Multiple crystalline solid-state forms of an active pharmaceutical ingredient; blue symbol is API and green symbol is second component, which may be neutral (crystalline solid, cocrystals, solvates, hydrates) or ionic state (salt).
“Probably every substance is potentially polymorphic. The only question is whether it is possible to adjust the external conditions in such a way that polymorphism can be realized or not.” Maria Kuhnert-Brandstätter, *Pharm. Z.* 1975, 4, 131.

### 1.1 Solid State Chemistry

Solid State Chemistry is the study of the synthesis, structure, and properties of solid phase materials. It has a strong overlap with Physics, mineralogy, crystallography, ceramics, metallurgy, thermodynamics, materials science and electronics with a focus on the synthesis of novel materials and their characterization. The design of organic crystalline materials requires understanding of non-covalent interactions between molecules. There have been major advances in solid state and materials chemistry in the last two decades and contributed that are an integral part of life. The properties of a crystalline solid depends not only on the constituent molecules, but also on their interactions in the crystal lattice. An understanding of the factors that determine crystal packing arrangement and the role of physicochemical properties is a challenging topic. Solid state chemistry is concerned with the development of new methods of synthesis, identifying and characterisation of new materials by advanced techniques for the control of useful properties.

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of dosage forms (e.g. tablets, capsules, granules, powders, etc) because of their easy uptake in the bodies. No matter whether as pure drug substances or in formulated products, APIs can exist in various solid forms, such as polymorphs, pseudopolymorphs (solvates and hydrates), salts, co-crystals and amorphous solids. Polymorphs are possible for each of these solid forms (Scheme 1). Along with crystalline materials, amorphous solids having short range order of periodicity, are also important in drug development because of their high free energy and hence solubility. Each form may possess its own unique mechanical, thermal, physical and chemical properties that can remarkably affect the solubility, bioavailability, hygroscopicity, melting point, stability, compressibility and other performance characteristics of the drug. A thorough understanding of the relationship between the particular solid form and its functional properties are crucial for selecting the most suitable form of the API
for scale up, formulation activities, clinical trials and finally manufacturing. This exercise requires inputs about crystallization, pharmacology and formulation.

1.2 Solid forms of Active pharmaceutical Ingredients

At present nearly 40% of the new chemical entities being discovered have poor water solubility drugs, which is a serious drawback for drug formulation and so many new potential drugs fail in the formulation stages because of poor aqueous solubility. More than 80% drugs are marketed as solid formulations and 90% of them are crystalline in nature. Remaining 10% are marketed as gel, injected form etc. An enhancement of drug solubility of therapeutic agents can possibly improve their bioavailability. Identifying the optimum solid form of an active pharmaceutical ingredient (API) is always desirable for clinical use. Frequently, the API exhibits low solubility, and it might be appropriate to use its more soluble amorphous phase or a more soluble multicomponent form, such as a salt form – for ionizable APIs – or cocrystal form for neutral APIs. Furthermore, APIs are typically amenable to formation of multiple component crystals such as solvates and hydrates.
1.2.1 Polymorphs

Polymorphism is defined as the ability of a compound to exist more than one crystalline arrangement in the solid state. Polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different crystalline arrangements of the molecule of that compound in the solid state (McCrone 1965). The number of crystalline forms or polymorphs of a compound are proportional to the time and resources dedicated to investigate to them (McCrone 1963). Allotropes and polymorphs are closely related. Polymorphism is used in general to refer to structural diversity of molecular compounds, whereas allotropy is the structural diversity of elements. For example, carbon has four allotropes diamond, graphite, fullerene and carbon nanotube. The carbon atom is the same in four crystal structures; however the arrangement of atoms is different in different crystal structures, which consequently lead to the differences in their properties like hardness and conductivity (Figure 1). Polymorphs may have different conformations (conformational polymorphism), packing (packing polymorphism) and supramolecular synthons (synthon polymorphism) in the crystal lattice. The different types of polymorphs has been displayed in Scheme 2. Conformationally flexible molecules have greater scope for polymorphic occurrence because of large number of degrees of freedom as the energy differences between conformational polymorphs generally lies in a small energy window of 0.5-3 kcal mol\(^{-1}\). A metastable conformation may be stabilized by stronger hydrogen bonds in the crystal structure while a stable conformer may not be able to form strong hydrogen bonds. The overall stability of a polymorph is accounted by the conformation energy and lattice energy (total) for a given polymorphic system. The energy compensation towards overall energy minimization in a polymorphic system is referred to as ‘systematic effect’. This phenomenon was recently reviewed by Nangia with several examples of conformational polymorphs. Polymorphism in drugs like nimesulide (chapter 2), furosamide, tolbutamide, ritonavir, chlortalidone and biologically active compound curcumin (chapter 3) are examples of conformational polymorphs.
Figure 1 Four allotropes of carbon, graphite (layered), diamond (tetrahedron), buckminsterfullerene C$_{60}$ (spherical) and carbon nanotube (cylindrical structure) culled from ref. 5e.

Scheme 2 Schematic illustrations of different arrangements of molecules in the crystalline lattice that lead to different kinds of polymorphism, taken from ref. 6a.

Polymorphism in organic solids is of fundamental importance because of its ability to alter physicochemical properties in different crystal structures, such as melting.
point, density, dipole moment, hardness, compressibility, solubility, dissolution rates and bioavailability. These differences impact on drug formulation and processing of the drug, due to which it has received particular attention in pharmaceutical industry. Stability is an important concern while dealing with polymorphs. Because their energy differences are relatively small, form inter-conversion is common. For e.g. Antitumor prodrug temozolomide exists as three crystalline polymorphs (with 3D coordinates) as form 1, 2 and 3 and their stability order is form 1>form 2>form 3. Grinding of metastable form 2 for half an hour in mortar pestle or in presence of small amount of acetonitrile transforms to stable form 1. The metastable nature of form 2 is ascribed to hydrogen-bonding differences in the two crystal structures. The amide syn NH moiety forms N–H···O hydrogen bonds in both structures. The anti NH moiety forms N–H···N hydrogen bonds in form 1, whereas the donor is not intermolecularly H-bonded in form 2 (Figure 2). Therefore risks of marketing a drug product without awareness and recognition of the thermodynamically most stable form are very high. Getting the right polymorph is not only important for drugs and pharmaceuticals but also for speciality chemicals like explosives, dyes, pigments, flavours and confectionery products. For example, anthelmintic drug mebendazole (Figure 3) exists in three polymorphic forms (A, B, C). Form A is the most stable polymorph, whereas form B and C are metastable ones. The solubility order of the three polymorphs in 0.03M hydrochloric acid is A<C<B. However, due to the increased toxicity of the highly soluble form B, form C is clinically preferred because its solubility is sufficient to ensure optimal bioavailability. This is important because polymorph A has no anthelminthic activity alone or when present above 30% in polymorphic mixtures. But form C has tendency to convert into stable inactive for A. So it is desirable to stabilize form C by additive, polymer, excipients or cocrystal coformers (CCF).

**Figure 2** (a) The carboxamide dimer of crystallographic unique molecules (shaded differently) in TMZ Form 1. Anti N–Hs are involved in N–H···O and N–H···N bonds. (b)
N–H···O and C–H···O dimers assemble in a tape motif in form 2. The anti NH of CONH₂ makes only intramolecular hydrogen bond in this crystal structure (taken from ref. 6c).

**Figure 3** Three polymorphic forms of anthelmintic drug mebendazole, among them metastable form C is therapeutically active.

The transformation to the undesired polymorph may take place through a solvent mediated phase transformation during manufacturing process. On the other hand, recognition of such processes may lead to its utilization to obtain a desired polymorph. For example L-glutamic acid have two polymorphs; metastable α and stable β form (Scheme 3). L-glutamic acid, later converted to the monosodium salt used for taste enhancement in food additive industry. It is crucial to obtain α polymorph rather β form. The latter can lead to a situation in which crystallization slurry coagulates into a gel and can no longer be processed. Garti et al showed the addition of selected surface active agents can lead to the preferential crystallization of the α polymorph of L-glutamic acid. Trimesic acid and transglutonic acid, which conformationally mimic α form of glutamic acid, selectively inhibit crystallization of β form and stabilize metastable α form.

**Scheme 3** Polymorphic Transformation of L-Glutamic acid from Conformation α to β

Drugs that were previously known to exist only one form are now shown to have various polymorphic forms. This has perplexed pharmaceutical companies and now they have investigated crystal polymorphism in order to optimize the physical properties of a pharamaceutical soild before the drug development. Otherwise late-stage phase
transitions to a new polymorph can become a big setback for the company like anti HIV drug ritonavir.\textsuperscript{12} To obtain exclusively metastable forms are recent techniques such as, crystallization with structurally related additives, epitaxial growth, laser induced nucleation, crystallization in capillaries, confinement within porous materials, using polymers as heteronuclei, mechanical grinding, using supercritical liquids, gels etc.\textsuperscript{13} High-throughput crystallization screens have been developed using a combinatorial approach to capture crystal form diversity.\textsuperscript{14}

\textbf{1.2.2 Thermodynamic relationships in polymorphs}

crystallization occurs in two processes, (i) nucleation and (ii) crystal growth. Although the exact mechanism of nucleation is not clear, a plausible mechanism is supported partly by some experimental evidence.\textsuperscript{15} From the thermodynamic point of view, a solution is an entropy-dominated situation and a crystal is largely the enthalpically determined outcome. In solution various clusters involving both solute molecules and solvent molecules are formed using intermolecular interactions. This brings elements of short range order in solution. These clusters are continuously breaking, forming and rearranging prior to nucleation stage. At supersaturation these clusters become larger in size and more short range order enters in the system. At this stage nucleation occurs either by homogeneous nucleation (no effect of any external factor) or by heterogeneous nucleation (effect due to foreign particle, physical disturbance, scratched surface of vessel etc.) and solvent molecules from solute-solvent clusters exit into the bulk solvent simultaneously forming the crystal, which is characterised by long range order.\textsuperscript{16}

Ostwald rule\textsuperscript{17} states that a system moves to equilibrium from an initial high-energy state through minimal changes in free energy. Therefore the structure that crystallizes first is the one which has the lowest energy barrier (highest energy, kinetically metastable). This form would then transform to the next lower energy state until a thermodynamically stable state (lowest energy) is reached, the so-called Ostwald’s Law of Stages (Scheme 1.4).
Scheme 1.4 Ostwald’s Rule of Stages. Initial high-energy state (metastable A) through minimal changes in free energy crystallizes first and is the one which has the lowest energy barrier. Metastable form A will then transform to the next lower energy polymorph (metastable B) and so on (metastable C) until thermodynamically stable crystal D appears, culled from ref. 17.

From thermodynamic consideration polymorphic pairs can be divided as monotropic and enantiotropic systems. Monotropic systems are defined as systems where a single form is more stable than others regardless of temperature. Enantiotropic systems are defined as systems where the relative stabilities of the two forms invert at some transition temperature before melting. Again heat of transition rule suggest that if an endothermic phase change is observed at a particular temperature, the transition point lies below that temperature, and the two polymorphs are enantiotropically related. If an exothermic transition is observed, then there is no phase transition point below that transition temperature. This can occur when two forms are monotypically related or when they are enantiotropically related and the thermodynamic transition point is higher than the measured transition temperature. Heat of fusion rule states that in an enantiotropic system the higher melting polymorphs will have the lower heat of fusion. If the higher melting polymorph has a higher heat of fusion, the two are monotypically related.

Several analytical techniques are used to establish the thermodynamic behaviour of polymorphs, e.g. Optical and/ or Hot Stage Microscopy (HSM), Differential Scanning Calorimetry (DSC) etc. HSM can be used to obtain qualitative information on polymorphic behaviour by visualising the morphology change under optical microscope.
However thermal analysis (DSC or DTA) provides quantitative information about the relative stability of polymorphic modifications, the energies involved in phase changes between them and the monotropic and enantiotropic nature of those transitions. Tolbutamide, an oral hypoglycaemic agent exists in five polymorphic modifications.\(^{19}\) The thermogram of Form I\(^I\) showed two peaks; a small endotherm at 40 °C followed by another endotherm at 128 °C. The first peak was ascribed to a kinetically reversible polymorphic transition to Form I\(^II\) and the second peak corresponds to melting of Form I\(^II\). Polymorph I\(^II\) is stable at high temperature and phase transition from polymorph II III, and IV can clearly be described by DSC thermograms (Figure 4). Transitions II→I\(^III\), III→I\(^III\), IV→I\(^III\) show those polymorph pairs are enantiotropically related. Enantiotropic and monotropic relation between polymorphs in several instances are observed and discussed in Chapter 2 and 3. HSM, DSC and X-ray diffractions measurements are analyzed. Spectroscopic methods include Fourier Transformed Infrared (FT-IR), Near Infrared (FT-NIR) and Raman spectroscopy etc., thermal analysis (DSC, TGA, HSM etc) and finally X-ray diffractions (single crystal and powder X-ray diffraction) are generally used to characterization of polymorphs.

![DSC thermogram of Tolbutamide polymorphs at heating rate of 10°/min. The polymorph conversions from other forms to form I (Ref. 19b).](image)

**Figure 4** DSC thermogram of Tolbutamide polymorphs at heating rate of 10°/min. The polymorph conversions from other forms to form I (Ref. 19b).

Powder X-ray diffraction (PXRD) method is one of the most reliable methods for identification and characterization of polymorphs based on line profile by taking a safe threshold of $\Delta2\theta > \pm0.2^\circ$. Traditionally PXRD have been used for the qualitative
identification of individual polymorphic phases or mixture of phases and considered as fingerprint pattern. As polymorphs comprise different solids with different unit cells and different arrangements of the molecules within the unit cell they have different fingerprints. For e.g. Chlorpropamide, anti-diabetic drug crystallizes as five polymorphs; α, β, γ, δ and ε.20 The PXRD of five polymorphs of chlorpropamide showed clear indication of at least five different solid phases of the API (Figure 5).

Figure 5 PXRD patterns of five polymorphs of chlorpropamide suggesting at least five different solid forms exists, taken from ref. 22a.

1.3 Multi-component system

- Host-guest compounds, salts and cocrystals

Multi-component system can be divided into host-guest compounds, molecular salts and cocrystals. The inclusion of small guest molecules in the open framework of a host molecule constitutes a host-guest compound. Some common host molecules are cyclodextrins, calixarenes, cucurbiturils, porphyrins, crown ethers, cryptophanes, bisphenols and zeolites etc.21 The difference between a host-guest adduct H•G and a binary molecular complex A•B is that, in a host guest adduct there are either no H···H and G···G interactions, or H···H interactions along with weak H···G association stabilizing the structure. But in case of binary molecular complex A•B, there is a definite A···B interaction comparable in strength to A···A or B···B aggregation. When the guest molecule is a solvent of crystallization and present in the cavity of a crystal lattice, the
structure is referred to as solvate or pseudopolymorph. When the guest molecule present in the crystal structure is water, it is referred to ashydrate.

Solvates, hydrates (pseudopolymorphs)\textsuperscript{22} are of great importance in the pharmaceutical industry. The drug development process exposes active pharmaceutical ingredients (APIs) to various organic and aqueous solvents during crystallization, wet granulation, storage and dissolution can lead to the formation of pseudopolymorphs. The most important point is that some APIs form solvates while others do not. The propensity of an API molecule to form solvates has been related to molecular structural features, hydrogen bond patterns, donor-acceptor imbalance and crystal packing. About one third of the drugs are able to form hydrate. Generally hydrates are less soluble than anhydrous compound because of repulsion of water molecules present in the crystal lattice and external solvent molecules. But interestingly norfloxacin hydrate and tegaserod monohydrate showed better solubility than its corresponding anhydrous forms.\textsuperscript{22f,g} Hence hydration plays an important role in altering solubility and stability of a drug. Some important drugs which are marketed as solvates are Indinavir sulphate ethanolate (Crixivan), Darunavir ethanolate, Doxycycline HCl ethanolate, Mirtazapine hemihydrate (Remeron), Paroxetine HCl hemihydrate (Paxil), Atorvastatin calcium trihydrate (Lipitor) and Cephradine dihydrate (Velosef).\textsuperscript{23}

A cocrystal can be defined as multi-component assembly of two or more solid crystalline materials involving in noncovalent interactions in a definite stoichiometric ratio results homogeneous phase and solid at ambient conditions.\textsuperscript{24} Co-crystals can be constructed through several types of non-covalent interactions, including hydrogen bonding, $\pi$ stacking, and vander Waals forces. Again salt is defined as multi-component system where proton is transferred from acidic to the basic moiety. Salts and cocrystals are the extreme cases of proton position between an acid and a base in multi-component crystals. At the salt end the proton transfer is complete, and on the opposite end proton transfer is absent in cocrystals where the acid ionization constant ($pK_a$) governs the formation of a salt or cocrystal.\textsuperscript{25} Both of them are very useful for alteration of physicochemical properties of an API. Salts of API are used in pharmaceutical industry for the past many decades but pharmaceutical cocrystals are still in the pipeline and much widely studied in the last decade.\textsuperscript{26}
1.3.1 Pharmaceutical cocrystals

Pharmaceutical cocrystal is a subclass of cocrystals that are formed between an Active Pharmaceutical Ingredient (API) and generally regarded as safe (GRAS) molecule or biologically acceptable to the human body. Cocrystallization is a process to combine together different molecular species within one periodic crystalline lattice by noncovalent interactions without making or breaking of covalent bonds. As a result, it is expected that API should retain its biological activity as before cocrystal formation. During cocrystallization, two things can happen: interacting molecules may separate yielding individual solids or crystallize together as a cocrystal. During falling apart of individual component may crystallize into metastable forms also. The goal of the recrystallization is to obtain homogeneous phase, whereas cocrystallization produces a heteromeric product or a binary phase (Figure 6). The most common method of obtaining cocrystals is to dissolve the components in a suitable solvent system and allowing for crystallization to take place. Gentle warming is necessary to dissolve the solids and sometimes an anti-solvent is added or the solution is subjected to sonication to accelerate crystallization. This empirical, trial-and-error method is referred as solution crystallization. Jones showed that by adding a few drops of solvent during grinding/kneading, referred to as solvent-drop or solvent-assisted grinding, one can accelerate adduct formation due to lubrication. Again recently utilizing Kofler mixed fusion method, nicotinamide cocrystals with seven active pharmaceutical ingredients were prepared. Here higher melting point component (A) melted and recrystallized before molten component (B) is brought into contact with it, creating a zone of mixing, shown in Figure 6.

![Figure 6](image)

**Figure 6.** (a) Events that take place during co-crystallization. Two components may fall apart yielding individual phases or obtain as a cocrystal. (b) Various methods (solution, slurry, grinding, ball milling or melt) used to prepare
1.3.2 Pharmaceutical salts

Salt formation is a useful method for isolation and purification of substances. The formation of a pharmaceutical salt can modify the physicochemical as well as the biological properties of an ionizable drug, which cannot be predicted from the properties of the parent drug and of the counter ion. Salt formation is an acid base reaction and a compound having an acidic or basic group can participate in salt formation. Improvement of solubility and dissolution rate of weakly acidic or basic drug having poor water solubility is the primary reason for preparation of pharmaceutical salt forms. In addition salt formation also influences many other properties like melting point, hygroscopicity, chemical stability, solution pH, crystal form, and mechanical properties. An estimated half of the drugs in the market are administered in the salt form. It is easier to select a salt forming agent by knowing the acid ionization constant (pKa) value of each ionizable group present in API. It is generally accepted that reaction of an acid with a base will be expected to form a salt if the ΔpKₐ (ΔpKₐ = pKₐ(conjugate acid of base) – pKₐ(acid)) is greater than 3. Nangia and coworkers noted that a smaller ΔpKₐ (less than 0) will almost exclusively result in cocrystal formation, the parameter is inappropriate for accurately predicting salt formation in the solid state when ΔpKₐ is between 0 and 3, as some examples are there where partial proton transfer is the case. Salt former selection is an important aspect in preparing pharmaceutical salts from toxicological and pharmacological point of view. Salt formers can be subdivided into a number of categories, depending upon their functionality and purpose. Some of the most frequently used pharmaceutical salts are listed in Table 1.

Table 1 Classification of some common pharmaceutical salts (ref. 30g)

<table>
<thead>
<tr>
<th>Salt Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inorganic acids</td>
<td>hydrochloride, hydrobromide, sulfate, nitrate, phosphate.</td>
</tr>
<tr>
<td>Sulfonic acids</td>
<td>mesylate, esylate, isethionate, tosylate, napsylate, besylate.</td>
</tr>
<tr>
<td>Carboxylic acids</td>
<td>acetate, propionate, maleate, benzoate, salicylate, fumarate.</td>
</tr>
<tr>
<td>Anionic amino acids</td>
<td>glutamate, aspartate.</td>
</tr>
<tr>
<td>Hydroxyacids</td>
<td>citrate, lactate, succinate, tartrate, glycollate.</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>hexanoate, octanoate, decanoate, oleate, stearate.</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Insoluble salts</td>
<td>paemoate (embonate), polystyrene sulfonate (resinate).</td>
</tr>
<tr>
<td><strong>Cations</strong></td>
<td></td>
</tr>
<tr>
<td>Organic amines</td>
<td>triethylamine, ethanolamine, triethanolamine, meglumine, ethylenediamine, choline.</td>
</tr>
<tr>
<td>Metallic</td>
<td>sodium, potassium, calcium, magnesium, zinc.</td>
</tr>
<tr>
<td>Cationic amino acids</td>
<td>arginine, lysine, histidine.</td>
</tr>
</tbody>
</table>

### 1.4 Solubility and dissolution rate

According to the simplest definition, the thermodynamic solubility of a compound in a solvent is the maximum amount of the most stable crystalline form of the compound that can remain in solution under equilibrium conditions. Aqueous solubility is essential for drug candidates. Poor aqueous solubility is likely to result in poor absorption, even if the permeation rate is high, since the flux of a drug across the intestinal membrane is proportional to the concentration gradient between the intestinal lumen and the blood. The FDA regulations concerning oral medications require more extensive investigation of compounds with low solubility, and it may have an even greater impact in the case of its dosage forms. Again high concentrations of poorly soluble drugs in organisms may result in crystallization and acute toxicity, as in the case of uric acid and gout. Overall, poor solubility of drug candidates has been identified as the cause of numerous drug development failures.\(^{31}\) The traditional approach of salt formulation to improve drug solubility is unsuccessful with molecules that lack ionisable functional groups, have sensitive moieties that are prone to decomposition/racemization, and/or are not sufficiently acidic/basic to enable salt formation. Cocrystals are preferred over salts because of stability towards hydration of the former. Cocrystals have the ability to tune physicochemical properties e.g. solubility, stability, bioavailability etc. which are the major concern in most APIs.

According to the Biopharmaceutics Classification System (BCS),\(^{32}\) drugs are classified into four categories depending on their solubility and permeability parameters (Table 2). The seminal work of Amidon\(^{32b}\) showed that drug absorption in the gastrointestinal (GI) tract is controlled by membrane permeability and solubility/dissolution rate. Permeability is measured as the partitioning of the drug.
molecule in its uncharged or neutral state between n-octanol and water, represented by log P. The reference standard for defining high or low permeability boundary is the n-octanol/water partition coefficient for metoprolol (log P 1.72). Drugs having log P > 1.72 are categorized as high-permeability because metoprolol is known to be 95% absorbed in the GI tract. High/low solubility is defined with reference to the Dose number, Do, which is the ratio of the highest drug dose strength in the administered volume (taken as 250 mL = a glass of water) to the saturation solubility of that drug in water (measured in mg/L). A Do value of <1 means a highly soluble drug whereas Do is >1 for low solubility compounds. In simple terms, Do is the number of glasses of water required to dissolve the tablet at its highest dose. Do values of 25-100 are considered low solubility drugs and this number can even exceed 1000. The serious problem posed by low solubility drugs was highlighted in recent articles, over 80% drugs are sold as tablets. About 40% of marketed drugs have low solubility problems. More alarming is double the percentage of drug candidates in the R&D pipeline (80-90%) which could fail due to solubility problems (Table 3).

Table 2 The Biopharmaceutics Classification System of drugs (ref. 34) according to intestinal absorption and oral administration parameters.

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>% drugs on market</th>
<th>% drugs in R &amp; D pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>high</td>
<td>high</td>
<td>35</td>
<td>5-10</td>
</tr>
<tr>
<td>II</td>
<td>low</td>
<td>high</td>
<td>30</td>
<td>60-70</td>
</tr>
<tr>
<td>III</td>
<td>high</td>
<td>low</td>
<td>25</td>
<td>5-10</td>
</tr>
<tr>
<td>IV</td>
<td>low</td>
<td>low</td>
<td>10</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Table 3 Low Solubility Drugs in the Market and in the Development Pipeline According to the Biopharmaceutics Classification System (ref. 35).
The solubility and dissolution are related to each other. The concentration of the solute in the solvent, at which the rate of molecules leaving the bulk solute surface becomes equal to the rate of redeposition, is the thermodynamic solubility. The rate at which this equilibrium is achieved is defined as the dissolution rate. Therefore solubility is an equilibrium process while dissolution is a kinetic phenomenon. According to Noyes–Whitney, dissolution rate of a solute in a solvent is directly proportional to its solubility described by the equation

\[ \text{Dissolution rate} = \frac{dQ}{dt} = \frac{DA}{h} (C_s - C_b) \]

where,
\( dQ/ dt \) is the rate of mass transfer
\( D \) is the diffusion coefficient (cm\(^2\)/ sec)
\( A \) is the surface area of the drug (cm\(^2\))
\( h \) is the diffusion layer thickness (cm)
\( C_s \) is the saturation solubility of the drug
\( C_b \) is bulk solution concentration.

When particles dissolve by pure diffusion, the concentration at every point away from the solid-liquid interface increases, but the concentration gradient decreases with time. Therefore overall dissolution rate decreases and becomes constant with time and a pseudo-steady state is reached. Noyes and Whitney proposed the diffusion layer model. When surface area is constant, the dissolution rate is proportional to the difference between solubility and the bulk solution concentration.

\[ \text{Dissolution rate} = k (C_s - C_b) \]

where, \( k \) is a constant (mass transfer coefficient)

1.4.1 Types of Dissolution

There are two different types of experimental dissolution methods (1) Planar surface dissolution and (2) Powder dissolution.

- **Planar Surface Dissolution**

  For experimental determination of dissolution rate the planar surface model is the simplest one having simple mathematics for calculation. For calculating dissolution rate the Noyes-Whitney equation can be used. Generally for pharmaceutical solids
measuring dissolution rate from a well defined surface is a popular way, for that intrinsic dissolution rate (IDR) determination is one example.

**Intrinsic Dissolution Rate**

When agitation intensity and surface area are fixed, dissolution rate can be considered as a property of solid. This loosely defined property is called the Intrinsic Dissolution Rate (IDR). Due to the close relation between IDR and solubility, it can be used as a method of solubility estimation, when equilibrium solubility cannot be obtained experimentally. For the intrinsic model the container shape, agitation intensity (rotation per minute, rpm), bulk solvent volume, temperature of the medium etc. are kept constant to calculate the dissolution rate. The rotating disk apparatus for measuring IDR and the liquid flow are shown in the Figure 7.

![Figure 7](image)

Figure 7 (a) Rotating disk apparatus for measuring IDR. (b) Liquid flow pattern around the rotating disk apparatus (ref. 35c).

**Powder Dissolution**

To calculate dissolution rate experimentally the planar surface model is useful but in a real sense the drug dissolution involves solid particles and is very complicated process as the total surface area changes during dissolution. Powder dissolution is based on the real dissolution phenomenon occurs inside the body. In this model the effect of particle size and shape play a crucial role. Generally for high soluble APIs, intrinsic dissolution experiment is better than powder dissolution because it provides dissolution rate in 4-5 h period, which is critical time for a fast dissolving drug. The drug will act accordingly in the biological system and it is preferred as tablet formulation. But for low
soluble APIs, powder dissolution experiment is more appropriate to obtain maximum solubility with respect to time and capsule formulation is better approach here. To improve solubility of specially BCS class II and IV APIs, cocrystals design approach is a preferred option. Recent examples of cocrystals of anti-depressent drug, fluoxetine hydrochloride, anti-fungal drug itraconazole (sporanox), chronic pain killer AMG 517, and anti-epileptic drug lamotrigine (Lamictal) and carbamazepine showed better solubility than the API. Antifungal drug Itraconazole extremely water insoluble and administered both orally and intravenously. The oral formulation of itraconazole is the amorphous form coated on the surfaces of sucrose beads, and marketed as the Sporanox® capsule. Interestingly, no crystalline salt of itraconazole has been reported in the patent literature, even though salt formation using itraconazole and an acidic salt former would seem to be a logical approach to improve the absorption properties of the API. Remener et al. prepared stable pharmaceutical cocrystals and especially itraconazole–L-malic acid cocrystal, exhibits a similar dissolution profile to that of the sporanox beads in 0.1 (N) HCl medium, is an alternative to the existing amorphous formulation (Figure 8). The cocrystals improved the solubility 4-20 fold higher concentration than the crystalline drug form and the peak values were maintained for up to 8 h.

![Figure 8](image)

**Figure 8** Dissolution curves in 0.1 N HCl at 25°C. Sporanox capsule amorphous form (■), crystalline itraconazole (♦), L-malic acid cocrystals (▼), tartaric acid cocrystal (●), and succinic acid cocrystal (▲) (ref. 37a).

Again epileptic drug Lamotrigine showed possibility of cocrystals with methyl paraben, nicotinamide and salt with saccharin. The saccharinate salt exhibited the
highest concentration in water and maintained its peak profile for 4 h (Figure 9a). The decrease in pH from 5.5 to 5.1 was attributed as a reason for the highest dissolution rate of the saccharinate salt. The increase in the solubility of lamotrigine is higher in acidic medium compared to pure water by about 10%, it being a basic drug. The methyl paraben cocrystal had the highest dissolution profile in acidic medium and maintained its level for 4 h (Figure 9b). Nicotinamide cocrystal had the second highest concentration profile in neutral medium whereas its hydrate form was higher in acidic solution. Rodríguez-Hornedo\textsuperscript{38} recently proposed that cocrystal solubility is directly proportional to the solubility of its components. However, the available data on lamotrigine cocrystals discussed above shows mixed results. Nicotinamide has the highest solubility (1 g/mL); it is used as a hydrotrope for solubility improvement, but its cocrystals exhibited the second highest solubility after saccharinate and methyl paraben in neutral and acidic medium, respectively. It appears that the theoretically expected linear relationship between the solubility ratio of the components plotted against the solubility of the cocrystal former divided by the solubility of the API\textsuperscript{38} will be realized only when the crystal structures have similar hydrogen bonding and molecular packing. This results showed clearly that solubility/dissolution is pH dependent.
Figure 9 Dissolution profile of lamotrigine crystal forms in (a) water and (b) pH 1 buffer. Lamotrigine, 2 = lamotrigine–methyl paraben (form II), 3 = lamotrigine–nicotinamide (anhydrate), 4 = lamotrigine–nicotinamide (monohydrate), and 5 = lamotrigine–saccharinate salt (ref. 37b).

1.4.2 Spring and Parachute model

Recently Nangia et al.\textsuperscript{39} explained the reason behind the solubility enhancement of pharmaceutical cocrystals which are bound through weak intermolecular interaction through Spring and Parachute model. The enhanced solubility of drug cocrystals is similar to the supersaturation phenomenon characteristic of amorphous drugs. However, in contrast to the metastable nature of amorphous phases, cocrystals are stable owing to their crystalline nature. Yet, cocrystals can exhibit dramatic solubility advantage over the stable crystalline drug form; often comparable to amorphous pharmaceuticals.\textsuperscript{39a} The “spring and parachute” concept for amorphous drug dissolution is adapted to explain the solubility advantage of pharmaceutical cocrystals. Thus (1) the cocrystal dissociates to amorphous or nanocrystalline drug clusters (the spring), which (2) transform via fast dissolving metastable polymorphs to the insoluble crystalline modification following the Ostwald’s Law of Stages, to give (3) high apparent solubility for cocrystals and optimal drug concentration (the parachute) in the aqueous medium (Figure 10). They proposed possible mechanism for the solubility advantage of pharmaceutical cocrystals (Figure 11). The dissociation of the hydrogen bonded cocrystals in the aqueous medium liberates the more soluble coformer into the solution, whereas the less soluble drug molecules
aggregate as an amorphous phase because of the sudden crashing out from solution. These aggregates lack the long-range order and periodicity characteristic of the crystalline state. The amorphous phase gives peak drug solubility for a short period (the spring), which will gradually transform to metastable polymorph(s) and thereby extend the metastable zone width (the parachute effect). Finally, the drug will transform to the stable, insoluble polymorph, but by this time the bulk of the drug has been absorbed through the fast dissolving metastable state(s). The Ostwald’s Law of Stages could stretch the metastable zone width to several hours. If the amorphous phase directly transforms to the stable crystalline form without the intermediacy of metastable polymorphs (dash arrow), the drug will exhibit spring effect only.

Figure 10 The spring and parachute concept to achieve high apparent solubility for insoluble drugs. (1) The crystalline (stable) form has low solubility. (2) A short-lived metastable species (i.e., amorphous phase) shows peak solubility but quickly drops (within minutes to an hour) to the low solubility of the crystalline form. (3) Highly soluble drug forms are maintained for a long enough time (usually hours) in the metastable zone (ref. 39).
Dissolution experiments of pharmaceutical cocrystals of biologically active molecule curcumin (chapter 4), antitumor prodrug temozolomide (chapter 5) and anthelmintic niclosamide (chapter 6) will be discussed.

1.5 Stability issue of pharmaceutical cocrystals

The stability of a solid drug substance in the presence of atmospheric moisture is of concern to the pharmaceutical industry as it has practical implications for processing, formulation, packaging, and storage. It is sometimes the case that an anhydrous crystal form is stable below a certain critical relative humidity (RH), but at higher RH it converted to a crystalline hydrate. In these cases, solid form selection is often employed to search for a polymorph or cocrystal form that exhibits greater stability at high RH values. According to International Conference on Harmonization (ICH) guidelines, three storage conditions for APIs are 25°C and 60% RH; 30°C and 65% RH and 40°C and 75% RH (Table 4). The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For APIs with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.
Table 4 Different storage conditions according to ICH guidelines (ref. 41)

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period covered by data at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term*</td>
<td>25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate**</td>
<td>30°C ± 2°C/65% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% RH ± 5% RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>

For e.g. Nitrofurantoin (NF) is a well known antibacterial drug extensively used as an oral treatment for urinary tract infections. The physical stability of NF-4HBA (1:1) co-crystal was tested against that of NF (β-form) at various relative humidity (RH) and temperature conditions recommended by the ICH guidelines for pharmaceutical stability testing. Incubated samples were analyzed by PXRD at designated time points. There were no detectable changes with NF (β-form) stored at 24 °C and RH (<10, 33, 57, 75%) and at 40 °C and 75% RH as per the PXRD. However, NF anhydrous (β-form) converted to NF hydrate (Form II) at 24 °C and 97% RH in 7 weeks whereas at 40 °C and 96% RH, phase transformation was rapid and it occurred within one week. Figure 12 shows the PXRD patterns analyzed for stored samples of NF (β-form) and NF-4HBA at 24 °C and 97% RH up to 13 weeks and compared against native samples and pure NF–H2O (Form II). The start of phase transformation was observed at 7 weeks for NF (β-form) in PXRD. Interestingly, NF-4HBA was robust and was found to remain unchanged in all the tested stress conditions. Stability study of antitumor prodrug temozolomide (chapter 5) and anthelmintic niclosamide (chapter 6) and their pharmaceutical cocrystals will be discussed.
To summarize, solid form selection is an important aspect of drug development. Although polymorph screening is required, preformulation activity, the scopes and experimental breadths of screens vary. It is important to do experiments as many as possible to obtain all possible crystalline forms before marketing the most stable API with optimum solubility, bioavailability and stability for further development. A metastable polymorph often has higher solubility and hence it is the desired polymorph for better bioavailability. In balance, however, the practical advantage of greater stability takes precedence over a more soluble but metastable polymorph. Using additive, polymer, excipients, stabilising metastable polymorphs will be good option for marketing. Again through the last decade, pharmaceutical cocrystals proved betterment of solubility, bioavailability, compressibility, stability etc. for an API. Still not a single cocrystal is marketed till clinical trials and dissociation of cocrystals to API to be confirmed before reaching the target side. To conclude, Solid State Chemistry has immense potential in the pharmaceutical Industry. Different solid forms of APIs (polymorphs, cocrystals, salts, hydrates, solvates etc.) can provide drugs with improved physicochemical properties.
1.6 References


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Chapter 1


