryanarayanan, S. R. Byrn, *Adv. Drug Deliv. Rev.*, **2001**, *48*, 1. (o) T. L. Threlfall, *Analyst*, **1995**, *120*, 2435.
24. G. R. Desiraju, *Nature Materials*, **2002**, *1*, 77.

25. A. V. Trask, G. M. Day, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2006**, 54.
26. P. K. Thallapally, R. K. R. Jetti, A. K. Katz, H. L. Carrell, K. Singh, K. Lahiri, S. R. Kotha, R. Boese and G. R. Desiraju, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1149.
27. (a) P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson and M. J. Zaworotko, *J. Am. Chem. Soc.*, **2005**, *127*, 16802. (b) A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem. Int. Ed.*, **2006**, *46*, 615. (c) A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem. Int. Ed.*, **2006**, *46*, 618.
28. W. I. F. David, K. Shankland, C. R. Pulham, N. Blagden, R. J. Davey and M. Song, *Angew. Chem. Int. Ed.*, **2005**, *44*, 7032.
29. J. T. Carstensen, *Pharmaceutics of solids and solid dosage forms*, John Wiley & Sons, New York, **1977**.
30. P. N. Zannikos, W. I. Li, J. K. Drennen and R. A. Lodder, *Pharm. Res.*, **1991**, *8*, 974.
31. G. Ahr, B. Voith and J. Kuhlmann, *Eur. J. Drug. Metab. Pharmacokinet.*, **2000**, *25*, 25.
32. M. Draguet-Brughmans, R. Bouche, J. P. Flandre and A. van den Bulcke, *Pharm. Acta helv.*, **1979**, *54*, 140.
33. T. Yokoyama, T. Umeda, K. Kuroda, T. Nagafuku, T. Yamamoto and S. Asada, *J. Pharm. Soc. Jpn.*, **1979**, *99*, 837.
34. T. Yokoyama, T. Umeda, K. Kuroda, T. Kuroda and S. Asada, *Chem. Pharm. Bull.*, **1980**, *29*, 194.
35. J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter and J. Morris, *Pharm. Res.*, **2001**, *18*, 859.
36. a) J. F. Remenar, J. M. MacPhee, B. K. Larson, V. A. Tyagi, J. H. Ho, D. A. McIlroy, M. B. Hickey, P. B. Shaw and Ö. Almarsson, *Org. Proc. Res. Dev.*, **2003**, *7*, 990. (b) R. J. Bastin, M. J. Bowker and B. J. Slater, *Org. Proc. Res. Dev.*, **2000**, *4*, 427.

37. (a) C. H. Gu and D. J. W. Grant in *Handbook of Experimental Pharmacology: Stereochemical Aspects of Drug Action and Disposition* Eds.; M. Eichelbaum, B. Testa and A. Somogyi, Springer, Berlin, **2003**. (b) M. Puddipeddi, A. T. M. Serajuddin, D. J. W. Grant and P. H. Stahl in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* Eds.; P. H. Stahl and C. G. Wermuth, Wiley, Weinheim, **2002**; pp 19–38. (c) S. H. Neau in *Water-Insoluble Drug Formations* Ed.; R. Liu, Interpharm, Buffalo Grove, **2000**, pp 405–425. (d) A. V. Trask, D. A. Haynes, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2006**, 51. (e) D. A. Haynes, W. Jones and W. D. S. Motherwell, *CrystEngComm*, **2005**, *7*, 538. (f) S. L. Morissette, Ö. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A.V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, *Adv. Drug Deliv. Rev.*, **2004**, *56*, 275. (g) E. C. Ware and D. R. Lu, *Pharm. Res.*, **2004**, *21*, 177. (h) S. M. Berge, L. D. Bighley and D. C. Monkhouse, *J. Pharm. Sci.*, **1977**, *66*, 1.

38. P. L. Gould, *Int. J. Pharm.*, **1986**, *33*, 201.

39. G. R. Desiraju, *CrystEngComm*, **2003**, *5*, 466.

40. J. D. Dunitz, *CrystEngComm*, **2003**, *5*, 506.

41. (a) N. Shan, F. Toda and W. Jones, *Chem. Commun.*, **2002**, 2372. (b) A.V. Trask, N. Shan, W. D. S. Motherwell, W. Jones, S. Feng, R. B. H. Tan and K. J. Carpenter, *Chem. Commun.*, **2005**, 880. (c) A.V. Trask and W. Jones, *Top. Curr. Chem.*, **2005**, *254*, 41. (d) A. V. Trask, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2004**, 890. (e) T. Friščić, L. Fábián, J. C. Burley, W. Jones and W. D. S. Motherwell, *Chem. Commun.*, **2006**, 5009. (f) T. Friščić, A. V. Trask, W. Jones and W. D. S. Motherwell, *Angew. Chem. Int. Ed.*, **2006**, *45*, 7546.

42. (a) X. Gao, T. Friščić and L. R. MacGillivray, *Angew. Chem. Int. Ed*, **2004**, *43*, 232. (b) B. Q. Ma and P. Coppens, *Cryst. Growth Des.*, **2004**, *4*, 211. (c) B. Olenik, T. Smolka, R. Boese and R. Sustmann, *Cryst. Growth Des.*, **2003**, *3*, 183. (d) C. B. Aakeröy, A. M. Beatty, B. A. Helfrich and M. Nieuwenhuyzen, *Cryst. Growth Des.*, **2003**, *3*, 159. (e) B. R. Bhogala and A. Nangia, *Cryst. Growth Des.*, **2003**, *3*, 547. (f) R. D. Walsh, M. W. Bradner, S. Fleischman, L.

A. Morales, B. Moulton, N. Rodriguez-Hornedo and M. J. Zaworotko, *Chem. Commun.*, **2003**, 186. (g) L. S. Reddy, A. Nangia and V. M. Lynch, *Cryst. Growth Des.*, **2004**, *4*, 89. (h) P. Vishweshwar, J. A. McMahon, M. L. Peterson, M. B. Hickey, T. R. Shattocka and M. J. Zaworotko, *Chem. Commun.*, **2005**, 4601. (i) W. W. Porter III, S. C. Elie and A. J. Matzger, *Cryst. Growth Des.*, **2008**, *8*, 14. (j) F. Lara-Ochoa and G. Espinosa-Perez, *Cryst. Growth Des.*, **2007**, *7*, 1213. (k) S. L. Childs and K. I. Hardcastle, *Cryst. Growth Des.*, **2007**, *7*, 1291. (l) G. P. Stahly, *Cryst. Growth Des.*, **2007**, *7*, 1007. (m) M. L. Cheney, G. J. McManus, J. A. Perman, Z. Wang and M. J. Zaworotko, *Cryst. Growth Des.*, **2007**, *7*, 616. (n) J. A. Bis, O. L. McLaughlin, P. Vishweshwar and M. J. Zaworotko, *Cryst. Growth Des.*, **2006**, *6*, 2648. (o) M. Dabros, P. R. Emery and V. R. Thalladi, *Angew. Chem., Int. Ed.*, **2007**, *46*, 4132. (p) B. R. Bhogala, S. Basavoju and A. Nangia, *Cryst. Growth Des.*, **2005**, *5*, 1683. (q) C. B. Aakeröy, J. Desper and J. F. Urbina, *Chem. Commun.*, **2005**, 2820. (r) C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem., Int. Ed.*, **2001**, *40*, 3240.

43. Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.,* **2004**, 1889.
44. S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des.*, **2003**, *3*, 909.
45. J. F. Remenar, S. L. Morissette, M. L. Peterson, B. Moulton, J. M. MacPhee, H. R. Guzman and Ö. Almarsson, *J. Am. Chem. Soc.*, **2003,** *125*, 8456.
46. S. L. Childs, L. J. Chyall, J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly and G. P. Stahly, *J. Am. Chem. Soc.*, **2004**, *126*, 13335.
47. (a) J. L. Atwood, J. E. D. Davies and F. Vogtle, *Comprehensive Supramolecular Chemistry*; Pergammon: New York, **1996**, vol. 6. (b) R. Bishop, *Chem. Soc. Rev.*, **1996**, 311. (c) D. D. MacNicol, F. Toda and R. Bishop, *Comprehensive Supramolecular Chemistry*; vol. 6, *Solid-state Supramolecular Chemistry: Crystal Engineering*, Pergamon Press: Oxford, **1996**. (d) E. Zaborowski, H. Zimmermann and S. Vega, *J. Am. Chem. Soc.*, **1998**, *120*, 8113. (e) R. Bishop, *Synlett.*, **1999,** *9*, 1351. (f) T. Müller, J. Hulliger, W. Seichter, E. Weber, T. Weber and M. Wübbenhorst, *Chem. Eur. J.*, **2000**, *6*, 54. (g) R. K. R. Jetti, A.

Nangia, F. Xue and T. C. W. Mak, *Chem. Commun.*, **2001**, 919. (h) A. Nangia, *Curr. Opin. Solid State Mater. Sci.*, **2001**, *5*, 115. (i) S. Kim, R. Bishop, D. C. Craig, I. G. Dance and M. L. Scudder, *J. Org. Chem.*, **2001**, *67*, 3221. (j) E. Weber, S. Nitsche, A. Wierig and I. Csöregh, *Eur. J. Org. Chem.*, **2002**, 856. (k) H. I. Süss, M. Lutz and J. Hulliger, *CrystEngComm*, **2002**, *4*, 610. (l) R. K. R. Jetti, P. K. Thallapally, C -K. Lam, T. C. W. Mak and A. Nangia, *Chem. Commun.*, **2002**, 952. (m) T. Hertzsch, F. Budde, E. Weber and J. Hulliger, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2281. (n) D. V. Soldatov, E. V. Grachev and J. A. Ripmeester, *Cryst. Growth Des.*, **2002**, *2*, 401. (o) J. L. Atwood, L. J. Barbour and A. Jerga, *Science*, **2002**, *296*, 2367. (p) C. M. Reddy, A. Nangia, C-K. Lam and T. C. W. Mak, *CrystEngComm,* **2002**, *4,* 323. (q) S. Apel, M. Lennartz, L. R. Nassimbeni and E. Weber, *Chem. Eur. J.*, **2002**, *8*, 3678. (r) J. G. Selbo, J. J. Haycraft and C. J. Eckhardt, *J. Phys. Chem. B*, **2003**, *107*, 11163. (s) G. V. C. Cave, J. Antesberger, L. J. Barbour, R. M. McKinley and J. L. Atwood, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5263. (t) M. R. Caira, Y. Paul Chang, L. R. Nassimbeni and H. Su, *Org. Biomol. Chem.*, **2004**, *2*, 655. (u) C. -K. Lam and T. C. W. Mak, *J. Am. Chem. Soc.*, **2005**, *127*, 11536. (v) B. K. Saha, R. K. R. Jetti, L. S. Reddy, S. Aitipamula and A. Nangia, *Cryst. Growth Des.*, **2005**, *5*, 887. (w) B. K. Saha, S. Aitipamula, R. Banerjee, A. Nangia, R. K. R. Jetti, R. Boese, C. -K. Lam and T. C. W. Mak, *Mol. Cryst. Liq. Cryst.,* **2005**, *440*, 295.

48. (a) J. A. R. P. Sarma and G. R. Desiraju, In *Crystal Engineering: The Design and Application of Functional Solids*; M. J. Zaworotko and K. R. Seddon, Eds; Kluwer: Dordrecht, **1999**, 325. (b) V. S. S. Kumar, S. S. Kuduva and G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1069. (c) R. Thaimattam, F. Xue, J. A. R. P. Sarma, T. C. W. Mak and G. R. Desiraju, *J. Am. Chem. Soc.*, **2001**, *123*, 4432. (d) V. S. S. Kumar and A. Nangia, *Chem. Commun.*, **2001**, 2392. (e) K. A. Udachin, G. D. Enright, P. O. Brown and J. A. Ripmeester, *Chem. Commun.*, **2002**, 2162. (f) S. H. Dale, M. R. J. Elsegood and C. Redshaw, *CrystEngComm*, **2003**, *5,* 368. (g) J. Ashmore, R. Bishop, D. C. Craig and M. L. Scudder, *Mendeleev Commun.*, **2003**, *13*, 144. (h) R. Banerjee, G. R. Desiraju,

R. Mondal, A. S. Batsanov, C. K. Broder and J. A. K. Howard, *Helv. Chim. Acta*, **2003**, *86*, 1339. (i) Y. -S. Kim and R. W. Rousseau, *Cryst. Growth Des.*, **2004**, *4*, 1211. (j) T. Hosokawa, S. Datta, A. R. Sheth, N. R. Brooks, V. G. Young and D. J. W. Grant, *Cryst. Growth Des.*, **2004**, *4*, 1195. (k) Y. Imai, T. Sato and R. Kuroda, *Chem. Commun.*, **2005**, 3289.

49. K. R. Seddon, *Cryst. Growth Des.*, **2004**, *4*, 1087.
50. G. R. Desiraju, *Cryst. Growth Des.*, **2004**, *4*, 1089.
51. J. Bernstein, *Cryst. Growth Des.*, **2005**, *5*, 661.
52. A. Nangia, *Cryst. Growth Des.*, **2006**, *6*, 2.
53. (a) T. L. Threlfall, *Org. Proc. Res. Dev.*, **2000**, *4*, 384. (b) S. Garnier, S. Petit and G. Coquerel, *J. Thermal Anal. & Calorimetry,* **2002**, *68*, 489. (c) Y. -S. Kim and R. W. Rousseau, *Cryst. Growth Des.*, **2004**, *4*, 1211. (d) T. Hosokawa, S. Datta, A. R. Sheth, N. R. Brooks, V. G. Young and D. J. W. Grant, *Cryst. Growth Des.*, **2004**, *4*, 1195. (e) M. R. Caira, T. le-Roex, L. R. Nassimbeni, J. A. Ripmeester and E. Weber, *Org. Biomol. Chem.*, **2004**, *2*, 2299.
54. (a) R. K. Khankari and D. J. W. Grant, *Thermochim. Acta*, **1995**, 61. (b) A. L. Gillon, N. Feeder, R. J. Davey and R. Storey, *Cryst. Growth Des.*, **2003**, *3*, 663. (c) L. -F. Huanga and W. -Q. Tong, *Adv. Drug Deliv. Rev.*, **2004**, *56*, 321. (d) D. A. Haynes, W. Jones and W. D. S. Motherwell, *CrystEngComm*, **2005**, 462.
55. (a) B. C. Hancock and G. Zografi, *J. Pharm. Sci.*, **1997**, *86*, 1. (b) S. R. Elliott in *Physics of amorphous materials*, 2nd ed., Longman Scientific & Technical, Essex, **1990**. (c) P. G. Debenedetti and F. H. Stillinger, *Nature*, **2001**, *410*, 259. (d) L. R. Hilden and K. R. Morris, *J. Pharm. Sci.*, **2004**, *93*, 3. (e) L. Yu, *Adv. Drug Deliv. Rev.*, **2001**, *48*, 27. (f) S. R. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg and G. Poochikian, *Pharm. Res.*, **1995**, *12*, 945. (g) D. Q. M. Craig, P. G. Royall, V. L. Kett and M. L. Hopton, *Int. J. Pharm.*, **1999**, *179*, 179. (h) R. Lefort, A. D. Gusseme, J. F. Willart, F. Danede and M. Descamps, *Int. J. Pharm.*, **2004**, *280*, 209. (i) B. C. Hancock and M. Parks, *Pharm. Res.*, **2000**, *17*, 397. (j) D. Zhou, G. G. Z. Zhang, D. Law, D. J. W. Grant and E. A. Schmitt, *J. Pharm. Sci.*, **2002**, *91*, 1863. (k) A. Saleki-Gerhardt, J. G. Stowell, S. R. Byrn and G. Zografi, *J.*

Pharm. Sci., **1995**, *84*, 318. (l) J. F. Willart, N. Descamps, V. Caron, F. Capet, F. Danede and M. Descamps, *Solid State Comm*., **2006**, *138*, 194. (m) H. Suga, *J. Phys*.: *Condens. Matter*, **2003**, *15*, S775. (n) M. Yoshioka, B. C. Hancock and G. Zografi, *J. Pharm. Sci*., **1994**, *83*, 1700.

56. (a) M. Mansfield, *J. Chem. Phys.*, **1995**, *103*, 8124. (b) C. A. Angell, *Proc. Nat. Acad. Sci*., *U.S.A.*, **1995**, *92*, 6675. (c) C. A. Angell, *Science*, **1995**, *267*, 1924. (d) C. A. Angell, D. R. MacFarlane and M. Oguni, *Ann. N.Y. Acad. Sci*., **1986**, *484*, 241. (e) M. D. Ediger, C. A. Angell and S. R. Nagel, *J. Phys. Chem*., **1996**, *100*, 13200.

CHAPTER TWO

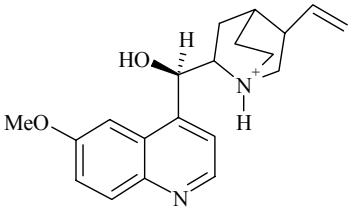
SACCHARIN SALTS OF ACTIVE PHARMACEUTICAL INGREDIENTS, THEIR CRYSTAL STRUCTURES AND INCREASED WATER SOLUBILITIES

2.1 Introduction

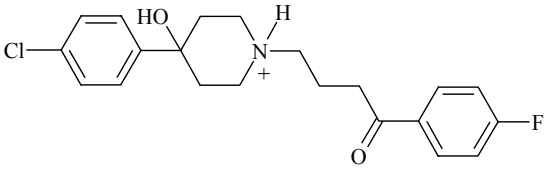
Importance of the solid dosage forms of drugs is well known and has been discussed in detail in chapter 1. Among various solid modifications of drugs, salts are the most common and have been used for years. Salts of drugs are primarily made to make the drug water soluble as most of the drugs are neutral organic molecules and have limited water solubility.[1] This increased solubility may sometimes result in better bioavailability. Sometimes salts are prepared for other reasons like increased chemical or physical stability, taste masking, to increase the melting point of low melting drugs and so on. Salts can be also advantageous in industrial process because they are generally hard and brittle, being ionic in nature.[1]

Many inorganic and organic acids like HCl, HBr, H_2SO_4, benzoic acid and acetic acid are used as salt formers. The salt having the most desirable properties is selected for formulation. An estimated half of all drug molecules used in medicine are administered as salts so that the formation and the selection of a suitable salt for a drug candidate is recognized as an essential step in the preclinical phase of modern drug development.[2,3] Saccharin (pK_a 2.2) has been used in the past as an acid (salt former) in the pharmaceutical industry but the literature is scanty. It has been reported that the alkaloid vincamine is rendered more soluble by salt formation with saccharin.[4] There is also a report that an API saccharinate (buspirone saccharinate) is less soluble than the hydrochloride, and this was claimed as a desirable property.[8,9] On the converse side, saccharinate formation of an API was an unintended consequence resulting in a recall of a commercial product**.** Midazolam hydrochloride was formulated with saccharin in an attempt to sweeten the product for pediatric medication.[10] During this process, midazolam saccharinate, with a lower solubility than the hydrochloride, precipitated rendering the formulation unacceptable. In view of the limited literature on API

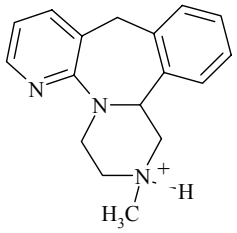
saccharinates, this chapter describes crystal structures, solubility and solution pH characteristics of saccharinate adducts (salt and co-crystal) of 11 APIs of current interest (Scheme 1 and Figure 1) and establishes the general use of saccharin as an acid in pharmaceutical chemistry.



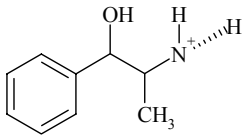
Quinine



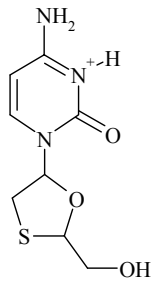
Haloperidol



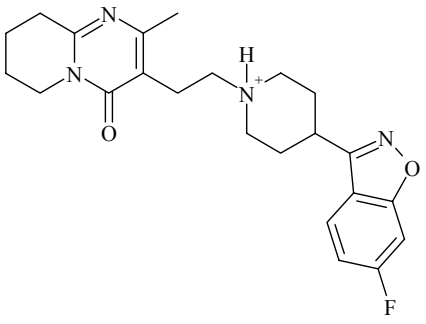
Mirtazapine



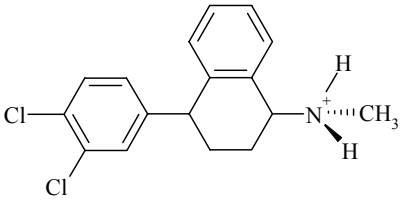
Pseudoephedrine



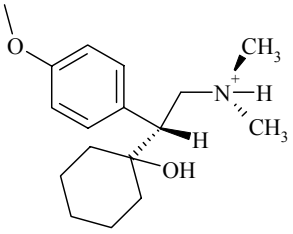
Lamivudine



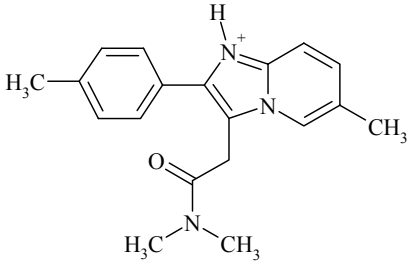
Risperidone



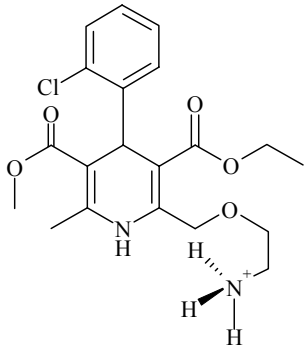
Sertraline



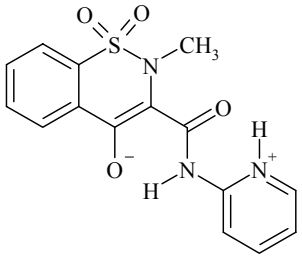
Venlafaxine



Zolpidem



Amlodipine



Piroxicam

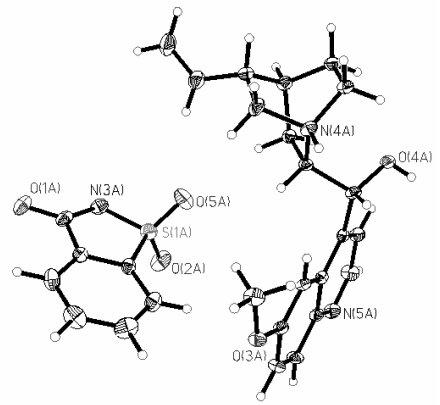
Scheme 1. APIs in this study as found in their saccharin adduct (cation or neutral).

2.2 Crystal structures of API saccharinates

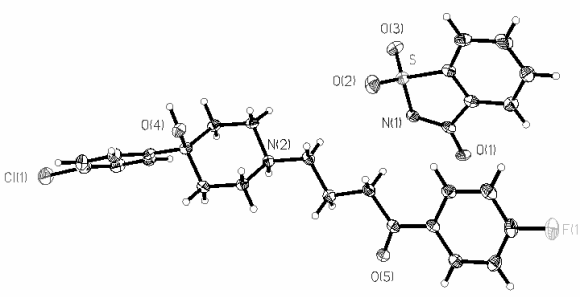
Table 1 gives salient properties of the APIs in this study and their saccharinates. An API of sufficient basicity will form a saccharinate. Otherwise, treatment with saccharin and subsequent crystallization leads to no chemical outcome or to co-crystal

formation (piroxicam). In a co-crystal, proton transfer does not take place between the acidic and basic components; rather, a hydrogen bond of the type A–H…B is formed between them. Co-crystal formation (with an acid like saccharin) requires therefore that the API be of sufficiently low basicity. Additionally, there are other requirements for co-crystal formation such as functional group complementarity and viable packing interactions (synthon compatibility).[8] Formation of co-crystals of APIs (or indeed, of any compound) is a delicate exercise, and there is no guarantee that when two (even predesigned) compounds are taken together in solution, a co-crystal will result.[9] An example of a co-crystal formed by saccharin is with carbamazepine[10] and general principles for co-crystal formation of APIs have been described by Almarsson and Zaworotko in their important review.[11]

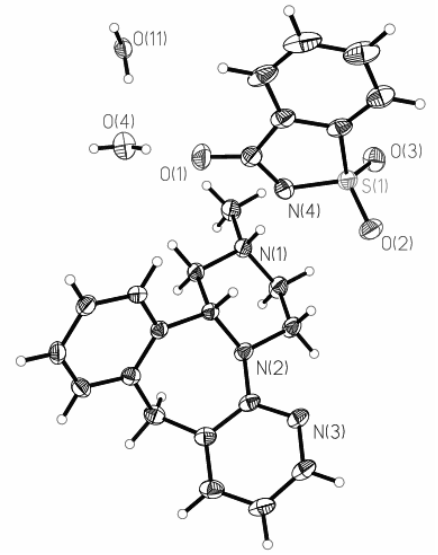
The structures contain organic cations and anions, and sometimes water; the API and saccharin fragments are rich in hydrogen bond donor and acceptor functionalities. Therefore it is no surprise that the crystal structures contain many hydrogen bonds that are quite strong (Table 2). Typically, one finds O–H…$N^{(-)}$, $N^{(+)}$–H…$N^{(-)}$, $N^{(+)}$–H…O, N–H…O, O–H…O and N–H…N bonds, with auxiliary C–H…$N^{(-)}$ and C–H…O interactions in some cases.



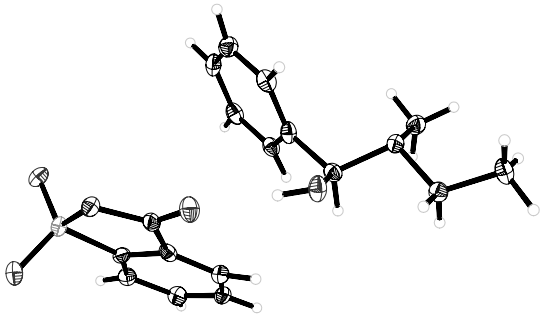
Quinine saccharinate (**I**)



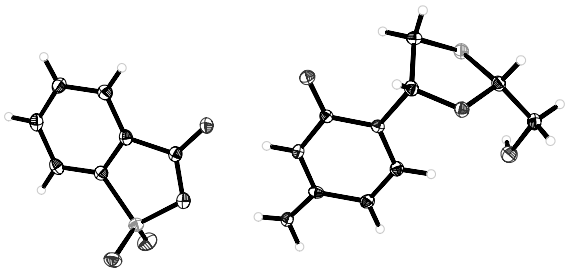
Haloperidol saccharinate (**II**)



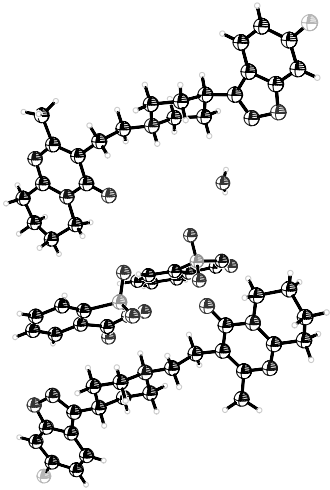
Mirtazapine saccharinate (**III**)



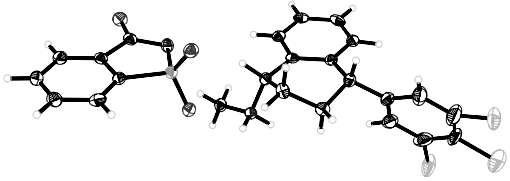
Pseudoephedrine saccharinate (**IV**)



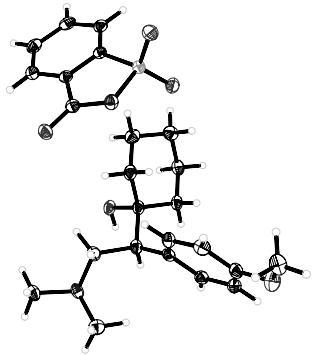
Lamivudine saccharinate (**V**)



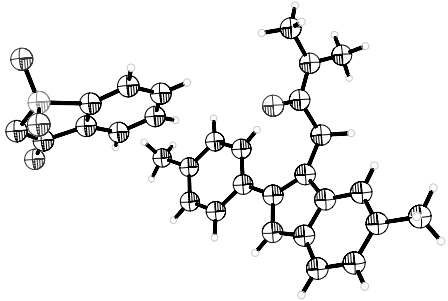
Risperidone saccharinate (**VI**)



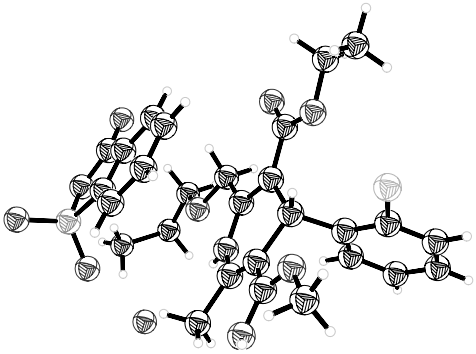
Sertraline saccharinate (**VII**)



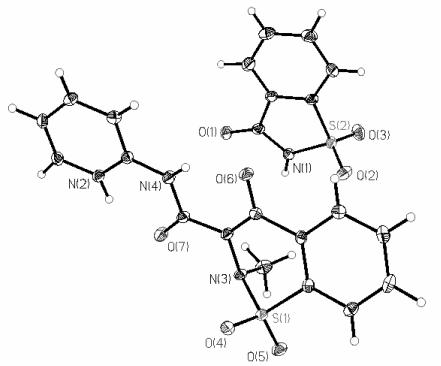
Venlafaxine saccharinate (**VIII**)



Zolpidem saccharinate (**IX**)



Amlodipine saccharinate (**X**)



Piroxicam-saccharin co-crystal (**XI**)

Figure 1. ORTEP diagrams of saccharin adducts of the APIs in this study.

Table 1. Salient properties of selected APIs and their saccharinates.

API							API saccharinate		
Name	**Marketed product**	**Disease treated**	**pK_a**	**LogP (octanol /water)**	**Solubility[c] (mg/mL)**		**m.p °C**	**Solubility (mg/mL)**	**pH**
					API	Marketed product			
Quinine	Quinine sulfate	Malaria	5.1	3.40	< 0.10	1.20	185.9	5.40	5.55
Haloperidol	Haloperidol	Schizophrenia	8.3	3.23	< 0.01	<0.01	139.6	6.08	5.44
Mirtazapine	Mirtazapine	Clinical depression	–	7.10	< 0.05	< 0.05	122.6	2.08[e]	5.85
Pseudoephedrine	Pseudoephedrine HCl	Nasal congestion	9.8	0.90	< 0.50	2000	145.1	>300.00	6.25
Lamivudine	Lamivudine	AIDS	–	2.38[d]	70.00	70.00	182.3	10.56	3.35
Risperidone	Risperidone	Delusional psychosis	8.2	3.49	< 0.10	< 0.10	178.2[f]	2.87[f]	5.25
Sertraline	Sertraline HCl	Obsessive-compulsive disorder	9.5	5.29	< 0.10	3.80	202.8	6.45	5.85
Venlafaxine	Venlafaxine HCl	Depression	9.4	0.43	< 0.10	572.00	152.1	30.06	5.95
Zolpidem	Zolpidem tartrate	Insomnia	6.2	3.85	< 0.01	23.00	184.9	11.90	6.05
Amlodipine[a]	Amlodipine besylate	Hypertension	8.6	3.00	< 0.01	< 1.00	–	–	–
Piroxicam[b]	Piroxicam	Arthritis	6.3	3.10	<0.10	<0.10	220.2	<0.10	3.27

a. The single crystal used for X-ray diffraction was of poor quality.
b. This API forms a co-crystal with saccharin.
c. Determined with UV spectroscopy.
d. Calculated value.
e. Mixture of dihydrate and anhydrate.
f. Anhydrate

2.2.1 Quinine saccharinate (**I**)

Quinine is still used to treat resistant malaria and is available in various salt forms. Quinine is very bitter in taste and so are its salts; however quinine saccharinate is sweeter in taste, and patient compliance might improve. Quinine saccharinate crystallizes from 1:1 $CHCl_3$-MeOH in the non-centrosymmetric space group $P2_12_12_1$ with one $(quinine)^+$ cation and one $(saccharin)^-$ anion in the asymmetric unit. This structure contains two types of hydrogen bonds, an $N^{(+)}$–H…$N^{(+)}$ interaction between $N^{(+)}$–H of $(quinine)^+$ and $N^{(-)}$ of $(saccharin)^-$ and an O–H…N between two quinine units. The O–H…N bonds give a helical arrangement (Figure 2).

2.2.2 Haloperidol saccharinate (**II**)

Haloperidol is a conventional butyrophenone antipsychotic drug.[12] Haloperidol saccharinate crystallizes in the centrosymmetric space group $P2_1/n$ with one $(haloperidol)^+$ cation and one $(saccharin)^-$ anion in the asymmetric unit. The crystal structure of the salt is characterized by an eight membered $[R^2_2(8)]$ supramolecular synthon consisting of $N^{(+)}$–H…O and C–H… $N^{(-)}$ hydrogen bonds (Figure 3). Additional O–H…O=S bonds complete the structure.

2.2.3 Mirtazapine saccharinate dehydrate (**III**)

Mirtazapine is a prescription antidepressant. The saccharinate crystallizes easily from water as a dihydrate. It is not surprising that the dihydrate is formed because there are many more hydrogen bond acceptors than donors in the system. Indeed the dihydrate is obtained even when saccharin and the API are crystallized together from solvents other than water (EtOH, DMSO, DMF); trace amounts of water present in the respective solvents are incorporated stoichiometrically in the crystal. The strongest hydrogen bond in the crystal structure is an $N^{(+)}$–H…$N^{(-)}$ between ions (Figure 4). One of the water molecules donates an O–H…N hydrogen bond to the pyridine nitrogen of the API, and an O–H…O=C bond to a $(saccharin)^-$ anion, and accepts an O–H…O hydrogen bond from the other water molecule resulting in a two dimensional arrangement. The second water molecule additionally forms an O–H…O=S bond with a $(saccharin)^-$ anion.

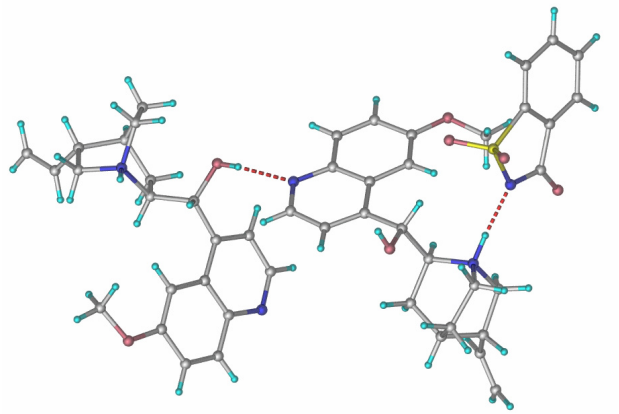


Figure 2. Quinine saccharinate. Note the helical array of hydrogen bonds.

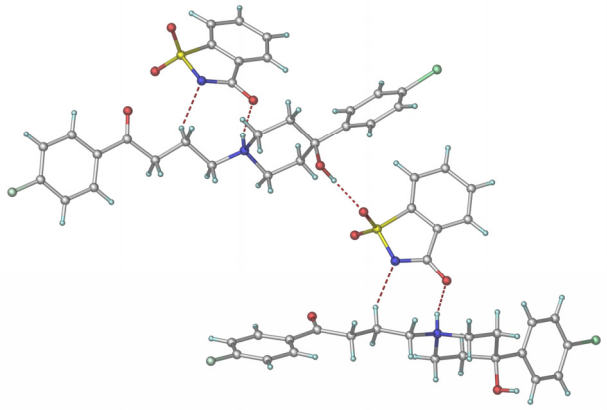


Figure 3. Haloperidol saccharinate. Note the eight membered supramolecular synthon consisting of $N^{(+)}$–H…O and C–H… $N^{(-)}$ hydrogen bonds.

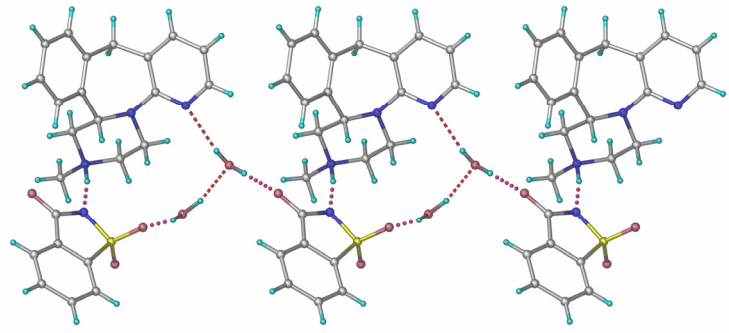


Figure 4. Mirtazapine saccharinate dihydrate. Note how water molecules bind the structure.

The dihydrate converts easily to an anhydrous form upon standing; this conversion is very rapid when the salt is heated to 50°C. Photographs of a crystal on a hot stage microscope are given in Figure 5. At the same time, the anhydrate is hydrated in an ambient atmosphere. Despite several attempts, it was not possible to obtain a solid sample that could positively be identified as the pure dihydrate or the pure anhydrate. The dihydrate and the anhydrate can clearly co-exist and therefore we could not determine the solubilities of either the pure dihydrate or the pure anhydrate. However, the solubility of the recrystallized material (mixture of dihydrate and anhydrate) was found to be higher than that of the free base, and this keeps with the broad theme of the present study.

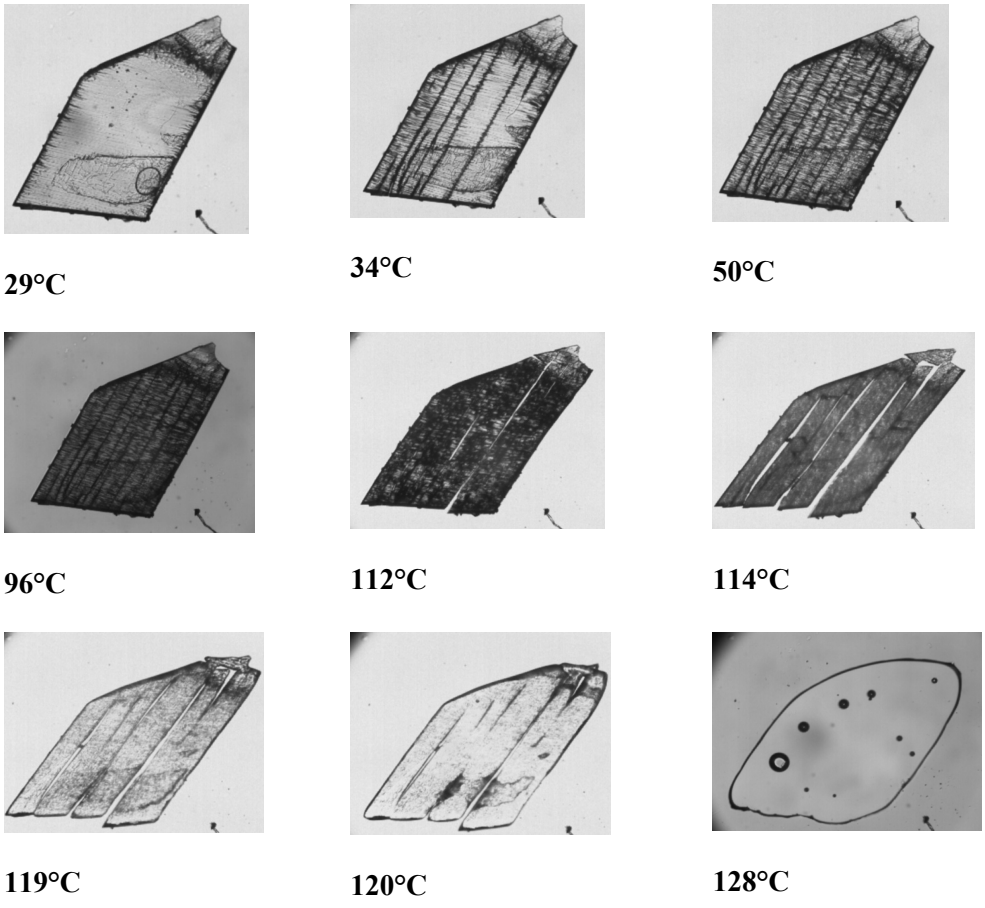


Figure 5. Hot stage microscope photographs of mirtazapine saccharinate.

2.2.4 Pseudoephedrine saccharinate (IV)

Pseudoephedrine (ψ-ephedrine) is a sympathomimetic amine commonly used as a decongestant.[13] Pseudoephedrine saccharinate crystallizes in the non-centrosymmetric space group $P2_1$ with one $(\text{Pseudoephedrine})^+$ cation and one $(\text{saccharin})^-$ anion in the asymmetric unit. The saccharinate has a two dimensional layered structure involving $N^{(+)}$–H… $N^{(-)}$, O–H…O=C, N–H…O=S and C–H…O=S hydrogen bonds (Figure 6).

2.2.5 Lamivudine saccharinate (V)

Lamivudine is a potent reverse transcriptase inhibitor.[14] Lamivudine saccharinate crystallizes in the non-centrosymmetric space group $P2_12_12_1$ with one $(\text{lamivudine})^+$ cation and one $(\text{saccharin})^-$ anion in the asymmetric unit. The saccharinate forms a layered structure which is characterized by a very stable two-point synthon constituted with $N^{(+)}$–H…O and N–H…$N^{(-)}$ hydrogen bonds. These dimers are further linked with N–H…O=C and O–H…O=S hydrogen bonds to form a layer like structure. The hydrogen bonding capability of the various donors and acceptors is saturated (Figure 7). Interestingly, the salt is less soluble than the free base. This example demonstrates that not all salts are more soluble than the free base (or acid).

2.2.6 Risperidone saccharinate hydrate (VI)

Risperidone is an atypical antipsychotic or a second generation antipsychotic medication.[15] Three polymorphs of risperidone free base are reported but atomic coordinates are reported for only one of them (Form A).[16] Risperidone saccharinate hydrate crystallizes in the space group $P2_1/n$ with two $(\text{risperidone})^+$ cations, two $(\text{saccharin})^-$ anions and two water molecules in the asymmetric unit. The structure has $N^{(+)}$–H…O=C, C–H…O=C, N–H…O=S and C–H…O=S hydrogen bonds. The two disordered water molecules form O–H… O bonds (3.03 Å, 2.18 Å, 144°) with the API. A $(\text{saccharin})^-$ anion connects two $(\text{risperidone})^+$ cations with C–H…O=S and N–H…O=S interactions (Figure 8). The hydrate loses water rapidly and converts to the anhydrate when kept in the open, and the solubility measurement is for the anhydrate.

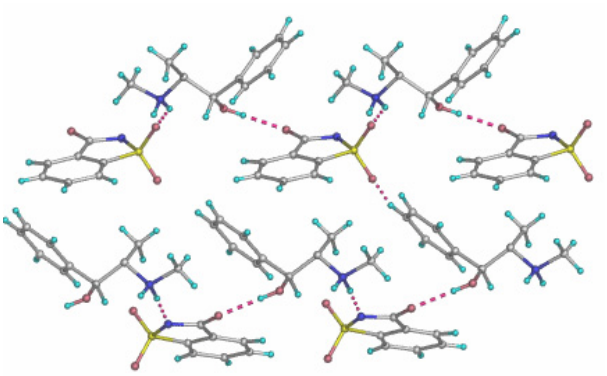


Figure 6. Pseudoephedrine saccharinate. Note the two dimensional layered structure.

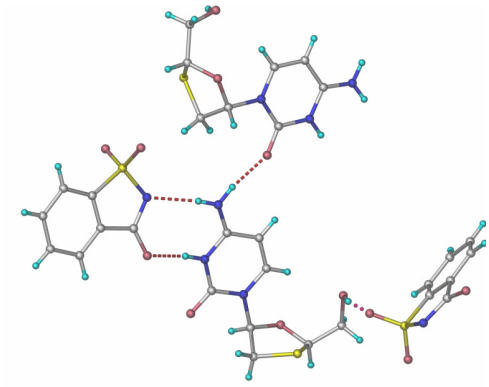


Figure 7. Lamivudine saccharinate. Note the two-point supramolecular synthon.

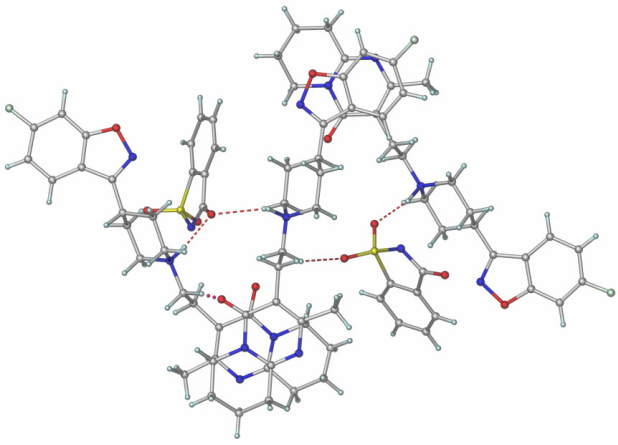


Figure 8. Risperidone saccharinate. Notice the $N^{(+)}$–H…O=C, C–H… O=C, N–H… O=S and C–H… O=S interactions. Disordered water molecules have been removed for clarity.

2.2.7 Sertraline saccharinate (VII)

Sertraline is an orally administered antidepressant.[17] It crystallizes in a non-centrosymmetric space group $P2_12_12_1$ with one $(\text{sertraline})^+$ cation and one $(\text{saccharin})^-$ anion in the asymmetric unit. The crystal structure of sertraline saccharinate is layered with alternating $N^{(+)}$–H…O=S and C–H…O interactions. The other $N^{(+)}$–H proton interacts with a $(\text{saccharin})^-$ of the next layer via a $N^{(+)}$–H…O=C bond (Figure 9). The crystal structure was determined at 100K and also at room temperature and in both cases it was observed that proton transfer has occurred from saccharin to the free base. An important part of this entire exercise is the claim that salt formation changes the solubility of the API. Salt formation is confirmed by locating the acidic H-atom on the API. Accordingly, low temperature single crystal X-ray diffraction is used. However, solubilities are measured at room temperature, and in any case it is the room temperature solubility of the salt that is pharmaceutically relevant. Noting that proton transfer across hydrogen bridges is sometimes a function of temperature, it is important to confirm that the form of the salt for which the solubility is measured (room temperature form) is identical to the form of the salt for which the location of the H^+ is confirmed (low temperature form). Therefore, and as a representative case, the crystal structure of sertraline saccharinate was determined at both 100K and room temperature and the identity of the crystal at both temperatures was demonstrated.

2.2.8 Venlafaxine saccharinate (VIII)

Venlafaxine hydrochloride is a prescription antidepressant.[18] Venlafaxine saccharinate crystallizes in the centrosymmetric space group $P2_1/n$. Although the molecule is chiral, the centrosymmetric space group indicates that commercial drug is a racemic mixture. The $(\text{venlafaxine})^+$ and $(\text{saccharin})^-$ ions form a dimer via a ten membered supramolecular heterosynthon consisting of $N^{(+)}$–H… $N^{(-)}$ and O–H… O interactions (Figure 10). The dimers are connected to each other with C–H… O hydrogen bridges. The salt is moderately soluble in water (30.06 mg/mL) when compared to the hydrochloride salt (572 mg/mL). Less water soluble salts are sometimes more suitable for extended release formulations such as hydrogel tablets. The advantage

of slow release is that the dosage of the drug may be lowered. Since venlafaxine hydrochloride is highly water soluble, efforts have been made to develop less water soluble forms. Venlafaxine maleate is one such form but it still has a fairly high water solubility of 370 mg/mL.[19] Venlafaxine saccharinate with a still lower solubility may therefore be useful for improving extended release formulations of the API. This example shows that lower solubility of a salt could also be important. Salt formation results in an increase (mostly) or decrease (sometimes) of solubility relative to the API. What is important is that a change in solubility takes place.

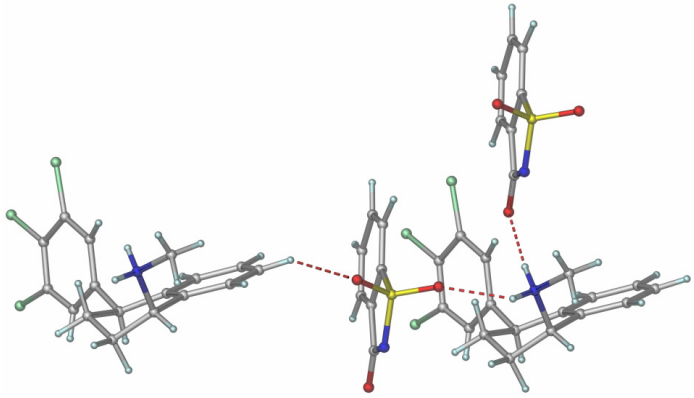


Figure 9. Sertraline saccharinate, with $N^{(+)}$–H… O=S, $N^{(+)}$–H…O=C and C–H…O interactions.

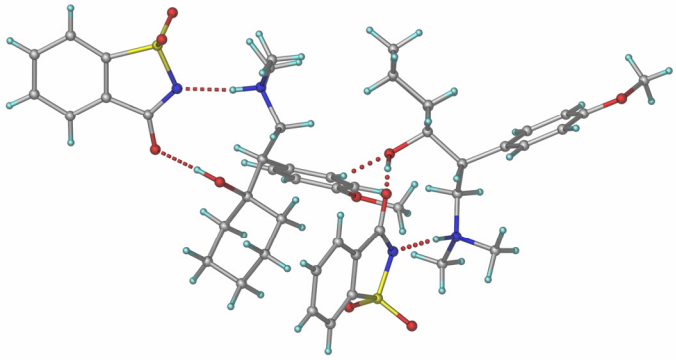


Figure 10. Venlafaxine saccharinate. Note the ten member supramolecular synthon consisting of $N^{(+)}$–H… N, and O–H…O=C interactions.

2.2.9 Zolpidem saccharinate (IX)

Zolpidem is a prescription drug used for short-term treatment of insomnia.[20] The crystal structure of zolpidem saccharinate can be visualized in terms of closed loops that involve two $(\text{zolpidem})^{+}$ and two $(\text{saccharin})^{-}$ ions. These loops are constituted with $N^{(+)}$–H…O and C–H…O interactions (Figure 11).

2.2.10 Amlodipine saccharinate hydrate (X)

Amlodipine is a long acting calcium channel blocker and is used as an anti-hypertensive in the form of its besylate salt.[21] Amlodipine saccharinate, being hygroscopic in nature, is difficult to characterize and crystallize. However, we succeeded with data on a poorly diffracting crystal and confirmed salt formation. Amlodipine saccharinate monohydrate crystallizes in the space group $P\bar{1}$ with one $(\text{amlodipine})^{+}$ cation, one $(\text{saccharin})^{-}$ anion and one water molecule in the asymmetric unit. In the crystalline saccharinate there is a tetramer of ions connected with $N^{(+)}$–H…$N^{(-)}$ and $N^{(+)}$–H…O hydrogen bonds (Figure 12). Other interactions, not shown in the figure, include a $N^{(+)}$–H…O hydrogen bond between $(\text{amlodipine})^{+}$ and a water molecule. These occur in the peripheries of the tetramers.

2.2.11 Piroxicam-saccharin co-crystal (XI)

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) used to relieve the symptoms of arthritis, dysmenorrhoea and pyrexia. Several forms of piroxicam are known.[22] Under mechanical activation, piroxicam passes from the stable β form (which contains neutral molecules of the API) to the active zwitterionic form that has enhanced solubility.[23] In contrast to the other APIs in this study, piroxicam forms a zwitterionic co-crystal with saccharin. This co-crystal is as insoluble as the marketed product. The asymmetric unit of the piroxicam saccharin co-crystal consists of one molecule of saccharin and one piroxicam zwitterion. There are two intramolecular N–H…O and one intermolecular N–H…O hydrogen bonds. One intramolecular N–H…O bond is between the enolic $O^{(-)}$ and N–H of the amide and the other is between the pyridinium $N^{(+)}$–H group and the C=O group of the amide. The N–H group of saccharin forms the

intermolecular hydrogen bond with the enolic $O^{(-)}$ of piroxicam, while the C=O functionality forms a C–H…O bond with a phenyl C–H group of piroxicam. Taken together, these interactions form a two-point supramolecular synthon. The piroxicam–saccharin dimers are linked with C–H…O bridges (Figure 13).

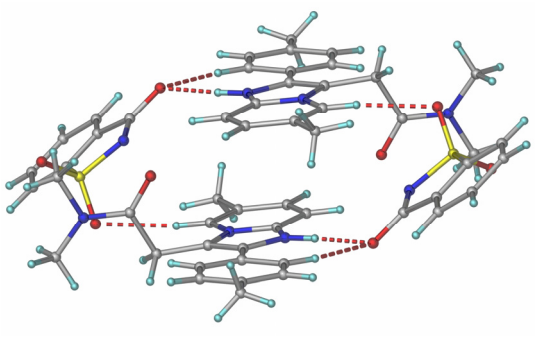


Figure 11. Zolpidem saccharinate. Note the supramolecular loop formed by two $(zolpidem)^+$ and two $(saccharin)^-$ anions. Here $(zolpidem)^+$ and $(saccharin)^-$ anions interact via $N^{(+)}$–H…O=C and C–H…O interactions.

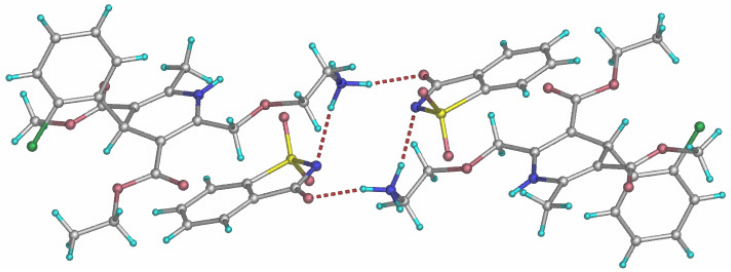


Figure 12. Amlodipine saccharinate. Note the tetramer synthon comprised of $N^{(+)}$–H… $N^{(-)}$ and $N^{(+)}$–H…O interactions.

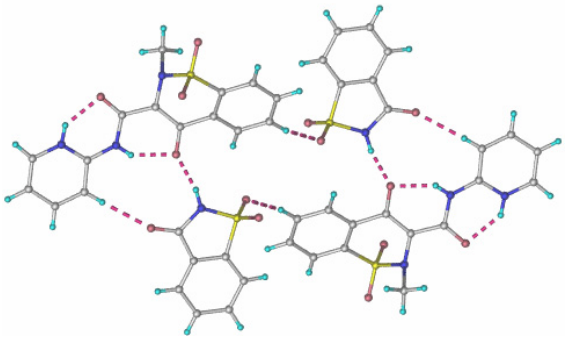


Figure 13. Piroxicam saccharin co-crystal. Saccharin and this zwitterionic API are held by $N^{(+)}$–H…O and C–H…O hydrogen bonds.

The crystal structures of these API saccharinates show that there is no distinctive preference for a particular hydrogen bond or a particular synthon between API cations and saccharinate anions. For example $N^{(-)}$ of saccharinate anion accepts hydrogen bonds from $N^{(+)}$–H, N–H and C–H groups in different structures. This is also true of the O=C and O=S acceptors. This structural variety is because of the diverse nature of the API cations. The approximate order of hydrogen bond acceptor capabilities between the different functionalities in the saccharinate anion in these API saccharinates, can be given as $N^{(-)}$ > O=C > O=S.

Table 2. Hydrogen bond metrics for the API-saccharinates in this study.

Salt	Interaction	*d*/Å (H…A)	*D*/Å (X…A)	*θ*/deg ∠X–H…A
Quinine saccharinate	N–H…N	1.86	2.849(6)	165.3
	O–H…N	1.84	2.819(5)	172.1
	C–H…O	2.31	3.374(6)	166.6
	C–H…O	2.29	3.236(6)	145.5
Haloperidol saccharinate	N–H…O	1.82	2.797(3)	160.8
	O–H…O	1.75	2.723(3)	170.9
	C–H…N	2.38	3.451(4)	171.1
Mirtazapine saccharinate	O–H…N	2.04	2.997(3)	163.4
	O–H…O	1.85	2.821(3)	171.3
	N–H…N	1.74	2.746(2)	171.4
	C–H…O	2.38	3.458(3)	172.1
Pseudoephedrine saccharinate	N–H…O	2.25	3.000(4)	130.4
	N–H…N	1.89	2.891(4)	172.7
	O–H…O	1.79	2.765(4)	170.2

	C–H…O	2.33	3.312(4)	149.9
	C–H…O	2.45	3.412(5)	147.9
Lamivudine saccharinate	N–H…O	1.85	2.838(2)	165.6
	N–H…N	1.94	2.946(2)	171.4
	N–H…O	1.64	2.644(2)	170.4
	O–H…O	1.96	2.928(2)	169.4
	C–H…O	2.26	3.207(2)	145.5
Risperidone saccharinate	O–H…O	2.18	3.037(9)	144.9
	O–H…N	1.90	2.843(8)	159.3
	N–H…O	1.79	2.793(4)	171.0
	N-H…O	1.82	2.792(4)	161.0
Sertraline saccharinate	N-H…O	2.25	3.000(4)	130.4
	N–H…O	1.89	2.891(4)	172.7
	O–H…O	1.79	2.765(4)	170.2
	C–H…O	2.33	3.312(4)	149.9
Venlafaxine saccharinate	N–H…N	1.79	2.791(1)	179.2
	O–H…O	1.75	2.750(2)	176.8
	C–H…O	2.30	3.375(8)	172.6
Zolpidem saccharinate	N–H…O	1.68	2.691(2)	176.1
	C–H…O	2.12	3.176(3)	164.1
	C–H…O	2.19	3.275(2)	172.4
Amlodipine saccharinate	N–H…N	2.02	3.018(11)	169.2
	N–H…O	1.85	2.760(12)	147.8

	N–H…O	1.84	2.793(10)	155.6
	C–H…O	2.01	2.835(18)	130.6
Piroxicam saccharinate	N–H…O	1.63	2.623(3)	165.8
	N–H…O	1.82	2.636(3)	135.8
	N–H…O	1.73	2.597(3)	141.4
	C–H…O	2.18	3.260(3)	171.5

2.3 X-ray powder diffraction

PXRD patterns of bulk samples of the API saccharinates were recorded and compared with the simulated PXRD obtained from the single crystal data of the respective API saccharinates. Least square refinement on respective experimental and simulated PXRD (Figures 14-22) affirms that in most of the cases material used for solubility determination is identical as that of single crystal. In case of risperidone saccharinate, bulk material obtained is most probably anhydrate while crystal structure obtained is that of hydrate hence experimental and simulated PXRDs are totally different.

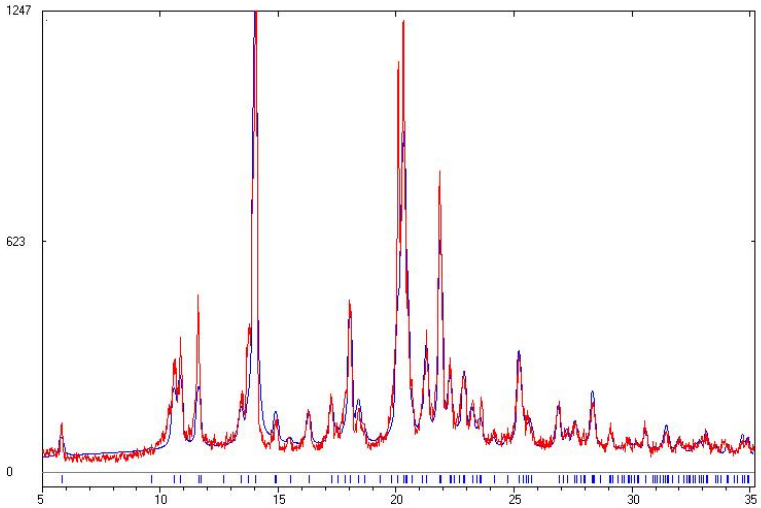


Figure 14. Comparison of simulated (blue) and experimental (red) PXRD patterns for quinine saccharinate.

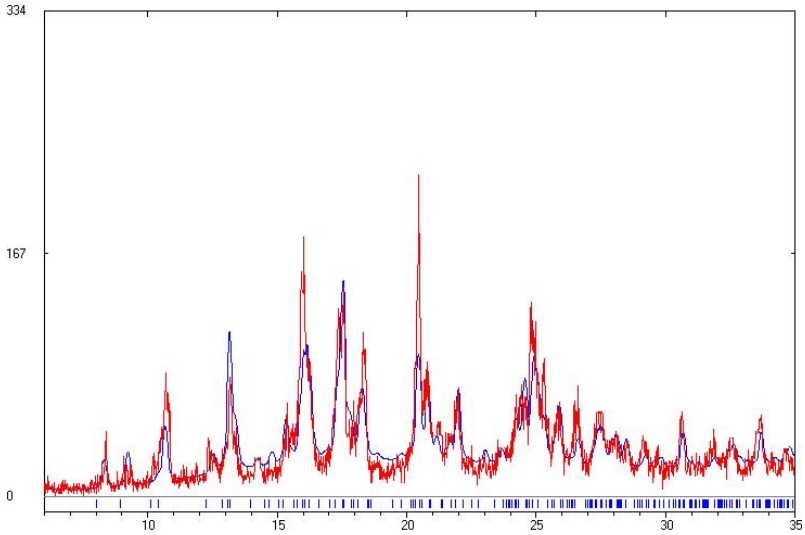


Figure 15. Comparison of simulated (blue) and experimental (red) PXRD patterns for haloperidol saccharinate.

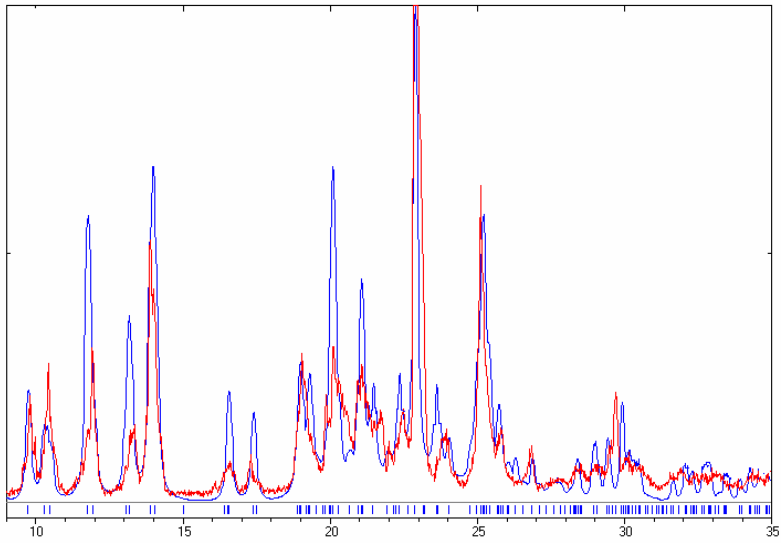


Figure 16. Comparison of simulated (blue) and experimental (red) PXRD patterns for mirtazapine saccharinate.

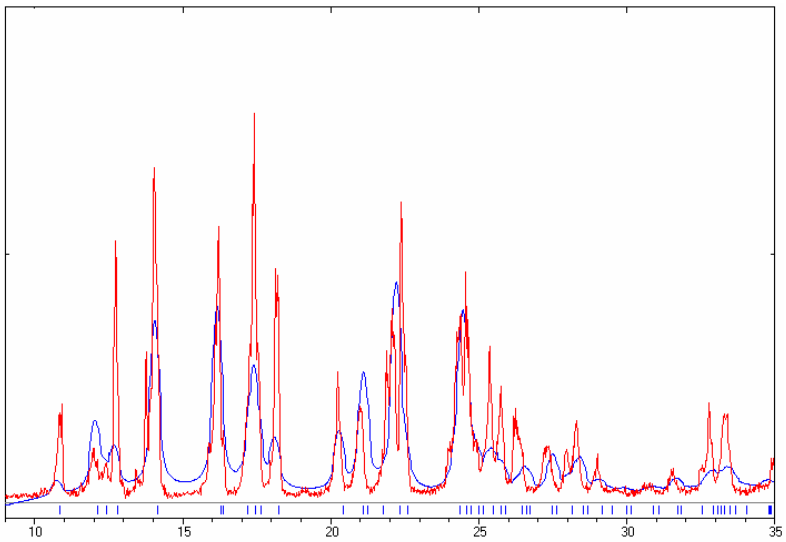


Figure 17. Comparison of simulated (blue) and experimental (red) PXRD patterns for pseudoephedrine saccharinate.

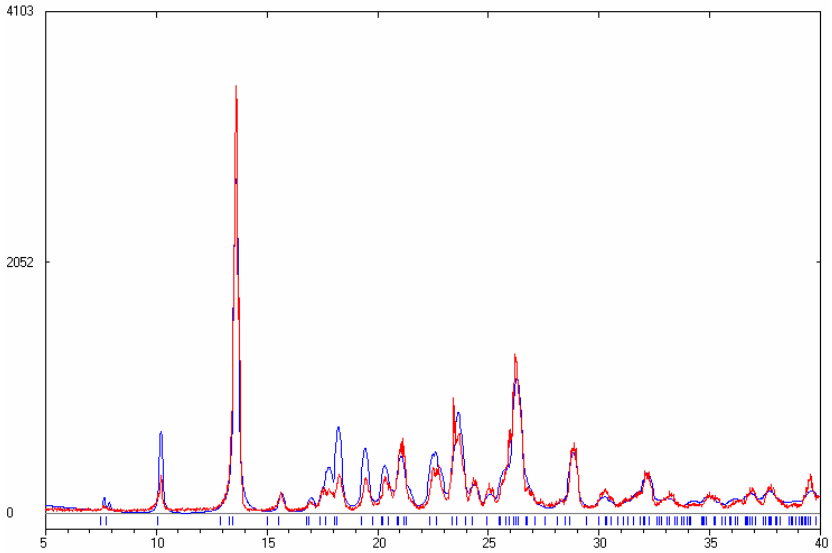


Figure 18. Comparison of simulated (blue) and experimental (red) PXRD patterns for lamivudine saccharinate.

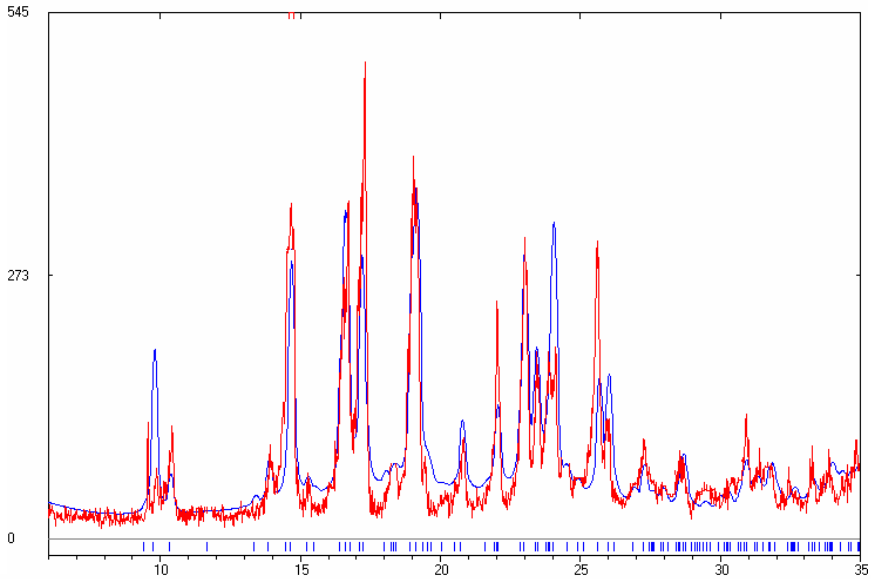


Figure 19. Comparison of simulated (blue) and experimental (red) PXRD patterns for sertraline saccharinate.

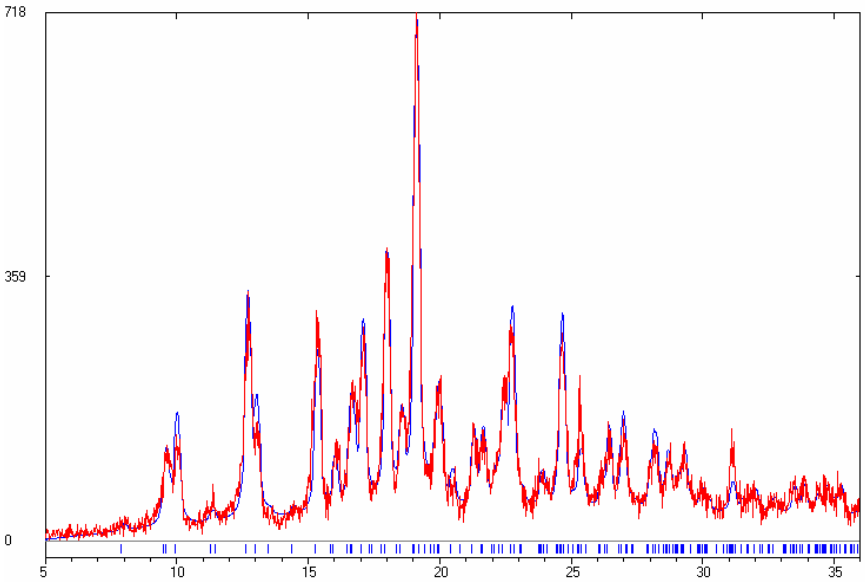


Figure 20. Comparison of simulated (blue) and experimental (red) PXRD patterns for venlafaxine saccharinate.

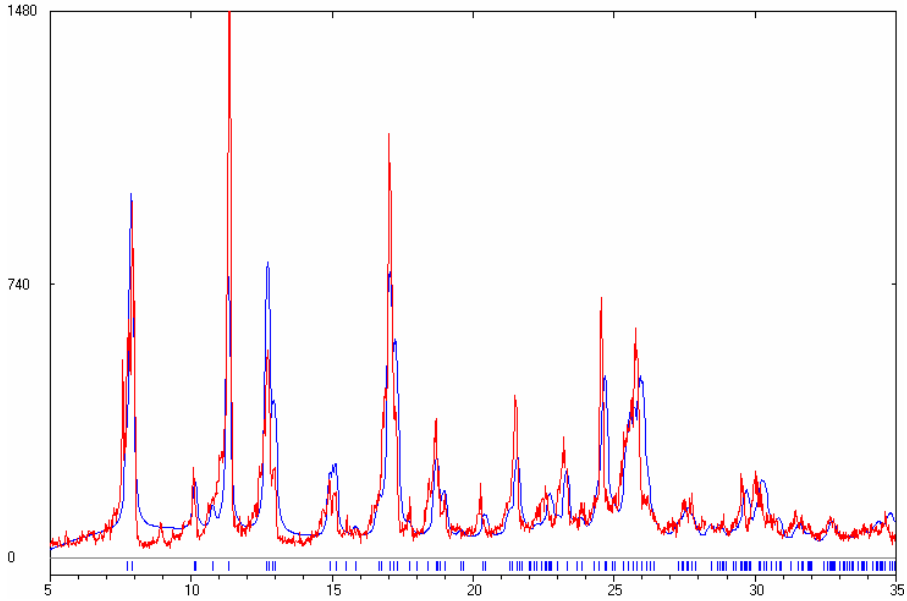


Figure 21. Comparison of simulated (blue) and experimental (red) PXRD patterns for zolpidem saccharinate.

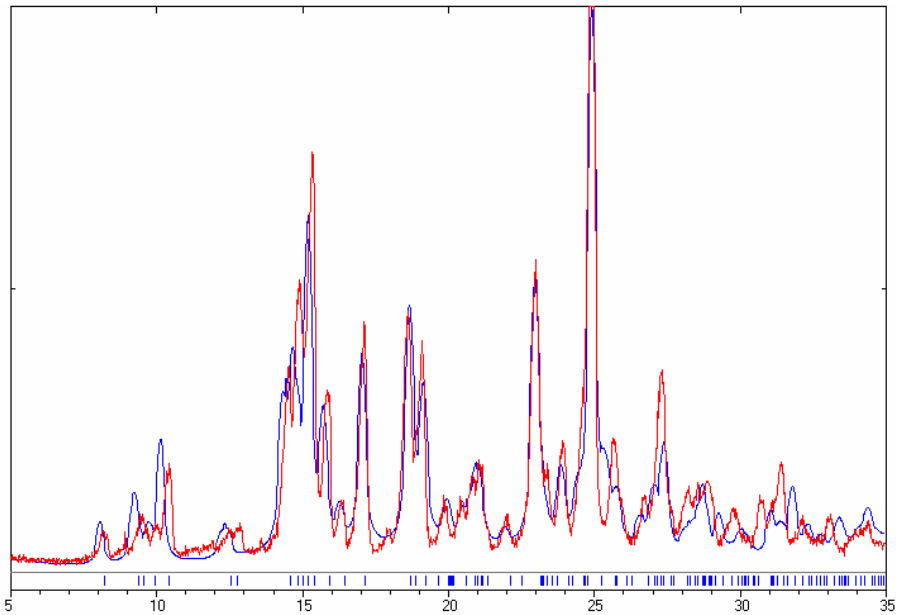


Figure 22. Comparison of simulated (blue) and experimental (red) PXRD patterns for Piroxicam- saccharin co-crystal.

2.4 Solubility and structure-solubility relationships of API saccharinates

One of the motivations in preparing saccharinates of APIs was that these salts have appreciable water solubilities, which are nearly always higher than the solubilities of the corresponding API free base (Table 1). Although saccharin itself is only moderately water soluble, the saccharinate anion has a high affinity for water. The exceptionally high water solubility of sodium saccharinate dihydrate is evidence of this affinity and it has been shown that this compound exists in equilibrium with water in a water saturated environment.[24] This behaviour is manifested in its unusual crystal structure which contains 64 Na^+ cations, 64 sac^- anions and 120 water molecules in the unit cell. Accordingly, we believe that many other saccharinates will also be water soluble to a significant degree. This follows from the molecular structure of the anion which is donor-poor and acceptor-rich in terms of hydrogen bonding functionalities.

It is difficult to correlate solubility with crystal structure. No satisfactory general correlation has yet been achieved between crystal structures and solubilities of organic solids. We attempt here to rationalize the solubility data of some of the outlier API saccharinates in our study (venlafaxine, lamivudine, piroxicam). It is emphasized that one is not trying to predict solubility on the basis of structure. Solubility is related to both enthalpic and entropic factors (hydrogen bonds, solvation). It appears that both enthalpic and entropic factors are important in determining solubilities and if one set of factors is held nearly constant, it might be possible to obtain satisfactory structure–solubility correlations. Saigo and co-workers correlated solubilities of some diastereomeric salts with their crystal structures,[25] and they got a good correlation because each pair of salts is diastereomeric.[26] They observed that the less soluble of the diastereomers is better stabilized by hydrogen bonding and close packing. In the present case, it is not possible to give this kind of explanation because of the comparatively large differences between the molecular structures, but some reasons may be suggested.

For appreciable water solubility, the hydrogen bonds formed by the hydrated ions (in solution) should be better than the hydrogen bonds in the crystal and/or the entropy of solvation of the ions must be favourable. Chloride ions are small in size and hence they are strongly hydrated, leading to higher solubility. Venlafaxine hydrochloride

exists as three polymorphs (I, II and VI) [27] and both form I and II have a higher solubility [28] than the saccharinate. The hydrogen bond energies of the hydrochloride polymorphs are I, 22 kcal/mole and II, 19 kcal/mole. The values are less than the value for the saccharinate (28 kcal/mole). Similarly, the packing coefficients of polymorphs I and II (0.66, 0.67) are less than that for the saccharinate (0.69). In form I of the hydrochloride, there are 1-D zigzag chains of $N^{(+)}$–H…$Cl^{(-)}$ and O-H…$Cl^{(-)}$ hydrogen bonds. The structure is held by hydrogen bonds only in one direction. However, the hydrogen bond network in the saccharinate is two dimensional with $N^{(+)}$–H… $N^{(-)}$, O–H… O and C–H…O=C hydrogen bonds. Possibly the lower solubility of the saccharinate is an account of its more extensive hydrogen bond arrangement.

The crystal structure of lamivudine saccharinate is saturated in terms of hydrogen bonding and there is no free hydrogen bond donor or acceptor site with which water may interact. More importantly, synthon $N^{(+)}$–H…O/N–H… $N^{(-)}$ is very stable and may remain intact in aqueous solution. Therefore lamivudine saccharinate may not be able to interact with water as strongly as lamivudine free base, leading to a decrease in solubility. Although the hydrogen bond energy of lamivudine (58 kcal/mol) is comparable to that of lamivudine saccharinate (56 kcal/mol), the packing coefficient of the saccharinate salt (0.74) is higher than that of the API itself (0.69) also accounting for its lower solubility.

The piroxicam saccharin co-crystal is notable. Piroxicam itself is poorly soluble in water and its saccharin adduct also has poor water solubility. The co-crystal contains zwitterionic piroxicam and neutral saccharin. There is no modification at the molecular level on co-crystal formation and no significant enhancement in water solubility is observed. This example suggests the advantages of saccharinate (salt) formation over co-crystal formation in the context of modifying solubilities.

2.5 Solubilities of salts and co-crystals

As mentioned earlier, when an acidic and basic substance are taken together in solution and crystallized from an appropriate solvent, the outcome is salt formation, co-crystal formation or the compounds crystallize out separately. The formation of a salt is

more or less assured if the pK_a difference between the acid (saccharin) and the conjugate base (of the API) is more than 3.0, and it is a very general phenomenon. Formation of a co-crystal is a more unpredictable event. In the present study, 11 APIs were treated with saccharin. Ten of the APIs form salts, while one (piroxicam) forms a co-crystal. Of the ten salts, eight have solubilities that are appreciably higher than the free base (whether they are anhydrates, hydrated or mixtures of these). Of the two remaining salts, one of them (lamivudine saccharinate) has a lower solubility while the other (amlodipine saccharinate) was so hygroscopic that we were unable to determine its solubility. So, in general, the device of saccharinate salt formation will increase the solubility of an API.

In the connection of co-crystal solubility Almarsson and Zaworotko have stated that "while equilibrium solubility of drug compounds in co-crystals may be less affected than in the context of salt forms, the kinetic aspects of solubilization provide the key to many successful formulation strategies".[11] We take the first portion of this sentence to mean that changes in solubility upon salt formation (increase or decrease) are usually higher than in co-crystal formation. As for the second portion of the sentence, it is true that bioavailability and solubility are not always connected. However, we feel that these "kinetic aspects" will need to be assessed on a case by case basis and that increased solubility still means increased bioavailability in many cases. What is invariably true is that: (1) saccharin is a very good salt former; (2) salt formation always changes the solubility of an API; (3) most API saccharinates have higher solubilities than the parent APIs.

As for the solubilities of co-crystals, we feel that the solubility of a co-crystal will be similar to the individual solubilities of its constituents.[29] Co-crystals are hydrogen bonded assemblies between two molecular entities: they will come apart while interacting with water/solvent and the solubility of the system will then be a function of the individual entities. We found that the solubility of the piroxicam–saccharin co-crystal is as low as that of piroxicam.

2.6 Other advantages of API saccharinates

These salts do not need to always have a high solubility to be useful. In one example we have described (venlafaxine saccharinate) the lower solubility of the salt (relative to the hydrochloride) is of significance. API saccharinates have many other advantages in that saccharin is a GRAS (generally recognized as safe) compound, and also in that the pH of the saccharinate solutions are higher (pH 5-6) than the corresponding hydrochlorides and other salt formulations (pH 2-3); this may make them more suitable for injections and drops. Unlike API salts of mineral acids, API saccharinates may be prepared by grinding. This does not require solvents and is important from the viewpoint of process development and green chemistry. As saccharin is a potent sweetener, it may mask the bitter taste of a drug and improve patient compliance. A good example in this regard is vincamine saccharinate.[4] Vincamine is an alkaloid, which has been used for the treatment of cerebral circulatory and neurological disorders. The free base is insoluble in water and other pharmaceutically acceptable solvents and has been primarily administered orally in solid dosage forms. In this regard, a further significant problem has been that even the few salts or complexes of vincamine which have been found to be relatively soluble in pharmaceutically acceptable solvents (vincamine citrate or tartrate in glycerol–ethanol mixtures), and which would therefore provide an adequate concentration of the drug in solution, have an extremely bitter and unpleasant taste which has been impossible to mask by the addition of flavoring agents. The failure to find a form of vincamine that has both the desired solubility and acceptable taste characteristics has precluded the development of medicinally acceptable liquid pharmaceutical compositions for oral administration. It was suggested that vincamine saccharinate has favourable solubility and taste to be used in a drop formulation.[4]

2.7 Conclusion

This study shows the generality of saccharinate formation with different basic APIs used in the treatment of a variety of diseases, and also shows change in solubility and pH increase via saccharinate formation. If increased solubility of an API formulation

is the desired aim, salt formation with saccharin may be a preferred strategy. However, our findings do not necessarily negate the investigation of co-crystals of APIs (which might be relatively insoluble) for drug delivery, as they could, in principle, have other desirable properties e.g. sustained release features, dissolution profiles. Such properties are very difficult to predict, and each case would of course have to be investigated individually. In the light of recent literature on the generation and potential of co-crystals of APIs,[11] saccharinate formation with the accompanying merits of enhanced solubility and concomitantly favourable solution pH values provides a very sound balance, putting the general strategy of supramolecular modification of APIs in perspective.

Chemically and legally, the saccharinates of the type that we report are fundamentally different from the co-crystals described earlier.[30] Most significantly a co-crystal as defined in these applications consists of two components each of which is capable of a unique existence. API saccharinates consist of cations and anions, which are not capable of unique existence. In the co-crystals, the constituents are held by hydrogen bonds in multipoint assemblies and all the molecules are neutral (except where a co-crystal former is crystallized with a salt). Hydrogen bonding is also important in our saccharinates but there is no necessity that an $N^{(+)}$–H…$N^{(-)}$ hydrogen bond is formed. Our salts contain $N^{(+)}$–H…O and O–H…$N^{(-)}$ hydrogen bonds and proton transfer has occurred in solution prior to crystallization.

2.8 Experimental section

Sample preparation and crystallisation

The APIs were obtained as complimentary samples from local pharmaceutical companies. Saccharin was purchased from Loba chemicals and recrystallized from acetone prior to use. Saccharinate salts of APIs were prepared by taking the appropriate quantities of the API and saccharin and cocrystallising from 1:1 $CHCl_3$-MeOH.

IR spectroscopy

All infrared spectroscopic experiments were performed on a Jasco 5300 IR spectrometer. A good indication for API saccharinate formation is obtained from the

bathochromic shift in the C=O stretching frequency (1720 cm^{-1} in saccharin to around 1690 cm^{-1} in the salts). We note that for the piroxicam saccharin co-crystal, the band at 1720 cm^{-1} was shifted hypsochromically to 1734 cm^{-1} indicating that salt formation had not taken place. Subsequent X-ray analysis showed that this API is an outlier forming a co-crystal with saccharin rather than a salt.

X-ray crystallography

X-ray diffraction intensities for the API saccharinates were collected at 100K (Bruker Cryosystems cooler) on a Bruker SMART 4K CCD diffractometer (Bruker Systems Inc.) using Mo K_α X-radiation.[31] The crystal data of sertraline saccharinate was collected additionally at room temperature (see discussion for the reason for so doing). Data were processed using the Bruker *SAINT* package[32] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[33] The structures of all the compounds were solved by direct methods and refined by full-matrix least-squares on F^2. H-atoms were located from the difference Fourier map in all 11 structures and refined freely with isotropic displacement parameters. Crystal data and details of data collections, structure solutions and refinements are summarized in appendix.

X-ray Powder Diffraction

Powder X-ray diffraction (PXRD) were recorded on a Pnalytical 1830 (Philips Systems Inc) diffractometer using Cu K_α X-radiation at 35 kV and 25 mA. Diffraction patterns were collected over a range of 5-40º 2θ at a scan rate of 1º 2θ min^{-1}. The software Powder Cell 2.3 was used for least square refinement.[34]

Solubility Determination

The shake-flask method was used to determine the equilibrium solubility.[35] An excess of sample was taken in double-distilled water and the resulting suspension was shaken for 24 h at room temperature. The aim was to form a saturated solution, as indicated by the observation of surplus undissolved material. After equilibration, the sample was filtered and the concentration of the compound in the filtrate was quantified

using UV spectroscopy on a Shimadzu UV-VS spectrophotometer after appropriate (1000-2000 fold) dilution. Thus, the thermodynamic solubility was determined rather than a kinetic solubility. The risk of obtaining a supersaturated solution is low in this method and, in addition, the solubility of the stable form of the substance examined has been determined. Since there is a possibility of saccharin absorbing at the λ_{max} of the API thus interfering with the determination of the API concentration, the absorbance values for all API saccharinates were related to the solution concentrations using a calibration curve.

pH Determination

The pH determination was carried out using a Digisum^{7007} digital pH meter. The saturated solution obtained in the above shake-flask method was filtered and used without any further processing.

2.9 References and notes

1. (a) J. F. Remenar, J. M. MacPhee, B. K. Larson, V. A. Tyagi, J. H. Ho, D. A. McIlroy, M. B. Hickey, P. B. Shaw and Ö. Almarsson, *Org. Proc. Res. Dev.*, **2003**, *7*, 990. (b) R. J. Bastin, M. J. Bowker and B. J. Slater, *Org. Proc. Res. Dev.*, **2000**, *4*, 427.
2. (a) C. H. Gu and D. J. W. Grant in *Handbook of Experimental Pharmacology: Stereochemical Aspects of Drug Action and Disposition* Eds.; M. Eichelbaum, B. Testa and A. Somogyi, Springer, Berlin, **2003**. (b) M. Puddipeddi, A. T. M. Serajuddin, D. J. W. Grant and P. H. Stahl in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* Eds.; P. H. Stahl and C. G. Wermuth, Wiley, Weinheim, **2002**, pp 19–38. (c) S. H. Neau in *Water-Insoluble Drug Formations* Ed.; R. Liu, Interpharm, Buffalo Grove, **2000**, pp 405–425. (d) A. V. Trask, D. A. Haynes, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2006**, 51. (e) D. A. Haynes, W. Jones and W. D. S. Motherwell, *CrystEngComm*, **2005**, *7*, 538. (f) S. L. Morissette, Ö. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A.V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, *Adv. Drug*

Deliv. *Rev*., **2004**, *56*, 275. (g) E. C. Ware and D. R. Lu, *Pharm*. *Res*., **2004**, *21*, 177. (h) S. M. Berge, L. D. Bighley and D. C. Monkhouse, *J*. *Pharm*. *Sci*., **1977**, *66*, 1.

3. Poor solubility of the parent API (free acid or free base) is a long-standing problem. More than 40% of newly discovered drugs have little or no water solubility (less than 0.1 mg/mL).
4. K. Räder and P. Stoss, US. Publication number, US 4362730, (07/12/1982).
5. J. W. Rayburn, Int. Publication number, WO 00/12067, (09/03/2000).
6. Even when increased solubility increases bioavailability it may not lead to a desired situation. For example see C. H. Schwalbe, *Cryst*. *Rev*., **2005**, *11*, 49.
7. The use of saccharin as a sweetener of food stuffs is very extensive and a review of this aspect is beyond the scope of the present work.
8. Selected recent references on co-crystals include. (a) A. V. Trask and W. Jones in *Top*. *Curr*. *Chem*. Springer-Verlag Berlin Heidelberg, **2005,** pp 41–70. (b) X. Gao, T. Friščić and L. R. MacGillivray, *Angew*. *Chem*. *Int*. *Ed*., **2004**, *43*, 232. (c) B. Q. Ma and P. Coppens, *Cryst*. *Growth Des*., **2004**, *4*, 211. (d) B. Olenik, T. Smolka, R. Boese and R. Sustmann, *Cryst*. *Growth Des*., **2003**, *3*, 183. (e) C. B. Aakeröy, A. M. Beatty, B. A. Helfrich and M. Nieuwenhuyzen, *Cryst*. *Growth Des*., **2003**, *3*, 159. (f) B. R. Bhogala and A. Nangia, *Cryst. Growth Des*., **2003**, *3*, 547. (g) L. S. Reddy, A. Nangia and V. M. Lynch, *Cryst*. *Growth Des*., **2004**, *4*, 89. (h) P. Vishweshwar, J. A. McMahon, M. L. Peterson, M. B. Hickey, T. R. Shattocka and M. J. Zaworotko, *Chem*. *Commun*., **2005**, 4601. (i) W. W. Porter III, S. C. Elie and A. J. Matzger, *Cryst*. *Growth Des*., **2008**, *8*, 14. (j) F. Lara-Ochoa and G. Espinosa-Perez, *Cryst*. *Growth Des*., **2007**, *7*, 1213. (k) S. L. Childs and K. I. Hardcastle, *Cryst*. *Growth Des*., **2007**, *7*, 1291. (l) G. P. Stahly, *Cryst*. *Growth Des*., **2007**, *7*, 1007. (m) M. L. Cheney, G. J. McManus, J. A. Perman, Z. Wang and M. J. Zaworotko, *Cryst*. *Growth Des*., **2007**, *7*, 616. (n) J. A. Bis, O. L. McLaughlin, P. Vishweshwar and M. J. Zaworotko, *Cryst*. *Growth Des*., **2006**, *6*, 2648. (o) M. Dabros, P. R. Emery and V. R. Thalladi, *Angew*. *Chem*. *Int*. *Ed*., **2007**, *46*, 4132.

9. Even three components have been assembled together in a co-crystal but this is a very delicate exercise. See (a) B. R. Bhogala, S. Basavoju and A. Nangia, *Cryst. Growth Des*., **2005**, *5*, 1683. (b) C. B. Aakeröy, J. Desper and J. F. Urbina, *Chem. Commun*., **2005**, 2820. (c) C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem., Int. Ed*., **2001**, *40*, 3240.
10. S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des*., **2003**, *3*, 909.
11. Ö. Almarsson and M. J. Zaworotko, *Chem. Commun*., **2004**, 1889.
12. P. Seeman, T. Lee, M. Chau-Wong and K. Wong, *Nature*, **1976**, *261*, 717.
13. I. Kanfer, R. Dowse and V. Vusumuzi, *Pharmacotherapy*, **1993**, *13*, 116S.
14. (a) R. van Leeuwen, C. Katlama and V. Kitchen, *J. Infect. Dis*., **1995**, *171*, 1166. (b) G. J. Yuen, D. M. Morris and P. K. Mydlow, *J. Clin. Pharmacol*., **1995**, *35*, 1174.
15. (a) S. Grant and A. Fitton, *Drugs*, **1994**, *48*, 253. (b) L. Cohen, *J. Pharmacotherapy*, **1994**, *14*, 253.
16. O. M. Peeters, N. M. Blaton and C. J. Ranter, *Acta Crystallogr*., *Sect. C*, **1993**, *49*, 1698.
17. (a) D. Murdoch and D. McTavish, *Drugs*, **1992**, *44*, 604. (b) B. K. Koe, A. Weissman and W. M. Welch, *J. Pharmacol. Exp. Ther*., **1983**, *226*, 686.
18. (a) G. E. Clerc, P. Ruimy and J. Verdeau-Pailles, *Int. Clin. Psychopharmacol*., **1994**, *9*, 139.
19. M. J. M. Oosterbaan and R. Keltjens, Int. Publication number, US 20030190353 A1, (09/10/2003).
20. (a) H. D. Langtry and P. Benfield, *Drugs*, **1990**, *40*, 291. (b) J. D. Hoehns and P. Perry, *J. Clin. Pharm*., **1993**, *12*, 881.
21. (a) R. A. Burges, *J. Hum. Hypertens*., **1991**, *5*, 49. (b) D. Murdoch and R. C. Heel, *Drugs*, **1991**, *41*, 478.
22. A. R. Sheth, S. Bates, F. X. Muller and D. J. W. Grant, *Cryst. Growth Des*., **2004**, *4*, 1091.
23. V. V. Boldyrev, *J. Mat. Sci*., **2004**, *39*, 5117.

24. R. Banerjee, P. M. Bhatt, M. T. Kirchner and G. R. Desiraju, *Angew. Chem., Int. Ed.*, **2005**, *44*, 2515.
25. K. Kinbara and K. Saigo, in *Topics in Stereochemistry*, Ed.; S. E. Denmark, Wiley, New York, **2003**, pp 207-265.
26. In this case, the solvation energy for both salts in the pair should be the same or very similar. Therefore solubility differences can be directly correlated with differences in crystal packing.
27. (a) A. Sivalakshmidevi, K. Vyas, S. M. Rao and G. O. Reddy, *Acta Crystallogr., Sect. E*, **2002**, *58*, 1072. (b) D. Vega, D. Fernandez and G. Echeverria, *Acta Crystallogr., Sect. E*, **2000**, *56*, 1009. (c) S. Roy, P. M. Bhatt, A. Nangia and G. J. Kruger, *Cryst. Growth & Design*, **2007**, *7*, 476.
28. S. M. Rao, K. Vyas, A. Sivalakshmidevi and G. O. Reddy, Intl Pat. Appl. No. WO02/46140 A1, (13-6-2002).
29. We determined the solubilities of carbamazepine (calculated pK_a=13.94) and carbamazepine : saccharin 1:1 co-crystal and found both of them to be practically insoluble in water.
30. (a) M. J. Zaworotko, B. Moulton and N. Rodriguez-Hornedo, Int. Publication number, WO 03/074474 A2, (12/09/2003). (b) Ö. Almarsson and M. J. Zaworotko, Int. Publication number, WO. 2004/078161 A1, (16/09/2004). (c) S. L. Childs, Int. Publication number, WO 2004/064762 A2, (05/08/2004).
31. *SMART, Version 5.05*; Bruker AXS, Inc.: Madison, Wisconsin, **1998**.
32. *SAINT, Version 6.2*, Bruker AXS, Inc.: Madison, Wisconsin, **2001**.
33. G. M. Sheldrick, *SHELXTL V5.1*; Madison, WI, **1998**.
34. N. Kraus and G. Nolze, *POWDER CELL,* version 2.3; Federal Institute for Materials Research and Testing: Berlin, Germany, 2000.
35. A. Glomme, J. Marz and J. B. Dressman, *J. Pharm. Sci.*, **2005,** *94*, 1.

CHAPTER THREE

STUDY AND CHARACTERISATION OF CRYSTALLINE DESLORATADINE, ITS HYDROCHLORIDE AND STABLE AMORPHOUS SACCHARINATE SALT

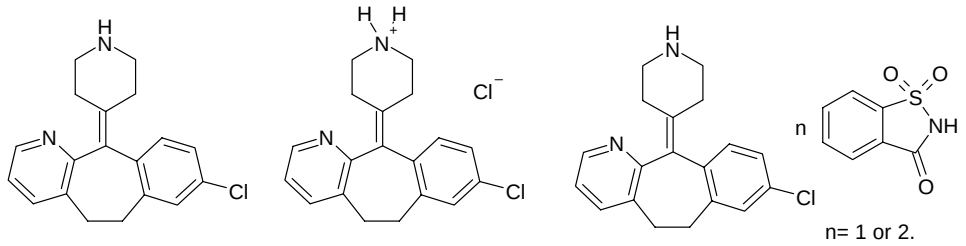
3.1 Introduction

As seen in the earlier chapters, the solid-state chemistry of active pharmaceutical ingredients (APIs) is of tremendous current interest, both from fundamental and applied viewpoints. Constant efforts are devoted to find new forms of APIs with better properties, leading in turn to superior formulations and improved medications.[1] Desloratadine is an antihistamine used to treat allergies. It is sold under brand names such as Clarinex and Aerius. It is an active metabolite of loratadine, which is also on the market. Desloratadine is a tricyclic antihistamine, and it has a selective and peripheral H_1-antagonist action. It has a long-lasting effect and does not cause drowsiness because it does not readily enter the central nervous system. Desloratadine is 10-20 times more potent as an antihistamine than loratadine and it is available as tablets and oral suspension.

Reported salts of desloratadine include the acetate, hemifumarate, hemisulfate and hydrochloride.[2] Most of these reported salts (and desloratadine itself) are crystalline in nature.[2,3] However the literature suggests that amorphous modifications of desloratadine may increase its prospects and effectiveness as a medicine. A recent patent application describes methods to prepare amorphous desloratadine.[4] However, this patent employs special procedures for obtaining the amorphous form and it does not mention anything about the stability of the amorphous form and how easily it converts to any of the crystalline forms.

Amorphous form of an API is a subject of high interest in the pharmaceutical industry,[5-18] especially from the viewpoint of drug delivery. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability.[5,10,11,13] However, it can also create the possibility that during processing or storage, the amorphous state may spontaneously

convert back to the crystalline state. Indeed, this is the case most of the time. This is one of the main reasons why many drugs are not sold as amorphous forms despite their favourable properties for drug delivery. The stabilization of the API is the key issue. Generally, the problem of crystallisation has been overcome by the addition of some polymers as stabilizer. In recent years some APIs have been marketed as amorphous forms. These include Accolate (zafirlukast), Ceftin (cefuroxime axetil), Accupril (quinapril hydrochloride), and Rezulin (troglitazone).



I **II** **III and IV**

Scheme 1. Desloratadine (**I**), desloratadine hydrochloride (**II**) and desloratadine saccharinate (**III, IV**).

During our study on desloratadine and API saccharinates,[19,20] we prepared crystals of desloratadine and desloratadine hydrochloride. However we could not prepare crystals of desloratadine saccharinate (des sac) and we found that it was amorphous. We tried a series of exhaustive crystallisation experiments in different solvents and different conditions to get the crystalline form of des sac to extend our ongoing study of API saccharinates. However, the results were frustrating, and we never got any crystalline product. Accordingly, we felt that the amorphous form of des sac is very stable and that its amorphous character could be utilized for useful applications. In present chapter, amorphous des sac is discussed along with the crystalline modifications of desloratadine namely desloratadine and desloratadine hydrochloride

.

3.2 Crystalline modifications of desloratadine

Crystal structures of desloratadine and desloratadine hydrochloride were determined and the hydrogen bonding and packing were studied in detail.

3.2.1 Crystal structure of desloratadine (I)

It crystallises in the non-centrosymmetric space group $P2_1$ with one molecule of desloratadine in the asymmetric unit. Value of the Flack parameter (0.04(5)) suggests that absolute structure assignment is correct. The molecular geometry and atom numbering are given in Figure 1. The only hydrogen bond present in the structure is a C–H...N interaction between the phenyl hydrogen (H11) and the pyridine nitrogen (N1). This interaction gives rise to an infinite zigzag chain with piperidine rings alternating and pointing outwards on either side of the chain. Two such adjacent chains pack by placing the piperidine fragments in the space between two fragments of the adjacent chain and vice-versa as shown in Figure 2. This is basically a close-packed arrangement.

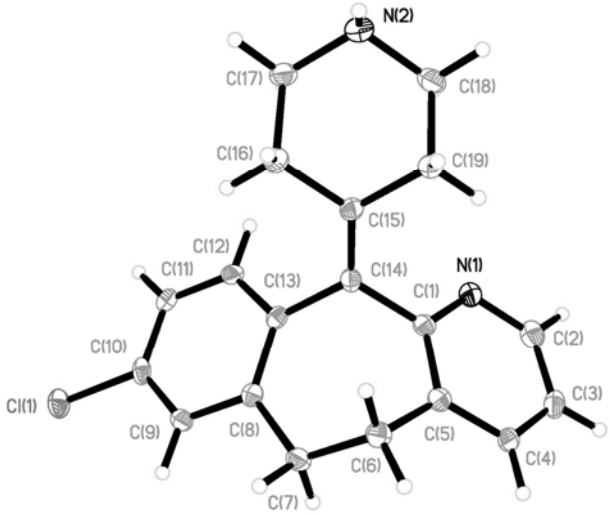


Figure 1. ORTEP diagram of desloratadine with atom numbering.

The most interesting feature of the crystal structure is that the piperidine N–H group is not hydrogen bonded in a conventional sense (N–H...N) although there are two N-atom acceptors in the molecule. A CSD search was carried out for entries which contain only N–H as a hydrogen bond donor and where this N–H is not hydrogen bonded to any acceptor. The constraints used in this search were as follows: $R < 0.05$, no errors, not polymeric, no ions, only organics. 543 hits were obtained. However, analysis showed that in almost all these cases, the N–H group is sterically hindered. It is therefore

surprising that in the case of desloratadine, which has a sterically unhindered N–H group, no hydrogen bonds are formed. The reason for this may lie in the awkward shape of the molecule. This reasoning was supported with a computational study with the Polymorph Predictor software.[21] The polymorph prediction was carried out with the DREIDING2.21 force-field in five space groups $P2_1$, $C2/c$, $P\text{-}1$, $P2_1/c$ and $P2_12_12_1$. Except in $C2/c$, the most stable structure predicted was very similar to the experimental structure in that no N–H...N hydrogen bond is present. Crystal structure prediction in the experimental space group ($P2_1$) gave the stablest structure which was identical to the experimental structure. This is a good validation of the force field.

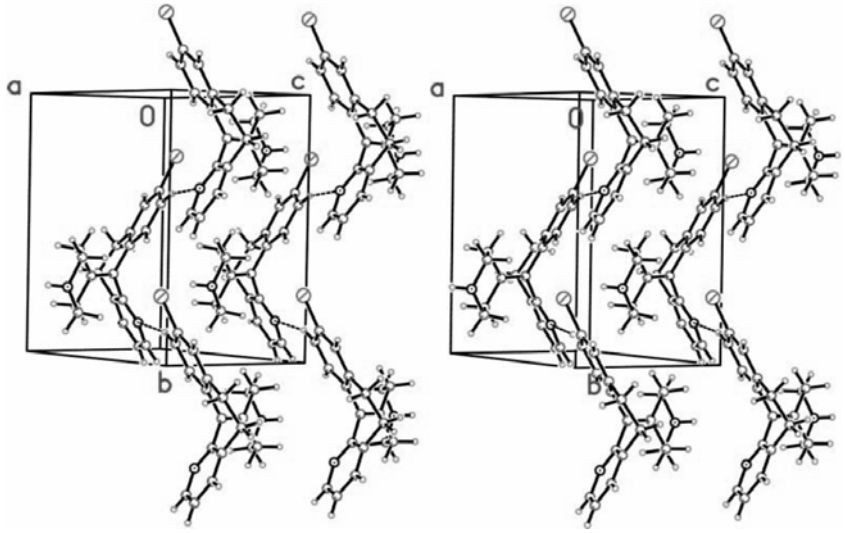


Figure 2. A stereoview of the packing arrangement of desloratadine, showing two close-packed zigzag chain of desloratadine molecules.

Desiraju[22] has discussed a similar issue in his article entitled "Bond free" with respect to the literature example of the oxalic acid–phthalocyanine complex[23] and also alloxan.[24] He concluded that crystal structures are determined by an interplay of both space filling and hydrogen bonding such that the free energy is a minimum and that the very occasional appearance of a crystal structure where sterically unhindered X–H groups do not form strong X–H...A interactions is a statistical issue, brought about by the fact that a very large number of crystal structures of small organic molecules are being determined today.

So far two polymorphs of desloratadine have been reported in a patent application[25] but no crystal structure data is available. A comparison of the powder X-ray spectrum given in the patent and that simulated from the single crystal data of the present study showed that the single crystal obtained by us corresponds to form 1 of desloratadine. We feel it is possible to experimentally realise the hydrogen bonded structure obtained computationally in the *C*2/*c* space group because it is only 2 kcal/mol/molecule less stable than the experimental $P2_1$ structure reported here.

3.2.2 Crystal structure of desloratadine hydrochloride (II)

It crystallises in centrosymmetric space group $P\bar{1}$ with one $(\text{desloratadine})^+$ cation and one chloride anion in the asymmetric unit. The molecular geometry and atom numbering are given in Figure 3. The $-NH_2^+$ group of $(\text{desloratadine})^+$ and Cl^- give rise to 1-D infinite chain via $N^{(+)}$–H…$Cl^{(-)}$ hydrogen bonds as shown in Figure 4. This chain is further stabilised by weak C–H...N hydrogen bonds between adjacent $(\text{desloratadine})^+$ cations (Table 1). These chains then close pack to give rise to the 3D structure as shown in Figure 5.

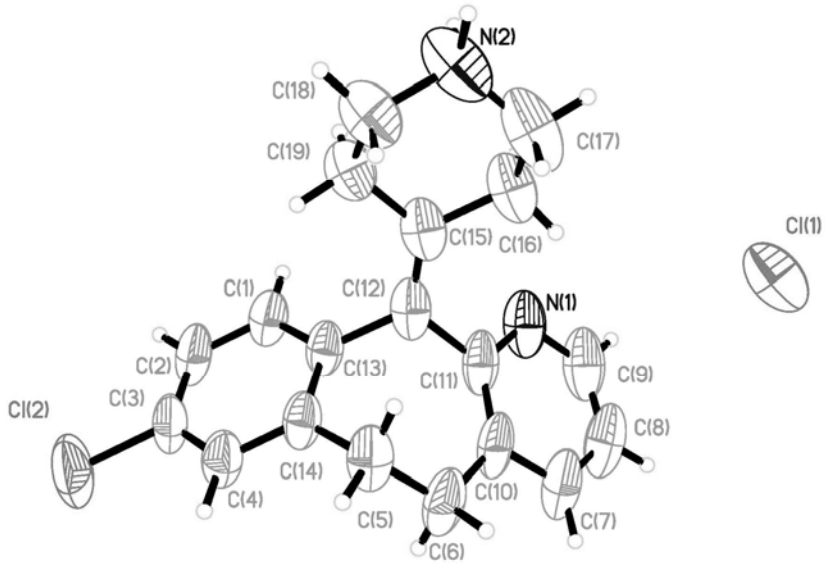


Figure 3. ORTEP diagram of desloratadine hydrochloride with atom numbering.

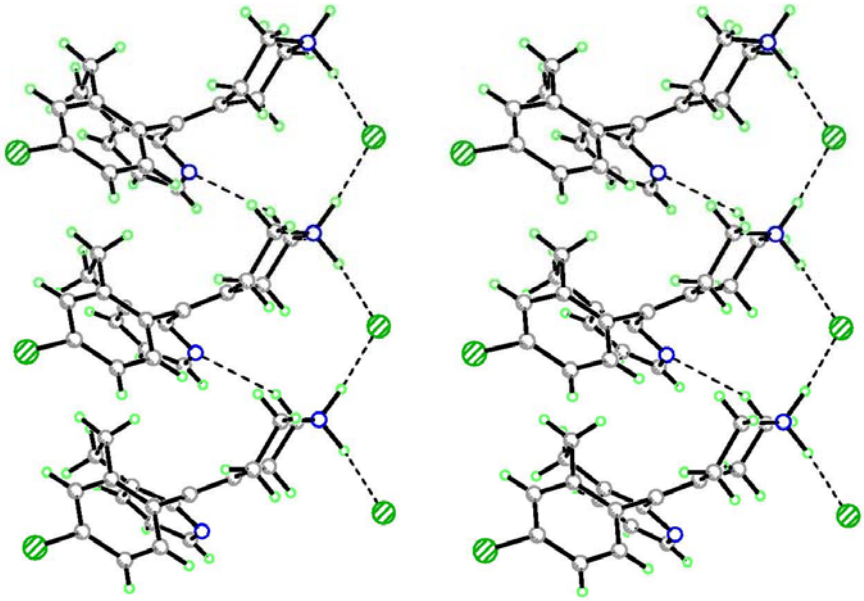


Figure 4. A stereoview of the 1D infinite chain of desloratadine hydrochloride.

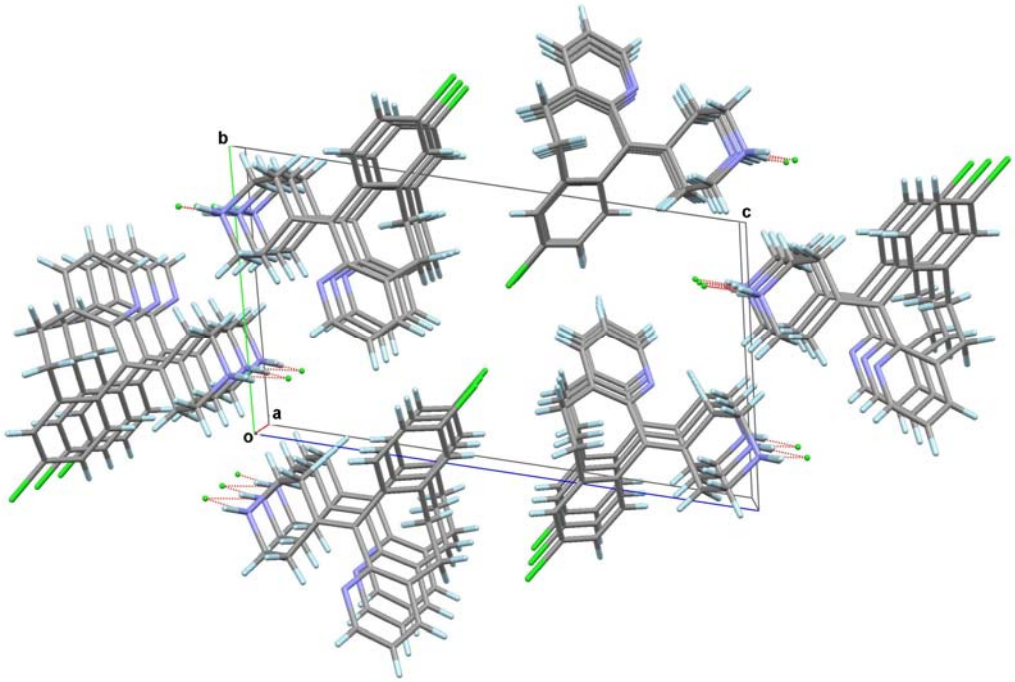


Figure 5. Packing of 1D infinite chains of desloratadine hydrochloride.

Table 1. Hydrogen Bond Metrics for the desloratadine and desloratadine hydrochloride.

Compound	Interaction	*d* (Å)	*D* (Å)	*θ* (˚)
Desloratadine	C–H…N	2.36	3.359(3)	153
Desloratadine hydrochloride	$N^{(+)}$–H…$Cl^{(-)}$	2.09	3.093(4)	173
	$N^{(+)}$–H…$Cl^{(-)}$	2.12	3.118(4)	168
	C–H…N	2.50	3.503(6)	154
	C–H…N	2.72	3.614(4)	140

[a] N–H and C–H distances are neutron normalized to 1.01, 1.08 Å.

3.3 Desloratadine saccharinate-A stable amorphous material

Des sac (**III**) is always obtained in an amorphous form; it can be prepared by a simple method such as solvent drop grinding.[26-28] To confirm that des sac does not crystallize, at least under normal conditions, we carried out around 30 different crystallisation experiments involving different solvents and different crystallisation techniques such as slow evaporation, solvent drop grinding, sintering and hydrothermal crystallization. Samples were analysed by PXRD and none of the samples showed any trace of crystalline material. These experiments indicate that des sac is stable in the amorphous state and that it does not revert easily to a crystalline form. There are not many such examples of small organic molecules which exist in stable amorphous forms that do not convert easily to crystalline material.[29,30] We also prepared amorphous {des sac + saccharin} (1:1) (**IV**) by the same method we used for des sac by adding an extra equivalent of saccharin, triturating etc. The IR spectrum indicates that in **IV** the second saccharin molecule remains unionized. We have also prepared amorphous materials having varying ratios of des sac and saccharin. These materials have desloratadine sacharinate and saccharin in (80:20) (**Va**), (70:30) (**Vb**) and (60:40) (**Vc**) ratios respectively (Figures. 10, 11 and 12). All these materials are amorphous. These experiments demonstrate that we can obtain a continuum of amorphous material with the ratio of des sac and saccharin varying from around (50:50) to (100:0).

3.3.1 X-ray powder diffraction

X-ray powder diffraction is important tool for identification and characterisation for crystalline and amorphous materials. PXRD pattern of crystalline material contains many peaks with varying intensity which is characteristic of particular crystalline material, while in PXRD patterns of amorphous materials such peaks are absent and only broad humps are observed. Powder XRD patterns of des sac (**III**) and **(IV**) show no peaks in the given *2θ* range but a broad hump was observed (Figures 8 and 9) which is typical for an amorphous phase. This may be compared with PXRD patterns of crystalline desloratadine and saccharin in Figures 6 and 7 respectively. Similar broad humps were obtained in PXRDs of **Va**, **Vb** and **Vc** also.

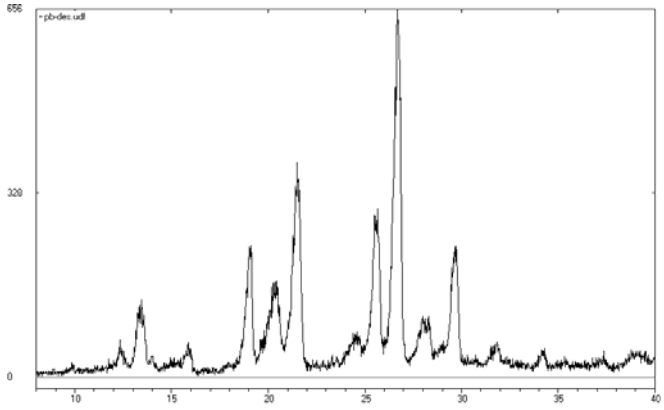


Figure 6. PXRD pattern of crystalline desloratadine.

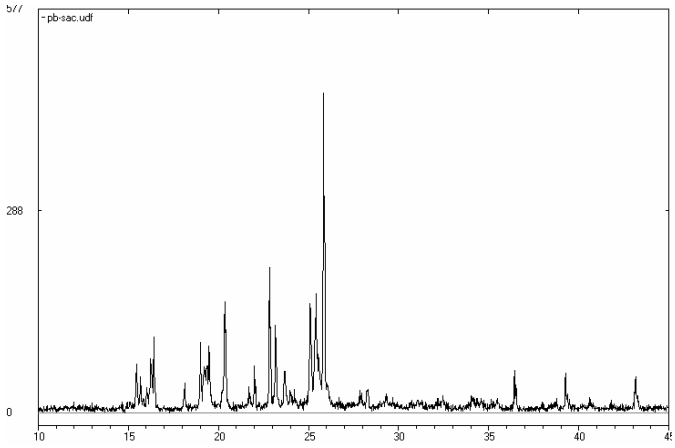


Figure 7. PXRD pattern of crystalline saccharin.

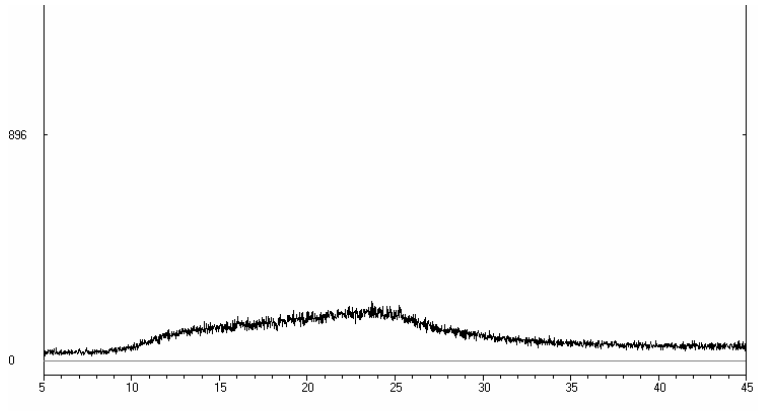


Figure 8. PXRD pattern of des sac (1:1). Note the absence of a diffraction pattern, which is characteristic of an amorphous material.

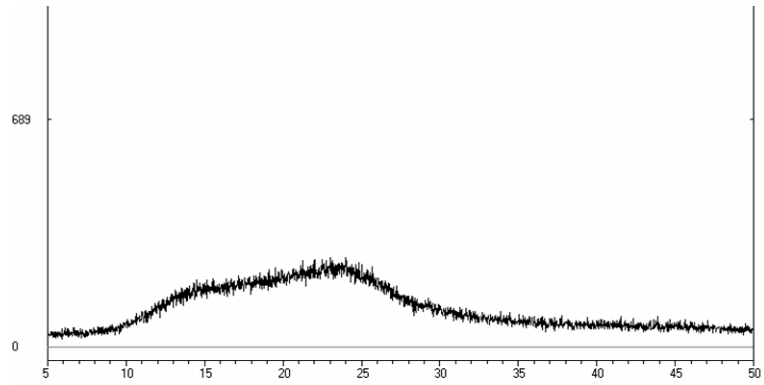


Figure 9. PXRD pattern of {des sac + saccharin} (1:1). Note that this material is not a 1:1 physical mixture of amorphous des sac and crystalline saccharin.

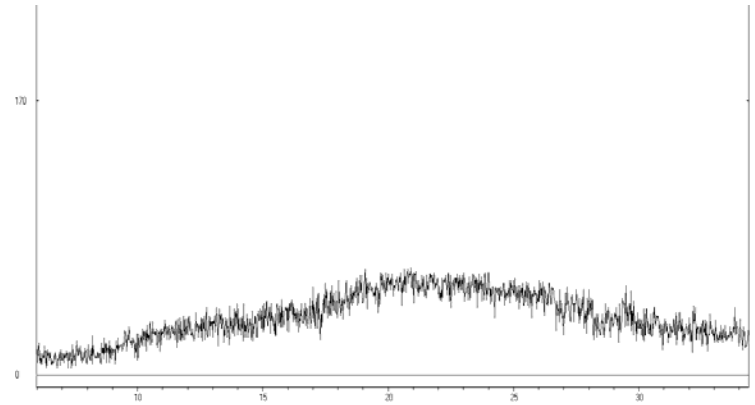


Figure 10. PXRD pattern of des sac and saccharin (80:20).

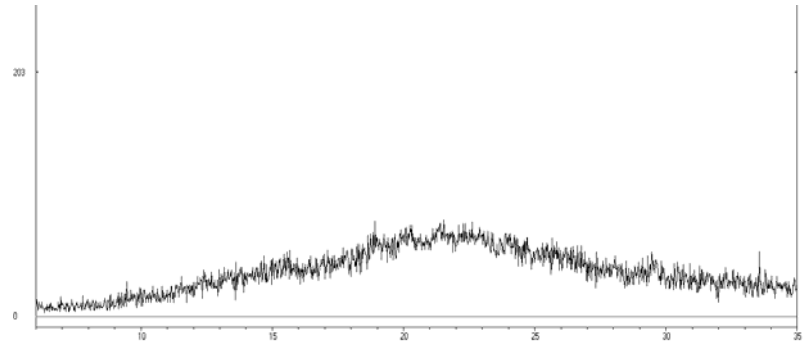


Figure 11. PXRD pattern of des sac and saccharin (70:30).

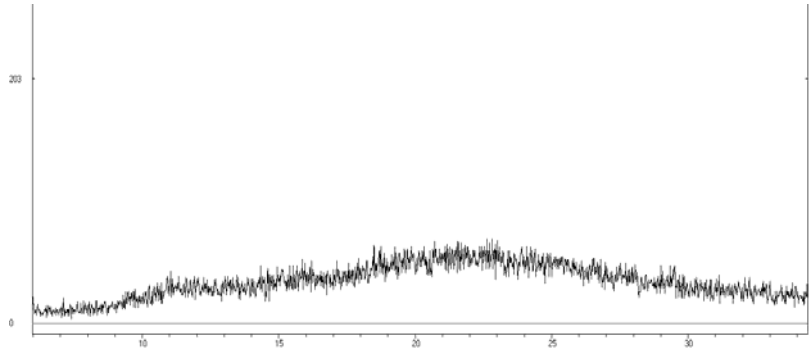


Figure 12. PXRD pattern of des sac and saccharin (60:40).

3.3.2 Thermal Analysis

Thermal characterisation is very important for amorphous materials as there are very few methods for the characterisation of amorphous materials. Glass transition (*T*g) temperature is the characteristic of the particular amorphous material. At *T*g the properties of the glassy material deviate from those of the equilibrium supercooled liquid to give a nonequilibrium state having even higher *H* and *V* than the supercooled liquid. *T*g can be determined from DSC curve. Generally amorphous material having *T*g 40-50˚ higher than the storage temperature is considered a strong glass former while *T*g below that is considered as fragile glass former.[5] *T*g of des sac (**III**) is determined from DSC and it is around 68˚C (Figure 13), which is a borderline case. However, repeated DSC

experiments with heat cool cycle does not show any sign of crystallisation or sharp melting. *T*g of **IV** is also determined from DSC and it is around 96˚C (Figure 14)

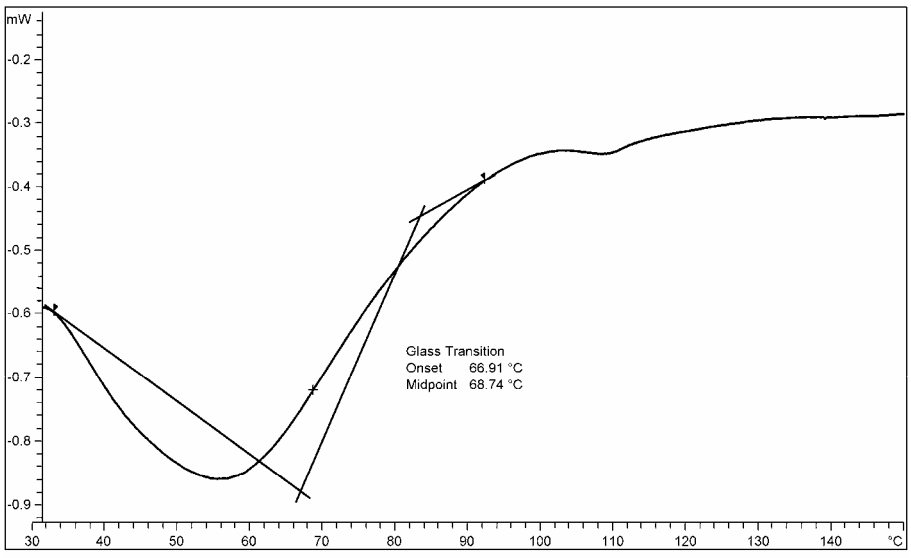


Figure 13. DSC curve of des sac (1:1) (**III**). The curve is characteristic of amorphous material with a glass transition temperature 68 ºC.

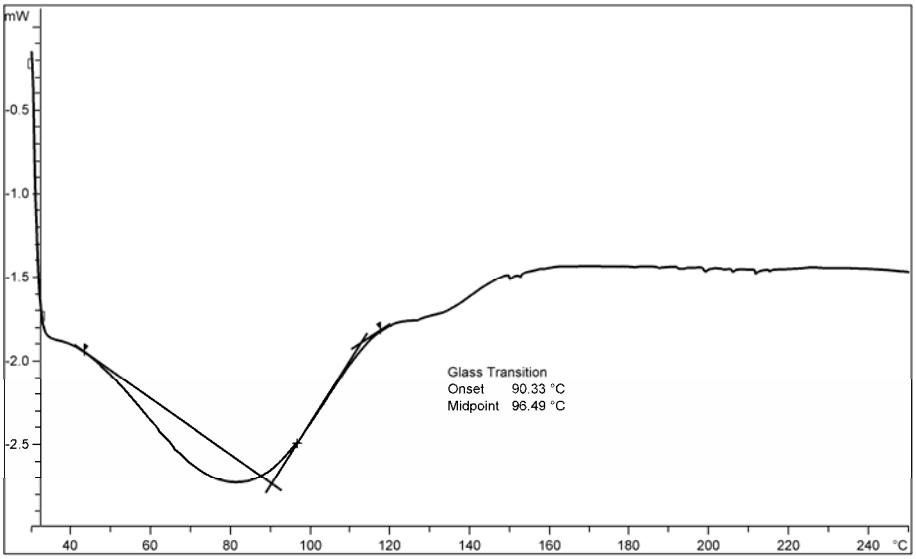


Figure 14. DSC curve of {des sac + saccharin} (1:1) (**IV**). The curve is characteristic of amorphous material with a glass transition temperature 96 ºC.

3.3.3 NMR Spectroscopy

Comparison of NMR spectra of des sac (with those of sodium saccharinate and desloratadine formate and also with NMR spectra of saccharin and desloratadine confirms the 1:1 stoichiometry of substance. All NMR spectra were recorded using DMSO-d6 as a solvent.

Sodium saccharinate: (400 MHz, dimethyl sulphoxide (DMSO)-d_6, δ ppm): 7.58 (s, 3H), 7.65 (d, 1H).

Desloratadine formate: (400 MHz, dimethyl sulphoxide (DMSO)-d_6, δ ppm): 2.29 (m, 2H), 2.83 (m), 2.84 (q, 2H), 3.05 (t, 2H), 3.32 (m), 7.11 (d, 1H), 7.21 (d, 2H), 7.32 (s, 1H), 7.58 (d, 1H), 8.34 (d, 1H).

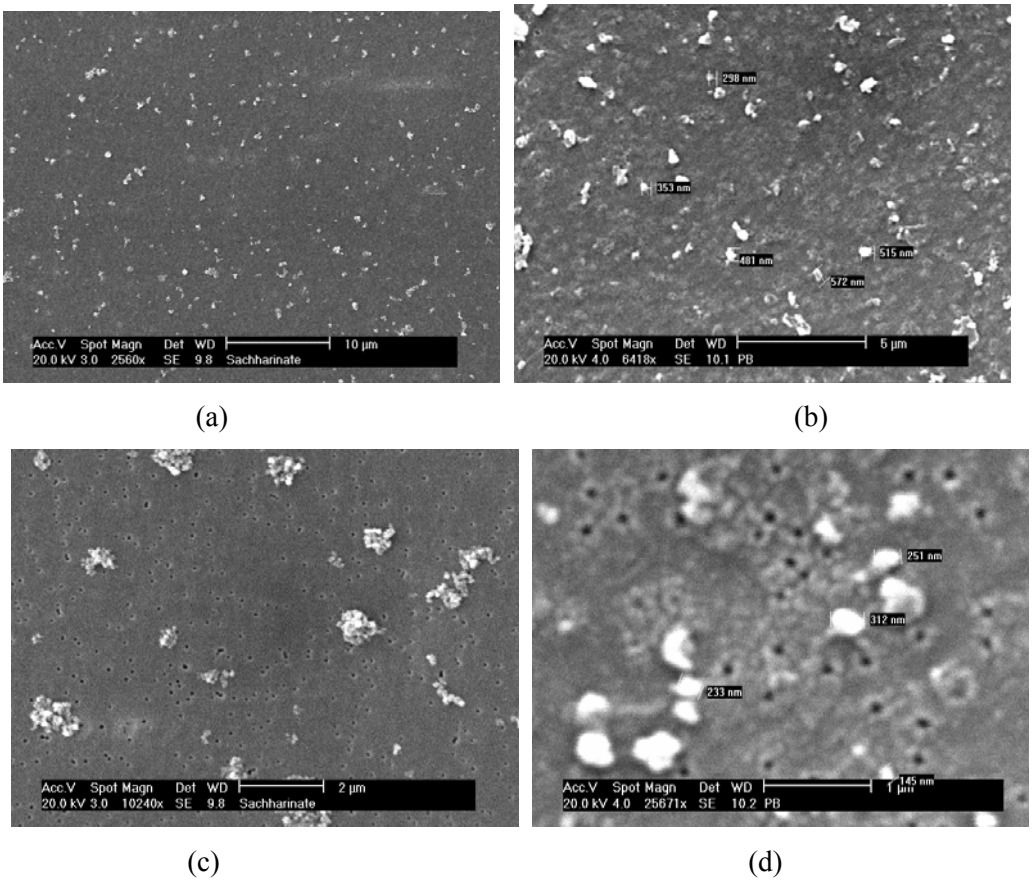
Des sac: (400 MHz, dimethyl sulphoxide (DMSO)-d_6, δ ppm): 2.35 (m, 2H), 2.57 (m), 2.84 (q, 2H), 3.02 (t, 2H), 3.25 (m), 7.15 (d, 1H), 7.24 (d, 2H), 7.35 (s,1H), 7.60 (m, 4H), 7.64(d,1H), 8.36 (d, 1H), 8.6(b, NH_2).

3.4 Advantages of amorphous desloratadine saccharinate

An obvious question would be to show how amorphous des sac is superior to other modifications of desloratadine. It is clear from the patent literature that there is a need for an amorphous form of desloratadine. A recent patent application describes an amorphous form of desloratadine, and says that, “It has been found that obtaining an amorphous solid of desloratadine is not a simple matter.”[4] This patent does not comment about the stability of the amorphous material.

Drug delivery by inhalation route is very important for many drugs, especially antihistaminic drugs, because rapid peak plasma concentrations of the drug can be achieved with a faster onset action. A recent patent application discusses the use of desloratadine in intranasal therapy for allergic rhinitis and nasal polyps and discusses its advantages over other drugs used in intranasal therapy. This work gives a method of preparing drops and spray of desloratadine for intranasal use. Desloratadine is poorly soluble in water and soluble only in acidic solutions but the intranasal formulation ideally requires a pH of around 6.0 to avoid nasal irritation. Hence, it requires the use of a buffer for maintaining pH and also solubilisers and other ingredients. Des sac is highly

water-soluble and its solubility is around 16 mg/mL. The pH of the saturated solution is 5.8. Moreover once in solution it is very difficult to solidify it, and hence the use of solubilisers may be avoided, giving a more straightforward method.



(a) (b)

(c) (d)

Figure 15. SEM images of des sac colloids in different magnifications.

In addition, desloratadine can be used in a powder formulation that is comparatively cheaper and easier to handle. However, for powder formulation the particle size should be below 1 µ. We were able to prepare colloids of des sac by injecting 4ml of methanolic solution (20 µM) into 25 ml water. SEM experiments showed that particles of the size less than 1 µ were formed (Figure 15). The SEM pictures show that although particles do not have particular shape they have size in the same range and can be considered as candidates for powder formulation.

3.5 Conclusion

Apart from the crystalline modification of desloratadine reported in this chapter and elsewhere there is a strong need for stable amorphous modification of desloratadine. In this chapter we are proposing new pharmaceutical modifications of desloratadine with improved properties. Amorphous des sac is very stable and we were not able to obtain any crystalline form. This is a positive feature because the biggest drawback of amorphous materials, namely their tendency to crystallize, is absent. Amorphous des sac has a considerably higher water solubility compared to its other salts. We note here that free base is practically insoluble in water. Amorphous des sac also shows promise to be used for drug delivery by inhalation route as a spray or powder formulation, and this has many advantages over the conventional oral route. The amorphous des sac can also be prepared as (1:1) amorphous mixture of {des sac + saccharin}, where one saccharin molecule exists in an unionized form.

3.6 Experimental section

Sample Preparation

Desloratadine : Desloratadine was crystallised from EtOAc solution by slow evaporation method.

Desloratadine hydrochloride: It was crystallised from MeOH solution by slow evaporation method.

Desloratadine saccharinate (1:1): 1 mmol desloratadine (310 mg) and 1 mmol saccharin (183 mg) were mixed and ground in a mortar and pestle for 15 min. The mixture was dissolved in 1 ml CH_2Cl_2, then 2 ml hexane (anti-solvent) were added into the solution which was triturated for 10 min. A white powder separated out on evaporation of solvent. Again, 2 ml hexane were added to the solid and it was triturated for 10 min. On evaporation of solvent, the white powder that was left was transferred to a 25 ml round bottomed flask and degasified under vacuum at 50ºC for 1 hour. The resulting amorphous desloratadine saccharinate (1:1) was characterized by PXRD, DSC, IR and NMR.

{Desloratadine saccharinate + saccharin} (1:1): 1 mmol desloratadine (310 mg) and 2 mmol saccharin (366 mg) were mixed and ground in a mortar and pestle for 15 min. The mixture was dissolved in 1 ml CH_2Cl_2 and then 2 ml hexane (anti-solvent) were added into the solution which was triturated for 10 min. A white powder separated out on evaporation of solvent. Again 2 ml hexane were added to the solid and it was triturated for 10 min. On evaporation of solvent, the white powder that was left was transferred to a 25 ml round bottomed flask and degasified under vacuum at 50ºC for 1 hour. The resulting amorphous {Desloratadine saccharinate + saccharin} (1:1) was characterized by PXRD, DSC, IR and NMR.

X-ray Crystallography

X-ray diffraction intensities for **I** and **II** were collected at 100K (Bruker Cryosystems cooler) and 298K respectively on a Bruker SMART 4K CCD diffractometer (Bruker Systems Inc.) using Mo K_α X-radiation.[33] Data were processed using the Bruker *SAINT* package[34] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[35] The structures of both the compounds were solved by direct methods and refined by full-matrix least-squares on F^2. In **I** the H1 and H11 atoms of the N–H and C–H groups respectively and in **II** H1a and H1b of the $^+NH_2$ were located from difference Fourier maps and refined isotropically. All other H atoms of both the structures were found in a difference map but then placed in calculated positions and included in the refinement. Crystal data and details of data collections, structure solutions and refinements are summarized in appendix.

Thermal Analysis

A Mettler Toledo Differential Scanning Calorimeter was used in this study. N_2 was used as the inert gas to flush through the DSC furnace (purge rate 150 ml/min) to prevent condensation. The experimental temperature ranged from 30ºC to 250˚C. Samples were analyzed using closed aluminum pans at a heating rate of 2˚C min^{-1}.

IR Spectroscopy

All infrared spectroscopic experiments were performed on a Jasco 5300 IR spectrometer. IR spectra give good indication of salt formation. The shift of bands around 3456 cm^{-1} (N-H) and 1720 cm^{-1} (C=O) in saccharin to around 3396 $cm^{-1}$and 1630 cm^{-1} respectively in des sac confirms proton transfer from saccharin to desloratadine. For {des sac + saccharin} (1:1), a band at 1734 cm^{-1} is also observed in addition to the band at 1630 cm^{-1} indicating that the second saccharin molecule is probably non-ionized.

X-ray Powder Diffraction

Powder X-ray diffraction patterns were recorded on a PANalytical (Phillips Systems Inc) diffractometer using Cu *Kα* X-radiation using a voltage of 25 kV and a current of 40mA. Diffraction patterns were collected over a range of 5-45º *2θ* at a scan rate of 2º *2θ* min^{-1}. Powder XRD patterns of des sac (1:1) and (1:2) show no peak in the given *2θ* range but a broad hump was observed which is typical for an amorphous phase.

Solubility Determination

The solubility of des sac was determined using a Shimadzu LC-MS., UV detector at 254 nm. The shake-flask method was used to determine the solubility in HPLC grade water at equilibrium. The sample was added to the medium in a flask/vial, in excess, and the resulting suspension was shaken for 24 hours at room temperature. The objective was to form a saturated solution, as indicated by observation of surplus undissolved material. After equilibration, the sample was filtered and the concentration of the compound in the filtrate was quantified using LC-MS after dilution. Here we would like to mention that there is a chance that some of the colloidal particles can also pass through the filter paper along with the solution. Although the obtained solution had the visual appearance of a true solution, we cannot overlook the presence of colloidal particles completely. However, even if there is some contribution from colloidal particles it would not be big enough to change the solubility completely and the solubility is expected to be in the same range.

The obtained solution was filtered and diluted 100 times. A stock solution of 1 mg/mL was prepared by dissolving 100 mg of des sac in 100 ml of HPLC grade water. The standard solutions of known concentration were prepared by diluting 5 mL, 10 mL, 20 mL and 40 mL to 100 mL, to give 0.05, 0.10, 0.20, 0.40 mg/mL solutions respectively. The concentration of unknown diluted sample was calculated using the calibration curve.

The area under the peak was determined using LC-MS with the following parameters.

Injection volume 5.0 μL

Solvent Methanol

UV Detector at 254 nm and mass spectrum detector.

Sl No	Concentration mg/mL	Area under Peak Units
1.	0.05	1174594
2.	0.10	1471972
3.	0.20	3207991
4.	0.40	6182946
5	Unknown	2724947

$y = ax + b$

Linear Regression $a = 1.479 \times 10^7$

$b = 234580$

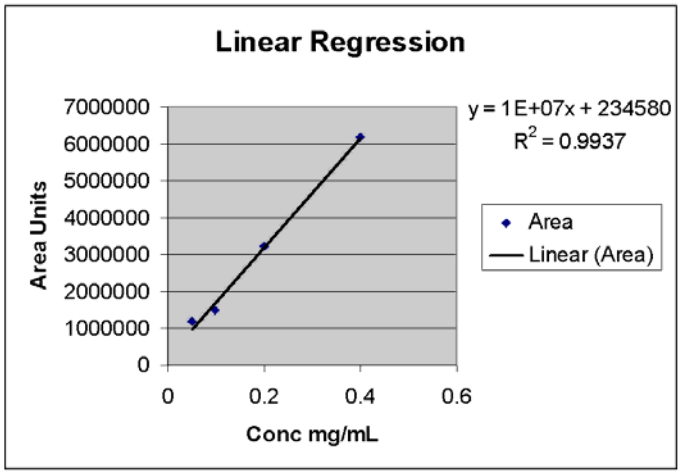
$r = 0.99684$

$(y - b) / a = x$

Concentration of unknown diluted solution 0.1683 mg/mL

Concentration of unknown saturated solution 0.1683 x 100 = 16.83 mg/mL

∴ Solubility is 16.83 mg/mL.



pH Determination

pH determination was carried out using Digisum[7007] digital pH Meter. A 1% solution of des sac was prepared and used without any further processing for pH determination. pH of 1% solution of des sac is 5.8.

3.7 References and notes

1. S. R. Byrn in *Solid-state chemistry of drugs*, Academic Press, London, **1982**.
2. J. Fischer and T. Fodor, Int. Publication number, WO 2005/0203116 A1, (15/09/2005).
3. P. M. Bhatt and G. R. Desiraju, *Acta Crystallogr*., *Sect*. *C*., **2006**, *62*, o362.
4. S. Venkatraman and G. Srinivasulu, Int. Publication number, WO 2005/084674 A1, (15/09/2005).
5. B. C. Hancock and G. Zografi, *J*. *Pharm*. *Sci*., **1997**, *86*, 1.
6. S. R. Elliott in *Physics of amorphous materials*, 2nd ed., Longman Scientific & Technical, Essex, 1990.
7. P. G. Debenedetti and F. H. Stillinger, *Nature*, **2001**, *410*, 259.
8. L. R. Hilden and K. R. Morris, *J*. *Pharm*. *Sci*., **2004**, *93*, 3.
9. L. Yu, *Adv*. *Drug Deliv*. *Rev*., **2001**, *48*, 27.

10. S. R. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg and G. Poochikian, *Pharm. Res*., **1995**, *12*, 945.
11. D. Q. M. Craig, P. G. Royall, V. L. Kett and M. L. Hopton, *Int. J. Pharm*., **1999**, *179*, 179.
12. R. Lefort, A. D. Gusseme, J. F. Willart, F. Danede and M. Descamps, *Int. J. Pharm*., **2004**, *280*, 209.
13. B. C. Hancock and M. Parks, *Pharm. Res*., **2000**, *17*, 397.
14. D. Zhou, G. G. Z. Zhang, D. Law, D. J. W. Grant and E. A. Schmitt, *J. Pharm. Sci*., **2002**, *91*, 1863.
15. A. Saleki-Gerhardt, J. G. Stowell, S. R. Byrn and G. Zografi, *J. Pharm. Sci*., **1995**, *84*, 318.
16. J. F. Willart, N. Descamps, V. Caron, F. Capet, F. Danede and M. Descamps, *Solid State Comm*., **2006**, *138*, 194.
17. H. Suga, *J. Phys*.: *Condens. Matter*, **2003**, *15*, S775.
18. M. Yoshioka, B. C. Hancock and G. Zografi, *J. Pharm. Sci*., **1994**, *83*, 1700.
19. P. M. Bhatt, N. V. Ravindra, R. Banerjee and G. R. Desiraju, *Chem. Commun*., **2005**, 1073.
20. R. Banerjee, P. M. Bhatt, N. V. Ravindra and G. R. Desiraju, *Cryst. Growth Des*., **2005**, *5*, 2299.
21. Accelrys, **2003**, *POLYMORPH PREDICTOR* in *Materials Studio* software suit. Accelrys Ltd., 334 Cambridge Science Park, Cambridge CB4 0WN, U.K. www.accelrys.com.
22. G. R. Desiraju, *CrystEngComm*, **2002**, *4*, 499.
23. W. Liu, C. -H. Lee, H. -W. Li, C. -K. Lam, J. Wang, T. C. W. Mak and D. K. P. Ng, *Chem. Commun*., **2002**, 628.
24. D. S. Coombes, G. K. Nagi and S. L. Price, *Chem. Phys. Lett*., **1997**, *265*, 532.
25. Z. G. Toth, V. Gyollai, A. Kovacsne-Mezei, C. Szabo, J. Aronhime and C. Singer, US Patent Application No. US2004242619, (02/12/2004).
26. T. Friščić, A. V. Trask, W. Jones and W. D. S. Motherwell, *Angew. Chem. Int. Ed Engl*., **2006**, *45*, 7546.

27. T. Friščić, L. Fábián, J. C. Burley, W. Jones and W. D. S. Motherwell, *Chem. Commun.*, **2006**, 5009.
28. A. V. Trask, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, **2004**, 880.
29. Y. Shirota, *J. Mater. Chem.*, **2005**, *15*, 75.
30. Y. Shirota, *J. Mater. Chem.*, **2000**, *10*, 1.
31. S. Bhattacharya, K. Lagu and S. Chhabada, Int. Publication number, WO 2003/101434 A2, (11/12/2003).
32. L. M. Salmun, P. Rohane and R. R. Lorber, Int. Publication number, WO 2003/000264 A1, (03/01/2003).
33. *SMART, Version 5.05*; Bruker AXS, Inc.: Madison, Wisconsin, **1998**.
34. *SAINT, Version 6.2*, Bruker AXS, Inc.: Madison, Wisconsin, **2001**.
35. G. M. Sheldrick, *SHELXTL V5.1*; Madison, WI, **1998**.

CHAPTER FOUR

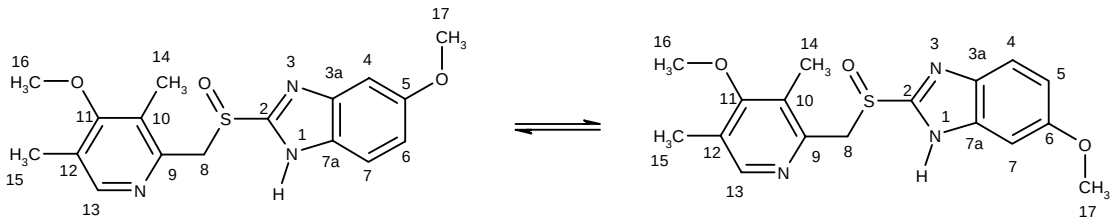
TAUTOMERIC POLYMORPHISM IN OMEPRAZOLE

4.1 Introduction

In recent times, polymorphism of drugs has emerged as a major topic of research because crystal forms with novel and interesting properties may qualify for independent patent protection, effectively extending the marketable life of the active pharmaceutical ingredient (API).[1,2] While there are many definitions for the terms 'polymorph' in organic solid state chemistry, the gist of all these definitions is that polymorphism involves different arrangements of the same molecule in the solid state. This definition is quite clear and uncontroversial as far as the molecules concerned are rigid and there are no great ambiguities in their crystal structures. However number and complexity of the crystal structures determined has increased to the extent in recent years that definition of polymorph has to be reconsidered. There are two issues here; how similar should be the molecules to be considered as same? and how different should be the two crystal structures to be considered as polymorphs?[3] The present chapter discusses the former question in the context of tautomeric polymorphism of Omeprazole, 5(6)-methoxy-2-{(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl}-1*H*-benzimidazole **1** (**2**) which is a blockbuster anti-ulcer drug.

Tautomers are dynamic isomers of the molecule and are interconvertible chemical entities. A crystal containing a different tautomer could be considered as polymorph or as a crystal of two different compounds. It has been argued that if a pair of tautomers are in rapid equilibrium in solution or in the melt, then they should be considered to be polymorphic.[4] In general, the crystals of isomers that interconvert rapidly in solution would be classified as polymorphs while crystals of slowly interconverting isomers would be considered as different compounds. However there is no timeframe defined for fast and slow interconversion. Moreover, rate of interconversions are generally temperature dependent. Accordingly depending on temperature of the experiment pairs of crystal structures could be called polymorphic or different compounds! In short the borderline is still not very clear.

Since tautomerism is widely prevalent in the solution one might have expected many well documented examples of tautomeric polymorphism. However, this is not the case in reality. There are at best two unambiguous examples of this phenomenon reported in the literature. The first report dates back to 1983 and is concerned with 2-amino-3-hydroxy-6-phenylazopyridine which exists as hydroxyazo and quinonehydrazone crystals, with different colours.[5] The second case has been reported in recent years and deals with sulfasalazine, which exists as an amide and an imide tautomer, and also as a hydrated as well as a DMF-solvated imide tautomer.[6,7] This phenomenon has also been referred to as desmotropy with reference to 3-phenyl-1*H*-pyrazole and 5-phenyl-1*H*-pyrazole,[8] and to irbesartan, a tetrazole-containing pharmaceutical compound.[9] Other examples are not very clear and have some sort of ambiguity: in anthranilic acid, one polymorph contains neutral as well as a zwitterionic molecule in the asymmetric unit while the other polymorph contains only neutral molecules;[10] the dipeptide L-His-Gly crystallises as a hemihydrate with both the more favourable Nε–H and the less favourable Nδ–H tautomers in the same crystal;[11] similar situations wherein two tautomers are present in the same crystal prevail in *N*-(3-hydroxysalicylidene)-4-methoxyaniline where enol-imine and keto-enamine tautomers exist in a same crystal,[12] 3(5)-phenyl-4-bromo-5(3)-methylpyrazole[13] and 4(5)-nitro-5(4)-methoxyimidazole;[14] form II of ranitidine hydrochloride might exist as a mixture of eneamine and nitronic acid tautomers.[15] In this chapter, we present evidence that the crystal forms of omeprazole contain different tautomeric compositions, and that the phenomenon of *tautomeric polymorphism* in this system also leads to further questions regarding the definition of term *polymorph* itself.



Scheme 1. Tautomeric interconversion in omeprazole.

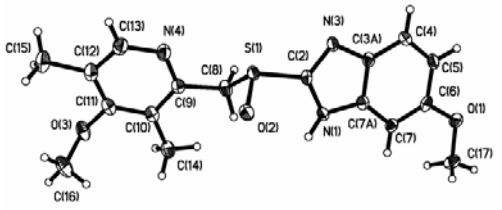
4.2 Crystal structures of forms I-V of omeprazole

We obtained single crystals of five different forms of omeprazole with the **1**:**2** ratio varying from 0:100 to 15:85 (Figure 1). Crystals of the pure 6-methoxy tautomer **2** (**I**) were obtained from a 2% methanolic solution of NaOH by slow evaporation over two days. It crystallises in the $P\bar{1}$ space group with one molecule in the asymmetric unit. The crystal structure is mainly made up of N–H…O=S dimmers (Figure 2). There are no strong interactions in the structure except for these N–H…O=S hydrogen bonds (Table 1). There is a weak C–H…O dimer between the hydrogen of the methylene group of one molecule and the oxygen of the sulfoxide group of the other molecule. This structure is the prototype for the rest of the group. Crystals containing increasing amounts of **1** were obtained following procedures in the US 6,780,880 patent. All these crystals are essentially isostructural to **I** and the diffraction data were modelled by refinement of the site occupancy factors of the MeO–group between the 5- and 6- positions in the benzimidazole ring (Figure 3). It may be noted, however, that the proportions of **1** in the crystals obtained were different from those reported in the literature. Crystals **II** through **V** were obtained as follows: **II** (8% **1**, 92% **2**, from concentrated ammoniacal MeOH in 3 days at r.t.); **III** (10% **1**, 90% **2**, from dilute ammoniacal MeOH in 3 days at r.t.); **IV** (12% **1**, 88% **2**, from acetone or 70:30 MeOH-CCl_4 at 5˚C); **V** (15% **1**, 85% **2**, from $CHCl_3$ in 2 days at r.t.)

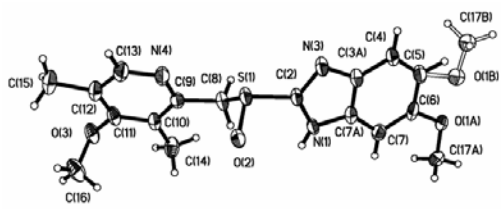
Table 1. Geometrical parameters of H- bridges of the hydrates in this study.

Omeprazole Form	**H-bridge**	***d*/Å (H…A)[a]**	***D*/Å (X…A)**	***θ*/deg ∠X–H…A**
I	N–H…O	1.74	2.743(3)	175
	C–H…O	2.41	3.445(4)	159
	C–H…O	2.43	3.443(4)	155
	C–H…N	2.43	3.458(4)	159

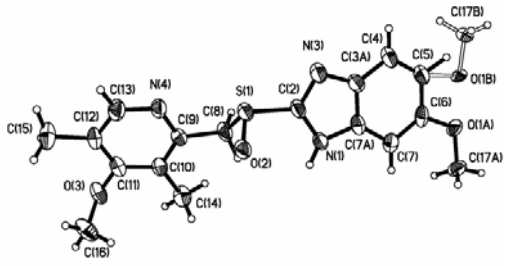
[a] N–H and C–H distances are neutron normalized to 1.01, 1.08 Å.



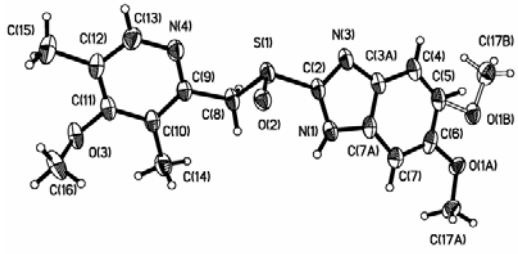
I



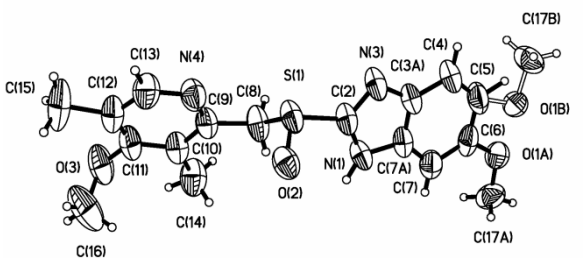
II



III



IV



V

Figure 1. ORTEP diagram of omeprazole (**I-V**) at 50% probability level.

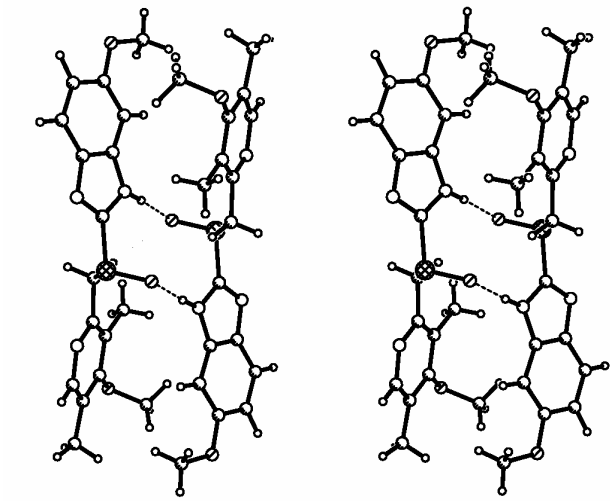


Figure 2. Omeprazole as the 6-methoxy tautomer in the crystal structure of **I**. Note the N–H…O=S hydrogen bonds in the dimer.

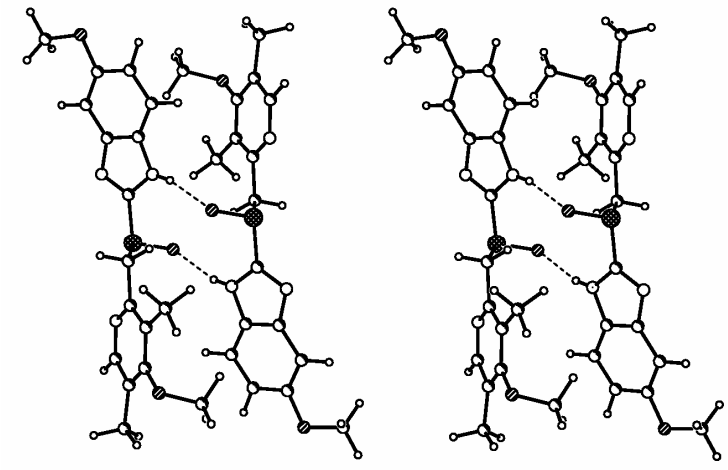
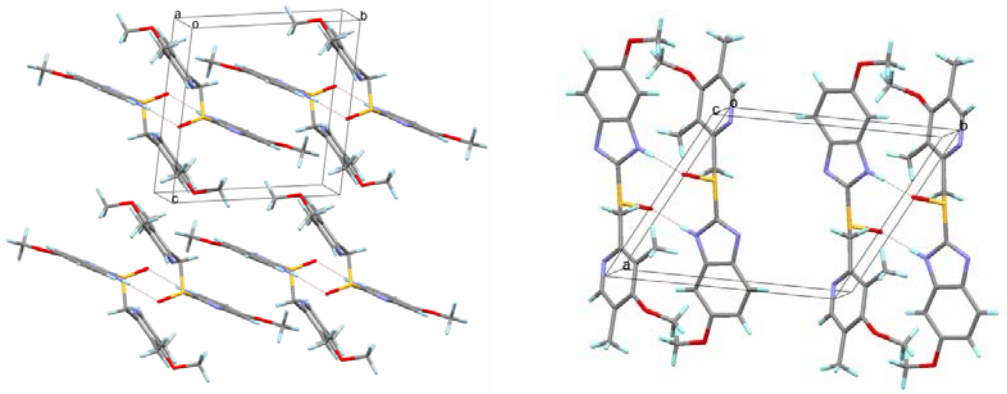
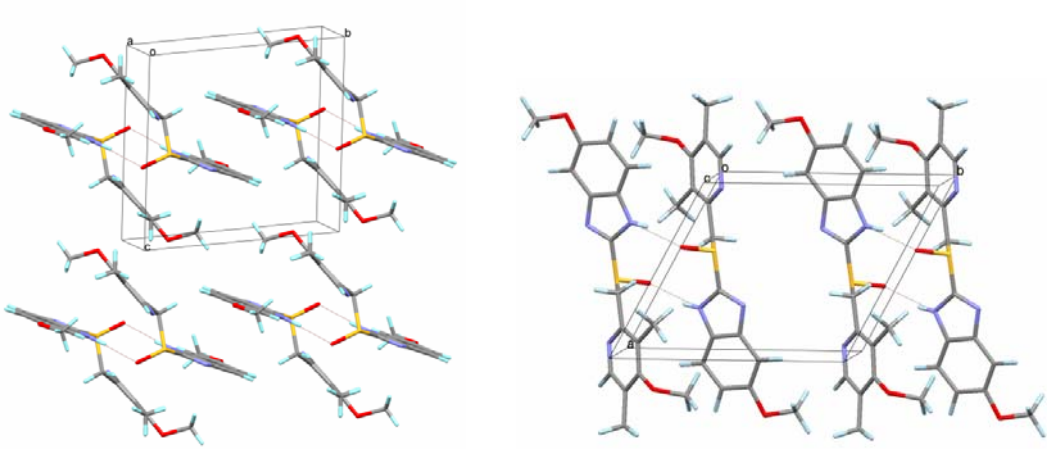


Figure 3. Idealised view of the 5-methoxy tautomer of omeprazole in the crystal structure of **V**. The percentage of this tautomer is so low that only the methoxy group is "seen" as an entity distinct from the atoms of the 6-methoxy tautomer. Even then, refinement at variable occupancies provides inaccurate exocyclic angles for the 5-methoxy group. The coordinates used to generate this figure were accordingly obtained by treating the 5-methoxy group as a rigid body with fixed geometry with respect to the benzo-ring.



a **b**

Figure 4. Packing of 6-methoxy dimers (a) viewed down the a-axis and (b) viewed down the c-axis.



a **b**

Figure 5. Packing of idealised 5-methoxy dimers (a) viewed down the a-axis and (b) viewed down the c-axis.

4.3 Crystal structure of chloroform solvate of omeprazole

As described in the earlier section, crystallization from chloroform at room temperature leads to unsolvated form **V** with 15% **1** content. However crystallisation form chloroform at lower temprature (around 5 °C in a refrigerator) leads to crystals of chloroform solvate of omeprazole. These crystals are very sensitive to temperature and

physical disturbance and became opaque rapidly before they could be mounted on the diffractometer. Single crystal X-ray data obtained from these crystals were poor and of very limited accuracy (R factor 0.34). However the model obtained is good enough to provide some qualitative insight to the structure. It shows that asymmetric unit contains two molecules of chloroform and two molecules of omeprazole as shown in Figure 6. Although the hydrogen atoms could not be assigned to this structure, the packing shows that asymmetric unit contains one molecule of **1** and one molecule of **2**.

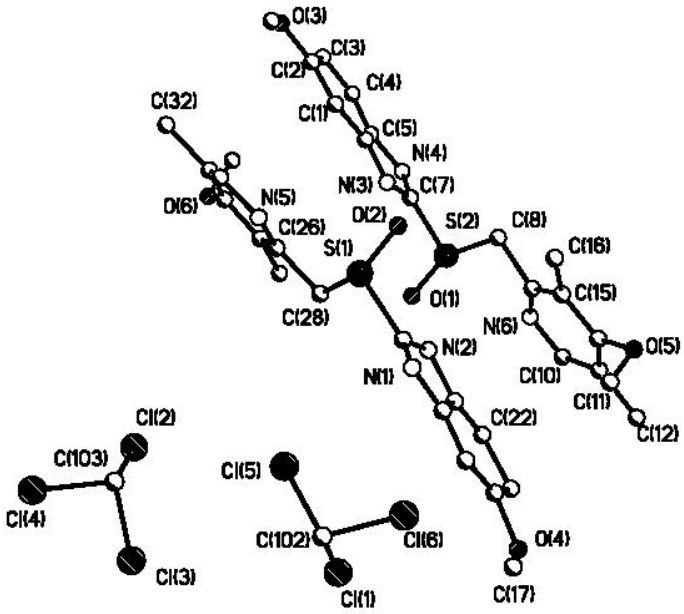


Figure 6. Crystal structure of chloroform solvate of Omeprazole.

4.4 Tautomeric polymorphism of omeprazole

The tautomers of omeprazole (**1** and **2**, Scheme 1) have been detected previously in solution. In solution omeprazole exists as both 5-methoxy and 6-methoxy tautomers. NMR study showed that at 195 K in THF solution ratio of 6-methoxy and 5-methoxy tautomer of omeprazole is 63:37.[16,17] Solid forms of omeprazole have been investigated according to two approaches— (1) with PXRD, and (2) with single crystal XRD and Raman analysis—but there is little correlation between these two approaches.

Three forms A, B and C have been patented and are characterized by their PXRD traces. In patent application WO 99/08500, it is stated that form A is more stable than form B.[18] In patent application US 2004/0122056 it is stated that form C is easier to prepare than A and B.[19] The previously reported crystal structure which appears to be the 6-methoxy tautomer[20,21] (mistakenly called the 5-methoxy compound in one of the original papers[20,21] and corrected subsequently by Claramunt et al.[16]), is identified in the WO 99/08500 patent application as form B. Another patent US 6,780,880 claims that omeprazole crystals contain mixtures of **1** and **2** and states that single crystal X-ray methods may be used to estimate the relative amounts of the two tautomers, without providing any further information.[22] In short, literature is confusing.

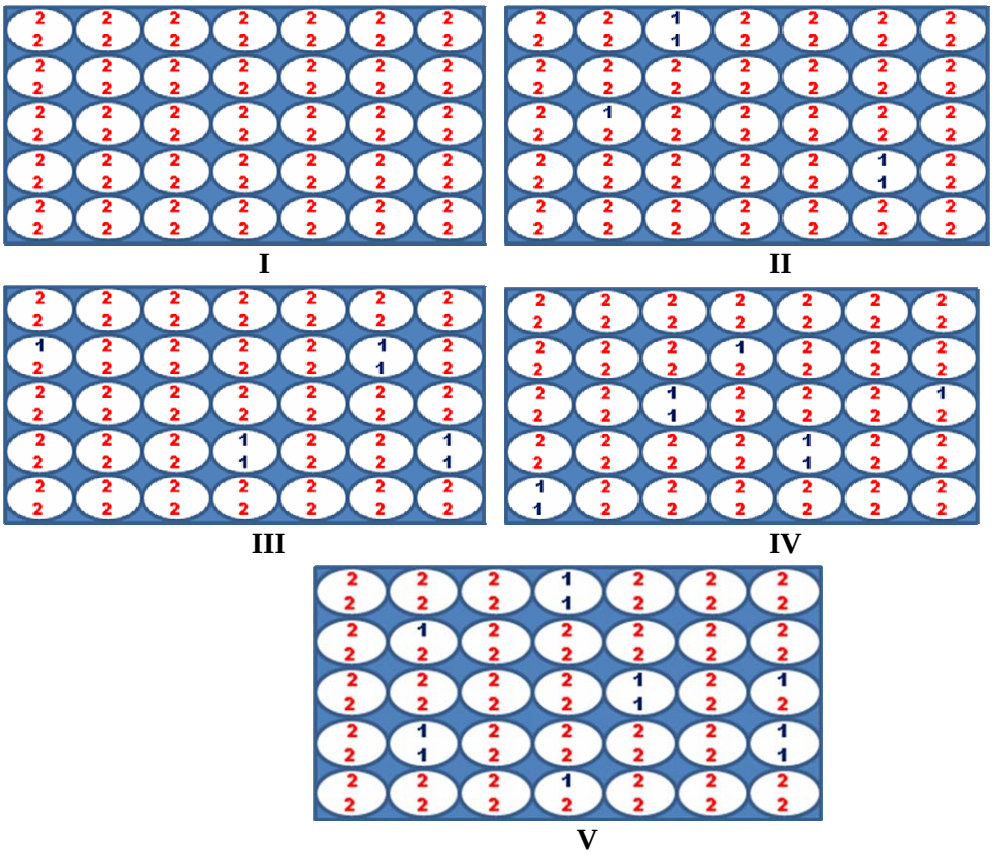


Figure 7. Cartoon depiction of crystal lattices of **I** through **V**, representing substitutional solid solutions of **1** in **2** with varying amounts of **1** in structures **I** through **V.**

There is adequate evidence that **2** is more stable than **1** and correspondingly that crystals containing greater proportions of **2** are more stable than those that contain less.[22] According to the literature, **2** is photostable while **1** is photosensitive. Crystals of **I** are white and do not change colour. It was observed that as the proportion of **1** increases (**II** → **V**) the crystals darken with increasing ease upon standing. It is also possible that at the crystal level, **2** packs slightly better than **1**. What is interesting is that the crystal packing is such that the MeO-group may be situated either at the 5- or 6- position of the benzimidazole ring without affecting the overall packing of molecules (Figures 4 and 5). Accordingly, these crystals **I** through **V** may be viewed as substitutional solid solutions of **1** in **2**. This can be visualized as varying amount of 5-methoxy tautomers **1** randomly located in the crystal lattice of **2**. Figure 7 shows cartoon depiction of crystal lattices of **I** to **V.** As **I-V** are crystals with differing amounts of tautomeric structures, the term *tautomeric polymorphism* is justified.

4.5 Simulated PXRD and comparison with patented forms

Simulation of the PXRD patterns of crystals **I** through **V** showed that **III** corresponds to Form A of the WO 99/08500 patent application, **IV** corresponds to Form C and **V** is form B. Simulated PXRD patterns are given in Figures 8-12. It may be noted that the previously reported crystal structure of omeprazole is innocent of the possibility that the crystal contains both **1** and **2**.[20,21] This structure was refined as if it contains only **2** but the simulated PXRD matches the crystal with 15 % of tautomer **1.** It is interesting that forms A, B and C seem to be sufficiently distinctive in terms of their stabilities and other properties, anyway distinctive enough that they enjoy independent patent protection (Figure 13). Structurally speaking, however, they occur in a structural continuum that begins with a pure 6-OMe crystal and ends with an 85:15 mixture of 6-OMe and 5-OMe tautomers.

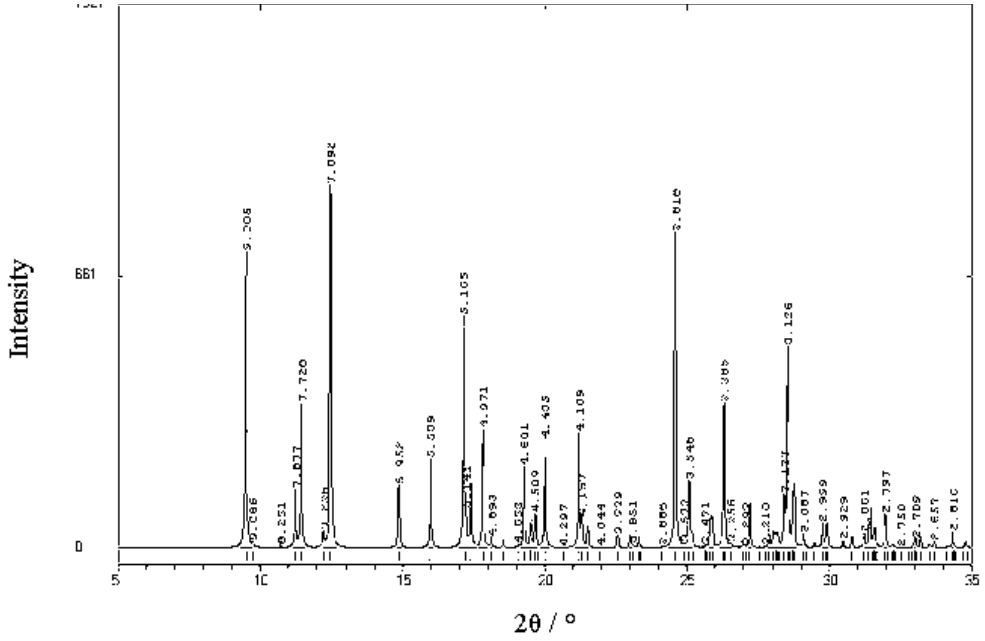


Figure 8. Simulated PXRD from single crystal X-ray data of omeprazole (**I**)

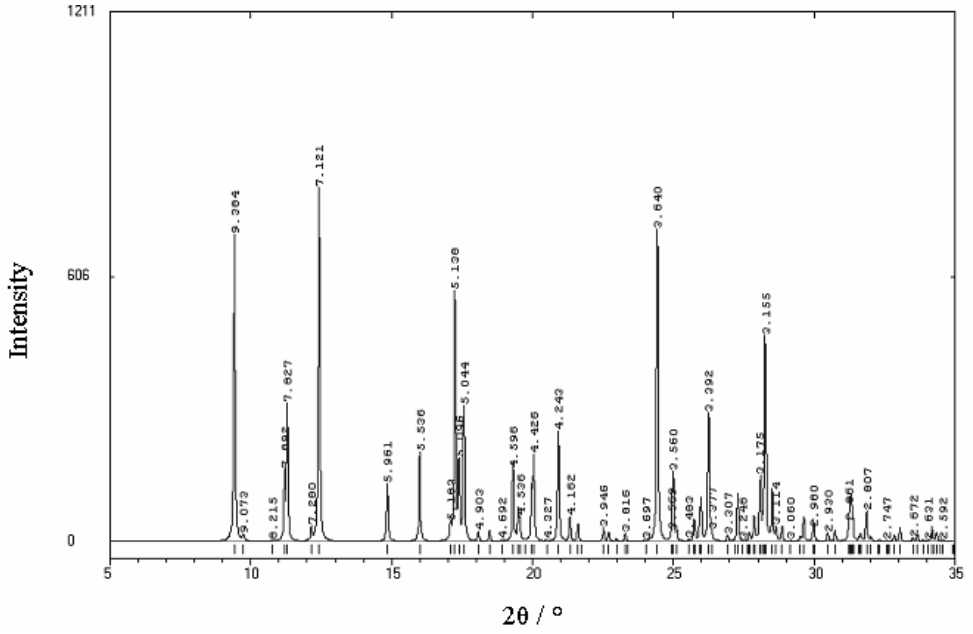


Figure 9. Simulated PXRD from single crystal X-ray data of omeprazole (**II**)

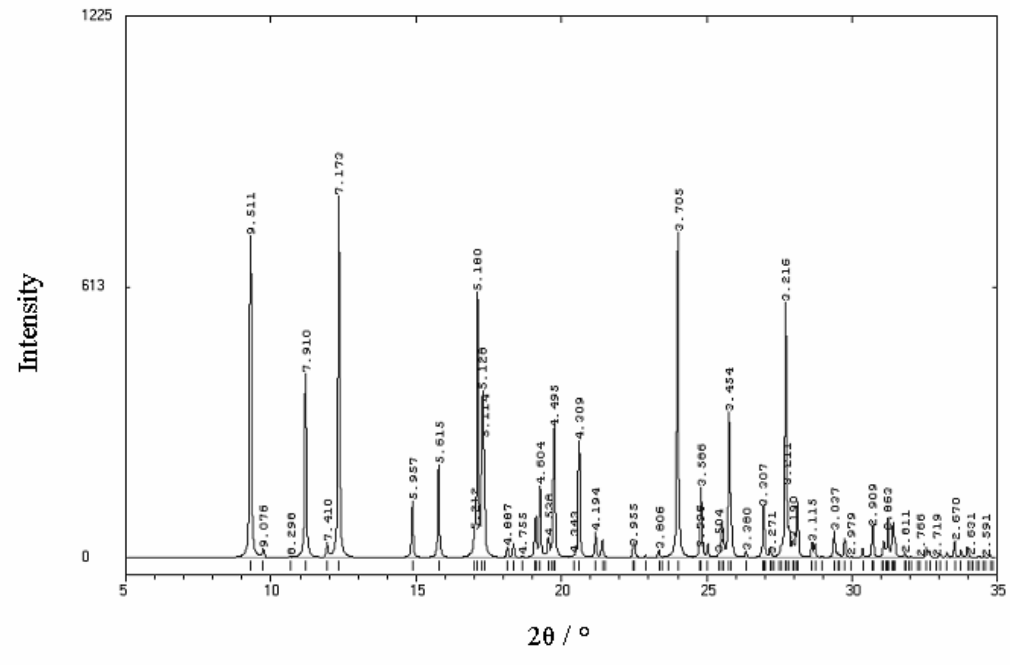


Figure 10. Simulated PXRD from single crystal X-ray data of omeprazole (**III**)

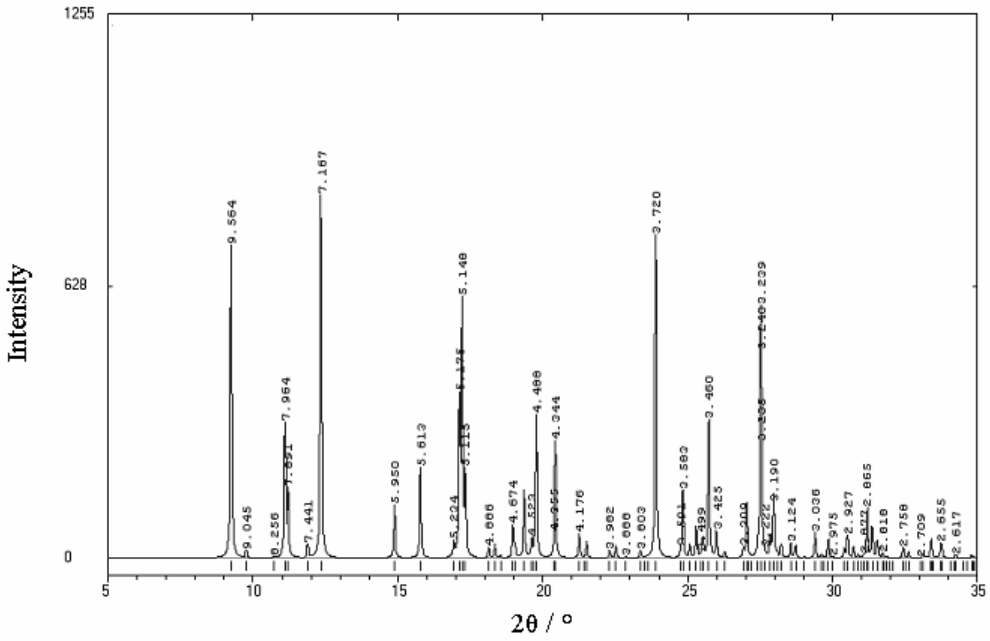


Figure 11. Simulated PXRD from single crystal X-ray data omeprazole (**IV**)

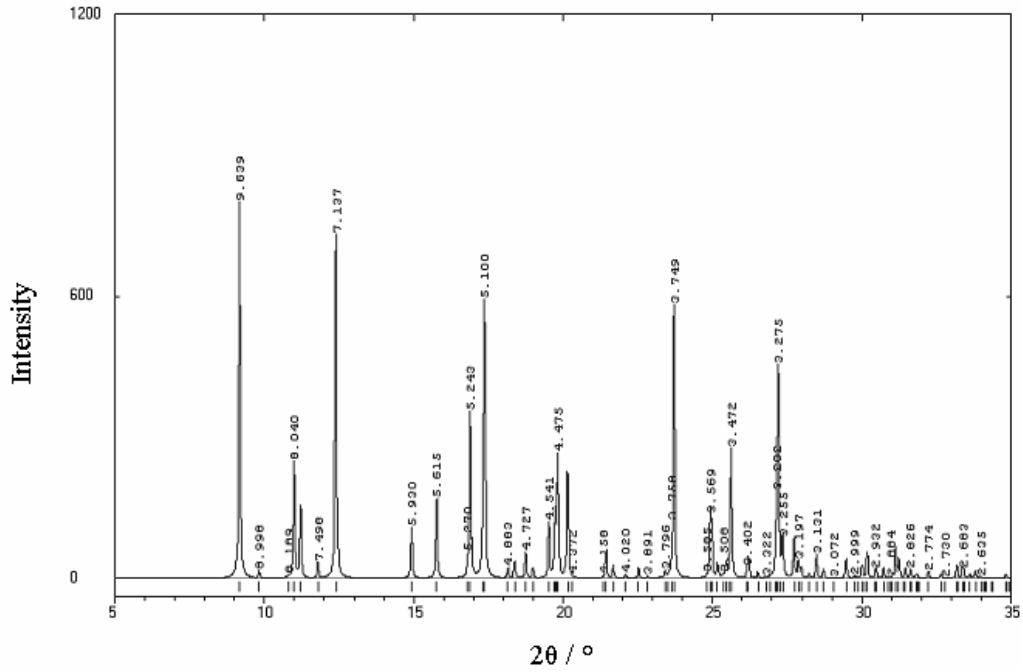


Figure 12. Simulated PXRD from single crystal X-ray data omeprazole (**V**)

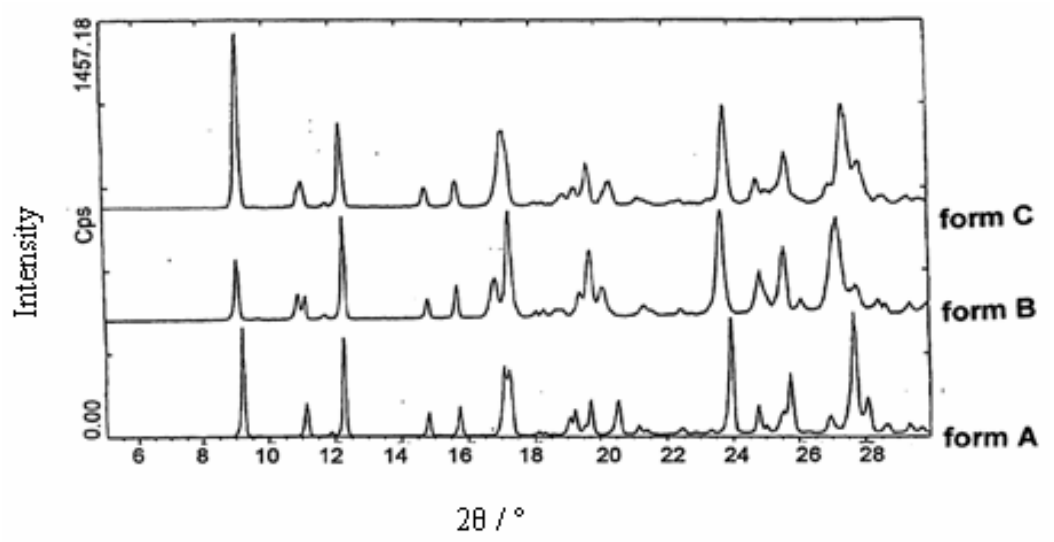


Figure 13. PXRD spectra of forms A, B and C given in the patent application US 2004/0122056 A1.

4.6 Conclusion

This example highlights several interesting features of general significance. Desiraju, Boese and Bond have recently described structural modulations in crystalline aspirin, where the crystals are best described as intergrowths of two domains, each of which if they existed independently, would constitute a pair of polymorphs.[23,24] In omeprazole, the situation is different in that the modulation is at the molecular level but there are some points of comparison. Forms **I** to **V** of omeprazole contain different tautomeric compositions therefore they are tautomeric polymorphs. In principle it is possible to make the whole spectrum of omeprazole forms ranging from 100% **2** and 0% **1** to 0% **2** and 100% **1**, where each form differ slightly to the adjacent one in **2**/**1** ratio. For example, consider F1→ F2→ F3→ → → F20→ → → F40→ → → Fn are different forms of omeprazole with slightly different **2**/**1** ratio in adjacent forms. Then F1 and F2 are same in practice and difficult to distinguish, similar for F2 and F3 and so on. However F1 and F20 can be called different and can have different PXRD pattern as well as they may have different physical properties. This raises a series of questions like: How many polymorphs of omeprazole really exist? Is it one or two or infinite? Would each **1**:**2** composition qualify for independent patent protection or would it be more meaningful to claim protection for compositional ranges? It is interesting to note here that patented forms (A, B, C) are defined in terms of properties like stability, ease of preparation etc. rather than in terms of structure. The role of the PXRD trace is merely as a fingerprint of a form with a particular property rather than diagnostic of a particular structure type, because these PXRD traces also constitute a structural continuum like the crystals they seek to characterise. This emphasises that function is more meaningful criterion of polymorph patentability than the structure. Indeed this is clearly indicated in Buerger's definition of polymorphs as different forms of the same chemical compound which have distinctive properties.[25] If function then is more significant than structure, this raises more provocative issues: (1) should the definition of polymorphism rely so heavily on structural differences? (2) are subtle structural differences really meaningful especially in the context of the kind of modulation which is seen in omeprazole and aspirin? (3) just as minor differences in crystal structure may be interpreted subjectively,

may this also be said of molecular sameness? (4) accordingly, how important is the criterion that the molecular structure should be exactly the same if two crystals are to be called polymorphs? (5) in the context of polymorphism is it more reasonable then to speak of a structural landscape that includes a number of solvated and unsolvated variations of the same molecular species without insisting on rigorous stoichiometric and chemical identity? In the end, one is reminded of Bernstein's realistic assessment that "an all-encompassing definition of polymorphism is elusive".[4]

4.7 Experimental section

Crystallisation procedures:

(1) Crystals of **I** were grown by dissolving 30 mg of omeprazole in 10 ml 2% methanolic solution of NaOH in a 25 ml conical flask and then allowing it to evaporate slowly for a period of 2 days at ambient condition.

(2) Crystals of **II** were grown by dissolving 30 mg of omeprazole in 10 ml methanol containing 8-9 drops of 25% ammonia solution in a 25 ml conical flask and then allowing it to stand for a period of 3 days at ambient condition.

(3) Crystals of **III** were grown by dissolving 30 mg of omeprazole in 10 ml methanol containing 4-5 drops of 25% ammonia solution in a 25 ml conical flask and then allowing it to stand for a period of 3 days in a refrigerator at around 5 °C.

(4) Crystals of **IV** were grown by dissolving 20 mg of omeprazole in 10 ml acetone in a 25 ml conical flask and then allowing it to stand for a period of 3 days in a refrigerator at around 5 °C.

(5) Crystals of **V** were grown by dissolving 30 mg of omeprazole in 10 ml chloroform in a 25 ml conical flask and then allowing it to stand for a period of 3 days at ambient temperature.

X-ray crystallography

The X-ray data of omeprazole (**I-V**) were collected at the University of Hyderabad. Intensity data were collected on a Bruker Nonius Smart Apex CCD with graphite monochromated Mo-K_α radiation at 100K (**I-IV**) and at 298K (**V**).[26] Data were

processed using the Bruker *SAINT* package[27] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[28]. In all these cases, disorder was modelled with the constraints DELU and SIMU in the refinement. The relevant crystallographic information is given in the appendix.

Simulated PXRD

PXRDs were simulated from crystal structures using the Powder Cell 2.3 software. The wavelength 0.1540598 nm (Cu Kα) was used to generate simulated PXRD plots. For comparison of simulated PXRD with experimental PXRD, a temperature correction was made in the former by replacing the low temperature unit cell parameters with the room temperature ones.

4.8 References and notes

1. *Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences*, ed. H. G. Brittain, Marcel Dekker, New York, **1999**, vol. 95.
2. *Solid state characterization of pharmaceuticals*, eds. A. Zakrzewski and M. Zakrzewski, Assa international Inc., Danbury, Connecticut, USA, **2006**.
3. T. L. Threlfall, *Analyst*, **1995**, *120*, 2435.
4. J. Bernstein, *Polymorphism in Molecular Crystals*, Clarendon, Oxford, **2002**, pp 2-4, 240-255, 297-307.
5. G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2.*, **1983**, 1025.
6. L. A. Filip, M. R. Caira, S. I. Fărcaş and M. T. Bojiță, *Acta Crystallogr.*, *Sect. C*, **2001**, *57*, 435.
7. A. J. Blake, X. Lin, M. Schröder, C. Wilson and R. X. Yuan, *Acta Crystallogr.*, *Sect. C*, **2004**, *60*, o226.
8. M. A. Garcia, C. Lopez, R. M. Claramunt, A. Kenz, M. Pierrot and J. Elguero, *Helv. Chim. Acta*, **2002**, *85*, 2763-76.
9. M. Bauer, R. K. Harris, R. C. Rao, D. C. Apperley and C. A. Rodger, *J. Chem. Soc., Perkin Trans. 2*, **1998**, 475.
10. W. H. Ojala and M. C. Etter, *J. Am. Chem. Soc.*, **1992**, *114*, 10288.

11. T. Steiner and G. Koellner**,** *Chem. Commun*., **1997**, 1207.
12. H. Pizzala, M. Carles, W. E. E. Stone and A. Thevand, *J. Mol. Struct*., **2000**, *526*, 261.
13. A. L. Llamas-Saiz, C. Foces-Foces, C. Fontenas, N. Jagerovic and J. Elguero, *J. Mol. Struct*., **1999**, *484*, 197.
14. M. Kubicki, *Acta Crystallogr.*, *Sect. B*, **2004**, *60*, 191.
15. M. Mirmehrabi, S. Rohani, K. S. K. Murthy and B. Radatus, *J. Cryst. Growth*, **2004**, *260*, 517.
16. R. M. Claramunt, C. López, I. Alkorta, J. Elguero, R. Yang and S. Schulman, *Magn. Reson. Chem*., **2004**, *42*, 712.
17. R. M. Claramunt, C. López and J. Elguero, *ARKIVOC*, **2006**, *5*, 5.
18. L. Karin; N. David; S. Gunnel and Y. Ingvar, Int. Publication number, WO 99/08500, (25/02/1999).
19. N. H. Milac and A. Copar, Int. Publication number, US 2004/0122056 A1, (24/06/2004).
20. H. Ohishi, Y. In, T. Ishida, M. Inoue, F. Sato, M. Okitsu and T. Ohno, *Acta Crystallogr.*, *Sect. C*, **1989**, *45*, 1921.
21. J. Deng, Y. Chi, F. Fu, X. Cui, K. Yu, J. Zhu and Y. Jiang, *Tetrahedron: Asymmetry*, **2000**, *11*, 1729.
22. R. R. Whittle, F. D. Sancilio and G. W. Stowell, US patent number, US 6,780,880 B1 (24/08/2004).
23. A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem. Int. Ed.* **2006**, *46*, 615.
24. A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem. Int. Ed*. **2006**, *46*, 618.
25. M. J. Buerger and M. C. Bloom, *Z. Kristallogr*., **1937**, *96*, 182.
26. *SMART, Version 5.05*; Bruker AXS, Inc.: Madison, Wisconsin, **1998**.
27. *SAINT, Version 6.2*, Bruker AXS, Inc.: Madison, Wisconsin, **2001**.
28. G. M. Sheldrick, *SHELXTL V5.1*; Madison, WI, **1998**.

CHAPTER FIVE

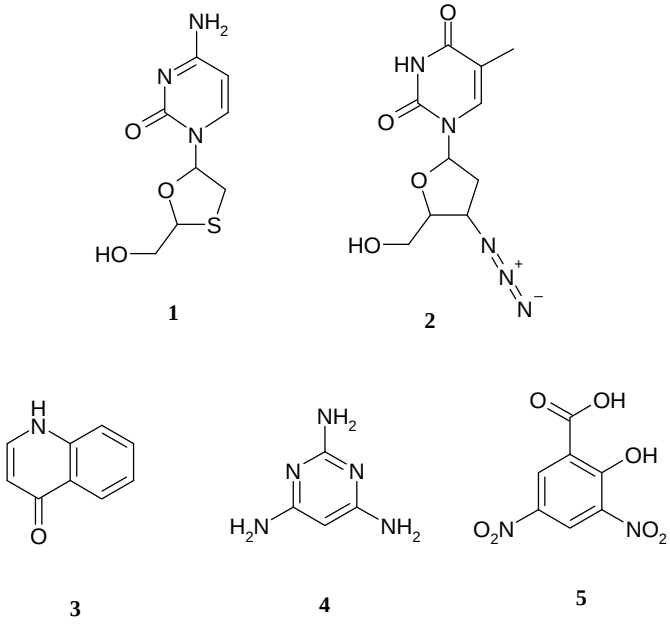
CO-CRYSTALS OF ANTI HIV DRUGS–LAMIVUDINE AND ZIDOVUDINE

5.1 Introduction

Co-crystal is defined as a material which contains two or more discrete molecular entities in the crystal structure. Co-crystals of many compounds are known for years in solid state chemistry. However, it is only recently that pharmaceutical co-crystals have generated much commercial and academic interest.[1-4] Pharmaceutical co-crystals are important because they can improve many properties of the parent API like solubility, dissolution rate, stability, crystallinity and many more.[1] This is particularly important for APIs, which do not have acidic or basic groups to form salts. Pharmaceutical co-crystals increase the chemical space of the API and co-crystals with favorable properties can also be patented.

Lamivudine (2',3'-dideoxy-3'-thiacytidine) and zidovudine {1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]- 5-methylpyrimidine-2,4(1*H*,3*H*)-dione} are potent nucleoside analog reverse transcriptase inhibitors. They are commonly used as anti HIV drugs. Lamivudine can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It needs to be phosphorylated to its triphosphate form before it is active. 3TC-triphosphate also inhibits cellular DNA polymerase.[5] Lamivudine is administered orally, and it is rapidly absorbed with a bio-availability of over 80%. Zidovudine does not destroy the HIV infection, but only delays the progression of the disease and the replication of virus.[6] The azido group increases the lipophilic nature of zidovudine, allowing it to cross cell membranes easily by diffusion and thereby also to cross the blood-brain barrier. Cellular enzymes convert AZT into the effective 5'-triphosphate form.

There are no co-crystals of lamivudine and zidovudine reported so far in the literature. A total of three co-crystals of lamivudine and zidovudine are reported and characterized in the present chapter.



I = 1+3 **II = 2+4** **III =1+5**

Scheme 1. Co-crystals of lamivudine **1** and zidovudine **2**.

5.2 Crystal structure of co-crystal I (lamivudine+4-quinolinone)

Co-crystal **I** crystallises in a space group $P2_1$ with one molecule of lamivudine and one molecule of 4-quinolinone in the asymmetric unit. The structure is stabilized by multiple N–H…O and O–H…O hydrogen bonds as shown in Figure 1. The amino group of lamivudine forms two N–H…O hydrogen bonds with the carbonyl oxygen of 4-quinolinone and hydroxy groups of another lamivudine molecule. This lamivudine molecule forms an O–H…O hydrogen bond with the carbonyl oxygen of another 4-quinolinone molecule resulting in a trigonal helical hydrogen bonding arrangement as shown in Figure 2. An N–H…O hydrogen bond between –NH of 4-quinolinone and carbonyl oxygen of lamivudine helps the structure in extending itself in the second direction (Figure 3).

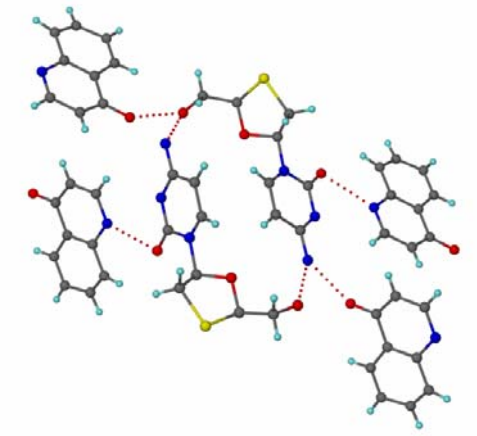


Figure 1. Hydrogen bonds in the crystal structure of **I**.

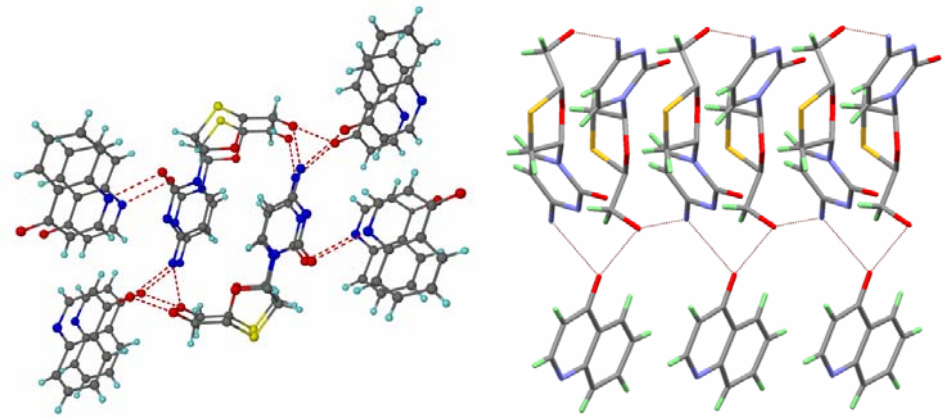


Figure 2. Helical hydrogen bonding arrangement made up of N–H…O and O–H…O seen from different views.

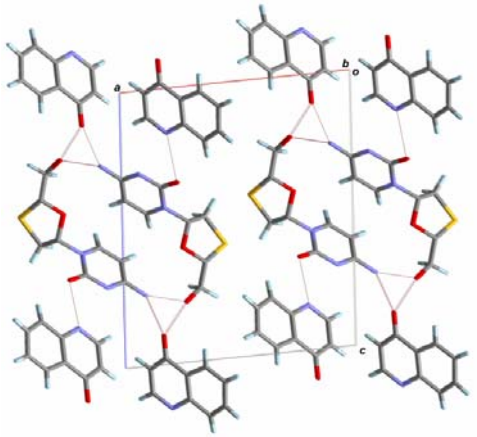


Figure 3. Packing of molecules in co-crystal **I**.

5.3 Crystal structure of co-crystal II (zidovudine+2,4,6-triaminopyrimidine 2:1)

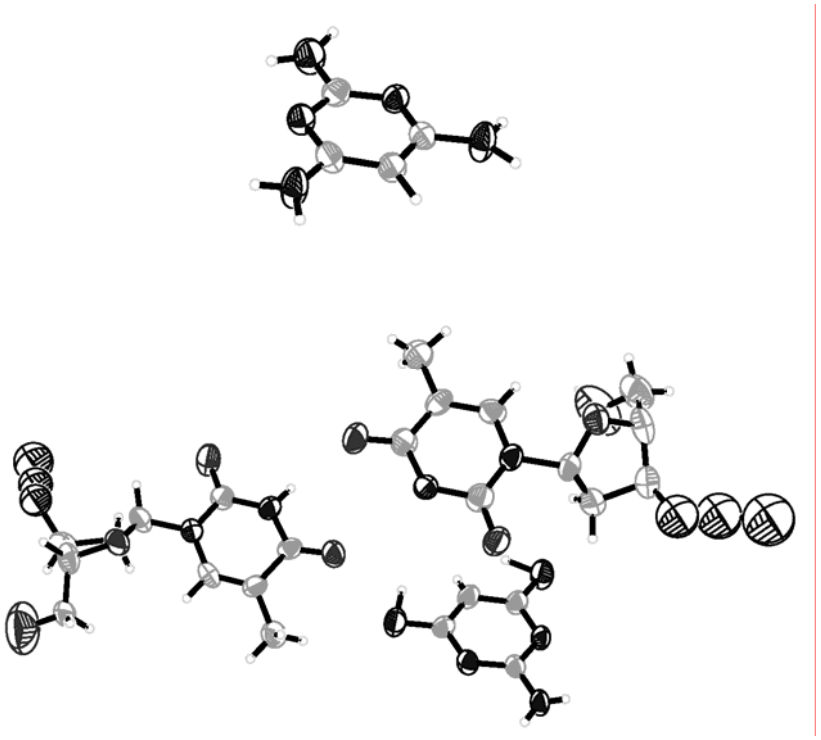


Figure 4. ORTEP diagram of co-crystal **II**.

Co-crystal **II** crystallises in space group *C*2 with two molecule of zidovudine and two half molecule of 2,4,6-triaminopyrimidine in the asymmetric unit (Figure 4). The trimer is made up of two zidovudine molecules and one 2,4,6-triaminopyrimidine and is held together by a three point (N–H…O, N… H–N, N–H…O) synthon which is a basic part of the crystal structure (Figure 5). These trimers are joined by two N–H…O hydrogen bonds to form an infinite 1D arrangement. This is further extended in 2D by O–H…N hydrogen bonds between different zidovudine molecules as shown in Figure 6. Additional O–H…O bonds between two zidovudine molecules in adjacent 2D layers extends the structure to the third dimension (Figure 7).

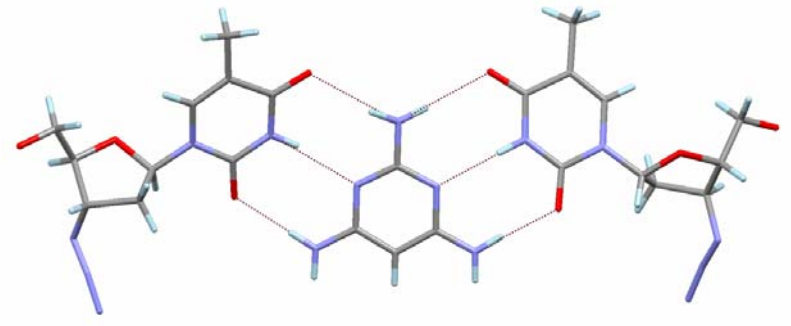


Figure 5. Trimer made up of two zidovudine molecule and one 2,4,6-triaminopyrimidine. Notice the three point synthon.

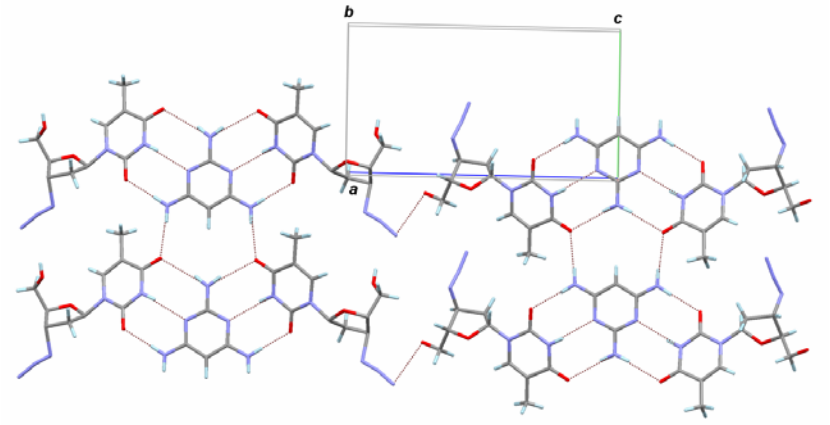
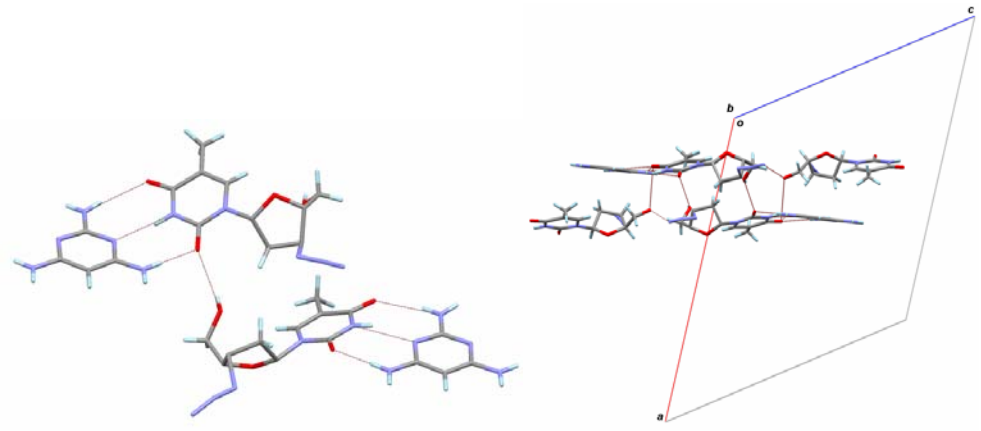


Figure 6. 2D arrangement of molecules in co-crystal **II**.



(a) (b)

Figure 7. (a) O–H…O hydrogen bond between zidovudine molecules of different layer and (b) two layers held together by O–H…O hydrogen bonds.

5.4 Crystal structure of co-crystal III (lamivudine+lamivudine dinitrosalicylate hydrate)

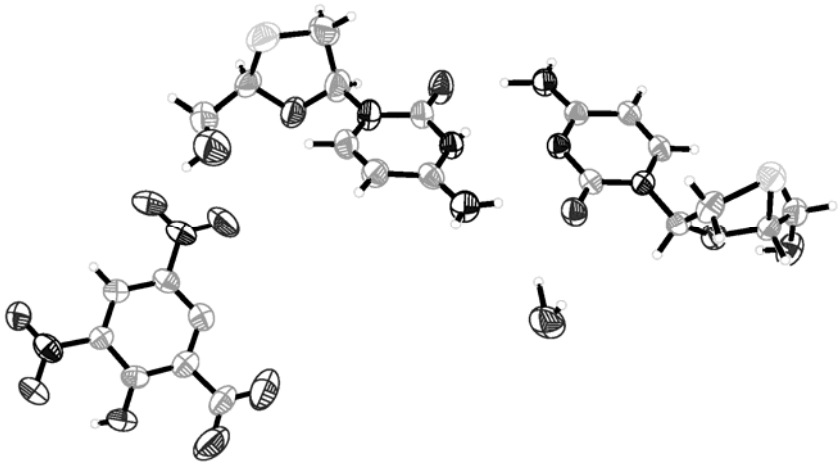


Figure 8. ORTEP diagram of co-crystal **III**.

Co-crystal **III** crystallises in space group $P2_1$ with one $(\text{lamivudine})^+$ cation, one $(\text{3,5-dintrosalicylic acid})^-$ anion, one molecule of lamivudine and one water molecule in the asymmetric unit (Figure 8). The structure contains a very complex hydrogen bonding pattern with multiple hydrogen bonding donors and acceptors. The dimer of $(\text{lamivudine})^+$ cation with a neutral lamivudine molecule is made up by a three point (N–H…O, $N^{(+)}$–H … N, O… H–N) synthon and is the basic structural unit of the structure as shown in Figure 9. These dimers give rise to a complex 3D structure by forming various hydrogen bonds with $(\text{3,5-dintrosalicylic acid})^-$ anion, water molecule and with other dimers (Figures 10 and 11).

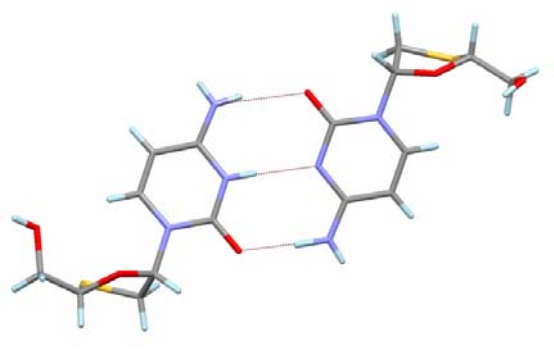


Figure 9. Dimer made up of neutral lamivudine molecule and one $(lamivudine)^{+}$ cation.

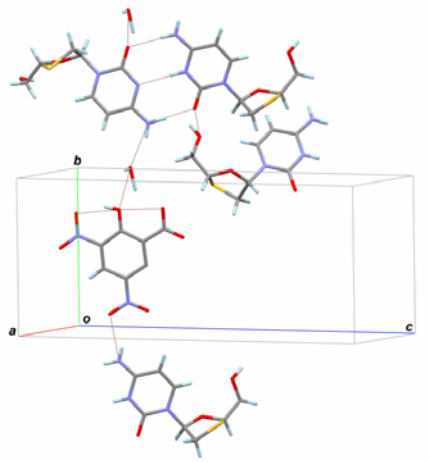


Figure 10. Some important hydrogen bonding interactions in co-crystal **III**.

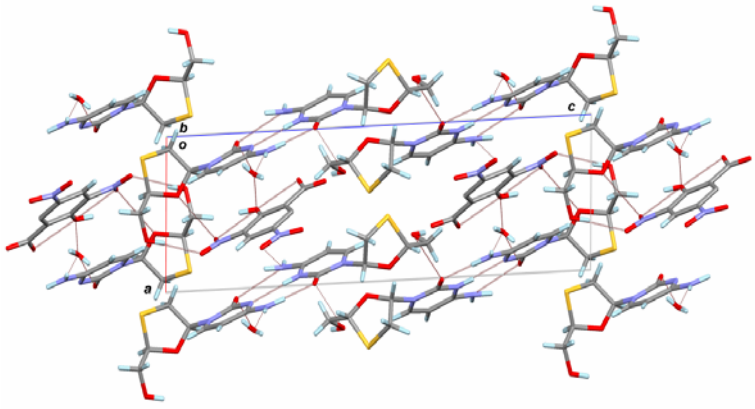


Figure 11. Packing of molecules in co-crystal **III**.

Table 1. Hydrogen bond metrics for the co-crystals in this study.

Co-crystal	Interaction	***d*/Å (H…A)**	***D*/Å (X…A)**	***θ*/deg ∠X–H…A**
I	N–H…O	1.97	2.951(4)	163
	N–H…O	1.90	2.824(3)	151
	N–H…O	1.77	2.774(3)	172
	O–H…N	2.24	2.824(3)	117
II	N–H…N	2.02	2.978 (4)	158
	N–H…O	2.22	3.213 (5)	169
	N–H…O	2.16	3.094(5)	154
	N–H…O	2.04	3.000(5)	159
	O–H…N	2.40	2.944(4)	114
	N–H…O	1.78	2.791(4)	178
	N–H…O	2.07	3.049(5)	164
	N–H…O	1.86	2.851(4)	168
	N–H…O	2.05	3.049(5)	169
	O–H…O	2.35	2.851(4)	111
III	N–H…O	1.88	2.839(7)	158
	N–H…O	2.12	2.983(7)	142
	N–H…O	1.79	2.797(6)	177
	N–H…O	2.03	2.853(6)	137
	N–H…N	1.83	2.836(5)	175
	O–H…O	2.27	2.916(6)	122
	O–H…O(intra)	1.73	2.511(7)	134
	O–H…O	1.89	2.860(5)	167

5.5 Thermal analysis

The thermal analysis of the co-crystal is very important as it gives an idea about the thermal stability and melting point. The result obtained from DSC experiments of co-crystals **I**, **II** and **III** are shown in Figures 12, 13 and 14 respectively. DSC experiments suggest that these co-crystals have considerable thermal stability. In case of co-crystals **II** and **III** co-crystal formation increase the melting point of the API.

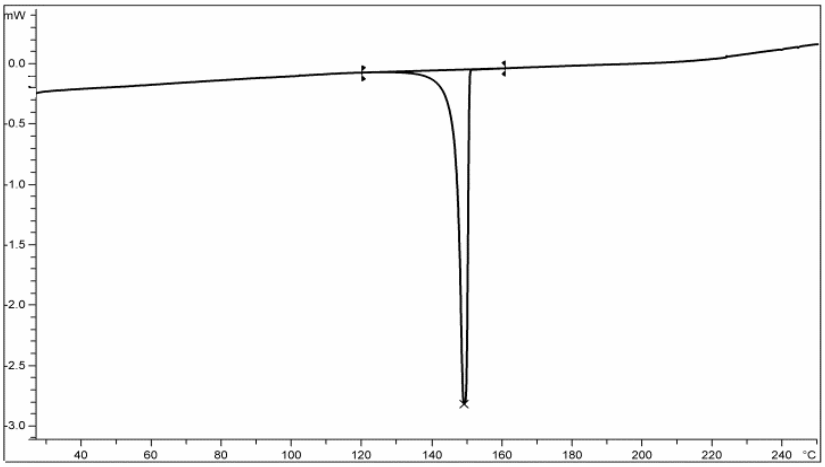


Figure 12. DSC curve of co-crystal **I**.

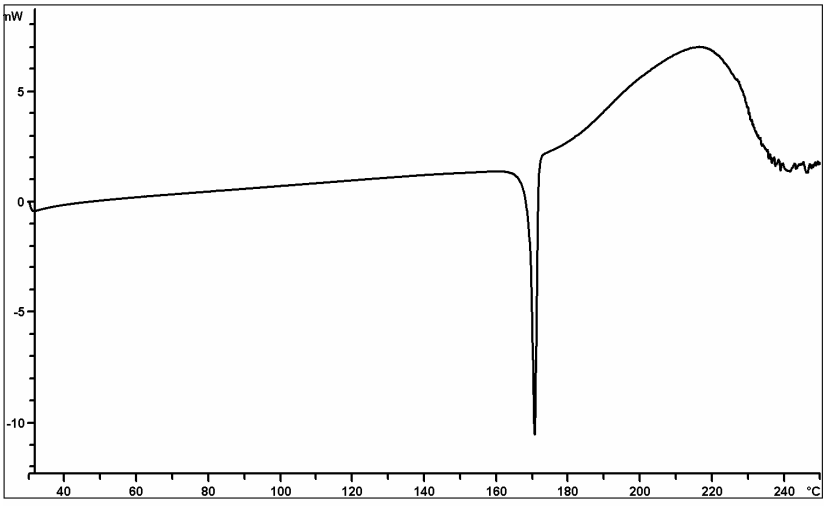


Figure 13. DSC curve of co-crystal **II.** Note that co-crystal **II** is higher melting than the API zidovudine (112˚C).

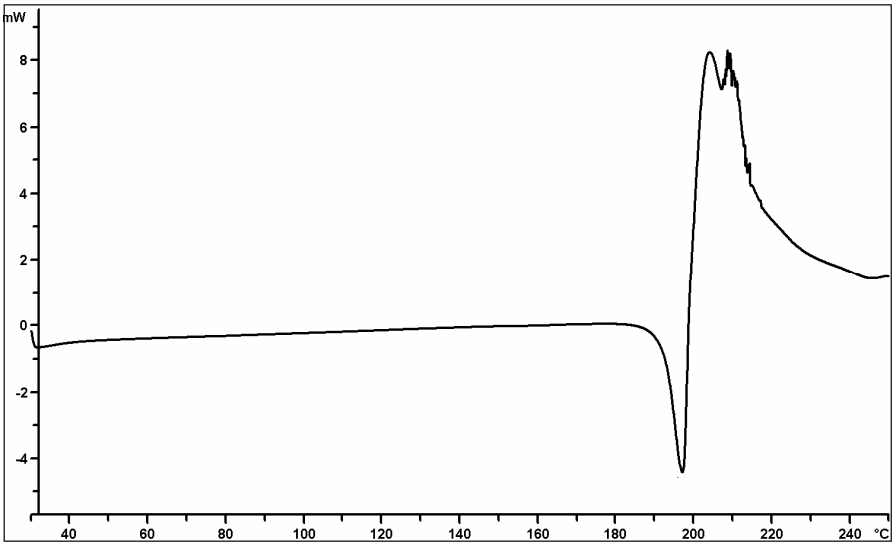


Figure 14. DSC curve of co-crystal **III**.

5.6 X-ray powder diffraction

PXRD patterns of bulk samples of the API co-crystals were recorded and compared with the simulated PXRD obtained from the single crystal data of the respective co-crystals. Least square refinement on respective experimental and simulated PXRD (Figures 15 and 16) affirms that in the case of co-crystals **I** and **II,** the bulk materials are identical to that of the single crystals. However, for co-crystal **III** the experimental PXRD pattern contains many extra peaks suggesting that the bulk material contains some material other than co-crystal **III**. This suggests that for co-crystal **I** and **II,** bulk crystallisation also produces the pure co-crystal.

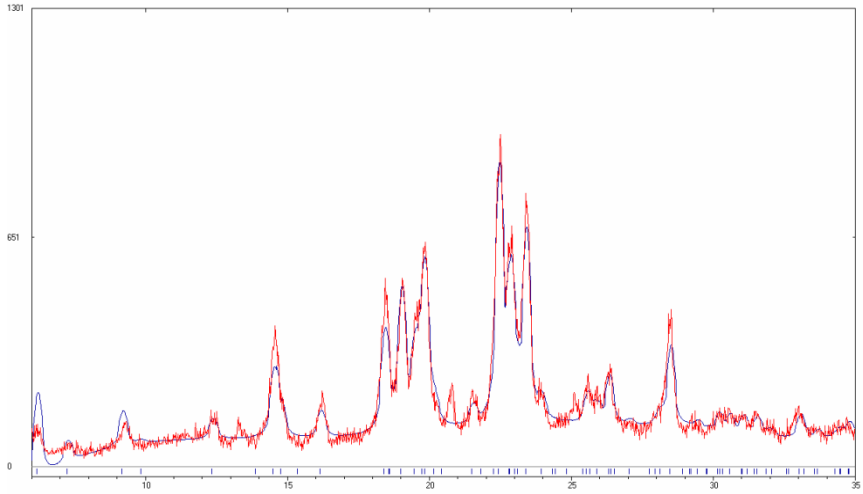


Figure 15. Comparison of simulated (blue) and experimental (red) PXRD patterns for co-crystal **I**.

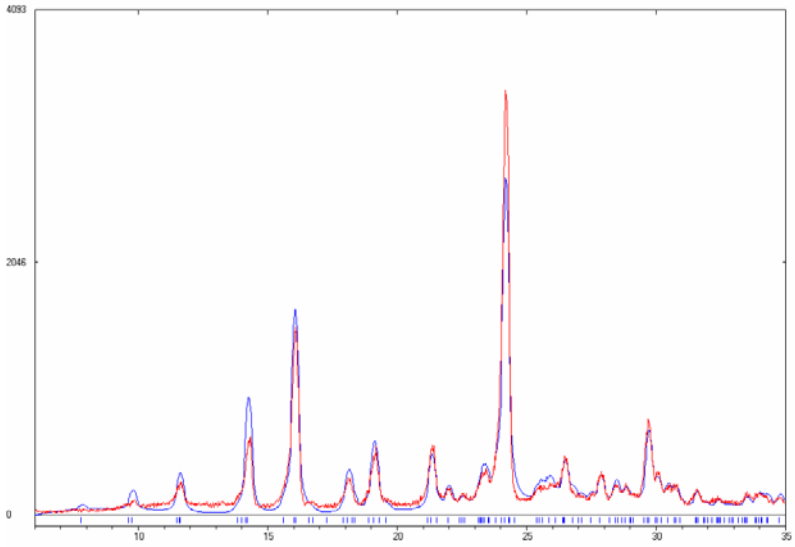


Figure 16. Comparison of simulated (blue) and experimental (red) PXRD patterns for co-crystal **II**.

5.7 Conclusion

Co-crystals reported here represent chemical extensions of lamivudine and zidovudine. These co-crystals can be further investigated for favorable properties with respect to the pure API. Co-crystals **II** and **III** contain three point synthons which can be

derived from molecular structures of co-crystal formers as suggested by Zaworotko and coworkers.[1,2] However, as it is well known many co-crystallization experiments based on synthon theory do not result in co-crystals. In contrast, co-crystal **I** although it contains many hydrogen bonds, there is no classical synthon in the structure.

5.8 Experimental section

Sample Preparation and Crystallisation

Co-crystals **I**, **II** and **III** were obtained by cocrystallisation of equimolar ratios of both components from EtOAc.

X-ray Crystallography

X-ray diffraction intensities for the co-crystals **I-III** were collected at 298K on a Bruker SMART 4K CCD diffractometer (Bruker Systems Inc.) using Mo K_α X-radiation.[7] Data were processed using the Bruker *SAINT* package[8] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[9] The structures of all the co-crystals were solved by direct methods and refined by full-matrix least-squares on F^2. Crystal data and details of data collections, structure solutions and refinements are summarized in appendix.

Thermal Analysis

Differential scanning calorimetry (DSC) was performed on a Mettler Toledo DSC 822e module. Crystals taken from the mother liquor were blotted dry on filter paper and placed crimped but vented aluminum sample pans for the DSC experiment. The sample amount in each case was 5-10 mg and temperature range was typically 30-250 °C at a heating rate of 0.5 °C min^{-1}. The samples were purged with a stream of N_2 flowing at 150 mL min^{-1}.

X-ray Powder Diffraction

Powder X-ray diffraction (PXRD) were recorded on a Pnalytical 1830 (Philips Systems Inc) diffractometer using Cu K_α X-radiation at 35 kV and 25 mA. Diffraction

patterns were collected over a range of 5-40º 2θ at a scan rate of 1º 2θ min^{-1}. The software Powder Cell 2.3 was used for least square refinement.[10]

5.9 References and notes

1. Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.,* **2004**, 1889.
2. S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des*., **2003**, *3*, 909.
3. J. F. Remenar, S. L. Morissette, M. L. Peterson, B. Moulton, J. M. MacPhee, H. R. Guzman and Ö. Almarsson, *J. Am. Chem. Soc*., **2003,** *125*, 8456.
4. S. L. Childs, L. J. Chyall, J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly and G. P. Stahly, *J. Am. Chem. Soc*., **2004**, *126*, 13335.
5. Z. Fox, U. B. Dragsted and J. Gerstoft, *Antiviral Therapy*, **2006**, *11*, 761.
6. H. Mitsuya, R. Yarchoan and S. Broder, *Science*, **1990**, *249*, 1533.
7. *SMART, Version 5.05*; Bruker AXS, Inc.: Madison, Wisconsin, **1998**.
8. *SAINT, Version 6.2*, Bruker AXS, Inc.: Madison, Wisconsin, **2001**.
9. G. M. Sheldrick, *SHELXTL V5.1*; Madison, WI, **1998**.
10. N. Kraus and G. Nolze, *POWDER CELL,* version 2.3; Federal Institute for Materials Research and Testing: Berlin, Germany, **2000**.

CHAPTER SIX

ALTERNATIVE METHOD FOR DETERMINATION OF ABSOLUTE CONFIGURATION OF CHIRAL COMPOUNDS BY CO-CRYSTAL FORMATION.

6.1 Introduction

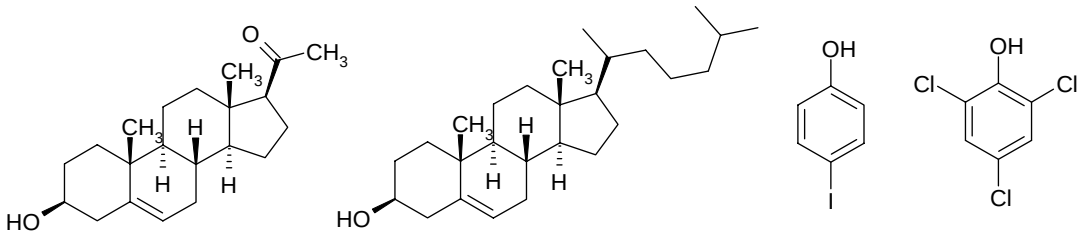
Determination of absolute configuration of a chiral compound is very important especially for pharmaceutical compounds as they are implicated in enzyme reactions, drug action and structure-function relationships.[1] There are many methods for determination of absolute configuration like circular dichroism (CD), NMR with chiral shift reagents, chemical correlation and X-ray crystallography.[2] Every method has its own set of advantages and limitations. Single crystal X-ray diffraction method is the most reliable and definitive method for determination of absolute configuration but it requires good quality single crystals and the compound should contain at least one atom heavier than Na for observing an appreciable amount of anomalous scattering of X-rays.[3]

When incident X-rays of moderately high energy are either scattered normally by an atom or absorbed and re-emitted at slightly different phase and intensity, this effect is called anomalous scattering. Since the anomalous photons are out of phase with the normal photons they will change both the intensity and phase of the scattered radiation. In a centrosymmetric crystal, the addition and subtraction of the anomalous photons will cancel out and they have no effect. However, for chiral crystals they will not cancel out hence Friedel's law would not be obeyed. In this case $|F_{h,k,l}| \neq |F_{\bar{h},\bar{k},\bar{l}}|$. Therefore one enantiomer will give a slightly better fit to the data because it will apply the correct sign to the interaction of the normal and anomalous radiation.[4] The Flack parameter is the best method to get correct absolute configuration.[5] This basically refines both forms at the same time and applies an occupancy of (1-x) to the form which is present and x to the other hand. Obviously x=0 suggests that assigned absolute configuration is correct and x=1 suggests that it is incorrect.

For reliable determination of absolute configuration it is necessary that the compound contains a heavy atom with a large anomalous component although there are

few isolated cases where the absolute configuration was determined by anomalous scattering from oxygen.[6] Because many organic compounds do not contain heavy atoms, such an atom can be introduced in the compound by salt formation. This is possible where the compound is capable of forming a salt. However, introduction of a heavy atom by chemical reaction is not always facile. The present chapter suggests an alternative method for the introduction of a heavy atom in the crystal structure by co-crystal formation. There are around 40 instances in the Cambridge Structural Database[7] (CSD) where the absolute configuration was determined by the help of a heavy atom present in the solvent included in the crystal structure. However solvent inclusion cannot be preplanned and only a small number of compounds form solvates. There are around seven co-crystals reported in the CSD where the absolute configuration was determined with the help of heavy atom present in co-crystal former. Refcodes for these co-crystals are BAHLAX10,[8] BUMPEE10,[8] CONPAW,[9] FEHMOU,[10] NUYBOY01,[11] SURLAS[12] and ZUSHEA.[13] However a closer look into the literature suggests that these co-crystals were not made to determine the absolute configuration but for other purposes like resolution and subsequently the absolute configuration was determined.

To establish this methodology, some steroid molecules were selected and cocrystallisation was attempted with compounds available in the laboratory. As a result, three co-crystals of pregnenolone and cholesterol were obtained.



1 **2** **3** **4**

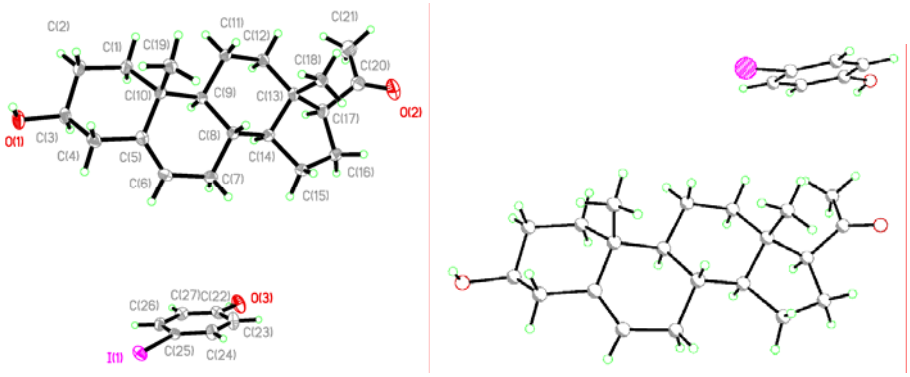
I = 1+3 **II = 1+4** **III = 2+3**

Scheme 1. Co-crystals of pregnenolone **1** and cholesterol **2** with 4-iodophenol **3** and 2,4,6 trichlorophenol **4**.

6.2 Crystal structure of co-crystal I (pregnenolone+4-iodophenol)

Co-crystal **I** crystallises in space group $P2_12_12_1$ with one molecule of pregnenolone and one molecule of 4-iodophenol in the asymmetric unit (Figure 1). Pregnenolone molecules form infinite 1D chains by head to tail recognition via O–H…O interactions between the –OH group and the >C=O group (Figure 2). 4-Iodophenol forms additional O–H…O hydrogen bonds with the pregnenolone molecules and close packs itself between the two adjacent chains of pregnenolone molecules as shown in Figure 3.

The determined absolute configuration of pregnenolone in co-crystal **I** is (3S, 8S, 9S, 10R, 13S, 14S, 17S) same to that of reported for pregnenolone.[14] The Flack parameter value 0.000(14) for assigned absolute configuration suggests that it is correct with high accuracy.



(a) (b)

Figure 1. Absolute configuration of pregnenolone in co-crystal **I**, shown as (a) 50% thermal ellipsoids and (b) ball and stick model.

Figure 2. Infinite linear arrangement of pregnenolone molecules and their interaction with 4-iodophenol in the crystal structure of **I**.

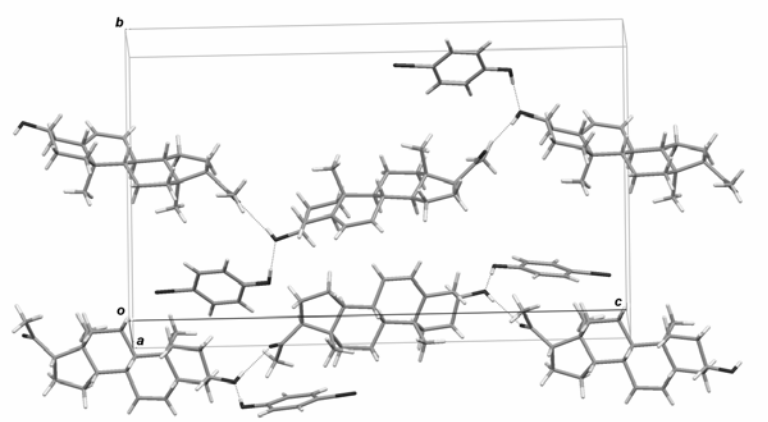
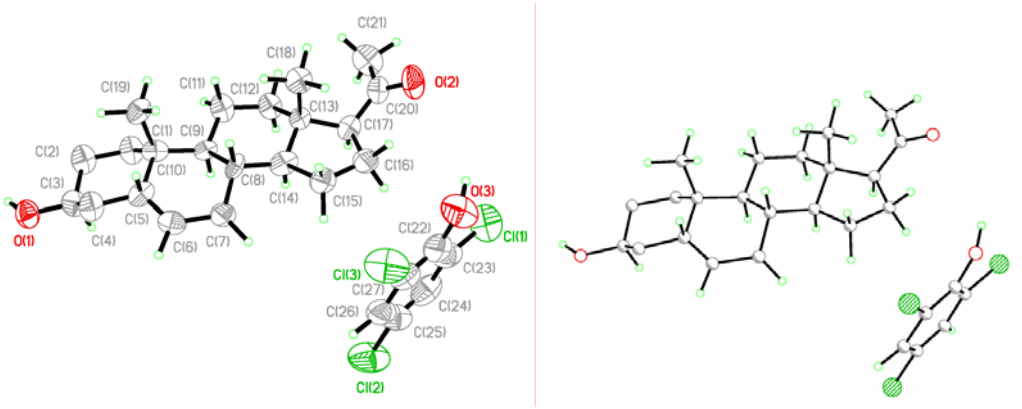


Figure 3. Packing of molecules in the crystal structure of **I**.

6.3 Crystal structure of co-crystal II (pregnenolone+2,4,6-trichlorophenol)

Co-crystal **II** crystallises in space group $P2_1$ with one molecule of pregnenolone and one molecule of 2,4,6-trichlorophenol in the asymmetric unit (Figure 4). The primary hydrogen bonding pattern in **II** is similar to that of **I** with pregnenolone molecules forming infinite 1D chains with O–H…O interactions and 2,4,6-trichlorophenol forming additional O–H…O hydrogen bonds with pregnenolone molecules and close packed itself between the two adjacent chains of pregnenolone molecules as shown in Figures 5 and 6. However the crystal structure of **II** differs with **I** in the shape of 1D chain and packing of the molecules.

The determined absolute configuration of pregnenolone in co-crystal **II** is (3S, 8S, 9S, 10R, 13S, 14S, 17S), which is the same as that reported for pregnenolone.[14] The Flack parameter value 0.0(2) for the assigned absolute configuration suggests that it is correct. This is further confirmed by the Flack parameter value 1.3(2) for the inverted structure.



(a) (b)

Figure 4. Absolute configuration of pregnenolone in co-crystal **II**, shown as (a) 50% thermal ellipsoids and (b) ball and stick model.

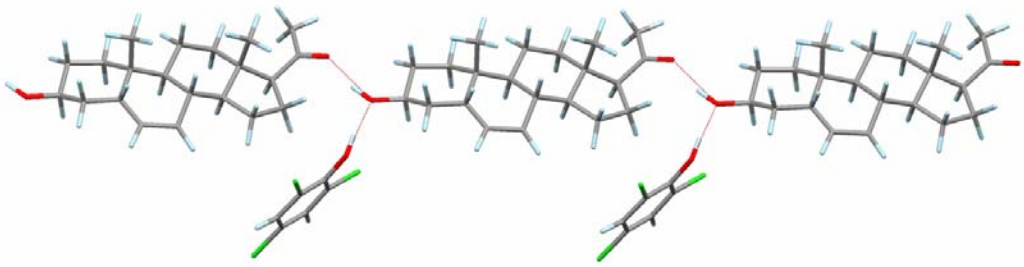


Figure 5. Infinite linear arrangement of pregnenolone molecules and their interactions with 2,4,6-trichlorophenol in the crystal structure of **II**.

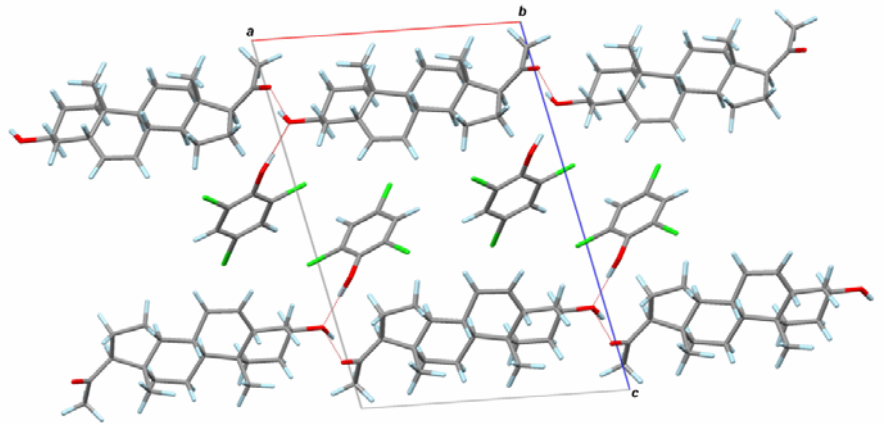
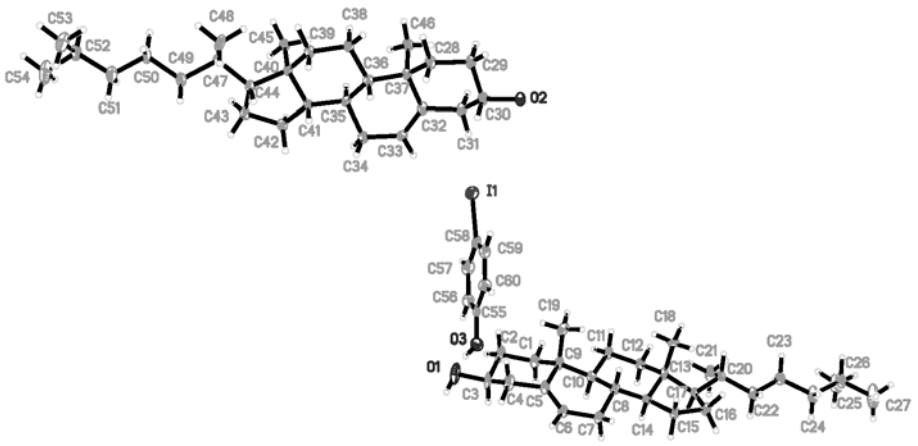


Figure 6. Packing of molecules in the crystal structure of **II**.

6.4 Crystal structure of co-crystal III (cholesterol+4-iodophenol 2:1)

Co-crystal **III** crystallises in space group $P2_1$ with two molecules of cholesterol and one molecule of 4-iodophenol in the asymmetric unit (Figure 7). Hydroxy groups of cholesterol and 4-iodophenol form infinite cooperative chains of O–H…O hydrogen bonds as shown in Figure 8. These 1D chains are further connected by I…O interactions between 4-iodophenol and cholesterol molecules respectively to give rise to a 2D network as shown in Figures 9 and 10.

The determined absolute configuration of cholesterol in co-crystal **III** is (3S, 8S, 9S, 10R, 13R, 14S, 17R), which is the same as that reported for cholesterol.[15] The Flack parameter value 0.008(13) for the assigned absolute configuration suggests that it is correct.



(a)

(b)

Figure 7. Absolute configuration of cholesterol in co-crystal **III**, shown as (a) 50% thermal ellipsoids and (b) ball and stick model.

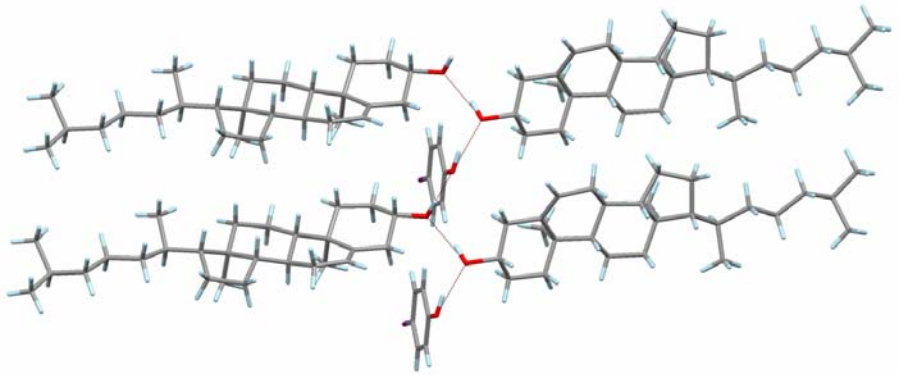


Figure 8. Infinite O–H…O hydrogen bond chain made up by hydroxyl groups of cholesterol and 4-iodophenol in the crystal structure of **III**.

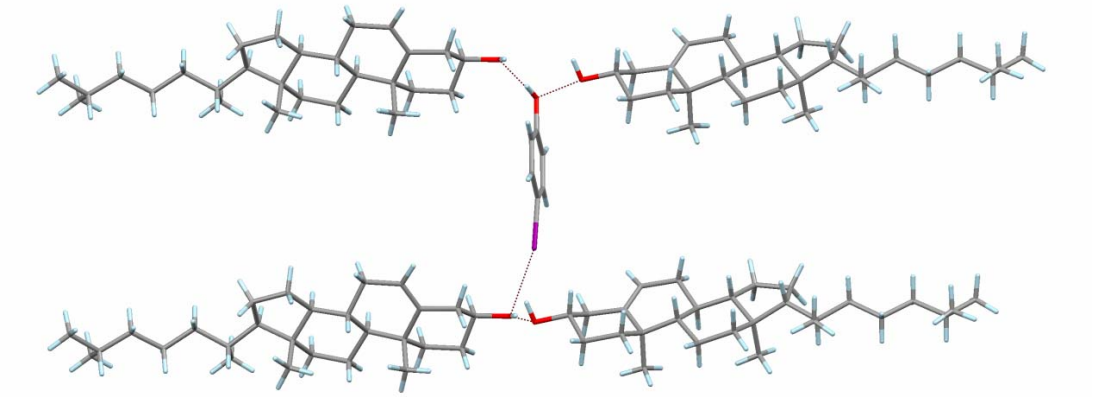


Figure 9. I…O interaction between 4-iodophenol and cholesterol molecules in the crystal structure of **III**.

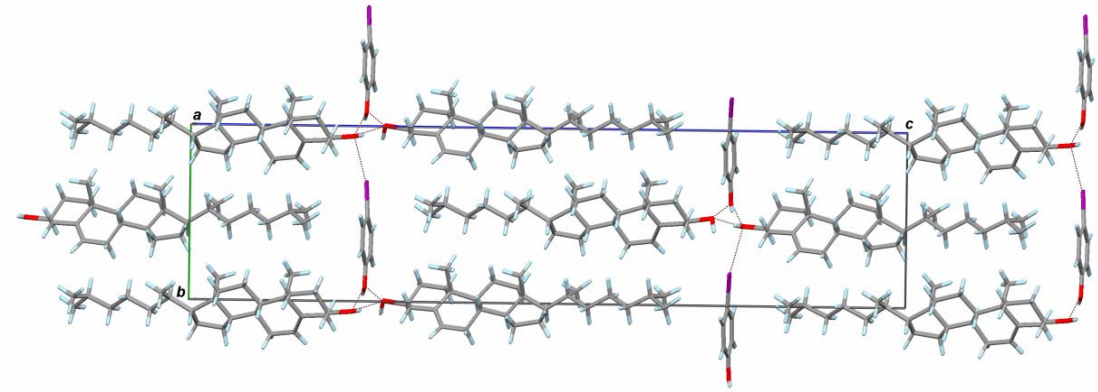


Figure 10. Packing arrangement of molecules in the crystal structure of **III**.

Table 1. Hydrogen bond metrics for the co-crystals in this study.

Co-crystal	Interaction	*d*/Å (H…A)	*D*/Å (X…A)	*θ*/deg ∠X–H…A
I	O–H…O	1.76	2.731(3)	170
	O–H…O	1.68	2.663(3)	176
II	O–H…O	1.82	2.851(4)	166
	O–H…O	1.66	2.613(4)	173
	C–H…Cl	2.74	3.700(9)	147
III	O–H…O	1.94	2.704(5)	133
	O–H…O	1.66	2.620(4)	165
	O–H…O	1.69	2.652(4)	164

6.5 Conclusion

Co-crystals **I**, **II** and **III** provide examples where the absolute configurations of target compounds were determined using heavy atoms of a co-crystal former and confirmed with the reported absolute configuration of the respective compounds. This method can be used for compounds with unknown absolute configuration which do not contain heavy atoms. In compounds containing acidic or basic groups, the heavy atom can be introduced by salt formation but in cases where salts do not form good single crystals or where the compounds are sensitive to pH, co-crystal formation can be tried. Compounds which do not contain heavy atoms and salt forming groups have to rely on chemical reactions for this purpose, which is not always feasible and in some cases reaction condition may lead to inversion or racemisation. Liquid compounds without salt forming groups can be also crystallised by co-crystal formation and absolute configuration can be determined.

However, co-crystals cannot always be designed. The synthon based strategy although it suggests possible co-crystal formers, cannot suggest whether a particular co-crystal will be formed or not.[16] Hence co-crystals are generally obtained by trial and error methods, and these may be time-consuming and tedious. However, with the advent of high-throughput technology it should not be very difficult to get co-crystals for a particular compound as large number of experiments can be carried out and the results analysed simultaneously.[17]

In short, an alternative methodology for the determination of absolute configuration by co-crystal formation is proposed in the present chapter. It is not always superior to existing methodologies for the determination of absolute configuration but in some cases it could be advantageous to choose this method as it can complement some of the drawbacks of existing methods.

6.6 Experimental section

Sample preparation and crystallisation

Co-crystals **I**, **II** and **III** were obtained by cocrystallisation of equimolar ratios of both components from EtOAc.

X-ray Crystallography

X-ray diffraction intensities for the co-crystals **I** and **III** were collected at 100K (Bruker Cryosystems cooler) and co-crystal **II** at 298K on a Bruker SMART 4K CCD diffractometer (Bruker Systems Inc.) using Mo K_α X-radiation.[18] Data were processed using the Bruker *SAINT* package[19] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[20] The structures of all the co-crystals were solved by direct methods and refined by full-matrix least-squares on F^2. Crystal data and details of data collections, structure solutions and refinements are summarized in appendix.

6.7 References and notes

1. C. McManus, *Right Hand, Left Hand*, Phoenix Publishers, Phoenix, **2003**. (b) M. Gardner, The *New Ambidextrous Universe: Symmetry and Asymmetry for Mirror Reflections to Superstrings*, Dover publications, Mineola, **2005**.
2. E. L. Eliel, S. H. Wilen and M. P. Doyle, *Basic Organic Stereochemistry*, Wiley Interscience, New York, **2001**.
3. W. Massa, *Crystal Structure Determination*, Springer, Berlin, **2000**.
4. (a) J. M. Bijvoet, *Proc. Kon. Ned. Akad. Wet.*, **1949**, *52*, 313. (b) A. F. Peerdeman, A. J. von Bommel and J. M. Bijvoet, *Nature*, *Lond*., **1951**, *165*, 271. (c) A. F. Peerdeman, A. J. von Bommel and J. M. Bijvoet, *Proc. Kon. Ned. Akad. Wet*., **1951**, *54*, 16. (d) J. M. Bijvoet, *Nature*, **1954**, *173*, 888.
5. H. D. Flack, *Acta Crystallogr.*, *Sect. A*, **1983**, *39*, 881.
6. (a) H. Hope and U. de la Camp, *Acta Crystallogr.*, *Sect. A*, **1972**, *28*, 201. (b) D. W. Engel, *Acta Crystallogr.*, *Sect. B*, **1972**, *28*, 1496. (c) D. Rabinovich and H. Hope, *Acta Crystallogr.*, *Sect. A*, **1980**, *36*, 670.
7. (a) F. H. Allen, O. Kennard and R. Taylor, *Acc. Chem. Res*., **1983**, *16*, 146. (b) F. H. Allen, *Acta Crystallogr. Sect. B*, **2002**, *58*, 380.
8. F. Toda, K. Tanaka, H. Ueda and T. Oshima, *Isr. J. Chem*., **1985**, *25***,** 338.
9. F. Toda, K. Tanaka and T. C. W. Mak, *Chem. Lett*., **1984**, 2085.
10. Y. Weisinger-Lewin, M. Vaida, R. Popovitz-Biro, H. C. Chang, F. Mannig, F. Frolow, M. Lahav and L. Leiserowitz, *Tetrahedron*, **1987**, *43*, 1449.
11. J. Zhu, Z. Zhou, F. Fu, J. Deng, A. Mi, Y. Jiang and T. Chau, *Chem. J. Chin. Univ*., *Chinese Edition*, **1999**, *20***,** 1081.
12. D. Hashizume, Y. Ohashi, K. Tanaka and F. Toda, *Bull. Chem. Soc*. Jpn., **1994**, *67*, 2383.
13. J. Bao, W. D. Wulff, J. B. Dominy, M. J. Fumo, E. B. Grant, A. C. Rob, M. C. Whitcomb, S. Yeung, R. L. Ostrander and A. L. Rheingold, *J. Am. Chem. Soc.*, **1996**, *118*, 3392.
14. A. Magyar, Z. Szendi, P. Forgó, M. Mák, H. Görls and F. Sweet, *Steroids*, **2004**, *69*, 35.

15. J. W. Cornforth, I. Youhotsky and G. Popják, *Nature*, **1954**, *173*, 536.
16. (a) Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.,* **2004**, 1889. (b) S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des*., **2003**, *3*, 909.
17. S. L. Morissette, Ö. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A.V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, *Adv. Drug Deliv. Rev*., **2004**, *56*, 275.
18. *SMART, Version 5.05*; Bruker AXS, Inc.: Madison, Wisconsin, **1998**.
19. *SAINT, Version 6.2*, Bruker AXS, Inc.: Madison, Wisconsin, **2001**.
20. G. M. Sheldrick, *SHELXTL V5.1*; Madison, WI, **1998**.

CHAPTER SEVEN
SUMMARY AND OUTLOOK

Crystal structures of the materials determine many physical properties like solubility, dissolution rate, bioavailability and stability which are very important especially for pharmaceutical materials. Hence it is crucial for pharmaceutical industries that properties of various solid state modifications like polymorphs, co-crystals, solvates, salts and amorphous forms of Active Pharmaceutical Ingredients (API) are investigated vigorously and that candidates with favorable properties are identified and used for further studies.

The ultimate goal of *Crystal Engineering* is to design and predict the crystal structure of an organic solid and its properties from the molecular structure but this goal is still not achieved in real sense. However, pioneering work by Pepinsky,[1] Schmidt,[2] Dunitz,[3] Desiraju[4] and others and a large amount of crystal structure data gathered in the Cambridge Structural Database[5] (CSD) over the years have enriched the subject enough so that it can provide guidelines in designing novel pharmaceutical materials with desired properties. In this thesis I have studied some solid state modifications of APIs and their favourable properties by using some of the crystal engineering principles.

Chapter 2 of the thesis describes less explored saccharinate salts of APIs and their favourable properties establishing saccharin as a salt former worth trying during salt selection studies of APIs by forming the saccharinate salts of quinine, haloperidol, mirtazapine, pseudoephedrine, lamivudine, risperidone, sertraline, venlafaxine, zolpidem and amlodipine. These salts have been characterized with single crystal X-ray methods. The structures contain many hydrogen bonds of the O–H…$N^{(-)}$, $N^{(+)}$–H…$N^{(-)}$, $N^{(+)}$–H…O, N–H…O, O–H…O and N–H…N type, with auxiliary C–H…$N^{(-)}$ and C–H…O interactions. These saccharinates are generally very water soluble when compared to the free base. Additionally, aqueous solutions of these API saccharinates are of moderate pH. Both these properties may be advantageous in the pharmaceutical industry. In general, most saccharinates would appear to have high water solubility, and this follows from the molecular structure of the anion which is donor-poor and acceptor-rich in terms

of hydrogen bonding functionalities. If an API of insufficient basicity is treated with saccharin it may form a hydrogen bonded co-crystal wherein proton transfer from saccharin to the API does not take place. This phenomenon was found in the co-crystal saccharin–piroxicam.

In the Chapter 3, two stable amorphous modifications of desloratadine saccharinate are reported as their normal and acid salts along with the desloratadine and desloratadine hydrochloride as crystalline modifications of desloratadine. The amorphous desloratadine saccharinates have higher solubilities than their marketed crystalline counterparts and they are also fairly stable in the dry condition. Amorphous des sac also shows promise to be used for drug delivery by inhalation route as a spray or powder formulation, and this has many advantages over the conventional oral route. The pH 5.8 of the saturated solution of des sac is ideal for its use for inhalation formulations. The most salient feature of the amorphous desloratadine saccharinates is that the amorphous forms are very stable and do not convert readily to the crystalline form. Indeed, several attempts to obtain the crystalline form of desloratadine saccharinate were unsuccessful.

Chapter 4 focuses on little known type of polymorphs namely *tautomeric polymorphism*[5] by taking the example of anti ulcer- drug Omeprazole. Omeprazole was crystallized in five different forms containing different compositions of 5-methoxy and 6-methoxy tautomers. Crystals containing 0%, 8%, 10%, 12% and 15% 5-methoxy tautomer were prepared by different methods. What is interesting is that the crystal packing is such that the MeO-group may be situated either at the 5- or 6- position of the benzimidazole ring without affecting the overall packing of molecules. Accordingly, these crystals may be viewed as substitutional solid solutions of 5-methoxy tautomers in 6-methoxy tautomers. This can be visualized as varying amount of 5-methoxy tautomers randomly located in the crystal lattice of 6-methoxy tautomers. Simulated PXRD patterns of the crystals showed that the forms reported in patents as A, B and C correspond to crystals **III**, **V** and **IV** respectively. Structurally speaking, forms A, B and C occur in a structural continuum that begins with a pure 6-methoxy tautomer crystal and ends with an 85:15 mixture of 6-methoxy and 5-methoxy tautomers. This raises a series

of questions like: How many polymorphs of omeprazole really exist? Is it one or two or infinite? Would each 5-methoxy:6-methoxy composition qualify for independent patent protection or would it be more meaningful to claim protection for compositional ranges?

Pharmaceutical co-crystals are important because they can improve many properties of parent API like solubility, dissolution rate, stability, crystallinity and many more.[6] Co-crystals of the anti HIV drugs lamivudine and zidovudine are discussed in Chapter 5. Cocrystallisation of lamivudine with 4-quinolinone and lamivudine with 3,5-dinitrosalicylicacid result in co-crystals. Zidovudine forms a co-crystal with 2,4,6-triaminopyrimidine. These co-crystals are characterized by crystallographic and thermal methods.

Chapter 6 exemplifies a new strategy for the determination of absolute configuration using anomalous scattering by co-crystal formation with the co-crystal former containing a heavy atom. Among various methods available for the determination of absolute configuration, single crystal x-ray diffraction using anomalous scattering is one of the easiest and most reliable. However, the limitations of this method are that the compound should contain an atom heavier than Si and further a single crystal of compound is required. There are a large number of organic compounds which do not contain heavy atoms and also do not contain any salt forming group so that the heavy atom cannot be introduced so easily. Co-crystal formation could be an alternate method for such compounds to introduce a heavy atom in the structure and consequently for the determination of absolute configuration. Cocrystallisation experiments with pregnenolone and cholesterol results in co-crystals with 4-iodophenol and 2,4,6-trichlorophenol. Determination of absolute configuration using the Flack parameter showed that the determined absolute configuration matches with the reported absolute configuration of pregnenolone and cholesterol with high accuracy. This method can be further used for the determination of absolute configuration of the compound with unknown stereochemistry in which heavy atoms cannot be introduced easily by traditional methods.

In summary various important aspects of solid state chemistry of APIs, mainly structural, are discussed in this thesis. Further biological and physiological study may

make it possible for some of the solid state modifications to use them for real applications.

References and notes

1. R. Pepinsky, *Phys. Rev*., **1955**, *100*, 971.
2. G. M. J. Schmidt, *Pure Appl. Chem*., **1971**, *27*, 647.
3. J. D. Dunitz, *Pure Appl. Chem*., **1991**, *63*, 177.
4. G. R. Desiraju, *Crystal Engineering*: *The Design of Organic Solids*, Elsevier: Amsterdam, **1989**.
5. (a) F. H. Allen, O. Kennard and R. Taylor, *Acc. Chem. Res*., **1983**, *16*, 146. (b) F. H. Allen, *Acta Crystallogr*., *Sect. B*, **2002**, *58*, 380.
6. Ö. Almarsson and M. J. Zaworotko, *Chem. Commun*., **2004**, 1889.

APPENDIX

Table 1. Crystallographic data for the structures discussed in this thesis.

Chapter 2			
	I	**II**	**III**
Empirical formula	$(C_{20}H_{25}N_2O_2)$. $(C_7H_4NO_3S)$	$(C_{21}H_{24}ClFNO_2)$ $(C_7H_4NO_3S)$	$(C_{17}H_{20}N_3)$. $(C_7H_4NO_3S)$ $(H_2O)_{1.34}$
Formula wt.	507.60	559.04	473.84
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1/n$	$P2_1/c$
a [Å]	9.607(3)	19.0609(10)	9.5791(12)
b [Å]	8.634(3)	7.2197(4)	26.733(3)
c [Å]	30.371(9)	21.5624	9.4055(12)
α [deg]	90	90	90
β [deg]	90	113.961(2)	90
γ [deg]	90	90	90
Z	4	4	4
V [Å^3]	2519.2(13)	2711.6(3)	2270.2(5)
D_{calc} [g/cm^3]	1.341	1.363	1.381
T [K]	100(2)	100(2)	100(2)
μ [mm^{-1}]	0.172	0.266	0.184
2θ range	2.64–52.04	4.68–51.98	3.04–52.04
Index ranges	$-8 \le h \le 10$	$-21 \le h \le 23$	$-11 \le h \le 11$
	$-9 \le k \le 10$	$-8 \le k \le 138$	$-28 \le k \le 32$
	$-33 \le l \le 37$	$-22 \le l \le 23$	$-11 \le l \le 11$
N-total	8453	11182	12697
N-independent	2445	4610	4002
N-observed	2953	3746	3485
Parameters	341	455	323
R_1	0.0709	0.0554	0.0422
wR_2	0.1690	0.1360	0.1335
GOF	0.971	1.032	1.055

Table 1. *Continued…*

Chapter 2			
IV	**V**	**VI**	**VII**
$(C_{10}H_{16}NO)$	$(C_8H_{12}N_3O_3S)$	$(C_{23}H_{28}FN_4O_2)_2$	$(C_{17}H_{18}Cl_2N)$
$(C_7H_4NO_3S)$	$(C_7H_4NO_3S)$	$(C_7 H_4NO_3S)_2$ 1.4 H_2O	$(C_7H_4NO_3S)$
348.42	412.44	1212.12	488.39
Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
$P2_1$	$P2_12_12_1$	$P2_1/n$	$P2_12_12_1$
6.9782(12)	5.3464(6)	14.4779(19)	6.4795(4)
14.496(3)	13.7459(14)	30.295(4)	9.6134(6)
8.2132(14)	22.738(2)	14.8080(19)	36.202(2)
90	90	90	90
92.983(2)	90	118.081(2)	90
90	90	90	90
2	4	8	4
829.7(3)	1671.1(3)	5730.4(13)	2255.0(2)
1.395	1.639	1.406	1.439
100(2)	100(2)	100(2)	100(2)
0.219	0.364	0.172	0.410
4.96–52.03	4.64–52.08	3.4–50.00	4.34–50.00
$-8 \le h \le 8$	$-6 \le h \le 6$	$-17 \le h \le 17$	$-7 \le h \le 7$
$-13 \le k \le 17$	$-16 \le k \le 16$	$-36 \le k \le 36$	$-11 \le k \le 11$
$-10 \le l \le 9$	$-17 \le l \le 26$	$-17 \le l \le 14$	$-43 \le l \le 38$
3465	6667	32247	9645
2411	3197	10079	3973
2229	3117	6382	3857
297	308	792	306
0.0383	0.0257	0.0679	0.0446
0.0918	0.0676	0.1756	0.0903
1.042	1.051	1.011	1.064

Table 1. *Continued…*

Chapter 2			
VIII	**IX**	**X**	**XI**
($C_{20}H_{27}ClN_2O_5$)	($C_{17}H_{28}NO_2$)	($C_{19}H_{22}N_3O$)	$C_{15}H_{13}N_3O_4S$).
(C_7H_4 NO_3S) H_2O	($C_7H_4NO_3S$)	($C_7H_4NO_3S$)	($C_7H_5NO_3S$)
609.07	460.58	490.57	514.52
Triclinic	Monoclinic	Monoclinic	Triclinic
$P\bar{1}$	$P2_1/n$	$C2/c$	$P\bar{1}$
7.8070(6)	11.8821(12)	31.293(4)	9.5117(8)
7.9325(6)	10.5439(11)	9.3226(10)	10.3862(9)
24.745(2)	19.195(2)	22.381(3)	12.6635(11)
97.185(4)	90	90	66.983(2)
93.027(4)	104.843(1)	133.388(3)	71.011(2)
112.628(4)	90	90	89.380(2)
2	4	8	2
1394.83(19)	2324.5(4)	4745.1(9)	2519.2(13)
1.450	1.316	1.373	1.589
100(2)	100(2)	100(2)	100(2)
0.271	0.177	0.178	0.303
3.66–50.00	3.58–50.00	5–49.42	3.72–52.03
$-14 \le h \le 14$	$-37 \le h \le 37$	$-9 \le h \le 8$	$-11 \le h \le 10$
$-12 \le k \le 12$	$-10 \le k \le 11$	$-8 \le k \le 9$	$-11 \le k \le 12$
$-22 \le l \le 22$	$-26 \le l \le 26$	$-29 \le l \le 29$	$-15 \le l \le 11$
10981	27177	22689	7625
4724	4087	4179	4011
2700	3788	3662	3208
417	420	369	388
0.1342	0.0487	0.0370	0.0479
0.3730	0.1111	0.0947	0.1262
1.050	1.112	1.045	1.017

Table 1. *Continued…*

Chapter 3		*Chapter 4*		
I	**II**	**I**	**II**	**III**
$(C_{19}H_{19}ClN_2)$	$(C_{19}H_{19}ClN_2)$ HCl	$(C_{17}H_{19}N_3O_3)$	$(C_{17}H_{19}N_3O_3)$	$(C_{17}H_{19}N_3O_3)$
310.81	347.2	345.42	345.42	345.42
Monoclinic	Triclinic	Triclinic	Triclinic	Triclinic
$P2_1$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
100(2)	298(2)	100(2)	100(2)	100(2)
6.9336(12)	5.1772(11)	9.6421(9)	9.667(7)	9.638(5)
11.998(2)	10.122(2)	10.3865	10.337(8)	10.264(5)
9.4691(16)	17.427(4)	10.1539	10.292(8)	10.324(5)
90	101.364(4)	89.929(2)	90.044(12)	90.085(9)
9.4691(16)	90.686(4)	110.939(2)	111.552(12)	111.732(8)
90	103.836(3)	116.937(2)	116.451(11)	116.288(8)
2	2	2	2	2
9.4691(16)	867.7(3)	830.78(14)	839.6(11)	833.7(8)
1.373	1.329	1.381	1.366	1.376
0.252	0.375	0.216	0.213	0.215
4.24 –52.28	4.5–52.08	4.22–52.14	4.34–52.14	4.52–46.94
$-8 \le h \le 8$	$-6 \le h \le 6$	$-11 \le h \le 11$	$-11 \le h \le 11$	$-11 \le h \le 10$
$-13 \le k \le 14$	$-12 \le k \le 12$	$-12 \le k \le 12$	$-12 \le k \le 12$	$-12 \le k \le 12$
$-8 \le 1 \le 8$	$-21 \le l \le 21$	$-12 \le l \le 12$	$-12 \le l \le 12$	$-12 \le l \le 12$
4424	9011	9197	7586	6800
2661	3439	3262	3248	3281
2550	1958	2723	1950	1824
207	217	225	237	249
0.0320	0.0647	0.0566	0.0532	0.0620
0.0754	0.1716	0.1268	0.1411	0.1795
1.047	1.069	1.106	0.981	0.988

Table 1. *Continued…*

Chapter 4		*Chapter 5*		
IV	**V**	**I**	**II**	**III**
$(C_{17}H_{19}N_3O_3)$	$(C_{17}H_{19}N_3O_3)$	$(C_8H_{11}N_3O_3S)$ (C_9H_7NO)	$2(C_{10}H_{13}N_5O_4)$ $(C_4H_7N_5)$	$(C_8H_{11}N_3O_3S)$ $(C_8H_{12}N_3O_3S)$ $(C_7H_4N_2O_7)$ H_2O
345.42	345.42	538.47	659.63	705.6
Triclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
$P\bar{1}$	$P\bar{1}$	$P2_1$	$C2$	$P2_1$
100(2)	298(2)	298(2)	298(2)	298(2)
9.6439(16)	9.701(3)	12.15(2)	22.737(5)	7.719(4)
10.2621(17)	10.259(3)	5.079(9)	8.422(2)	9.124(5)
10.3322(17)	10.694(3)	14.41(2)	19.036(5)	21.059(12)
90.216(2)	91.720(4)	90	90	90
111.762(2)	112.117(4)	94.47(3)	125.881(3)	93.296(8)
116.113(2)	115.642(4)	90	90	90
2	2	2	2	2
835.5(2)	864.8(4)	887(3)	2953.5(12)	1480.7(14)
1.373	1.326	1.394	1.477	1.578
0.214	0.207	0.213	0.115	0.263
4.04 –54.96	2.22–52.14	2.82–53.42	2.64–52.08	2.88–52.78
$-9 \le h \le 9$	$-11 \le h \le 11$	$-15 \le h \le 15$	$-14 \le h \le 14$	$-9 \le h \le 9$
$-19 \le k \le 19$	$-12 \le k \le 12$	$-6 \le k \le 6$	$-17 \le k \le 17$	$-10 \le k \le 11$
$-13 \le 1 \le 13$	$-13 \le l \le 13$	$-17 \le l \le 18$	$-21 \le 1 \le 21$	$-26 \le l \le 20$
11510	8775	6594	13213	7342
4895	3373	3412	4964	4705
4233	1736	2112	2120	3981
249	249	206	328	462
0.0576	0.0611	0.2123	0918	0.0596
0.1539	0.1666	0.3459	0.2914	0.1760
1.182	0.984	1.163	1.060	1.032

Table 1. *Continued…*

Chapter 6		
I	**II**	**III**
$(C_{21}H_{32}O_2)$	$(C_{21}H_{32}O_2)$	$2(C_{27}H_{46}O)$
(C_6H_5IO)	$(C_6H_3Cl_3O)$	(C_6H_5IO)
536.47	513.90	993.28
Orthorhombic	Monoclinic	Monoclinic
$P2_12_12_1$	$P2_1$	$P2_1$
100(2)	298(2)	100(2)
6.1375(6)	12.211(5)	6.3022(4)
15.5472(15)	6.166(2)	10.2952(6)
25.751(3)	17.398(7)	41.964(3)
90	90	90
90	102.607(7)	91.032(1)
90	90	90
4	2	4
2457.1(4)	1278.3(9)	2722.3(3)
1.450	1.335	1.212
1.329	0.385	0.630
3.06–52.04	2.4–52.08	2.92–51.14
$-7 \le h \le 7$	$-14 \le h \le 14$	$-7 \le h \le 7$
$-19 \le k \le 19$	$-17 \le k \le 17$	$-12 \le k \le 12$
$-31 \le l \le 31$	$-21 \le 1 \le 21$	$-51 \le l \le 51$
25526	13213	28020
4847	4964	10544
4710	2120	9819
306	328	642
0.0237	0.1092	0.0428
0.0572	0.2932	0.0978
0.868	1.040	1.098

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List of Publications

1. Saccharin as a salt former. Enhanced solubilities of saccharinates of active pharmaceutical ingredients.
   P. M. Bhatt, N. V. Ravindra, R. Banerjee and G. R. Desiraju
   Chem. Commun., **2005**, 1073.

2. Structural studies of the system Na(saccharinate)•*n* (H_2O): A model for crystallization
   R. Banerjee, **P. M. Bhatt**, M. T. Kirchner and G. R. Desiraju
   Angew. *Chem*. *Int*. *Ed*., **2005**, 44, 2515.

3. Saccharin salts of active pharmaceutical ingredients, their crystal structures, and increased water solubilities.
   R. Banerjee, **P. M. Bhatt**, N. V. Ravindra, and G. R. Desiraju.
   Cryst. Growth & Design, **2005**, 5, 2299.

4. Form I of Desloratadine, a tricyclic antihistamine.
   P. M. Bhatt and G. R. Desiraju.
   Acta Crystallogr. Sect. C, **2006**, *62*, o362.

5. Solvates of Sildenafil Saccharinate. A New Host Material
   R. Banerjee, **P. M. Bhatt** and G. R. Desiraju.
   Cryst. Growth & Design, **2006**, *6*, 1468.

6. Stable polymorph of venlafaxine hydrochloride by solid-to-solid phase transition at high temperature.
   S. Roy, **P. M. Bhatt**, A. Nangia and G. J. Kruger.
   Cryst. Growth & Design, **2007**, *7*, 476.

7. 5,5-Dibenzylbarbituric acid monohydrate
   P. M. Bhatt and G. R. Desiraju.
   Acta Crystallogr. Sect. E, **2007**, *63*, o771.
8. Variable-temperature powder x-ray diffraction of aromatic carboxylic acid and carboxamide cocrystals
   L. S. Reddy, **P. M. Bhatt**, R. Banerjee, A. Nangia and G. J. Kruger.
   Chem. Asian J., **2007**, *2*, 505.

9. Tautomeric polymorphism in Omeprazole
   P. M. Bhatt and G. R. Desiraju.
   Chem. Commun, **2007**, 2057.

10. Crystal structure of Na_4Li_4(saccharinate)$_8$·14H2O and its comparison with other alkali metal saccharinates
    P. M. Bhatt and G. R. Desiraju
    J. Mol. Struct., **2007**, *871*, 73.

11. Desloratadine saccharinate. A stable amorphous form of an active pharmaceutical ingredient (API).
    P. M. Bhatt, R. Banerjee and G. R. Desiraju
    (*in preparation*)

12. Co-crystals of anti HIV drugs–Lamivudine and zidovudine
    Y. Azim, **P. M. Bhatt** and G. R. Desiraju
    (*in preparation*)

13. Alternative method for determination of absolute configuration of chiral compounds by co-crystal formation.
    P. M. Bhatt and G. R. Desiraju
    (*in preparation*)