Schematic representation of the possible crystalline modifications (polymorphs, solvates, cocrystals, salts, solid solution and eutectic composition) and amorphous phase of any single and multi-solid component systems.
1.1 Supramolecular Chemistry

Jean-Marie Lehn (1969) defined the term supramolecular chemistry\textsuperscript{1} as the chemistry of molecular assemblies and of the intermolecular bond, and was awarded the Nobel Prize for his work in the same area in 1987. He expressed supramolecular chemistry as ‘chemistry beyond the molecule’ and this is extended by other chemists as the chemistry of non-covalent interactions and non-molecular chemistry.\textsuperscript{2} But simply and originally, it is described as the non-covalent interactions between a guest and a host molecule and product host-guest complex (Fig. 1.1) or supermolecule.\textsuperscript{3} The host is a molecular entity which provides the hydrogen bond donors (convergent binding sites) and the guest provides the hydrogen bond acceptors (divergent binding sites) for the inclusion of one molecule in another. Initially, this field began with the discovery of chlorine hydrate by Davy in 1810 and it has grown from the further development of macrocyclic ligands for metal ions by Curtis in 1961.\textsuperscript{4} Modern supramolecular chemistry is not limited only to host-guest systems but also includes molecular devices, molecular recognition, self assembly and self organization (self processes) and it has become interdisciplinary which includes complex matter and nanochemistry.\textsuperscript{5} Furthermore development of such devices requires the design of molecular components performing a given application and function such as photoactive, electroactive, ionic active, thermoactive, or chemoactive, and suitable for assembly into an organized array.\textsuperscript{6} Light-conversion devices and charge-separation centers have been developed with photoactive cryptates formed by receptors having photosensitive groups. It is extended in technological devices and is due to the functions of supermolecular recognition, catalysis and transport.\textsuperscript{3,7}
1.2 Solid State Chemistry

When we intend to understand the solid state chemistry, we need to have some perceptiveness about the solids, structures and the forces that hold them together in the solid-state. Indeed, the chemical bonding in solids is not well understood even today, in fact there is wide variation in the chemical properties of crystalline solids. Many difficult challenges and expectations remain in predicting the composition, structure, and the properties of some new materials. So the synthesis and design of novel solids with desired functions is as much an art as a science. Solid state chemistry is concerned mainly with the crystalline inorganic and organic materials, synthesis, characterizations, crystal structures, properties and applications in devices. Recently materials chemistry has emerged as a new distinctive branch of chemistry from solid state chemistry which covers molecular, non-molecular and solid materials. So these materials give overwhelming interests
in new chemistry, new structures and improved understanding of structure-property relationships.\textsuperscript{14}

The crystal structures are usually determined by X-ray crystallography and this technique relies on the fact that the distance between the atoms in the crystals are of the same order of magnitude as the wavelength (1 Å) of X-rays. Dunitz expressed the crystal as a supermolecule par excellence of macroscopic dimensions, millions of molecules held together in a long and periodic arrangement by the non-covalent bond interactions.\textsuperscript{15} A crystal thus behaves as a three dimensional diffraction grating to X-rays and the diffraction pattern can give the internal positions of atoms in the crystal very clearly. Throughout history, scientists have worked on the slow and serendipitous trial-and-error crystallization process for discovering and developing new crystalline materials using different laboratory crystallization techniques. However, an emerging theme in modern crystalline science is the notion of intelligent design of crystals such as molecular and non-molecular complexes with desired chemical and physical properties.\textsuperscript{16} The pharmaceutical industry is adapted for the purposes of materials science and crystal engineering and the combinatorial approach represents a watershed in the process of accelerated discovery, development and optimization of pharmaceutical materials using different crystal engineering strategies. Therefore, the crystallization process itself is an impressive model of supramolecular self assembly in solid state chemistry field involving specific molecular recognition.\textsuperscript{17} This is the advantage of crystalline solids in materials science and it differs from the other phases such as liquids and gases. The crystal property of phase transition differs from the liquids is due to the cooperativity of molecules in the crystal lattice otherwise the local effects in the liquids. Within a crystal, every displacement of a molecule from the equilibrium conformation, position and orientation in the crystal packing is immediately communicated to its immediate and distant neighboring molecules through the coupling of molecular motions in a set of lattice vibrations that extend through the entire crystal.\textsuperscript{18}
1.3 Crystal Engineering

Crystal engineering is an emergent subject in solid state chemistry for the design of new crystal structures with the same or different molecules as building blocks. This began with Robertson’s work to systematically correlate the molecular structures of organic compounds with their crystal structures.\textsuperscript{19} It demands a detailed understanding of intermolecular interactions because they act as the supramolecular glue that binds molecules into crystals.\textsuperscript{20} This became active and under investigation to analyze the interactions for around 30 years from the Bragg’s discovery of X-ray crystallography study for naphthalene and anthracene. Pepinsky introduced the term crystal engineering in 1955 as the crystallization of organic ions with metal complexes results the crystals with advantageous properties that can be engineered. Schmidt was also pioneered in this field in around 1950s for the systematic published works and topochemistry of crystalline alkenes.\textsuperscript{20b,c} Now the concepts of crystal engineering are applicable to any kind of intermolecular assembly such as protein ligand recognition, the design of supramolecular polymers, molecular complexes for drug delivery. Now this field has expanded its wide scope in many disciplines including organic chemistry, inorganic chemistry, physical chemistry, X-ray crystallography, materials sciences and computational chemistry.\textsuperscript{21}

Recently, Desiraju (1989) added the term crystal engineering as \textit{the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties}.\textsuperscript{10} This is well understood by many students because of the trio attributions such as analysis, design and functions was taken together in the definition. It has been further described as the careful understanding and the exploitation of non-covalent interaction between molecular or ionic components for the rational design of solid-state structures that could exhibit interesting electrical, magnetic, and optical properties.\textsuperscript{22} It is now recognized by
many scientists and it is becoming increasingly evident that the specificity, directionality, and predictability of intermolecular hydrogen bonds can be utilized to assemble supramolecular structures of controlled dimensionality to achieve the solids with the desired functions. Crystal engineering approaches are now potentially applied to a wide range of crystalline materials that offers an alternative and potentially fruitful solution for improving the solubility, dissolution rate and subsequent bioavailability of poorly soluble drugs in the market.

1.4 Classification of Crystalline Forms

Several novel crystalline forms are identified for organic and inorganic compounds in the recent literatures and they supposed to show different physical and chemical properties. These solid forms include polymorphs, solvates, cocrystals, salts, solid solution and eutectic mixtures (Fig. 1.2) are now modern solution to many solid state issues. Many crystallization techniques and different conditions are available for screening these solid forms to achieve the desired physical properties for some of the solids such as stability, solubility, hygroscopicity, and melting point to increase the bioavailability for weak acids and bases or neutral and zwitterionic compounds. The available techniques are solution crystallization, grinding, milling, sublimation and heating experiments are generally used to screen new crystalline solid forms. In this approach, the discovery and optimization of solid forms of pharmaceuticals are essential to achieve the optimal properties. In conclusion, we collect the right information of relevant solid forms for direct comparison and recommend the best solid form based on the improved properties of the material or else and next development plan of our ideas on finding alternative forms and other formulation methods for long term strategic considerations.
1.4.1 Polymorphism

Polymorphism is the usual occurrence in which same chemical substance exhibits different crystalline arrangements in the crystal lattice for any solid materials.\(^{27}\) In 1965, McCrone defined the *polymorph* as *it is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state*.\(^{29}\) Then it was simplified as “if these solids can exist in different crystal lattices, then we speak of polymorphism”.\(^{30}\) Polymorphism is a passionate research topic that covers the research interests of physical, organic, inorganic, metal-organic, supramolecular, computational, pharmaceutical and solid material scientists. It started with Robertson and Ubbelohde work in 1938 with determination of the crystal structures of two polymorphs of resorcinol as the first example after the first discovery of
polymorphism in sodium phosphate arsenate (1820) and benzamide (1832). Allotropes and polymorphs are closely related terms but they are different in terms of elements and molecules. In brief the word polymorph is used for structural differences in molecular compounds (paracetamol) whereas allotope is for the structural variations in elements such as C, Sn and Se. For example carbon has three well known allotropes called diamond, graphite and fullerenes. Interestingly, Tin pest is the allotropic transformation from metallic allotope of β-form- white tin to brittle, nonmetallic, α-form-grey tin upon cooling (13.2 °C). Selenium allotropes exhibit distinctive color variations of black and red colors and they can be visually identified (Fig. 1.3).

![Tin medal affected by tin disease](image1)

![Black and red colored allotropes of Se](image2)

**Figure 1.3** Allotropes of tin and selenium elements exhibiting different characteristics (Adapted from Wikipedia, Ref. 32)

Polymorphism can occur because the chance in changes in differences in the packing of molecules in the crystal lattice, conformational flexibilities, and supramolecular synthon competitions. They are classified accordingly with respect to changes called packing, conformational, and synthon polymorphism respectively. Polymorphism in organic compounds is very often and of course fundamental importance since its ability to change the physical and chemical properties such as solubility, dissolution, toxicity and bioavailability for different crystal forms (Ritonavir: solubility I > II and Mebendazole: toxicity B > A ≈ C). There is no
limit for number of polymorphs to obtain for any compounds but the Flufenamic acid is the only example having nine polymorphs\textsuperscript{34c} (graphical Fig. 1.4) having solved crystal structures in the CSD after second most 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, known as ROY for its red, orange, and yellow crystals, heptamorphic crystal structures.\textsuperscript{70}

\textbf{Figure 1.4} Nonamorphism in Flufenamic acid (FFA) and a new world record for a polymorphic compound with solved structures (Adapted from Re. 34c).

\textbf{1.4.1.1 Conformational Polymorphism}

According to IUPAC definitions, a conformation is “\textit{the spatial arrangement of the atoms affording distinction between stereoisomers which can be interconverted by rotations about formally single bonds\textsuperscript{35}}”, whereas a conformer “is one of a set of stereoisomers, each of which is characterized by a conformation corresponding to a distinct potential energy minimum\textsuperscript{35}”. Bernstein likened it with
Dunitz’s thoughts to define the conformer as *any change in a given single rotatable bond of a molecule always affords a new conformation, but it affords a new conformer only if the conformational change goes through a potential energy barrier into a different potential energy well.*\(^{36}\) Finally, any organic molecule with flexible torsions and low energy conformations in the crystal structures will have a greater likelihood of displaying polymorphism because (1) different conformations will lead to new hydrogen bonding and close packing modes and (2) the exchange of energy that reduces the total energy difference between alternative crystal structures. Molecular conformation is able to make noticeable distinctions but make significances in the property related to the chemistry of the organic solid state. The rotations are about single bonds worth of 1-3 kcal mol\(^{-1}\) but can be as high as 8 kcal mol\(^{-1}\) due to restricted rotation in organic molecules.\(^{33}\) The consequent compensation of Gibb’s free energy for these changes in conformer destabilization process by the crystal environment increases the propensity of polymorphism in organic molecules with flexible torsions. The study of conformational polymorphism is the reasonable one in crystal engineering approach and it has become improved further through the various crystallization methods to find various crystal forms and the correlation of their properties by techniques such as single crystal X-ray crystallography, powder X-ray diffraction, differential scanning calorimetry, infrared and Raman spectroscopy and rarely terahertz spectroscopy.\(^{37}\) A conformational polymorph renaissance have been developed for number of reasons: (1) different conformational polymorphs of the same substance can exhibit very different physical and chemical properties than the other polymorphs (2) the possibility of using those polymorphs as the ideal systems for the comparison and the study of structure–property correlations (3) the immense interest for carrying out single crystal structure determinations is the structural characterization and comparison of the polymorphs (4) the recognition of their purpose in pharmaceutical industries and the high-profile patenting on polymorphism (5) the ease of publishing these polymorphs having color and
solubility differences in the mainstream scientific literatures (6) some conformational polymorphs might be harder to crystallize because their conformers are less accessible experimentally.38

For instance, two polymorphs are conformational polymorphs only when their conformations are related by changes in torsion angles of those two crystal structures. These changes can be identified though the energy calculations because this change requires a change of gas-phase conformer and crossing of an energy barrier. Though the energy differences associated with conformational variations of small organic molecules in different polymorphs are usually small, higher energy conformations in crystalline polymorphs are rare but for few possible cases listed here, (i) molecules that are able to break an intramolecular interaction in favor of a strong intermolecular interaction to attain the new conformation i.e., polymorphism in cardiosulfa and its analogs39a and (ii) molecules that crystallize in special symmetry positions i.e., C2 and Ci in dimorphs of phenyl-2-pyridyl-ketone-azine39b (iii) Zwitterionic molecules i.e., tetramorphs of cysteine.39c If a change in conformations in any crystal structures, conformational adjustment and conformational change are the two postulated possibilities.38 Conformational adjustment always observed for any conformationally flexible molecule in a crystal to some extent of minimal and a small conformational energy penalty is paid for intermolecular interactions in the crystal. Therefore, the flexible molecule adjusts to the crystal environment by changing slightly its conformation to minimize the lattice energy of that particular crystal. In other case, conformational change involves a change of gas-phase conformer and so that it requires high energy over the energy barriers. Two conformations are related by conformational change then the torsion changes would be max (Δθ) > 95° otherwise it is a conformational adjustment. Additionally, the rmsd(r)-crystal cutoff of 0.375 Å is an indication for the type of conformational flexibilities when comparing two conformations and it is a very
convenient approximation for the large set of polymorphs and molecules of different nature (Fig. 1.5a). In similar way, there are thirty six percent of polymorphic compounds in the CSD showed conformational polymorphism and the best example is Chlorpropamide\textsuperscript{40a-c} drug. It has been reported as the largest number of conformational polymorphs (pentamorphs overlay, Fig. 1.5b) after Tolbutamide drug (tetramorphs) in the CSD.\textsuperscript{40f-g}

![Decision tree to identify the conformational polymorphs A and B with structural data.](image1)

**Figure 1.5** (a) Decision tree to identify the conformational polymorphs A and B with structural data. (b) Overlay of five different conformers in chlorpropamide polymorphs (Adapted from Ref. 38).

**1.4.1.2 Pseudopolymorphism**

Solvatomorphism or pseudopolymorphism arises due to the multi-point recognition with strong and weak intermolecular interactions between solvent and solute molecules facilitate the retention of aqueous or organic solvents in crystals during the nucleation step. The phenomenon *pseudopolymorphism is the major occurrence wherein a compound is obtained in crystalline forms that differ in the*
nature or stoichiometry of included solvent molecules.\textsuperscript{41} The process of crystallization is bringing the solute and the solvent together to interact first and forms the aggregates in the nucleation step. This whole aggregate contains solute–solute, solute–solvent and solvent–solvent interactions in the initial crystallization process.\textsuperscript{42} The supramolecular synths or intermolecular non-covalent interactions between the solute and solute provides an adequate driving force for nucleation and crystallization to overcome the solvent-solute interactions when there is simultaneous entropic gain in eliminating solvent molecules from these aggregates into the bulk solution and enthalpic gain in forming stable solute species as the crystals.\textsuperscript{43} This thermodynamic change results that most organic crystals are unsolvated in CSD. In solvates, the interaction are in multi-point manner through either strong O/N–H⋯O or weak C–H⋯O intermolecular hydrogen bonds with solvent molecules are present so the extrusion of solvent from the aggregates into the bulk solution becomes thermodynamically unfavorable. Hence, the solvent remains an integral part of the crystals during the nucleation step itself.\textsuperscript{44} Practically, the unsolvated forms is not possible to obtain in normal crystallization of solvated compounds such as fluoroquinone derivatives (norfloxacin, ciprofloxacin etc). Unfortunately, one third of pharmaceutical solids are prone to form or transform to hydrate species depending on the external environmental and other conditions.\textsuperscript{42b} This solid-state transformation will have vigorous effects on the physical and chemical properties of drugs and eventually modify the drug stability and biological properties such as solubility, dissolution and bioavailability.\textsuperscript{43} So the identification, characterization of solvates and understanding of their interactions of water and drugs is so important to control the transition and assure the quality of the drug products.\textsuperscript{44-45} In contrast to the solvates, the drug norfloxacin hydrates showed better solubility and stability compared to the anhydrous forms. The main functional groups of norfloxacin changed from COOH to COO\textsuperscript{−} and NH to NH\textsubscript{2}\textsuperscript{+} in hydrated structures and the proton transfer from COOH group to NH group caused by the
water molecules (Scheme 1.1). This suggests that the hydration can induce the interaction between norfloxacin molecules from hydrogen bonding to ionic bonding by an intramolecular proton-transfer process in the solid state. We found that water molecules is not only induced the proton transfer reaction between norfloxacin molecules in the solid state, but also changed the solid character from a neutral state to ionic state to make a higher dissolution rate of norfloxacin after hydration.

![Scheme 1.1](image)

**Scheme 1.1** Norfloxacin hydration involves the intra-proton transfer in the solid state

### 1.4.1.3 Desmotropism and Tautomeric Polymorphism

Desmotropy is a German term introduced by Jacobson in 1887 and it was formed from the Greek language meaning change of bonds. It was later explained as tautomers are constitutional isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. These interconversion reactions deals with the migration of a hydrogen atom or proton which is accompanied by a switch of a single bond in conjugation with adjacent double bonds. Desiraju said that a crystal structure with a particular tautomer is polymorphic to a different crystal structure that contains another tautomer. If they are different in nature of tautomer in different crystal structures then they are not polymorphs at all but crystals of different compounds. If there are structures of different molecules but they are isometric in nature in the same crystal structure. Then this phenomenon is called as synthomorphism means there is local similarity in the internal crystalline arrangement of atoms in structures because of the local similarity in the
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crystal structure. The other important terms in the crystalline studies are *isomorphism*, *isotypism*, *isostructuralism*, *homostructuralism*, and *approximate isomorphism*.\(^{51}\) Isomorphism is originally defined by Mitscherlich\(^{51e}\) in 1819 and it refers only to morphological similarities but in later isostructurality implies similar close packing within similar unit cells. Now the isomorphous crystals which differ by only one substituent have high degree of structural similarity. Isostructural crystal pairs formed by molecules differing only in the chirality of one atom are termed as configurationally isostructural.\(^{51}\) According to IUCr online dictionary,\(^{52}\) two crystals are said to be Isomorphic (isometric) if (a) both have the same space group and unit-cell dimensions and (b) the types and the positions of atoms in both are the same except for a replacement of one or more atoms in one structure with different types of atoms in the other (isomorphous replacement), such as heavy atoms, or the presence of one or more additional atoms in one of them (isomorphous addition).\(^{52}\) When the related molecules differing by substitutions on more than one atomic site have similar packing, it is called homeostructural crystals. In order to avoid the confusion with other important terms with respect to crystalline arrangements, the Conformational isomorphism and Conformational synmorphism are two phenomena are also are discussed here. Conformational isomorphism which may arise due to conformational differences present in the flexible molecules having more than one molecule in the asymmetric unit.\(^{31}\) The existence of different conformers of the same molecule in the same crystal structure represents conformational isomorphism for \(Z > 1\) type of molecules. Conformational synmorphism refers to a random distribution of different conformers within the crystal structure for \(Z > 1\) cases.\(^{31}\)

Solid-state tautomeric inter-conversion and tautomeric polymorphs are strictly related but they involve confusions to address in a general way of differentiating them. For tautomers, rapidly interconverting species in solution or in the melt would be accepted as polymorphs (2-thiobarbituric acid, Scheme 1.2a) and
called tautomeric polymorphs, although slowly interconverting species would be excluded. This is now little meaningful when we see the “safe” criterion for classification of a system as polymorphic would be if the crystal structures were different but lead to identical liquid and vapor state. Gavezzotti illustrated the polymorphs as polymorphs are a set of crystals (a) with identical chemical composition; (b) made of molecules with the same molecular connectivity, but allowing for different conformations by rotations about single bonds; (c) with distinctly different three-dimensional translationally periodic symmetry operations. Hantzsch and Herrmann insisted that if a substance could be isolated in two stable forms it should be called desmotropic (Piroxicam, Scheme 1.2b), while if it could not be isolated it should be termed tautomeric. Although there are no examples of desmotropy involving three tautomeric structures in different crystal structures but limited to only two isomeric structures in the literatures.

\[ \text{Scheme 1.2} \] (a) Tautomeric pentamorphs of 2-thiobarbituric acid, (b) Two desmotropes of piroxicam
1.4.1.4 Zwitterionic and Neutral Polymorphism (Desmotropism)

In chemistry, a zwitterion (in German word zwitter means hybrid) is a neutral molecule with a positive and a negative electrical charge simultaneously present in the same molecule. Amino acids and some of the ampholytes are the well known examples for zwitterions. Some of the ampholytes are crystallized as neutral polymorph in one crystal structure and zwitterionic polymorph in another crystal structure for the same molecule. There is an intramolecular proton transfer in nucleation and crystallization steps (2-(p-tolylamino)nicotinic acid, Scheme 1.3a). These polymorphs are not common for all organic amphoteric molecules and even in amino acids. Very few drug examples in the literature are reported as neutral and zwitterionic polymorphs including the amphoteric drugs ciprofloxacin, norfloxacin, torsemide, clonixin and tianeptine and remaining amphoteric drugs are reported as either neutral or zwitterionic in their crystal structures. Generally, the solubility and stability are inversely related for any drug polymorphs. However, the zwitterionic polymorphs are highly stable and soluble compared to neutral polymorphs. This is the main advantage of these ionic forms in the pharmaceutical industries to optimize the physical property without any chemical modification of drugs. Recently, Nangia et al proved experimentally in model and drug compounds that the twin characteristics of high solubility and good stability may be jointly optimized in the same zwitterionic polymorph for marketed amphoteric drugs. Thus, the drug property can be improved by zwitterionic polymorph optimization method for any amphoteric drug without altering the original drug formula. When we are able to separate these neutral and zwitterionic isomers in the crystal structures then they can be called as desmotropes. Surprisingly, there were no reports on the neutral polymorphs of 20 amino acids in the literatures; ten of those amino acids are resulting only zwitterionic polymorphic crystal structures till date (Scheme 1.3b). Once we optimize and understand the neutral polymorphs formation from amino
acids in crystallizations and may be the zwitterionic forms from the ampholytes could be explored further in applications. The optimization and control of zwitterionic polymorphs would be utilized in pharmaceutical industry because of the twin characteristics of these ionic polymorphs.

![Scheme 1.3](image)

**Scheme 1.3** (a) Two isomers of 2-(p-tolylamino)nicotinic acid for neutral and zwitterionic polymorphs (desmotropes) (b) Isomeric amino acids but only zwitterionic polymorphs present (no desmotropy in amino acids)

### 1.4.1.5 Concomittant and Disappearing Polymorphs

Bernstein and Davey elaborated the term ‘concomitant polymorphs’ in crystallization experiments that yield crystals of different polymorphic structures simultaneously and potentially offer both structural and thermodynamic information, not available when only one phase crystallizes.\(^6\) Crystallization is a remarkable process that brings approximately \(10^{20}\) molecules or ions into an essentially ordered array, and results in the same structure or limited number of structures, in the case of polymorphism for every crystal. In this process, the regions in which there is overlap of occurrence domains in nucleation one may expect that two or more polymorphs
would crystallize under essentially identical conditions thus leading to this concomitant polymorphism. The occurrence domain can be the solvent, temperature, rate of evaporation or cooling, and other conditions under which a material will crystallize for any substances. It is of more meaning when we discuss this with energy functions. The free energy associated with any chemical reaction is a transition state and an activation free energy which can decide the relative rates of formation of the two structures. Crystallization is not well understood by the nature of the activated state because it relates to a large collection of self-assembled molecules with precise packing arrangement a new separate nucleate or solid phase (Fig. 1.6).

![Figure 1.6](image)

**Figure 1.6** Crystallization energy profile of two polymorphs (Ref. 60).

The concept of critical size in which an assembly of molecules must have in order to be stabilized by further growth is the main part here to include in the crystallization process. The higher the operating level of supersaturation, the smaller this size is typically a few tens of molecules. In Figure 1.6, the supersaturation with respect to form I is simply $G_0 - G_1$ and is lower than $G_0 - G_{II}$ for structure II. However,
it can now be seen that if the critical size is lower for I than for II for a particular solution composition then the activation free energy for nucleation is lower and kinetics will favor form I. Finally form I will have to transform to form II, Overall the probability that a particular form will appear is explained by Equation (1),

\[ P(i) = f(\Delta G, R) \]  

in which \( \Delta G \) is the free energy for forming the \( i \)th polymorph and \( R \) is the rate of some kinetic process associated with the formation of a crystal by molecular self aggregation in Equation (2).

\[ G = H - TS \]

Thus, if we follow the above reasoning we could equate the rate process with \( J \), the rate of nucleation of the form. If all polymorphs had the same rates of nucleation then their appearance probability would be dominated by the relative free energies of the possible crystal structures.

\[ J = A_n e^{\left(-\frac{16\pi\gamma^3\sigma^2}{3kT^2}\right)} \]

The rates of nucleation is as expressed by the classical expression of Volmer related to various thermodynamic and physical properties of the system such as bulk and surface free energy (\( \gamma \)), temperature (\( T \)), degree of supersaturation (\( \sigma \)), solubility (hidden in the pre-exponential factor \( A_n \)) in Equation (3).  

Figure 1.7 shows three possible simultaneous solutions of the nucleation equations which involve the careful control of the occurrence domain, there may be conditions in which the nucleation rates of the two forms are equal and hence their appearance probabilities are nearly equal. Under these conditions we might expect the polymorphs to crystallize concomitantly. Many polymorphs are reported as concomitant polymorphs and For example, polymorphs I, II and III of 6-chloro-2,4-
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dinitroaniline are concomitantly crystallized from CH$_2$Cl$_2$ resulted the needles (Form II) and indistinguishable I and III polymorphs (Fig. 1.8) amongst the chunks.$^{119}$

![Figure 1.7](image1.png)

**Figure 1.7** Rates of nucleation (J) are plotted as functions of supersaturation (σ) for the dimorphic system and simultaneous nucleation of the forms at supersaturation levels corresponding to the (a) crossover (b) two crossovers of the curves (Ref 60).

![Figure 1.8](image2.png)

**Figure 1.8** (a) Mixture of polymorphs I, II and III of 6-chloro-2,4-dinitroaniline concomitantly from CH$_2$Cl$_2$: needles (Form II) and indistinguishable I and III polymorphs amongst the chunks (b) Molecular structure of 6-chloro-2,4-dinitroaniline (Ref 119).
Disappearing polymorphs are unfortunate events where the polymorph was previously considered to be stable and easy to make, suddenly becomes very difficult to obtain. The reasons for these problems may be poor understanding of mechanism involved in nucleation and crystallizations. The phenomenon of ‘disappearing polymorphs’ where a previously apparently stable form can no longer be routinely produced, is a scientific anathema.\textsuperscript{63a} Indeed it should be possible to reproduce any metastable polymorph by reproducing the appropriate crystallization conditions but not. The new outcome suffers from a ‘disappearing polymorph’, which can be found to our surprise that a second polymorph of maleic acid was obtained 124 years after evidence of the first crystal form was reported (Fig. 1.9).\textsuperscript{63b} To avoid this we need to understand the mechanism involved in the stabilization of crystallites in the nucleation and the proper solvent selection enables the solute solvent interaction to be tuned to promote: (i) the desired conformation, (ii) the mode of molecular assembly and (iii) modify the growth kinetics of the crystal as reflected in the crystal habit and the transformation of one phase to another. Further an effective crystal engineering strategy for polymorph isolation requires: (i) isolation or prediction of polymorphs, (ii) analysis of the similarities and differences between polymorphs, (iii) identification of functionality required by the additive or solvent, (iv) analysis of solvent or additive interaction with host lattice, and (v) experimental verification of selectivity.\textsuperscript{64}
1.4.1.6 Color Polymorphs

Organic solid-state luminescent materials are now attracting interest in various application fields and in fact the tuning of solid-state luminescence by controlling the mode of molecular packing, instead of the commonly used synthetic modification of molecules, has attracted great interest. The related potential application in the development of new organic luminescent materials based on the crystal engineering concept, which would lead to applications in novel photonic, photoelectronic, and sensory materials. In the beginning, Byrn et al described colorless and yellow forms of a terephthalic acid derivative 3,6-dichloro-2,5-dihydroxyterephthalat in 1972. Interestingly, many on this topic, “polymorph-dependent luminescence”, have appeared recently. In these systems, modification of inter-luminophore interactions or packing-induced conformational changes of any molecules are allowing for tuning the luminescence properties. However, development of such methods are still remains a challenging task because of the lack
of understandings in mechanisms that allow for alteration of molecular packing with different luminescence properties. A detailed study and plan on the relationships between the molecular packing modes and the luminescence properties are the topic of interest in dealing with multiple polymorph-dependent luminescence is desirable for the study of the structure–property relationships. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophene-carbonitrile has been crystallized in heptamorphs as yellow prisms (Y), red prisms (R), orange needles (ON), orange plates (OP), yellow needles (YN), orange-red plates (ORP), and red plates (RPL). It is named as ROY\textsuperscript{70} for its red, orange, and yellow crystal colors (Fig. 1.10a). The related interesting topic is photochromism. Light-induced reversible color change of substances is known as ‘photochromism’ and organic photochromic compounds have attracted much attention over the past decades for their applications in optic data storage, electronic display systems, optical switching devices, ophthalmic glasses, this in turn leads to changes in the physicochemical properties of such compounds including absorption, fluorescence, refraction index and electric permittivity.\textsuperscript{71} N-Salicylideneanilines exhibit photochromism in solution and in the solid state respectively. The trimorphs alpha, beta, gamma forms were formed in the crystallization of N-3,5-di-tert-butysalicylidene-3-carboxyaniline (SCA). When the crystals were irradiated with UV light, alpha and beta showed photochromism whereas gamma was unchanged (Fig. 1.10b). Moreover, the lifetimes of the colored species of alpha and beta forms were quite different.\textsuperscript{71a}
Figure 1.10 (a) Seven polymorphs: yellow prisms (Y), red prisms (R), orange needles (ON), orange plates (OP), yellow needles (YN), orange-red plates (ORP), and red plates (RPL), and Color changes of trimorphs alpha, beta and gamma forms (SCA); Ref. 70 (b) before UV irradiation, after UV irradiation; Ref. 71.

1.4.1.7 Crystallization of Polymorphs

A large number of controllable and uncontrollable factors can influence the outcome of polymorphic crystallization, including supersaturation, temperature, solution concentration, cooling rate, solvent, agitation, pH, additive, impurity, seeding, interface, etc. Kitamura came up with idea of grouping the controlling factors for polymorphic crystallization into two group of categories and it depends mainly on systems and crystallization methods. The primary factors are the operation
of the polymorphic crystallizations including supersaturation, temperature, seeds, the stirring rate, the addition rate of antisolvent, the cooling rate, the mixing rate of reactant solutions, etc. On the other hand, other factors are solvents, additives, interfaces, etc. are grouped in the secondary factor group. Both factors impart thermodynamic and kinetic effects on polymorphic crystallization. Nevertheless, the mechanism of the effect and the quantitative relationship between the operational factors and the crystallization characteristics of polymorphs is not well understood as usual. The modern techniques and methods that generally used to obtain the polymorphs are control of supersaturation level, control of nucleation temperature, solvent screening, Heating and sublimation of the materials, low temperature and high temperature evaporation, roto vapor fast evaporation, seeding technology, capillary crystallization, introduction of additives, polymer-induced heteronucleation, nucleation confined in nanopores, heteronucleation on substrates such as ionic liquids and gels, laser-induced nucleation and crystal structure prediction.

The new concept of high-throughput (HT) screening and combinatorial synthesis are applied recently to the development of drugs, high-throughput (HT) crystallization systems have recently been developed and are emerging as an accelerator for the discovery and screening of solid forms of an API. After a particular form at small scale is identified in the HT screening, scale-up studies will be conducted to further optimize the process for laboratory scale production. The HT crystallization has been applied to discover solid forms for a series of APIs, such as acetaminophen, sulfathiazole. Peterson et al. discovered the highly unstable form III of acetaminophen by use of the HT crystallization technique. In experimental and industrial practice, it has been commonly observed that the metastable form appears first and then transfer into a more stable structure. From this phenomenon, Ostwald concluded that “when leaving a metastable state, a given chemical system does not
seek out the most stable state, rather the nearest metastable one that can be reached without loss of free energy.” That is, in a crystallization from the melt or from solution, the solid first formed will be that which is the least stable of the polymorphs, the one with the largest Gibbs free energy (Fig. 1.11). As a result, the crystallization of the least stable form is expected to predominate at high levels of supersaturation. Meanwhile this effect is also dependent upon the solvent-solute interactions and other important factors.

![Diagram showing hypothetical transitions from solution to thermodynamic and kinetic crystals](image)

**Figure 1.11** Hypothetical transitions from solution to thermodynamic and kinetic crystals. Difference between $\Delta G^\#_{\text{thermodynamic}}$ and $\Delta G^\#_{\text{kinetic}}$ determines the ease of formation of kinetic crystals (Ref. 87)

### 1.4.1.8 Characterization of Polymorphs

In the pharmaceutical industry, identification and discovery of polymorphism during early stage development is critical, as unanticipated appearance of polymorph and polymorphic transitions of a drug substance can affect chemical and physical stability, solubility, morphology, hygroscopicity, and, ultimately, bioavailability. A number of analytical techniques have been employed for characterizing polymorphs
and *in-situ* monitoring the formation and transformation of polymorphs during the process. The analytical techniques and the information extracted from those instruments are available in the Table 1.1 below.

**Table 1.1 Analytical techniques and the observation for polymorphs**

<table>
<thead>
<tr>
<th>Category</th>
<th>Techniques</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray diffraction</td>
<td>Powder and Single crystal X-ray diffractions</td>
<td>Structure, crystallinity, chemical and phase composition, molecular weight, etc.</td>
</tr>
<tr>
<td>Vibrational spectroscopy</td>
<td>FT-Raman and Infrared spectroscopy</td>
<td>Structure, molecular conformation, chemical and phase composition, hydrogen bonding, etc.</td>
</tr>
<tr>
<td>Microscopy</td>
<td>Optical, Scanning electron and Atomic force microscopy</td>
<td>Crystal size and habit, etc.</td>
</tr>
<tr>
<td>Thermal methods</td>
<td>Hot-stage Microscopy</td>
<td>Melting point, transitions, etc.</td>
</tr>
<tr>
<td></td>
<td>Thermogravimetric analysis</td>
<td>Melting point, transitions, etc.</td>
</tr>
<tr>
<td></td>
<td>Differential scanning calorimetry</td>
<td>Thermal transitions.</td>
</tr>
<tr>
<td></td>
<td>Differential thermal analysis</td>
<td>Melting point, transitions, heat capacity, crystallinity, etc.</td>
</tr>
<tr>
<td></td>
<td>Isothermal calorimetry</td>
<td>Heat and rate of transition, crystallinity, etc.</td>
</tr>
<tr>
<td>NMR Spectroscopy</td>
<td>Solid-state nuclear magnetic resonance spectroscopy ($^{13}$C and $^{15}$N NMR)</td>
<td>Chemical and phase composition, structure, crystallinity, intermolecular interaction, conformational change, etc.</td>
</tr>
</tbody>
</table>
1.4.1.9 Thermodynamics of Polymorphs

The thermodynamic and kinetic properties of the polymorphic system is essential for the control of polymorphs accompanied by crystallization process and it requires a full understanding of the nucleation, crystal growth, and phase transformation in the crystallization. The Gibbs free energy change $\Delta G_c$ of a crystallization process at constant temperature and pressure is (4),

$$\Delta G_c = \Delta H_c - T\Delta S_c \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots (4)$$

Where $\Delta H_c, \Delta S_c$ are the enthalpy change and the entropy change of the crystallization process respectively. From the thermodynamic viewpoint, for a polymorphic system, the minimization of $\Delta G_c$ is the classical thermodynamic driver (eqn 5), which leads to the formation of stable form, whilst the maximization of the rate of entropy production is the driver in irreversible thermodynamics, which will lead to the formation of less stable form.

$$\Delta G_T = \Delta H_T - T\Delta S_T \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots (5)$$

Meanwhile, the relative thermodynamic stability of polymorphs and the driving force for a transformation at constant temperature and pressure is also determined by the difference in Gibbs free energy between the polymorphs $\Delta G_T$. Where $\Delta H_T$ the enthalpy difference between the polymorphs, reflects the lattice or structural energy differences and the entropy difference; $\Delta S_T$ the entropy difference between the polymorphs, is related to the disorder and lattice vibrations. When $\Delta G_T < 0$, the transformation can occur spontaneously; $\Delta G_T = 0$, the free energy of the two phases is the same; $\Delta G_T > 0$, the spontaneous transformation is not possible under the specific conditions. According to the corresponding thermodynamic relationships, polymorphs can be classified as either enantiotropes or monotropes, depending on one form can transform reversibly to another or not.
1.4.2 Prediction Rules for Polymorphs

Burger and Ramberger proposed a series of rules for predicting the relative thermodynamic stability of polymorphs and the nature of polymorphic system because the exact course of $G$ isobars cannot be followed experimentally, since the entropy cannot be determined. At a given temperature, the thermodynamically stable modification has always the lowest Gibbs free energy. Fig. 1.12a represents an enantiotropically related system of two modifications (polymorphs). Modification II shows the lowest Gibbs free energy until the $T_p$ is reached and is therefore thermodynamically stable from absolute zero up to $T_p$. Beyond $T_p$, the Gibbs free energy of mod. II is higher than for mod. I; therefore, the mod. II is thermodynamically unstable from $T_p$ up to its melting point. At $T_p$ polymorphs I and II have equal Gibbs free energy and equal thermodynamic stability. The two modifications are enantiotropically related. $\Delta H_t$ represent the enthalpy of transition for the transformation II/I, $\Delta H_{f,I}$ and $\Delta H_{f,II}$ represent the enthalpy of fusion for modifications I and II respectively. Figure 1.12c gives an energy/temperature diagram for tedisamil dihydrochloride demonstrating that its three polymorphic forms are enantiotropically related. Fig. 1.12b describes the relations in a monotropic system. Modification II shows a larger Gibbs free energy than mod. I and is therefore thermodynamically unstable compared with mod. I from absolute zero up to $M_p$. There is no $T_p$ over this temperature region, but a transition in the solid state of mod II into mod. I is possible; however, the reverse transition never occurs. It is worth noting that such a monotropic transition is always exothermic, as has been known for a long time but now is often forgotten in the interpretation of new experimental results. Fig. 1.12d gives an Energy/ Temperature diagram for flurbiprofen demonstrating that its polymorphic forms are monotropically related. Of course there are many reasons why during preparation of a solid substance polymorphic modifications are transformed.
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**Heat-of-Transition Rule:** This rule generalizes that, if an endothermic enthalpy of phase transition between two crystal forms is observed at a specific temperature, so then there is a transition point below this temperature and the two polymorphs are enantiotropically related.\textsuperscript{28c,30} If an exothermic enthalpy of phase transition is observed at a particular temperature, and there is no transition at higher temperatures, the two polymorphs may be monotropically related.

**Heat-of-Fusion Rule:** The heat-of-fusion rule indicates that in an enantiotropic system the higher-melting polymorph of a pair will have the lower enthalpy of fusion. If the higher-melting polymorph also has the higher enthalpy of fusion, the two polymorphs are monotropically related.\textsuperscript{28c,30} The rule will be valid so long as the Gibbs energy profiles of dimorphic systems can be described.

**Enthalpy-of-Sublimation Rule:** If the polymorph with the higher melting point has the lower enthalpy of sublimation, the two polymorphs are enantiotropic. Monotropism is realized if the lower melting form shows the lower enthalpy of fusion.\textsuperscript{28c,30}
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Figure 1.12 Energy–temperature diagrams. **Enantiotropy:** (a) general principles (*G*, Gibbs free energy; *H*, enthalpy; Δ*H*$_f$, enthalpy of fusion; liq, melt; *M*$_p$, melting point; *T*$_p$, thermodynamic transition point; Δ*H*$_t$, enthalpy of transition); (c) example of enantiotropic behaviour: three modifications of tedisamil dihydrochloride (*G*, Gibbs free energy and *H*, enthalpy of the melt (liq.); mod I (I), mod II (II); mod. III (III); (*M*$_p$) melting point; (III/II, III/I, II/I) thermodynamic transition points; Δ*H*$_f$, enthalpy of fusion; Δ*H*$_t$, enthalpy of transition) **Monotropy:** (b) general principles (*G*, Gibbs free energy; *H*, enthalpy; Δ*H*$_f$, enthalpy of fusion; liq, melt; *M*$_p$, melting point); (d) example of monotropic behaviour: crystalline modifications of flurbiprofen (symbols the same as in b), (Adapted from ref 31c).
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**Entropy-of-Fusion Rule:** The melting point is defined as the temperature at which the liquid is in equilibrium with the solid so that the difference in Gibbs free energy between the two phases is zero. According to the rule, if a polymorph has the higher melting point but has the lower entropy of fusion, the two polymorphs are enantiotropically related. Monotropism is inherent if the lower melting polymorph has the lower entropy of fusion. The entropy of fusion $\Delta S_f$ can then be expressed as $\Delta S_f = \frac{\Delta H_f}{T_f}$.

**Heat-Capacity Rule:** At a given temperature, if one polymorph has both the higher melting point and the higher heat capacity than another polymorph, these two polymorphs are enantiotropically related. For a pair of polymorphs, if the polymorph with the higher melting point also has a higher heat capacity at a given temperature, there exists an enantiotropic relationship between them. Otherwise, the system is monotropic.

**Density Rule:** If the polymorph with the higher melting point has the lower enthalpy of sublimation, the two polymorphs are enantiotropic. Monotropism is realized if the lower melting form shows the lower enthalpy of fusion. The most energetically stable structure is expected to correspond to the one that has the most efficient packing. The two polymorphs are monotropically related if the polymorph with higher melting point possesses the higher density. Otherwise, they are enantiotropically related. This rule is quit general for ordered molecular solids that are dominated by van der Waals interactions. Exceptions such as acetazolamide, are not unexpected when other interactions, such as hydrogen bonds, dominate the packing, since some energetically favourable hydrogen-bond dominated packing arrangements can lead to large voids in the crystal structure with correspondingly lower density.
Infrared Rule: The rule is normally for the hydrogen-bonded crystals and the highest frequency infrared absorption band in polymorphic structures containing strong hydrogen bonds. The formation of strong hydrogen bonds is associated with a reduction in entropy and an increase in the frequency of the vibrational modes of those same hydrogen bonds. The hydrogen bonded polymorphic structure with the higher frequency in the bond stretching modes may be assumed to have the larger entropy.

Solubility Rule: Since the solubility is directly proportional to the free energy of a polymorph, determination of solubility is the most reliable method of assessing $\Delta G_T$ between polymorphs. Generally the stable form has a lower solubility. It is important to note that although the absolute solubility of a polymorph will be solvent dependent, the relative solubility of different forms will not depend on the solvent used. If one form with a higher melting point has a higher solubility at temperatures above the transition temperature, polymorphs are enantiotropic. When the polymorphs are monotropic, the solubility of one form with the higher melting point is always lower than another form with the lower melting point.

1.4.2.1 Properties of Polymorphs

The particular advantage of polymorphism is that the chemical identity and utility of the materials remains unchanged from one polymorph to another, so that a direct correlation between activity and solid state structure are made for better understanding in the solid state. Polymorphism is very important in those areas of chemical research that covers characterization of a material has a pivotal role in determining its ultimate use of pharmaceutical, pigment, agrochemical, explosive and fine chemicals in industries. It is interesting to note that polymorphism has left an impression even on the history of our world (Ex. Sn allotropes).

Packing properties: Molar volume, Density, Refractive index, Optical properties conductivity, Electrical, Thermal and Hygroscopicity.
**Mechanical properties:** Hardness, Tensile strength, Compactibility, Tabletability, Handling, Flow and Blending.

**Surface properties:** Surface free energy, Interfacial tensions and Habit.

**Thermodynamic properties:** Melting and Sublimation temperatures, Internal energy, Enthalpy Heat capacity, Entropy, Free energy and Chemical potential, Thermodynamic activity, Vapour pressure and Solubility.

**Kinetic properties:** Dissolution rate, Rates of solid state reactions and Stability.

**Spectroscopic properties:** Electronic transitions, Ultraviolet-visible spectra, Vibrational transitions, Infrared and Raman spectra, Rotational transitions and Nuclear Magnetic Resonance chemical shifts.

### 1.4.2.2 Cocrystals and Salts

Solid-state chemists are focusing on different strategies when attempting to alter the chemical and physical solid-state properties of APIs or any materials, namely, the formation of salts, polymorphs, hydrates, solvates, cocrystals, eutectics and solid solution. Salt formation is the first and one of the primary solid-state approaches to modify the physical properties of APIs, and it is estimated that over half of the medicines on the market are administered as salts. However, a major drawback with this salt formation approach is that the API must possess a suitable basic or acidic ionizable site. The other immediate idea is that the cocrystals in which the multicomponent assemblies held together by freely reversible via non-covalent interactions offer a different pathway where any API regardless of acidic, basic, ionizable groups could potentially be cocry stallized. Aakeröy defined the term cocrystal as the structurally homogeneous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts. Again Jones elaborated cocrystal as “a crystalline complex of two or more neutral molecular constituents bound together in the lattice through non-covalent
interactions, often including hydrogen bonding.” Furthermore, the use of pharmaceutical cocrysal is a common platform and usually applied when an API is one of the molecules in the multicomponent crystalline system. In cocrysalization, evaluation of the API should be carried out with number and arrangement of hydrogen bond donors and acceptors whereas in salt forming ability that depends on $\Delta pK_a$ rule, conformational flexibility, and solubility requirements. The compounds including APIs that are rigid, highly symmetrical, possess strong non-bonded interactions, and low molecular weight are more apt to cocrysalize with GRAS (Generally Regarded as Safe Molecules). Suitable coformers are selected based on hydrogen bonding rules, probable molecular recognition events and toxicological profiles. To extend this idea of selection of the coformers based on the charge distribution, many prediction were made in the last two decades to understand the cocrysal synthesis and mechanism. The first one is that the Hammett substituent constants were used as the basis to model the formation of cocrysal products. By this way, 32 acid/acid combinations of substituted benzoic acids in the attempted cocrysalization it was interestingly found that 90% of the systems formed cocrysals if the Hammett constants of the coformers were of opposite sign, while only 25% of the systems where the constants were of the same sign yielded cocrysal. It was noted in the paper that a direct relationship exists between the Hammett constant and the ionization constant of the carboxylic acids, and hence systems characterized by large differences in substituent constants. The Hammett constant approach is successful in major level. Another approach for studying the salt-cocrysal continuum has involved the evaluation of protonation states using X-ray photoelectron spectroscopy, where the shifting in energy of the nitrogen 1s spectrum of theophylline was used to evaluate the degree of proton transfer. In the formation of an adduct with citric acid, and the equivalence in energies of the nitrogen 1s spectra in theophylline and its citric acid adduct was the substantial existence of a cocrysal formation and the lack of salt formation. Cocrysal eutectic
constants are calculated as the ratio of the solution-phase concentrations at the eutectic point of the compounds making up a cocrystal species which are the indicators of phase behavior. These constants were shown to be capable of providing guidance to the selection and synthesis of cocrystals.\textsuperscript{96} The third approach is Hansen solubility parameters, and it was used as part of an interaction study of 30 coformers with indomethacin, and it was proved to improve the efficiency of cocrystal screening.\textsuperscript{97} The degree of proton transference in a hydrogen-bonded synthon determines whether a particular solid should be classified as a cocrystal or as a salt or else continuum between salts and cocrystals retain their property. The fourth one is the degree of transfer between substituted pyridine derivatives and a series of carboxylic acids were evaluated using molecular electrostatic potential surface (MEPS) calculations,\textsuperscript{98} and it was reported that the calculated charges on the $N$-heterocyclic base bond acceptor could be used to predict the existence of a salt or a cocrystal. Formation of the salt was inevitable once the charge on the hydrogen-bond acceptor exceeded a critical value, while the intended cocrystal could not form if the charge was too low.

By converting APIs into pure salts/cocrystals if they are liquids at or below body temperature, some problems typically associated with solid APIs such as low solubility and polymorphism, may have to overcome. The non-covalent modification of APIs has become the immense interest in their regulatory and intellectual property ramifications, as well as the technological aspects. Already the new crystalline salts and solvates of a known API are considered as patentable new forms. But the cocrystals could also be considered as patentable but it can be the novel forms if they improve upon drug properties. Cocrystals are not yet approved and marketed as drugs but there is a lot of scope and reason for optimism. Much recognition for one of the first studies of comparing the pharmacokinetic profile of a novel carbamazepine: saccharin cocrystal\textsuperscript{99} to a marketed drug carbamazepine (Tegretol\textsuperscript{®})
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drew the industrial attention with economic aspects of this field. Indeed, some APIs currently marketed as salts such as caffeine citrate may assumed to be cocrystals. The co-crystals of fluoxetine-HCl (Prozac) and various organic acids reported by Childs et al. are the well known examples for ionic cocrystals. Co-crystals would be considered analogous to API-excipient systems such as inclusion compounds of drugs and so would not be considered new drugs as per the FDA norms. Rather, they would be eligible for approval under an Accelerated New Drug Application (ANDA), which only requires proving bioequivalence to a market drug (CBZ:SAC can be taken). However, the FDA regulates novel salts of an API as entirely new drugs which must undergo full testing. It means the full biological test is needed to prove the equivalence of drug activity with the new cocrystal and it requires several screening test to be approved as drugs. So the Selection of an appropriate salt or cocrystal form for a new drug entity provides the pharmaceutical and formulation scientist to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance. Salts are most commonly employed for modifying aqueous solubility. However, the salt form selected will influence a range of other properties such as melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties.

1.4.2.3 Cocrystal/ Salt Polymorphs

Polymorphs offer a unique way to study the structure–property relationships of the drug compound of single or multi component systems resulted from the different crystalline environments. As we know that characterizing and analyzing the polymorphic property of an API is important in the drug developments. It is estimated that more than 50% of drug molecules are polymorphic and studies concerning polymorphism in cocrystals and salts are not so explored well and very few studies are available for identifying novel polymorphs of cocrystals. As per
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the recent report, polymorphs of 17 cocrystals have been found to crystallize concomitantly out of the 114 polymorphic cocrystals reported. Cocrytallization experiments can be conducted from solvents of different polarities and solvent mixtures and a number of polymorphs were reported for cocrystals by conventional crystallization techniques. Parallel to solvent-based cocrytallization technique, solid state grinding is used extensively for cocrytall screening. Forms I and II of the 1:1 cocrytal of caffeine–glutaric acid was crystallized concomitantly from evaporative crystallization but form I was obtained by neat grinding or grinding with a few drops of non-polar solvents and then form II can be obtained by grinding with a few drops of polar solvents. Trask et al. have shown that the two polymorphs of the cocrytal of caffeine with glutaric acid showed differences in stability property under elevated relative humidity (RH) conditions. Goud and Nangia have recently reported two polymorphs of a cocrytal of a sulfonamide antibiotic, SACT with ACT with improved solubility and dissolution rates. The crystal structure analysis revealed that these two polymorphs were distinguished by N–H⋯O sulfonamide and N–H⋯O carbonyl hydrogen bonds and thus can be classified as synthon polymorphs. Desiraju coined the term supramolecular synthon and defined it as structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions. A different conformational polymorphism has been observed by Braga et al. for 1:1 cocrytal of pimelic acid with BP, which forms three polymorphs that show minor differences in their overall crystal packing but feature differences in the conformations of pimelic acid. When different tautomers of a compound crystallize in different crystal forms, they are termed as tautomeric polymorphs. In general, tautomerism occurs when the constitutional isomers of different hydrogen-atom connectivities are in dynamic equilibrium with one another. A 1:1 cocrytal of a nonsteroidal anti-inflammatory drug, piroxicam with 4-HBA represents a rare case of tautomeric polymorphism in cocrytals. Saha recently reported a methanol solvate of a
cocrystal of 1,3,5-benzenetricarboxylic acid (BTA) with 4,4’-methylenebis-(2,6-dimethylaniline) (MBDA) in a 1 : 1 : 1 molar ratio which exists in two polymorphic forms.\textsuperscript{104d} Ma et al found that cocrystallization of C-methylcalix[4]resorcinarene (CMCR) with BP in the presence of benzil resulted in concomitant crystallization of two polymorphs of a 1 : 1 : 1 ternary cocrystal, CMCR–BP–benzil.\textsuperscript{104e} In another ternary system, the crystal structures of two polymorph is shown to have 10 independent molecules in the asymmetric unit of trimesic acid (benzene-1,3,5-tricarboxylic acid, TMA), tert-butylamine (TBA), and methanol. Among polymorphic systems reported previously, there are very few examples for which two polymorphs have 10 or more independent molecules in the asymmetric unit and very few examples of co-crystals comprising three or more distinct organic molecules.\textsuperscript{104f} 

Salt polymorphs are also reported and limited to very few in the literatures. A second polymorphic form of a 1 : 2 : 3 pamoate : DABCO : water salt has been obtained by liquid-assisted grinding, and it is shown that interconversion between this salt and a salt with 1 : 1 : 2 stoichiometry is facile via liquid-assisted grinding with additional amounts of pamoic acid.\textsuperscript{104g} In other case, A metastable polymorph of metformin hydrochloride is identified in capillary crystallization technique and characterized by thermal microscopy.\textsuperscript{79} The stability relationship between the two polymorphs of metformin–embonate can be inferred from the solubility and dissolution measurements at room temperature in the aqueous medium. The above results indicate that form II is more stable at RT, which therefore has a lower solubility and lower dissolution rates compared to the less stable form I.\textsuperscript{105a} Both hydrochloride and hydrobromide carbamazepine salts (CBZHCl and CBZHBr) were initially isolated as metastable polymorphs that subsequently spontaneously transformed to the more favorable isomorphic forms, CBZ.HCl (II) and CBZ.HBr (II).\textsuperscript{105b} Six structures of new salt forms of CBZ and
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CYT are reported and their occurrence and structural similarities discussed by Kennedy et al. Piperazinium meclofenamate salt (1:1) crystallized as monoclinic ($P2_1/c$) and orthorhombic ($P2_12_12_1$) polymorphs concomitantly from acetonitrile solvent.$^{105c}$ Many other salt polymorphs are reported elsewhere and related the structural importance in deciding the solid state characteristics with polymorphs.$^{106}$

1.4.2.4 Solid Solution and Eutectic Composition

Solid solution are possible only between the materials that should have isomorphous$^{52}$ that means same space group and unit cell dimensions and/or almost same type and position of atoms or functional groups or isostructural having same structure but not necessarily the same unit cell dimensions present in the materials.$^{107}$ Hume-Rothery rules says that solid solution is often formed by isomorphous crystals where the crystal structures having the same space group and unit cell dimensions.$^{108}$ These solid solutions are sustained by strong cohesive interactions and retain the lattice structure of the parent (major) component as the inclusion of the second (minor) component happens substitutionally or interstitially in the parent crystal lattice. This topic is not explored so well for organic and pharmaceutical materials to understand their structure property relationships.$^{25}$ Thus, the distinction of components as solvent and solute is superficial in continuous solid solutions, since they can mix in any proportion. When the interacting materials have similar size and crystal structures, they can have unlimited solubility and accommodate and distribute well in the crystal lattice, either substitutionally or interstitially, without disturbing the parent lattice structure and thus form continuous solid solutions (Cu-Ni).$^{108c}$ They can form a homogeneous phase or solid solution throughout the lattice wherein no interface exists between the copper and nickel atoms, non-isomorphous crystals can give rise to a eutectic. Solid solutions are possible to characterize by single crystal X-ray diffraction as the site occupancy factor (s.o.f.) of atoms and it can be used to determine the integrity and stoichiometry of the components.$^{25}$ When the materials
have atomic/molecular size/shape mismatch and asymmetry in the crystal structures, they have limited solubility and thus cannot fit beyond a threshold in the crystal lattice of each other, since this will cause strain and disorganization of the lattice structure. Such systems cannot form continuous solid solutions and instead tend to form eutectics (Pb-Sn).\textsuperscript{108c}

The components of eutectic solid solutions can be differentiated as solvent/solute because of limited solubility in one another. Therefore, a eutectic can be envisaged as an ensemble of many/different solid solutions which are discontinuous.\textsuperscript{25} The individual components retain their crystal structures as discontinuous solid solutions and form the eutectic crystal lattice. A eutectic’s microstructure may be more precisely defined as ‘a conglomerate of solid solutions’ or ‘a conglomerate of lattice structures of different materials.’\textsuperscript{25} Fortunately, the atomic pair distribution function PDF is available to estimate the instantaneous atomic arrangements and reveals the local structure (low r region) from the average crystallographic structure. The utility of pair distribution function (PDF) in the characterization of felodipine–eudragit E solid dispersion is an early pharmaceutical example.\textsuperscript{108d} The characterization of eutectics is really a challenge because depression in melting point by thermal methods DSC, Kofler’s hot stage microscope, heat–cool–reheat is the only indicator of eutectic formation. Anti-tuberculosis combination drugs are found to form eutectics upon thermal treatment (pyrazinamide–isoniazid and rifampicin–isoniazid).\textsuperscript{109a} Apart from the fusion and solvent-based methods, eutectics can also be prepared by compaction (acetaminophen–propylphenazone) and grinding (curcumin–hydroquinone). Aspirin eutectics are reported by melting and grinding techniques.\textsuperscript{109b,c} To exploit the full potential of eutectics as novel organic materials, advances in XRD techniques must dovetail into the preparatory and property studies on eutectics. The several reports of
unsuccessful cocry stallization experiments could actually be latent eutectics, after a thorough analytical study.

1.5 Solubility and Dissolution

Solubility is a thermodynamic property while dissolution is a kinetic process. The equilibrium solubility of a compound is defined as the maximum quantity of that substance which can be completely dissolved at a given temperature and pressure in a given amount of solvent, and is thermodynamically valid as long as a solid phase exists which is in equilibrium with the solution phase. Drug bioavailability depends on adsorption that can be assessed by Fick’s First law, \( J = PC \) where the flux \( J \) of a drug through the gastrointestinal wall depends on the permeability coefficient \( P \) of the gastrointestinal barrier for the drug and the drug concentration \( C \). Generation and maintenance of the metastable supersaturated state is a strategy to improve intestinal absorption of poorly water soluble drugs. Two essential steps need to be considered and they are termed the “spring and parachute” approach (Fig. 1.13). A thermodynamically unstable, supersaturated solution of a drug can only be generated starting from a high energy form of a drug which is known as the “spring”. An example might be an amorphous API which is much more soluble than the crystalline material. A combination of excipients such as co-solvents, lipids, or polymer-based formulations can deliver the drug in solution as high energy solid forms that can easily provide an accelerated dissolution or a higher apparent solubility and is known as the “parachute effect”. The apparent solubility is the apparent equilibrium between drug in solution and a solid whose structure is in the high energy state. A high energy form of the drug (the spring) provides the driving force to solubilize the drug at a concentration greater than its equilibrium solubility level and a similar effect resulted by the combination of excipients (the parachute) by inhibiting or retarding precipitation. For a pure solid to be in equilibrium with a solution containing, the chemical potential of solid, \( \mu_s \), must be
the same in the solid (s) and liquid (l) phases; \( f^* \) —solubility. So the chemical potential of solid and liquids are same in equilibrium condition is given as follows (eqn 6),

\[
\mu_{\text{solid}} = \mu_{\text{solution}}
\]

\[
\mu_{0\text{solid}} = \mu_{0\text{solution}} + RT f^* \quad (6)
\]

**Figure 1.13** “Spring and parachute” approach to promote and maintain supersaturation of poorly soluble drugs (Ref. 113).

Kinetics is a time-dependent term and the dissolution rate of a solid in solvent is written by Noyes–Whitney equation, as follows (eqn 7),

\[
\frac{dc}{dt} = \frac{DS_w}{Vh} (C_s - C) \quad (7)
\]

where \( C \) and \( C_s \) represent the concentration of the dissolved substance at a given time \( t \) and the solubility concentration of the substance, respectively. The \( D, S_w, V, \) and \( h \) represent the diffusion coefficient of the substance, the surface area of exposed solid, the volume of solution, and the thickness of the diffusion layer, respectively.
For drugs that undergo phase change during the solubility experiment, the IDR of the drug must be measured (designated $J_m$ and $J_s$ for metastable and stable polymorphs), and these values in turn are used to estimate the apparent solubility of the metastable species. Equation 8 can be derived from the Noyes Whitney Nernst equation,

$$C_m = C_s \left( \frac{J_m}{J_s} \right) \quad \text{(8)}$$

The origins of the concept of dissolution impacting the absorption of a drug substance from the GI tract were attributed to a publication by Edwards in 1951 in an excellent historical perspective on dissolution by Dokoumetzidis and Macheras. However, the working apparatus and underlying concepts used by scientists to routinely assess the dissolution characteristics of drug substance and dosage forms have not evolved significantly over the same period. Indeed, the USP I/II apparatus typically used around the globe to measure product performance can trace its origins back to the 1960s with formal adoption of the basket stirred flask test by the USP and NF in 1970. The simple basket or paddle stirred USP I/II systems provide a well-stirred, medium-rich environment in which dosage form disintegration and dissolution can be evaluated. Such a static, closed environment is limited by the absence of an absorptive sink and the relevance of the resulting hydrodynamics is also questionable given the continuous stirring and large volumes of media often deployed. In vivo solubility and dissolution rates are affected by the unique physicochemical properties of the drug and dosage form and by physiological factors such as pH, fluid composition and hydrodynamics. The composition of intestinal fluids is likely to vary considerably due to meal ingestion, diet, gastric emptying, secretion, intestinal transit and motility. All of which can impact both saturation solubility and dissolution rate. A key exemplar of this class of system is the artificial stomach duodenal model (ASD) which has been used to evaluate the effect of gastric emptying on API dissolution, solubilization and precipitation in a separate
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duodenal compartment (Fig. 1.14). The in vivo relevance of ASD dissolution profiles is based on the assumption that the concentration of dissolved drug in the simulated duodenum is proportional to its bioavailability. The simplicity of this technique combined with biorelevant fluid transfer makes it a powerful tool to understand dynamic dissolution issues for compounds if they are subject to physical chemistry processes such as precipitation, dissolution or solubilization.

![Dynamic Processes in the Artificial Stomach Duodenal Model](image)

**Figure 1.14** Dynamic processes present in the artificial stomach duodenal model (ASD, Ref. 115a).

**Maximum Dose Strength.** For WHO oral drugs formulated in immediate-release dosage forms, values for maximum dose strength and lowest dose strength (milligrams) were obtained from the WHO Essential Medicines Core List. For the oral drugs in immediate-release dosage forms in the top 200 U.S. list, this information was obtained from the Orange Book (online version updated June 2003).

\[
D_o = \left(\frac{M_0}{V_0}\right)C_s \quad \text{.........(9)}
\]
The above equation 9 was used to calculate the dose number, where \(M_0\) is the highest dose strength (milligrams), \(C_s\) is the solubility (milligrams per milliliter), and \(V_0 = 250\) mL. A \(D_o\) value of <1 means a highly soluble drug whereas \(D_o\) is >1 for low solubility compounds. In simple terms, \(D_o\) is the number of glasses of water required to dissolve the tablet at its highest dose. \(D_o\) values of 25-100 are considered low solubility drugs and this number can even exceed 1000.\(^{13c}\)

### 1.6 Structure-property Relationships

Crystal engineering has reached the immense level of developments over few decades as a new subject of the interaction between crystallography and chemistry. Chemistry deals with molecules while crystallography has to do with crystals in which they are extended and long ordered assemblies of molecules in the crystal lattice. The interplay between chemistry and crystallography is just interaction between the structure and properties of molecules on one hand and those of extended assemblies of molecules on the other.\(^{116}\) Polymorphism can cause direct impact on physical properties, melting point \((T_m)\), density \((\rho)\), elastic modulus \((E)\), and hardness \((H)\) of the molecular crystals. In the structure-property context, the variation in the crystal packing or conformations of polymorphs can lead to variations in dissolution, solubility, grindability, and tabletability. So they affect the pharmaceutical industrial processes such as industrial scale ups and formulations.\(^{31}\) A new mechanochemical approach that is stress-induced phase transformations of polymorphs from one crystalline form to another during milling and tableting are generally undesirable in drug products. Nanoindentation provides useful information on the mechanical properties of polymorphic drugs, which in turn allows for developing an understanding of their stability in the solid state. Higher hardness, \(H\), and elastic modulus, \(E\), This can be addressed by seeking the correlation between \(H\) and solubility of molecular crystals. Both \(H\) and solubility depend broadly on crystal structure and the intermolecular interactions. Desiraju has found an inverse linear
correlation between H and solubility (i.e., the higher the H, the lower the solubility) in curcumin and sulfathiazole polymorphs (Fig. 1.15) and confirmed the Gibbs free energy of the polymorphs are close to one another in this study.\textsuperscript{117a}

![Figure 1.15](image)

**Figure 1.15** inverse correlations of hardness and solubility in (a) curcumin and (b) sulfathiazole polymorphs (Adapted from Ref. 117a).

In the similar way, Desiraju showed the correlation of elastic modulus, E, of the single crystals with $T_m$ measured by the nanoindentation technique and that both E and $T_m$ are strongly dependent on solid state molecular conformations.\textsuperscript{117b} A crystal with a higher E has a similarly larger set of restoring forces between molecules that may be measured with nanoindentation. The melting temperature $T_m$ depends on two thermodynamic factors called enthalpic and entropic factors.\textsuperscript{117c} A higher $T_m$ is associated with efficient three dimensional close packing and higher density. The even diacids have a crystal packing that is dominated by alkyl chain close packing and the melting points and E values are correspondingly high. In the odd acids, the packing follows from a high-energy strained conformation. Relief of this strain energy is provided by melting or by mechanical flexing. This accounts for their anomalously low $T_m$ and E values (Fig. 1.16). Nanoindentation may be used as a direct measure of molecular and crystal energies in molecular crystals.
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Figure 1.16 Variation of (a) E and (b) $T_m$ with N in $\alpha,\omega$-alkane dicarboxylic acids. (c) Linear correlation between E and $T_m$, (d) $E/\rho$ vs N and variation in $\rho$ and E with N (Adapted from Ref. 117b).

1.6.1 Compression Behavior

Crystal engineering can be an effective means in rectifying among many other properties, including the poor mechanical properties of a drug for smooth development of tablet dosage forms. The Influence of crystal structures and intermolecular interactions on the tableting properties of paracetamol and sulfamerazine polymorphs is compared here.\textsuperscript{118a} The purpose of this study was to investigate the compression behavior of orthorhombic polymorph and to compare with the monoclinic paracetamol. There are sliding planes present in the orthorhombic form responsible for an increase in crystal plasticity. Tabletability of the orthorhombic crystals was observed to be far better than that of the monoclinic...
ones. Orthorhombic paracetamol from II exhibited greater fragmentation at low pressure, increased plastic deformation at higher pressure, and lower elastic recovery during decompression compared to form I. A structure analysis of two polymorphs showed that the nature of intermolecular bonds was similar in two polymorphs and the number of bonds is being greater for orthorhombic paracetamol. The crystalline structure accounts for its better compression behavior, because of the presence of sliding planes and orthorhombic paracetamol is suitable for the direct compression process.

Recently the compression behavior of acetaminophen salt was compared with the monoclinic form I and protonated of Acetaminophen hydrochloride monohydrate is discovered to solve these compaction problems associated with paracetamol polymorphs.\textsuperscript{118b} This exhibits improved mechanical properties and superior tableting behavior as expected which can address the poor compaction in ACM polymorphs (Fig. 1.17). Like form II, the flat-layered structure in salt which allows facile plastic deformation of crystals when stressed and a much lower force is needed to make an indent of the same size on the crystal of salt. It is concluded that acetaminophen HCl monohydrate demonstrate its excellent tableting properties to the polymorphs.

![Tabletability plots of Form I acetaminophen Vs acetaminophen salt](image)

**Figure 1.17** Tabletability plots of Form I acetaminophen Vs acetaminophen salt (Adapted from Ref. 118b)
Bulk powders of sulfamerazine polymorph I and of two batches II(A) and II(B) of different particle size of polymorph II were crystallized for understanding the compression behavior. The powders were compressed to form tablets of known porosity and tensile strength. The tabletability of these polymorphs are following the order of I >> II(A) > II(B) and compressibility follows the order, I << II(A) < II(B). Therefore, the increased tabletability of form I over froms II(A) or II(B) is attributed to its greater compressibility. The crystal structure analysis reveals that the slip planes in crystals of I is the reason for good compressibility but this was absent in form II. Slip planes provide I crystals greater plasticity and therefore greater compressibility and tabletability. Thus, the slip planes confer greater plasticity to crystals of acetaminophen salt than polymorphs, and sulfamerazine polymorphs I than II and therefore greater tabletability achieved by using the crystal engineering strategies.

1.6.2 Mechanical Behavior

Polymorphs are quite different in terms of their mechanical hardness/softness, and this is a property of interest in the pharmaceutical and material industry, because the harder form will have better granularity, filterability and flowability properties. For example, the compound 6-chloro-2,4-dinitroaniline has three polymorphs which are obtained concomitantly from a variety of solvents. All of them are visually indistinguishable chunks in crystallization flask (Fig. 1.8a) and it is accomplished by picking them by their ability to withstand (Form III) or collapse (Form I) on application of mechanical shear. Form I has Layer structure to show N–H···O, C–H···O, C–H···Cl and C–Cl···O interactions in the crystal structure and forms the stacking in a [010] plane (Fig. 1.18). Significantly, Forms I and III are quite different in terms of their mechanical hardness/softness in this study and may open an interest in mechanical property. In conclusion, the strength of a tablet is expected to be directly proportional to the strength of intermolecular
interactions in the lowest energy slip planes in the corresponding crystal form. The established relationship between the presence of a thin flat 2D layer structure and high plasticity in molecular crystals of Form I showed that the bending type crystals have an alternate packing type for achieving high plasticity in crystals.

Figure 1.18 Crystal structure of Form I of 6-chloro-2,4-dinitroaniline (CDA). (a) Layer structure to show N–H⋯O, C–H⋯O, C–H⋯Cl and C–Cl⋯O interactions. (b) View down [010] to show stacking of antiparallel layers (c) Two different crystals of form I that are not only bent but are also cracked along the crystal length. Middle: Molecular structure of CDA (Adapted from 119ab).

Another interesting example is the crystals of C₆Cl₆ and it was deformed into Ω and Π shapes¹¹⁹c (Fig. 1.19a), depending on the direction and the points of
applying the support and stress on the crystals. When a crystal of C₆Cl₆ (Fig. 1.19b) was compressed carefully along its needle length [010] a bending deformation takes place. It is just continued in extreme level of bending the crystals can even be flattened upon themselves and reaches the zero bend radius. The reason for this extreme level bending nature is that the interactions among halogen atoms between the stacks are weaker and/or less specific than the π···π interactions within a stack.

![Image of C₆Cl₆ crystal bending](image)

**Figure 1.19** Bending of C₆Cl₆ crystal. (a) Before bending. Arrows show the point and direction of the stress applied. (b-d) Different snapshots in the bending process. Notice the very low bend radius (close to zero) in Figure d. Right hand side: Molecular structure of C₆Cl₆ (Ref. 119c)

### 1.6.3 Solid-state Emission Behavior

Many organic molecules and metal-containing hybrid ligands exhibit solid-state emissions in the field of fundamental research on photophysical properties and applications for electroluminescent devices, light-emitting diodes (LED), solid state dye lasers, and light-emitting electrochemical cells. Basically, this field originated from the intramolecular charge-transfer (ICT) state, excited-state intramolecular proton transfer (ESIPT), aggregation-induced enhanced emission (AIEE). The characteristics of solid-state emission are that the emitting behavior strongly depends on the molecular structure and molecular arrangement in crystal structures. In the course of development of emitting molecules, polymorph-dependent emissions were
proposed as a promising approach to control the emission properties.\textsuperscript{121a-b} For example, the quinoline derivatives with donor and acceptor substituents as new fluorophores were screened for polymorphic single crystals that could emit different colors.\textsuperscript{121c} Surprisingly, the crystals demonstrated SC-to-SC transformations between the polymorphs in response to heat, and the thermal alteration of molecular rearrangements in the single crystal polymorphs. They were successfully confirmed by X-ray diffraction and X-ray crystallography. The compound N-methyl and N-phenyl derivatives of 2,4-tri-fluoromethyl-7-aminoqumoline (1 and 2 in Scheme 1.4) and their absorption and emission properties in the solution and the crystalline state were compared and the emission change with the thermal SC-to-SC phase transition is also accounted. The absorptions for the powder and the emission spectra for the crystal samples of 1 namely polymorph GB and YG and 2 polymorphs B and G are shown in Figure 1.20. The large red shifts of emission maxima $\lambda_{\text{max}}^f(c)$ and reduction of emission intensity $\Phi^f(c)$ observed in the solid-state emission might be due to the intermolecular $\pi\cdots\pi$ interaction and the intermolecular hydrogen bond. Although the $\pi\cdots\pi$ interaction at distances between the quinoline rings greater than 3.6 Å were limited. The $\pi\cdots\pi$ interaction was considered to stabilize the photoexcited state and led to the red shift of $\lambda_{\text{max}}^f(c)$ and the reduction of $\Phi^f(c)$ in the solid state. In addition, the intermolecular hydrogen bonding might lead the non-radiative decay process. The crystal structure analysis showed the herringbone arrangements for polymorphs (1), slipped parallel and slipped-columnar modes for polymorphs G and B (2) respectively. The herringbone, slipped-columnar, and slipped-parallel modes showed partial overlapping of the quinoline rings with J-aggregate form. In this study, thermal SC-to-SC transformation between the crystal polymorphs that emitted different colors was successfully monitored in irradiation process. However, the observed thermal emission color changes were irreversible.
Scheme 1.4 Molecular structural unit of 2,4-tri-fluoromethyl-7-aminoquinoline

Figure 1.20 (I) Spectra of absorption for the powder and emission for the crystal samples of a) 2 (polymorph GB: solid line, and polymorph YG: dashed line), and b) 3 (crystal B: solid line, and crystal G: dashed line). Arrows in the spectra indicate the vertical axes. II. Time dependence of the views of a) crystal GB of 2 at 90.8 °C and b) crystal B of 3 at 110.8 °C. Top: irradiation at 365 nm. Bottom: Under ambient lighting. Scale bar beside 0 min indicates 1 mm (Adapted from Ref. 121c).
1.6.4 Solubility Behavior

In general, the aqueous solubility of small molecules depends on mainly their hydrophobicity (log P). The partition coefficient log P (eqn 10) can be defined as follows:

\[
\log P = \log \left( \frac{\text{solute in octanol}}{\text{solute in water}} \right) \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots (10)
\]

Increase of aqueous solubility leads to an increase of the denominator of the above equation and a decrease of log P. To decrease the value of log P by chemical modification, i.e., substitution of hydrophilic group(s) into molecules is a general strategy for improving aqueous solubility of organic compounds. But this approach is limited when we have hydrophilic group(s) in the substitution because sometimes this interferes with the target protein drug interaction and affects purpose of the lead compounds. This strategy is also not effective when both solubility and hydrophobicity need to be increased in special cases to improve the oral bioavailability of highly hydrophilic compounds having insufficient solubility. Furthermore, compounds with poor solubility in both octanol and water sometimes retain poor absolute values of aqueous solubility despite a decrease of log P values, because log P values are just the ratios of two parameters. So there is special focus to find a novel and general strategy to increase the aqueous solubility of drug and bioactive candidates that would have a great impact on drug discovery and medicinal chemistry.\textsuperscript{122a} Polymorphism can make an increase in dissolution rate and a temporary or apparent increase of solubility.\textsuperscript{122b} But it cannot produce a permanent alteration of solubility issues. The undissolved solute particles in the solution will revert to its most stable crystal form at any time and therefore the solubility will approach the true thermodynamic solubility. Hence, the role of crystal modification/polymorph is confined to increasing the dissolution rate of drugs. Finally, some of the solubility scientists collectively introduced an alternative
strategy for improving aqueous solubility by means of disruption of molecular planarity and symmetry. Molecular planarity and symmetry are known to influence crystal packing, and disruption of molecular planarity is expected to decrease the efficiency of crystal packing and the melting point.

By following this general strategy to address this solubility, Yalkowsky (1980) came up with the idea of general solubility equations (GSEs) derived on the basis of semi-empirical analysis (eqn 11).\textsuperscript{122c} GSE includes not only log P but also melting point:

$$\text{Log } [\text{solubility (M)}] = 0.5 - (\log P) - 0.01([\text{melting point (°C)}] - 25)$$ \quad (11)

The melting point and solubility is closely related to crystal lattice and crystal packing energies. In general, the solubility of a solid solute in water is dependent on two important factors: (a) the crystallinity of the solute and (b) the ability of the solute to interact with water molecules.\textsuperscript{122d} Therefore, the disruption of crystal packing would be an alternative solution for improving aqueous solubility of the drugs. A few chemical modifications focused on crystal packing have been discussed here to compare structure-property relationships. Gavezzotti emphasized that the melting point is one of the most difficult crystal properties to predict, and Lipinski mentioned that the prediction of crystal packing energies is at present extremely difficult.\textsuperscript{123} There is a wide scope to make a concrete and general strategy to decrease melting point and disrupt the crystal packing to address these issues by analyzing the crystal packing through crystal structure and melting point determination for solid state chemists. Recently, Lovering analyzed the drug and clinical candidate database and reported that an increase in the fraction of sp\textsuperscript{3} hybridized carbons is associated with a decrease in melting point.\textsuperscript{124a} In 1995, Gavezzotti noted that a very old rule of thumb says that symmetrical molecules pack in a three-dimensional periodic lattice more easily than less symmetrical ones and hence form more stable, higher-melting and less soluble crystals.\textsuperscript{124b} In 1996, Yalkowsky also reported a statistical study
showing that the entropy of melting of organic compounds is related to molecular symmetry number. \textsuperscript{124c} Thus, the relationship between molecular planarity and melting point could provide the basis for a strategy to increase solubility of drug candidates.

In this discussion, we will have to focus on chemical modification of bicyclic lead molecules in different ways to disrupt molecular planarity/symmetry by increasing the dihedral angle. In fact Dihedral angles are considered here for improving the solubility because (i) little is known about the effect of increased dihedral angle on solubility, and (ii) dihedral angle is a convenient numerical parameter that can be obtained by calculation or X-ray crystal analysis among parameters of molecular planarity. For example, \(\beta\)-Naphthoflavone \textsuperscript{125} (Scheme 1.5) was reported to be a more potent aryl hydrocarbon receptor (AhR) agonist than the usual AhR agonist TCDD. Its hydrophobicity is found to be lower than that of other AhR agonists that could make a potentially more useful tool for AhR research. The structural developmental studies of (1) were aimed to obtain AhR ligands with more potent activity and improved solubility. The structure of 1 includes a rotatable biaryl moiety to decrease the planarity of the molecule and later introduced substituent(s) (2-6) on the phenyl group of 1 to understand the structure-solubility relationships. The thermodynamic aqueous solubility of 1-6 was carried in phosphate buffer (pH 7.4) solution. The aqueous solubility of 1 was quite low (<0.15 \(\mu\)g/mL) compared to other derivatives. EtOH was used as an aqueous medium for the evaluation of thermodynamic solubility in addition to the buffer solution. The solubility improved to 84.6 \(\mu\)g/mL. Ortho-substituted derivatives 2-5 showed better solubility than 1 as expected. Indeed, dimethyl analogue 3 was 15 times more soluble (1270 \(\mu\)g/mL) than 1. Difluoro analogue 5 showed 3 times greater solubility (248 \(\mu\)g/mL) than 1. On the other hand, methoxy analogue 6 was less soluble than 1 (Table 1.2). Compounds 2, 3, and 4 possess increased hydrophobicity, larger dihedral angle, lower melting
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point, and improved aqueous solubility compared with 1. These results suggest that introduction of substituent into 1 disrupted the planarity by increasing the dihedral angle in turn to decreased crystal packing energy. This results in lower of melting point and increasing of solubility after this modification. Lack of molecular symmetry of 4 might lead to a lower melting point and greater solubility, or the changes of electron density arising from the introduction of fluorine might have resulted in increased solubility. In the first chapter we expanded this study of comparing the molecular planarity with solubility and dissolution study of cardiosulfa and its analogs to validate this new strategy to make modification in low aqueous soluble drugs for further improvements.

Scheme 1.5 Molecular structure of β-Naphthoflavone AhR agonist

Table 1.2 Thermodynamic solubility of β-Naphthoflavone derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>X</th>
<th>Dihedral angle</th>
<th>Melting point (°C)</th>
<th>Solubility (µg/mL)</th>
<th>CLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>C</td>
<td>17.8</td>
<td>165</td>
<td>84.6</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>C</td>
<td>37.9</td>
<td>135</td>
<td>262</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>C</td>
<td>70.0</td>
<td>92</td>
<td>1270</td>
<td>5.1</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>H</td>
<td>C</td>
<td>9.1</td>
<td>157</td>
<td>153</td>
<td>4.8</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>F</td>
<td>C</td>
<td>40.5</td>
<td>150</td>
<td>248</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>H</td>
<td>C</td>
<td>18.5</td>
<td>192</td>
<td>45.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>
1.7 CSD and Supramolecular Synthon

The Cambridge Structural Database CSD (1965) currently has structural information on over 700000 (2014)\textsuperscript{126a} crystal structures of organic molecules as polymorphs, cocrystals, salts and solvates, and also many organometallic complexes. In the CSD, all crystal structures are differentiated by unique refcode codes having six letters. Any new crystal structure is to be reported that will have this refcode family. In future if any further changes in the structures of the same chemical compound like redeterminations under the same or different conditions or, specifically in the current context, those structures will be given same those six letters plus additionally two more numbers. If there are no accurate structures in redetermination with proper refinement factor then only the unique structure with the lowest R factor will be kept. In addition to redeterminations, potentially wrong structures are also eliminated including structures with R factors of >10\% together with structures exhibiting positional disorder of heavy atoms. Therefore, the resulting list contains only structures of high quality with no disorder. Thus, any refcode family containing more than one refcode within the best-R-factor list corresponds to a polymorphic family.\textsuperscript{38}

Polymorphs: Only structures with all of their three-dimensional atomic coordinates determined with the exception of hydrogen atoms were retrieved, and polymeric structures were removed. The search returned 2935 different crystal structures containing 1366 polymorphic molecules. Gavezzotti stated that “structures without a substantial change in the three dimensional symmetry operations should strictly be referred to not as polymorphs but as modulations or phases.”\textsuperscript{126b} A 2011 data analysis set revealed that 1297 out of 1366 are originally polymorphic retrieved through COMPACK algorithm, 1157 (89.2\%) have two polymorphs, 114 (8.8\%) have three polymorphs, and only 26 (1.4\%) molecules have four polymorphs. Six molecules are there in the pentamorphic systems where as only one molecule has
hexamorph and heptamorph category. A new record of polymorphic molecule, Flufenamic acid (FFA), reported by Matzger is the example of nonamorphism in the CSD having nine solved crystal structures. However, there are some families of related molecules, such as the sulphonamides, ROY derivatives, barbiturates, carbamazepine derivatives, and fenamates, which appear to have a strong tendency for polymorphism. A new concept of a polymorphophore, first introduced by Matzger as a structural element that, when incorporated into a molecule, favors the formation of polymorphic crystal forms. This is analogous to “pharmacophores” as particular structures which are particularly useful in finding new leads in drug discovery, especially when the three-dimensional (3D) structure of the receptor is unknown. The concept recognizes that there are families of molecules containing a common substructure (polymorphophore) where many members exhibit polymorphism (Scheme 1.6). These common substructures to several polymorphic molecules have been referred to as polymorphophores.

For cocrytals, polymorphism in 114 of cocystal cases is a result of conformational flexibility and/or minor structural changes in the packing out of many organic co-crystals in the CSD. Synthon polymorphism in a co-crystal is more specific, and occurs when the primary synthons in the forms are different. Five polymorphs (FUR-NCT) reported for a cocystal of a loop diuretic drug, furosemide (FUR), and nicotniamide (NCT) and four polymorphs (GA-ACT) for cocystal of gallic acid with acetamide in the CSD (Scheme 1.7). Dimorphs of ternary cocystal has also been reported for C-methylcalix[4]resorcinarene (CMCR) compound in CSD.
Introduction

Scheme 1.6 Polymorphophores (substructure for polymorphic molecules) in CSD

Scheme 1.7 Highly polymorphic co-crystals of furosemide and gallic acid in the CSD

Intermolecular bonds: A bond brings together atoms, molecules, or ions in chemically acceptable and meaningful ways though different modes of orientation with the help of covalent bonds, ionic bonds, metallic bonds, and hydrogen bonds. In IUPAC Gold book, a hydrogen bond is defined as a form of association between an electronegative atom and a hydrogen atom attached to a second, relatively electronegative atom. It is best considered as an electrostatic interaction by hydrogen which permits proximity of the interacting dipoles or charges. Hydrogen bonds can
be inter-molecular or intramolecular. Generally, it is involving fluorine, the associated energies are less than 20-25 kJ/mol. The H atom is the seat of bonding of hydrogen bridge in $X-H\cdots Y-Z$ because it is the key ingredient that brings atoms $X$ and $Y$ together. Hydrogen bonds of the typically $N-H\cdots O$, $O-H\cdots O$, $O-H\cdots X$, $F-H\cdots F$ (Pauling’s definition)\textsuperscript{127a} do not violate the definition because they are short, linear, energetically very favorable, and can be identified spectroscopically. This strength follows from the electronegativities of the elements $X$ and $Y$. Typical “new” hydrogen bonds are the $C-H\cdots O$, $C-H\cdots N$, $O-H\cdots \pi$, $N-H\cdots \pi$, and $C-H\cdots \pi$ interactions\textsuperscript{127e} and still in the controversy to name them as hydrogen bonds. All these weak and strong bonds are mentioned in the table 1.3 for more information.

**Table 1.3 Characteristics of Hydrogen bonds**

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X-H\cdots Y$</td>
<td>Mainly covalent</td>
<td>Mainly electrostatic</td>
<td>Electrostatic</td>
</tr>
<tr>
<td>Bond energy (kJ/mol)</td>
<td>60-20</td>
<td>16-60</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Bond Lengths (Å)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H\cdots Y$</td>
<td>1.2-1.5</td>
<td>1.5-1.2</td>
<td>2.2-3.2</td>
</tr>
<tr>
<td>$X\cdots Y$</td>
<td>2.2-2.5</td>
<td>2.5-3.2</td>
<td>3.2-4.0</td>
</tr>
<tr>
<td>Bond angles $X-H\cdots Y$ (°)</td>
<td>175-180</td>
<td>130-180</td>
<td>90-150</td>
</tr>
<tr>
<td>IR stretching</td>
<td>25%</td>
<td>10-25%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>NMR shift</td>
<td>14-22</td>
<td>&lt;14</td>
<td>-</td>
</tr>
<tr>
<td>Examples</td>
<td>Gas phase dimers</td>
<td>Acids</td>
<td>C–H H and π-bonds</td>
</tr>
</tbody>
</table>
The systematic analysis on the probabilities of formation of supramolecular synthons and the Etter’s hydrogen ring motifs constructed from O–H···O, O–H···N, N–H···O and N–H···N hydrogen bonds in the crystal structures.\textsuperscript{21,127a-d} The maximum probabilities of formation of 75 bimolecular hydrogen-bonded ring motifs in organic crystal structures were determined to the robust supramolecular synthons. Among all of 34 different hydrogen bond acceptors (O, N, S, halogen and π-acceptors) for the strong carboxyl donor, carboxylic groups are among the best investigated hydrogen bond functionalities possess a hydrogen bond donor as well as an acceptor site that can readily form cyclic dimers (85\%) or open arrays or catemer (15\%).\textsuperscript{128a-b} However, the probability drops to 33\% for dimer and 2.8\% for catemer in presence of other functional groups. Zaworotko\textsuperscript{128c} showed 84\% probability for amide dimers and 14\% for catemers in the absence of competing hydrogen bond donors/acceptors. Again the probability of formation of amide dimer and catemer comes down to 35\% and 18\% respectively when there are competing groups such as carboxylic acid, secondary amide, aminopyridine, pyridine, water, alcohol, amines etc are present. For example, presence of pyridyl-N as a competitor makes the probability of formation of acid–pyridine heterosynthon 91\% than a carboxylic acid dimer or catemer. Hence it is known as the highly robust synthon that can be utilized for crystal design. Zaworotko\textsuperscript{128d} classified synthons as homosynthons and heterosynthons based on the interacting functional groups. Classified synthons as homosynthons and heterosynthons based on the interacting functional groups are given in Scheme 1.8. The known hydrogen bonds are acid–pyridine,\textsuperscript{129} phenol–pyridine,\textsuperscript{130} phenol–amine,\textsuperscript{131} acid–amide,\textsuperscript{132} aminopyridine–acid and amide–pyridine-N-oxide\textsuperscript{133} are robust heterosynthons.
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Scheme 1.8 Supramolecular synthons with their probabilities calculated from CSD statistical study.

1.8 Conclusions

Polymorphism plays an important role in pharmaceutical and other industries and therefore knowing the possible forms will help to choose the best form for development, determine the most stable form, develop a robust crystallization process, develop a suitable formulation process, avoid processing conditions that could produce another form, prevent latent polymorphs from appearing late in development or in marketed products, prepare an acceptable regulatory package, expand intellectual property for the compound and assess lifecycle management. The identification of zwitterionic polymorphs for amphoteric drugs may open a new way of modifying the drug property suitable for dosage forms without any chemical modification. The crystal engineering strategies are still useful to find out these polymorphs and need some more attention of understanding the mechanism to develop the method to stabilize this new category of polymorphs.
Cocrystals, salts and eutectic compositions are multi components used in the developmental stage of drug properties and it requires the specific strategies to select the conformer which can form cocrystals with API. Salts are the better formulation techniques compared to the cocrystals because of the FDA restrictions on the approval of cocrystal as drugs. It is believed to conduct many biological experiments on cocrystal would help us to reach the next level of marketing the cocrystal products. So the eutectics mixtures and cocrystals are in the clinical stage and now expected to show the equal or more efficiency in clinical performance.

Solubility is the main issue for many drugs in the drug discovery stage and it requires the novel strategies to predict the solubility of new molecules before it come to the synthesis stage. Either chemical modification or crystal engineering techniques should be focused more on this aspect to improve the solubility of lead molecules. This will save the time and investment on working with insoluble drug/lead molecules. This area is now interdisciplinary to biological testing for engineered materials and that would expand the wide scope of crystal engineering in many ways. The structure-property relationships would be useful to develop the material properties by using crystal structure analysis and theoretical predictions of cocrystals and polymorphs.

1.9 References


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