Chapter 1

Introduction

1.1 Introduction

Crystal engineering allows the rational design of multicomponent solids such as cocrystals, salts, and eutectics with desired properties [1–3]. The principles of crystal engineering together with supramolecular synthons play a vital role in the selection of the guest molecule, namely, the coformer that is incorporated into the host molecule through noncovalent interactions. The same has been widely employed in the novel formulation of drug molecules due to its ability to modulate physicochemical and pharmacokinetic performances without changing the structural integrity [3–6]. Apart from it has attracted the interest of researchers because of its application in designing multidrug combinations with synergistic effects to the known drug action and minimizing side effects [5,7]. Studies on pharmaceutical polymorphism, nanostructures, covalent organic frameworks, metal-organic frameworks, coordination polymers, chiral separation, etc. are a few evolving subject areas for academician and industries (Figure 1.1) [8–11]. Molecules in such solid systems are mainly sustained by weak noncovalent interactions such as hydrogen bonds, halogen bonds, van der Waals, π–π stacking, and coordination bonds in the case of metal complexes [3,9,12].

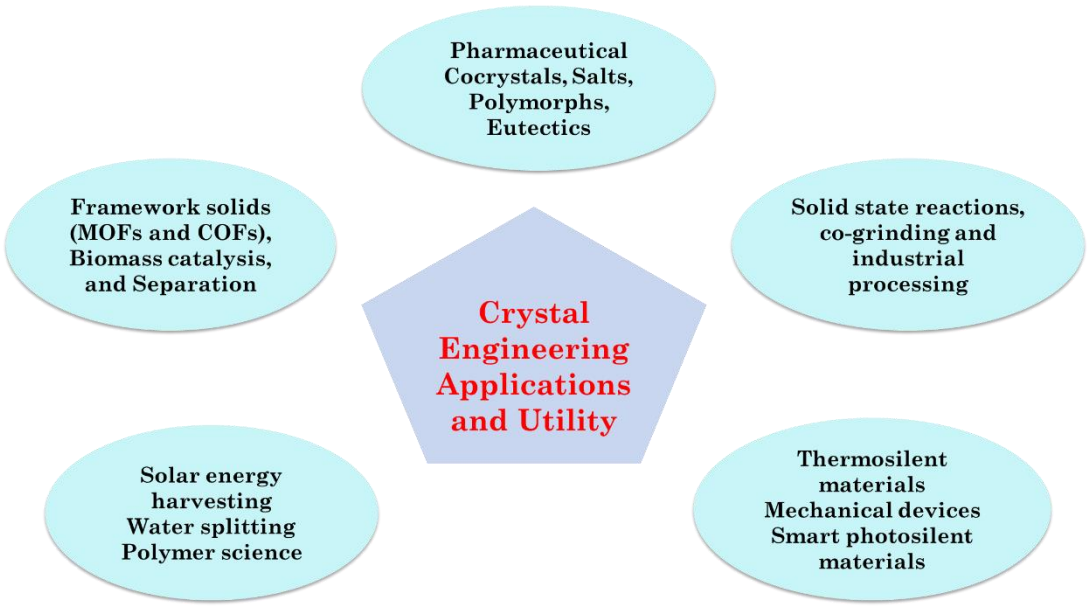


Figure 1.1 Various scope and important applications of crystal engineering [3].

The idea of 'crystal engineering' was introduced in 1955 by Pepinsky [13,14]. The solid-state structural engineering of *trans*-cinnamic acids by Gerhard Schmidt in the 1950s and 1960s laid the foundation for this subject [15,16]. The subject became popular after the publication of a book titled "*Crystal Engineering: The Design of Organic Solids"* by Desiraju in 1989 [1]. The book has demonstrated how the chemical factors (intermolecular interactions, Schmidt's viewpoint) and physical factors (size and shape, Kitaigorodskii's viewpoint) are jointly important to describe molecular crystal structures [16,17]. The term crystal engineering was defined as *"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."* A crystal is nothing but a supramolecular entity held together with noncovalent interactions that play a crucial role in the arrangement of the molecules [18,19]. Whereas the term supramolecular chemistry introduced by J.M. Lenh is defined as "*Chemistry Beyond the Molecule*" [19]. Crystal engineering utilizes the concepts of supramolecular chemistry to design and synthesize functional crystalline materials with desired properties.

1.1.1 Intermolecular Interactions

The hydrogen bond, halogen bond, van der Waals, and π–π stacking are important and commonly found intermolecular interactions in organic multicomponent solids [20]. The hydrogen bond energy ranges from 4–120 kJ mol^{-1} and depends on the hydrogen bond acceptor and donor strength (Table 1.1). The energy of the weakest van der Waals forces are less than 5 kJ mol^{-1} and the π–π stacking (< 50 kJ mol^{-1}) is also weaker than hydrogen bond. The strength and linear directionality of the hydrogen bonds makes it the most important interaction that controls the packing pattern in the crystal structures [10]. It has been a research topic ever since its inception because of its significance in a wide range of chemical systems starting from inorganic to biological [21]. The recent and most accepted definition of the hydrogen bond was recommended in 2011 by the IUPAC, which states as *"an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation"* [22]. Because of its tunable strength and linear directionality, the hydrogen bond is a useful tool to design and synthesize self-assembling multicomponent crystals.

Table 1.1 Strength of non-covalent interactions commonly found in organic crystals [20].

Intermolecular interactions	Strength (kJ mol^{-1})
Ion-Ion	100–350
Ion-Dipole	50–200
Hydrogen bond	4–120
Dipole-Dipole	5–50
π-π stacking	<50
Van der Waals	<5

1.1.2 Supramolecular Synthons and Graph Set Notation

The interactions of functional groups that are present in the starting components give way to the formation of multicomponent crystals. Molecules in the crystal structures are arranged via intermolecular interactions in a certain pattern that repeats regularly to form structural motifs. Desiraju used the term '*supramolecular synthon*' to describe such interaction motifs in crystal structures and defined them as "structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions" [23]. Supramolecular synthon is a spatial arrangement of structural motifs that describes recognition events that occur between functional groups when molecules build supermolecules. The ultimate goal of crystal engineering is to identify and design synthons that are strong enough to form new crystals with desired properties [24].

Based on the types of functional groups involved in molecular recognition to form crystal structures, supramolecular synthons are subdivided into homosynthon and heterosynthons [25]. Supramolecular homosynthon is formed when an interaction between molecules takes place with the same functional groups, whereas heterosynthon occurs when unlike functional groups of molecules are engaged to form supramolecular synthons. Amide–amide, acid–acid, guanidine–guanidine, and pyrimidine–pyrimidine are examples of supramolecular homosynthons which are common in single-component crystals. The most common supramolecular heterosynthons are acid–amide, acid–pyridine, hydroxyl–pyridine, carboxylate–pyridinium, guanidine–acid, and pyrimidine–acid (Figure 1.2). Survey analysis on the hydrogen-bonded co-crystals from the Cambridge Structural Database (CSD) has suggested that heterosynthons are more robust than

homosynthons [24]. Most of the reported cocrystals have been prepared by selecting cocrystal-forming components that combine heteromerically.

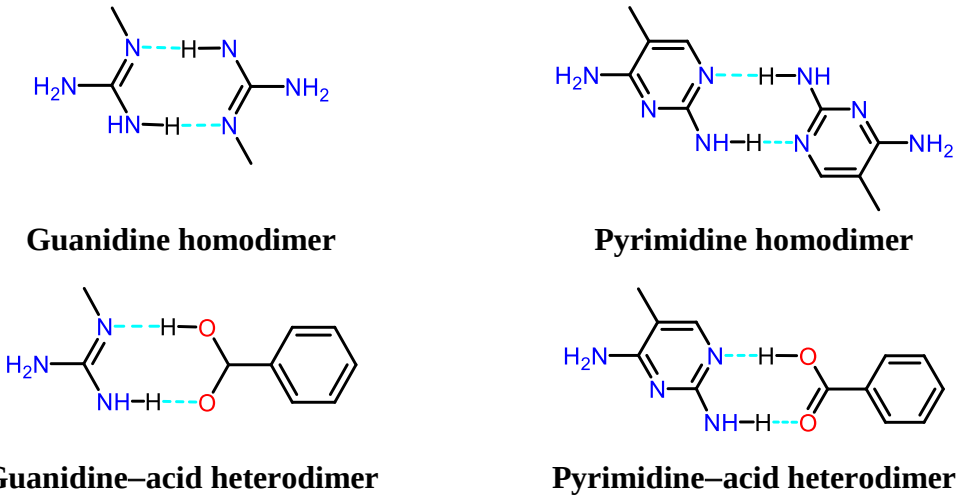


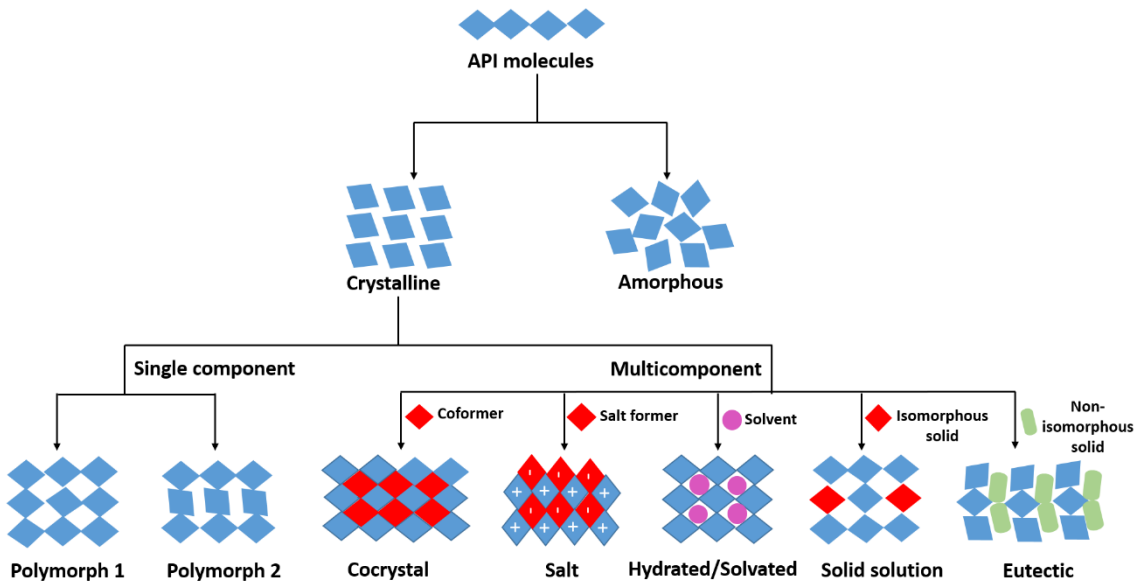
Figure 1.2 Examples of hydrogen-bonded supramolecular heterosynthons and homosynthons.

Margaret Etter identified the hydrogen bond as the most useful design element for the construction of molecular crystals and proposed a rule to assist the deliberate designing of hydrogen-bonded organic solids [26,27]. The rules assist to predict the synthon probabilities when multiple hydrogen bond-forming functional groups are present in the cocrystal-forming components. The first organic cocrystals synthesized using the hydrogen bond rules were reported in 1989 [28]. A graph set which is generally represented as $G_d^a(r)$ was used to describe interaction motifs in the crystal structures [26,29]. '**G**' stands for the hydrogen bond pattern and can be replaced by one of the letters: S, C, R, and D where S stands for intramolecular hydrogen bond, C stands for chain, R stands for ring, and D stands for dimer. '***a***' and '***d***' denote the number of hydrogen bond acceptors and donors respectively. The letter '***r***' represents the total number of atoms engaged in the formation of a particular interaction motif.

1.2 Organic Solid Forms

Organic solids are subdivided into two major categories, i.e., amorphous and crystalline states. Crystalline drugs are preferable in the pharmaceutical industry due to stability issues associated with the amorphous materials and separation, purification, and storage of the crystalline materials are relatively easier [4,30–33]. Crystallization of API molecules can offer various single-component polymorphic crystals and amorphous solids

[3,4,34]. Crystallization of API molecules by incorporating different types of guest molecules (solvent/other solid) in their crystal lattices through noncovalent interactions can lead to the formation of various multicomponent solids like salts, cocrystals, solvates, eutectics, solid solutions, polymorphs, and coamorphous (Scheme 1.1) [1,2]. These solids display distinct physicochemical and pharmacokinetic properties due to the differences in their molecular packing and structures. The intermolecular interactions that connect molecules in these solids play a crucial role in controlling the crystal packing which in turn determines their physicochemical properties. Multicomponent solid formulations give way to tune different drug properties such as solubility, permeability, bioavailability, stability, tabletability, etc. The significant role of multicomponent solids such as salts, cocrystals, hydrates, and solvates in the pharmaceutical industry is the focus of this research and is discussed in the following chapters of the thesis.



Scheme 1.1 Schematic representation of various single and multi-component solids.

1.2.1 Cocrystals/Salts

The therapeutic effect of drugs is mainly dependent upon their physicochemical properties. Solubility and permeability are the two important physicochemical parameters that determine the bioavailability of orally administered drugs [35]. In 1995, Amidon et al. categorized drugs into four classes based on their solubility and membrane permeability, and some examples are given in Table 1.2. According to this classification, more than 40% of marketed oral drugs and about 90% of drugs in the discovery pipelines display low solubility and/or poor permeability [36]. As a result, the bioavailability of these types of

API molecules is limited. Besides, a significant number of drugs have issues associated with chemical and hydration stability, tabletability, etc. These properties depend on the composition and molecular packing in the solid state and manipulating the composition and molecular packing of the drug enables tuning of the desired properties [4]. It was with such understanding that crystal engineering of pharmaceutical cocrystals began with the aim of optimizing different properties of the drug molecules [25,37,38].

Table 1.2 BCS Classification of drugs and representative examples of each class.

	Permeability		**Permeability**
Solubility	High	**Solubility**	Low
High	**Class I**	High	**Class III**
	Examples: Pyrazinamide, Theophylline, Doxycycline, Cetirizine, Tramadol, etc.		Examples: Isoniazid, Ranitidine, Lamivudine, Levetiracetam, Pyrazinamide, etc.
	High		low
Low	**Class II**	Low	**Class IV**
	Examples: Trimethoprim, Dapsone, Flufenamic acid, Glibenclamide, etc.		Examples: Famotidine, Cefixime, Ritonavir, Hydrochlorothiazide, Acetazolamide, etc.

1.2.1.1 Definition

The most accepted definition for cocrystals was forwarded in 2012 by 46 scientific communities in the crystal engineering fields [39]. They defined cocrystals as *"solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts".* Pharmaceutical cocrystals are a sub-class of cocrystals that consists of a stoichiometric ratio of an API and other pharmaceutically acceptable substance(s) in the crystal lattice [25]. The more recent definition of cocrystals proposed by the US FDA was found to be agreeable with the definition proposed by the scientists in the Indo-US bilateral conference in 2012 [39] and serves as a guideline for the approval of new cocrystal formulations of drugs. The guideline was published in 2018 and defines cocrystals as "*crystalline materials composed of two or more different molecules in the same crystal lattice*", whereas salt is *"any of numerous compounds that result from the replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal; an ionic or electrovalent crystalline solid".* Different salt forms of the same drug molecule are regarded as different APIs as per the regulatory guideline [40].

Different tools that are useful for the design of cocrystals have been developed. These tools give guidance to select suitable coformers that can interact with the API molecules for the cocrystal/salt formation. The molecular packing of the cocrystals is determined by intermolecular interactions such as hydrogen bonds, π–π stacking, and van der Waals interactions, halogen bonds. The availability of complementary functional groups that can form viable interactions between molecules of the API and coformers is mandatory for cocrystal formation. The selection of coformers is the most important stage in the pharmaceutical cocrystal design which includes analyzing the drug structure to find out possible functional groups for feasible molecular connections, potential supramolecular synthons for molecular recognition, and picking out suitable coformers.

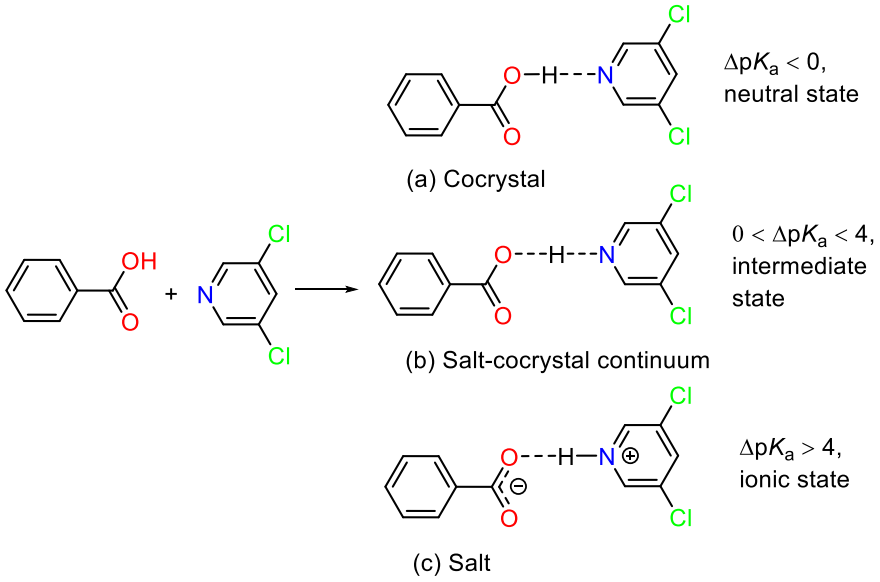
The coformers selected for the synthesis of pharmaceutical cocrystals must be non-toxic and pharmaceutically acceptable substances. They are generally selected from the GRAS list which consists of over 3000 compounds. Drug excipients, preservatives, vitamins, food additives, and bio-molecules are mainly used as coformers [4,41]. The selection of a coformer that forms robust synthon with API molecule requires effective screening techniques. The principles of supramolecular synthons serve as a guideline for the selection of coformers. However, it is difficult to forecast the synthon for the interacting molecules with multiple hydrogen bond donor and acceptor sites. In such a situation, coformers could be selected for the API cocrystallization based on the occurrence probability of different competing synthons extracted from the CSD data [42,43]. For instance, for 148 crystal structures taken from the CSD that have primary amide and acid functional groups, the amide···acid heterosynthon is 47% (69 structures), while the acid homosynthon is 6% (9 structures), and the amide homosynthon is 44%) (65 structures), indicating the cocrystal formation probability through the acid···amide heterosynthon is higher followed by the amide and acid homosynthons [3]. Such statistical data analysis of the hydrogen bond propensity from the CSD is useful to select the coformers based on the expected synthon and design cocrystals. Apart from that calculations of molecular electrostatic potential surfaces in the gas-phase can also help in ranking the hierarchy of synthons especially when the ΔpK_a rule is not adequate [44].

Other computational approaches have been also developed to assist the selection of coformers. The calculation of lattice energy can help to forecast the cocrystal formation between complementary molecules. The formation of a cocrystal is expected when its anticipated crystal structure is thermodynamically more stable than that of the individual

components. The COSMO (conductor-like screening model) software was devised to assist the design of cocrystals and has been proven to be useful in the evaluation of suitable coformer for drug cocrystal formation [45]. The probability of cocrystal formation between the molecules of API and coformer depends on the excess amount of enthalpy of the drug-coformer adduct in comparison to that of the individual components.

1.2.2 Salt-Cocrystal Continuum

Pharmaceutical cocrystals and salts can be identified based on the position of the proton between the API and the coformer. Salt formation takes place by a complete transfer of proton, whereas transfer of proton doesn't occur during the cocrystal formation. Some cases were reported in which the acid proton is equipoised in the salt-cocrystal continuum depending on the ΔpK_a value, stoichiometric ratio, temperature, and hydrogen bonding environment [46–48]. The location of the proton in such multicomponent systems can be determined using different spectroscopic and crystallographic techniques such as FT-IR, ss-NMR, single crystal X-RD, and X-ray photoelectron spectroscopy (XPS) [49–53].



Scheme 1.2 Schematic representation of the difference between (a) cocrystal, (b) salt-cocrystal continuum, and (c) salt [54].

The ΔpK_a rule is one of the useful tools to predict the position of the proton [49,55]. The ΔpK_a rule can also be employed to select coformers. ΔpK_a determines whether the salt or cocrystal formation occurs between API and coformer. Cocrystal formation is generally expected if the ΔpK_a values are less than 0, whereas the values of ΔpK_a greater than 4 usually lead to salt formation. The prediction of proton position is difficult when the ΔpK_a value is found between 0 and 3 and the product can be either a salt or cocrystal or salt-

cocrystal continuum (Scheme 1.2). The ΔpK_a rule was validated by extensive analysis of 6465 crystal structures of acid-base adducts from CSD [56]. These structures were divided into three categories and almost matched the ΔpK_a rule, while the intermediate zone falls between -1 and 4 (Figure 1.3).

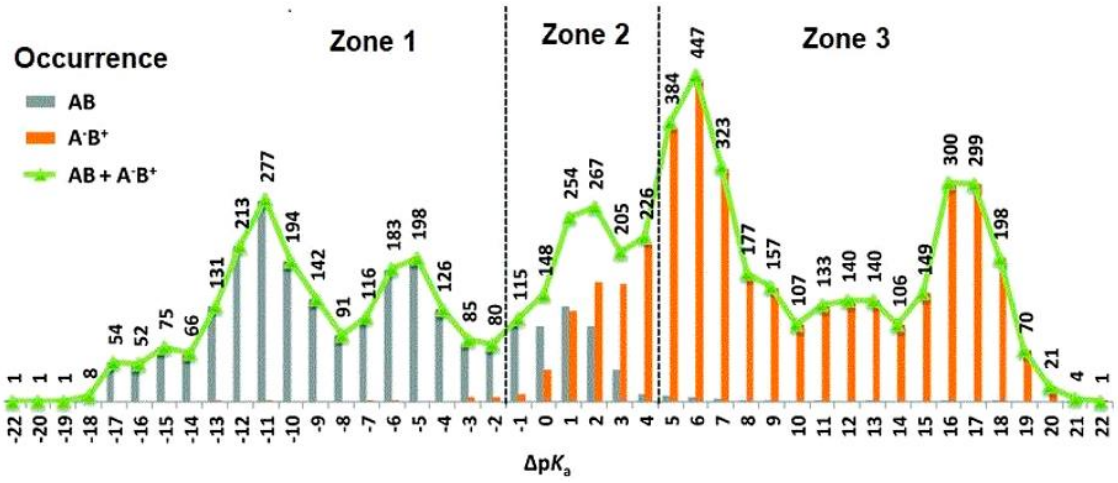


Figure 1.3 Occurrence of neutral AB (gray-zone 1) and ionic A^-B^+ (orange-zone 3) vs the calculated ΔpK_a values obtained from a CSD survey of 6465 acid-base adducts [56].

Braga and coworkers introduced the phrase 'ionic cocrystal' in 2010 [57]. Ionic cocrystals are multicomponent solids comprised of salts and neutral organic molecules in a fixed stoichiometric ratio (Scheme 1.3). Pharmaceutical ionic cocrystals can be obtained by deliberate cocrystallization of drug substances with inorganic or organic salts and are mainly connected via coordination bonds and/or ionic hydrogen bonds [3,4]. The major structural variation of the ionic cocrystals from molecular cocrystals is that ionic crystals comprise at least one ionic component, i.e., either metal halide or organic cation halide in the crystal structure. Ionic cocrystal formulations have been employed to modulate the physicochemical properties of API [58–62]. The alteration of drug properties is due to the replacement of the common O–H···N and N–H···O hydrogen bond interactions with the O–H···Cl^- and N–H···Br^- interactions.

Scheme 1.3 Schematic representation that demonstrates interactions between neutral molecules and metal complexes or salts in the ionic cocrystals [3].

Ionic cocrystal of sodium theophylline was synthesized with glycine to overcome the decomposition of theophylline complexes that causes gastric irritation [61]. The sodium theophylline glycinate ionic cocrystal demonstrated a typical theophylline response and less toxicity as compared to pure theophylline. Childs *et al*. reported organic cation halides based ionic cocrystals of fluoxetine hydrochloride with benzoic acid (Figure 1.4), fumaric acid, and succinic acid [62]. Optimization of solubility and dissolution rate was performed for this group of ionic cocrystals in comparison to fluoxetine hydrochloride. Ionic cocrystals are also used for the chiral separation of racemic mixtures. Cocrystallization of L- and DL-histidine with LiI by mechanochemical method gave L- and D-histidine conglomerate cocrystals in which separate enantiomers can be obtained with spontaneous chiral resolution [63].

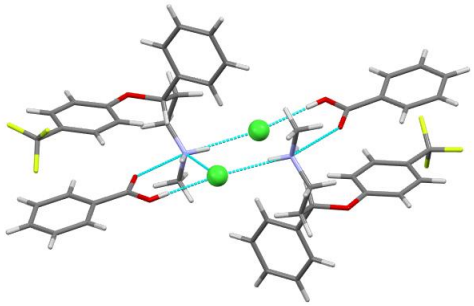


Figure 1.4 The ionic cocrystal of fluoxetine hydrochloride with benzoic acid is sustained by ionic hydrogen bonds [62].

1.2.3 Hydrates and Solvates

Hydrates/solvates are formed when solvent/water molecules are incorporated within the crystal lattice of API or cocrystal in the stoichiometric ratio [64]. The water or solvent molecule plays an important role in stabilizing the crystal whenever there is a disparity in the ratio of hydrogen bond donors and acceptors. The formation of solvates usually alters the physicochemical properties of the drug. For example, various solvated crystalline forms of the drug spironolactone displayed an improved dissolution rate [65]. Solvated materials are unstable during storage. They lose the solvent at elevated temperatures and low humidity which leads to changes in their stoichiometric ratio and physicochemical properties. However, hydrated drug products have been developed and are available in the market [4,66].

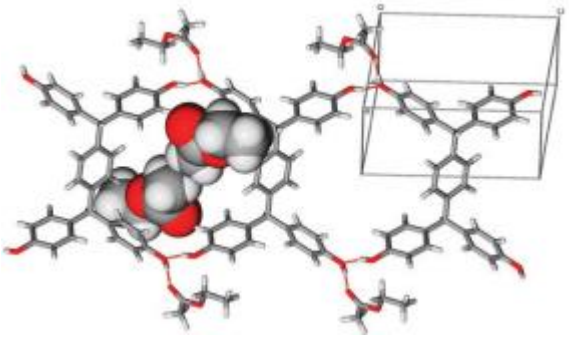


Figure 1.5 Crystal structure of ethyl acetate solvated 1,4-Di[bis(40-hydroxyphenyl)methyl]benzene [67].

1.2.4 Coamorphous Solids

Pharmaceutical coamorphous solids which are also known as amorphous solid dispersions are composed of the API and other pharmacologically acceptable substances in high thermodynamic states (high entropy and high energy) and thus demonstrate an improved solubility as compared to the parent crystalline form [68–70]. Coamorphous solids are single-phase multi-component systems that have a more aperiodic crystalline arrangement in the structure and are sustained by weak but discrete interactions (Scheme 1.1). Unlike crystalline solids such as cocrystals, salts, eutectics, and solid solutions, amorphous solids do not exhibit sharp diffraction profiles when analyzed with PXRD but display broad halo patterns. The primary issue of amorphous solids is that they are physically unstable and have the propensity to transform into a low-energy crystalline state and as a result lose their properties [71,72].

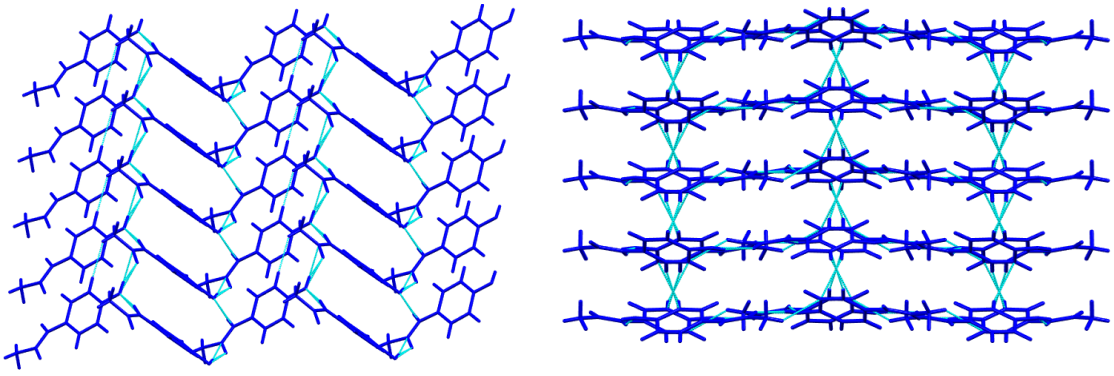
1.2.5 Eutectics and Solid Solutions

Crystallization of molecules that have complementary functional groups to form cocrystals may sometimes give a eutectic, a solid solution, or a simple physical mixture of individual components. Eutectics are multicomponent crystalline materials that are formed between two non-isomorphous compounds with a fixed stoichiometric ratio. Eutectics display lower melting points than those of the parent materials but their crystal packing resembles that of the individual components. A solid solution is a variable stoichiometric multicomponent crystalline solid formed when one component (minor) is included in the crystal lattice of another component (major) homogeneously. Solid solutions usually occur between molecules that have similar structures and their lattice structures are sustained by strong cohesive (homomolecular) interactions. Eutectic mixtures are sustained by weak

adhesive (heteromolecular) interactions and/or strong cohesive (homomolecular) interactions. In contrast, cocrystal formation occurs when unlike molecules are associated with strong adhesive (heteromoleular) interactions and the produced crystal packing is vary from that of the parent components. Hence, the cocrystal displays unique PXRD patterns and spectroscopic peaks from its pure constituents as it possesses a distinct crystal packing connected by hydrogen bonds and other weak interactions, whereas eutectics and solid solutions show similar to those of the parent components [2,10,73].

1.2.6 Polymorphism and Stoichiometric Cocrystals

Polymorphs are compounds with the same chemical composition but have distinct crystal packing or molecular conformation in the crystalline state [74]. Nearly 37% of organic compounds reported in CSD are polymorphic [3]. Research on drug polymorphism has become an essential part of the process of drug development since polymorphs of the same API display distinct drug properties such as stability, solubility, tabletability, bioavailability, melting point, etc. Apart from that the development of novel polymorph offers an opportunity to get a patent and intellectual property [75,76]. The impacts of polymorphism in single-component drug compounds concerning changes in their properties are widely studied [77–81]. For instance, the conformational polymorphism of an antiretroviral drug ritonavir is one of the early examples of a single-component system in which the stable form (form II) displays less dissolution rate than form I [77]. The metastable form II of the analgesic drug paracetamol exhibited better solubility and tabletability than stable form I (Figure 1.6) [78]. The stability variation of polymorphs of drugs such as sulfathiazole, carbamazepine, theophylline, etc. was studied [79–81].



(a) Form-I (b) Form-II

Figure 1.6 Crystal structures of dimorphic forms of the paracetamol. Form I doesn't have a slip plane in the crystal structure, whereas the layered structure of Form II has it and demonstrates better tablelability [78].

In comparison to the single-component systems, studies on polymorphism of the multicomponent solids are a few and quite recent [82–85]. They have an impact on the biopharmaceutical property of the APIs similar to that of the single-component crystals [86–89]. Caffeine displays dimorphic cocrystal structures with 3-nitrobenzoic acid in a ratio of 1:1 [97]. The supramolecular synthon that connects the components of the two modifications is the same, but their extended interactions are different. The layered structure of form I was found to have less energy barrier for plastic deformation and shows better tabletability than form II. Trimorphic cocrystal structures of ethenzamide with 2,4-dihydroxybenzoic acid were reported in which form I displayed better permeability [87]. Horst et al. demonstrated solvent-mediated conversion of dimorphic structures of carbamazepine cocrystal with isonicotinamide and evaluated their stability and solubility using a phase diagram [88]. They found that the metastable form II displayed higher solubility than the stable form I.

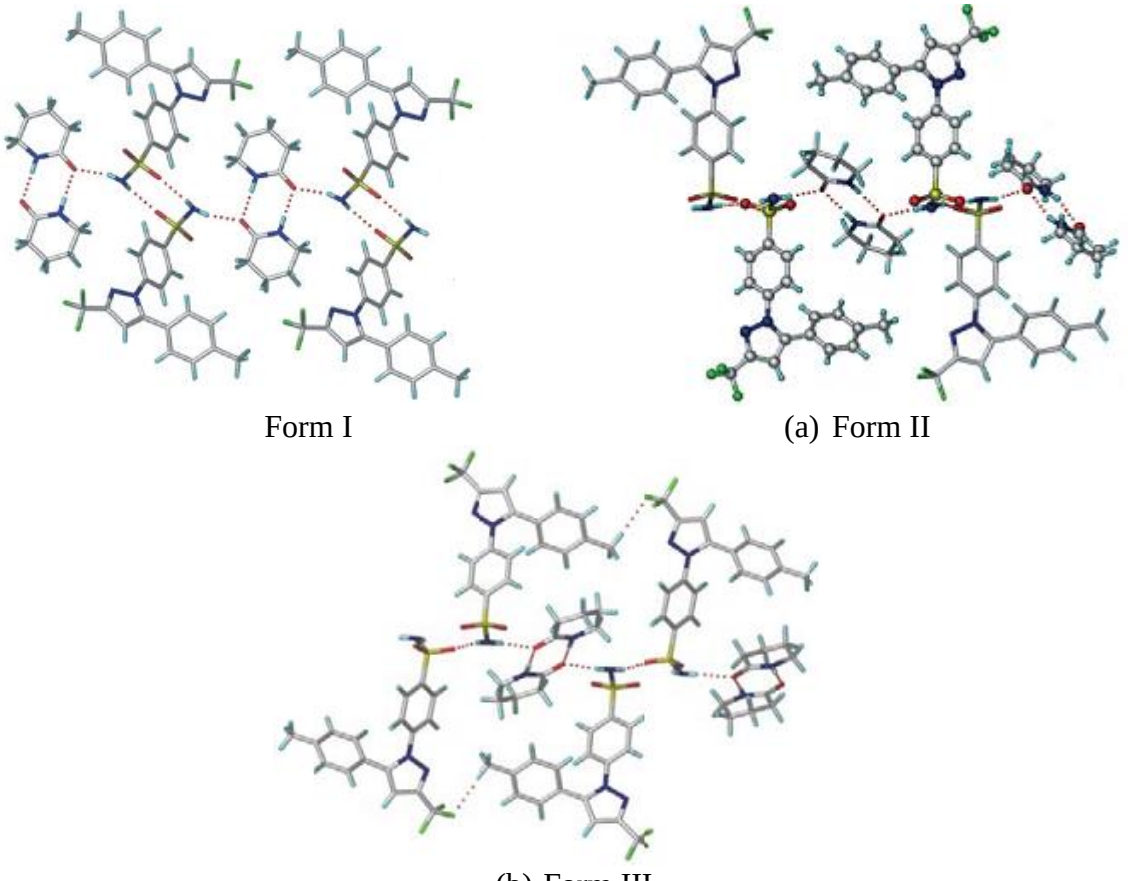


Figure 1.7 Crystal structures of trimorphic cocrystals of celecoxib with δ-valerolactam (1:1). (a) In the form I valerolactam dimmers are linked by sulfonamide dimer of celecoxib. (b) Celecoxib and valerolactam molecules in form II interact through N–H···O catemers. (c) Valerolactam dimers in form III are linked via an N–H···O catemer [89].

The anti-inflammatory drug celecoxib offers three cocrystal polymorphs with *δ*-valerolactam sustained through sulfonamide dimers and catemers of celecoxib as demonstrated in Figure 1.7 [89]. Among these, the unstable form II and form III were converted to the most stable form I whose solubility was 2-fold of the pure drug celecoxib. Polymorphism in cocrystals/salts increases the opportunity to formulate more solid forms with improved properties. In Chapter 2 we demonstrated the role of the topological distribution of hydrogen bond interactions on the phase stability and physiochemical properties of the dimorphic salt of famotidine with 2-aminobenzoic acid (2-ABA). Similarly, the cocrystallization of drug molecules with coformers results in stoichiometric cocrystals depending on the experiment conditions [90]. Cocrystallization of theophylline with 2-aminobenzoic acid in different solvents results in one anhydrous and three solvated cocrystals with 2:3, 2:2:2*iso*-BuOH, 3:2:4H_2O, 2:1:4H_2O [91]. Those cocrystals exhibit completely different solubility and permeability. Therefore, controlling the stoichiometry of the multicomponent systems is vital to ensure purity and homogeneity.

1.3 Preparation of Multicomponent Crystalline Phase

Different approaches have been devised for the synthesis of multicomponent solids because of their importance in the drug development processes. The methods can be broadly classified as solid-state grinding and solvent-mediated grinding.

1.3.1 Solid-state grinding

The most commonly practiced solid-state method to synthesize cocrystals is mechanochemical grinding. It involves grinding the stoichiometric cocrystal-forming components together either manually or mechanically. It is a relatively efficient and green approach for the cocrystal preparation because the product is not lost by the solvent due to solubility and organic solvent-free or limited use of organic solvent as compared to solution-mediated methods. Incomplete conversion to the product, scalability issues, and formation of some amorphous material is the limitation of this method. Extrusion, a twin-hot-melt extrusion, and screw extrusion are some of the other solid-state methods utilized for the synthesis of cocrystals [92–94].

1.3.2 Solvent-mediated grinding

Different types of solvent-mediated methods exist for generating cocrystals from the solution. The solubility of cocrystal-forming components plays a crucial role in the

crystallization process. Evaporative crystallization involves the dissolving of a stoichiometric amount of starting materials in a solvent in which the components have similar solubility and are kept for slow evaporation at ambient conditions. When the solubility of cocrystal components is not equivalent, the reaction cocrystallization approach is the preferred method to obtain cocrystals. Cocrystal synthesis through reaction crystallization can be carried out by mixing solutions of individual components. Cooling crystallization is another solvent-based approach that involves changing of crystallization temperature. Other methods such as slurry, antisolvent crystallization, freeze drying, spray drying, crystallization in supercritical fluid, etc. have been utilized for cocrystal synthesis [94,95].

1.4 Characterization

Novel cocrystals can be characterized by differential scanning calorimetry, thermogravimetric analysis, infrared spectroscopy, Raman spectroscopy, solid-state nuclear magnetic resonance spectroscopy, powder X-ray diffraction, single crystal X-ray diffraction, and X-ray photoelectron spectroscopy [4,95].

Table 1.3 Analytical techniques used to characterize the multicomponent solid state.

Analytical tools	Uses	Refs
Differential scanning calorimetry	obtain comprehensive melting point data and check phase purity	[96]
Thermogravimetric analysis	determine the quantity of solvent inclusion in the crystal lattice	[97]
Powder X-ray diffraction	evaluate the purity of the solid phase	[98]
Single crystal X-ray diffraction	determine the crystal structure and composition of the solid	[4]
Infrared spectroscopy	detect the hydrogen bonding interaction	[99]
Raman spectroscopy	study vibrational and rotational frequency for distinguishing isostructural phase	[100]
Solid-state nuclear magnetic resonance spectroscopy	diagnose the degree of hydrogen bonding transfer and local conformational changes	[101]
Microscopy	investigate crystal habit and purity	[102]

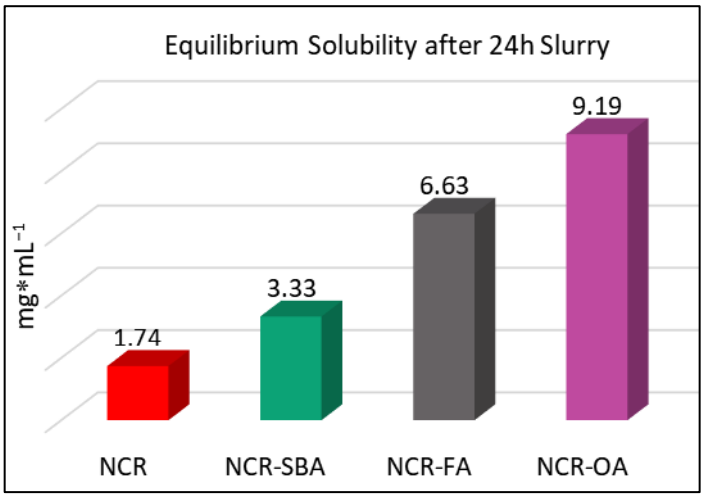
1.5 Physicochemical Properties

A significant number of drugs in the market as well as in the discovery pipelines show poor physicochemical properties such as aqueous solubility, membrane permeability, bioavailability, chemical stability, etc.[103–106]. The major objective of the formulation of multicomponent solids for drug molecules is to enhance those properties that have a significant impact on their therapeutic performance and shelf-life [3–5]. The pharmaceutically acceptable salt former or coformer is introduced in the crystal lattice of the API molecule via noncovalent interactions to generate new solid forms with improved stability, solubility, membrane permeability, bioavailability, and mechanical properties [3]. Such improvement in the properties is due to the alteration of intermolecular interactions that control the crystal packing in the crystalline state. In the following section, some examples of modulation of key drug properties through multicomponent crystal formulation are presented.

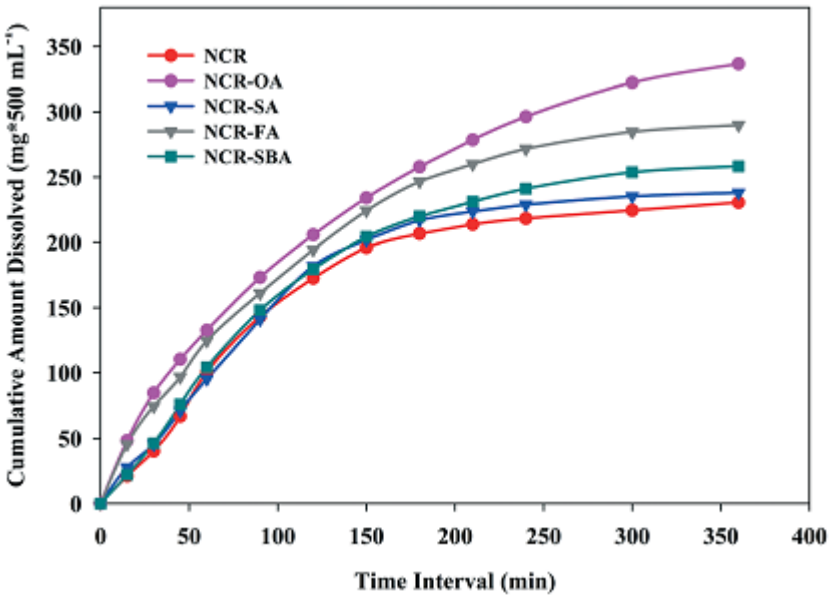
1.5.1 Dissolution Rate and Solubility

The majority of published articles on the applications of multicomponent cocrystals in the last two decades mainly focused on the improvement of solubility. The first article was about the enhancement of solubility of itraconazole through cocrystal formation with L-tartaric acid and L-malic acid which was published in 2003 [107]. These cocrystals displayed a similar solubility with the marketed amorphous formulation Sporanox and were better than the parent drug molecules. Following after that in 2004, Childs et al. demonstrated the dissolution rate improvement for the antidepressant Prozac (fluoxetine HCl) through cocrystallization with succinic acid [62]. After these pioneering works, multicomponent crystal technology has become an alternative method for modulating different pharmacokinetic and physicochemical properties of drugs [108–112]. For example, quercetin is a flavonoid compound that exhibits multiple therapeutic bioactivities, but its efficiency is low because of low bioavailability that is associated with limited solubility. The solubility of the compound was enhanced via cocrystal formation with caffeine, isonicotinamide, and theobromine [108]. The bioavailability of the cocrystals of quercetin with caffeine was found to be 10-fold that of the quercetin dihydrate. Cocrystal/salt formation of sildenafil (SLD) with dicarboxylic acids has improved its solubility [109]. The multicomponent solids of SLD displayed better solubility and dissolution profiles than the marketed citrate salt. The solubility of glutarate

salt (3.2-fold) is the highest among all the products. The solubility of cocrystals is in good agreement with their respective coformer solubility. Recently the solubility and dissolution profile enhancement of nicorandil (NCR) via multicomponent solid formulations with fumaric acid, succinic acid, suberic acid, and oxalic acid was reported [113]. It results in salts with fumaric acid and oxalic acid and cocrystals with succinic acid and suberic acid. The solubility and dissolution profiles of salts are higher than that of the cocrystals and the parent API (Figure 1.8). The ionic nature of salts due to the pyridinium···carboxylate synthon makes the solute···solvent interactions easier as compared to the neutral pyridine···acid synthon in the cocrystals.



(a)



(b)

Figure 1.8 (a) Solubility and (b) intrinsic dissolution rate comparison of pure nicorandil and its cocrystals/salts in phosphate buffer saline (pH 7) media at 37 ± 1 °C [113].

Rodríguez-Hornedo et al. studied the solubility trends in the cocrystals of nevirapine and acidic coformers with respect to the pH of the media [114]. The weakly basic nevirapine (NVP) formed cocrystals with saccharin (2:1, NVP-SAC), maleic acid (1:1, NVP-MLE), and salicylic acid (2:1, NVP-SLC). The solubility of the cocrystals dialed up and down depending on the pH condition of the solution. They derived theoretical equations by considering the solubility product of cocrystal and the ionization constant of coformer and drug to explain the relationship between cocrystal solubility and pH. The experimental cocrystal solubility was found to be in excellent agreement with the calculated value from the equation as shown in Figure 1.9, indicating the effect of pH on the cocrystal solubility can be predicted by using these equations.

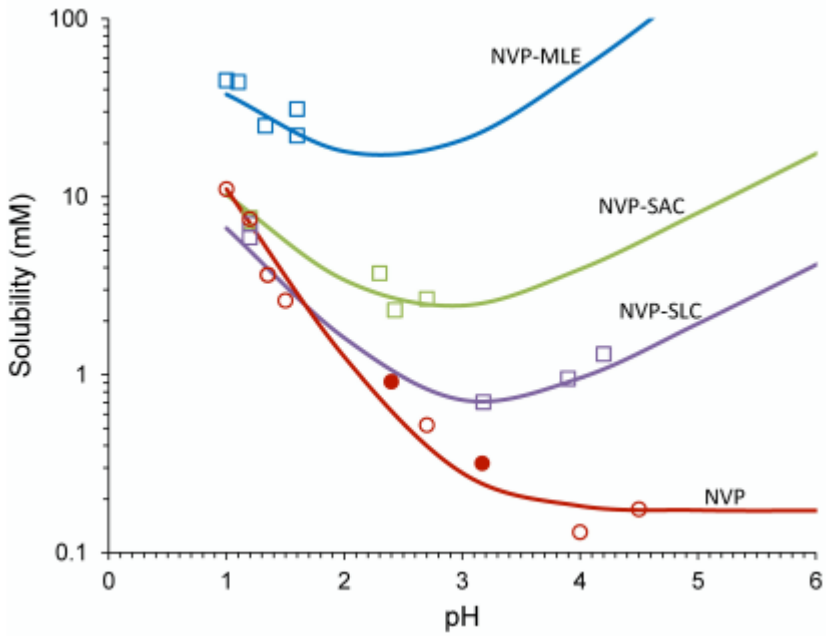


Figure 1.9 Solubility curves of nevirapine and its cocrystals vs pH of the media. Symbols refer to the measured solubility from saturated solutions at 25 °C. Curved lines represent the calculated solubility using the solubility-pH equations [114].

Besides enhancing the solubility and dissolution parameters of API molecules, multicomponent crystals are also utilized for reducing the release rate of drugs [115–118]. For example, Piperazine ferulate (PRZ-FLA) is an important API for the therapy of kidney diseases, however, its therapeutic application is hindered to some extent because of the short half-life and irregular drug concentration in the plasma. Dual-drug cocrystal of the PRZ-FLA and piperazine (PRZ) has demonstrated a slower dissolution rate as compared to that of the parent PRZ-FLA as shown in Figure 1.10, which is useful for sustained release of the drug [117]. The formation of a highly stable and tight networked structure

which is sustained via ionic and neutral hydrogen bonds is a reason for the reduced dissolution profile of the cocrystal. Recently, Xiao et al. reported the reduction of solubility and dissolution rate of propylthiouracil (PTU) via cocrystal formation with nutritional coformers such as cinnamic acid, ellagic acid, and kaempferol [118]. An antithyroid drug PTU has a rapid release rate and short half-life that requires more dosage delivery to the patient to maintain the therapeutic plasma concentration, resulting in hepatotoxicity and side effects. Those binary solids with reduced dissolution profiles can be potential candidates to formulate sustained-release medications to reduce the side effect.

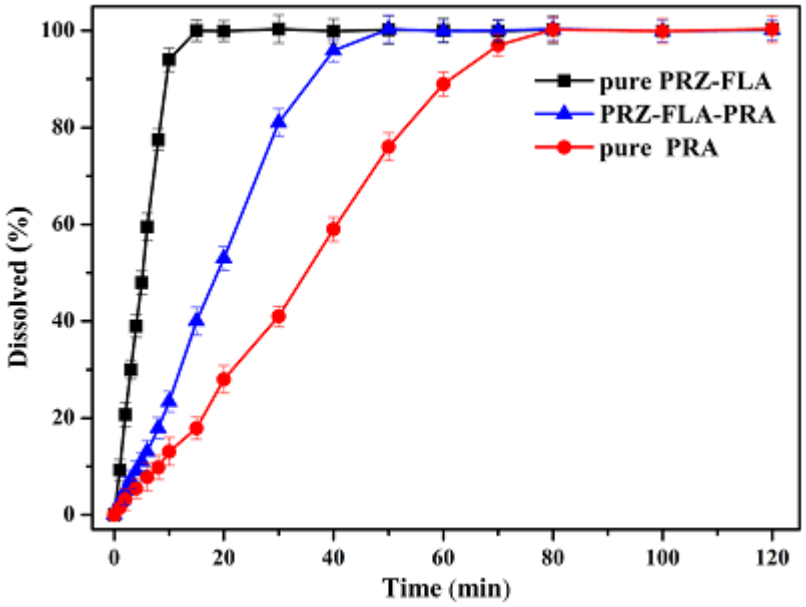


Figure 1.10 Dissolution rates comparison of compressed tablets of the two pure drugs and the ternary salt cocrystal in pH 1.2 buffer [117].

1.5.2 Membrane Permeability

Membrane permeability is another important parameter that determines the availability of oral drugs in the absorption sites along with the solubility [35,119]. Drug molecules under the category of BCS class IV have poor membrane permeation and need a formulation to avoid limited absorption problems via biological membranes. Multicomponent solids have been employed to enhance the permeation of those drugs [119]. For instance, the permeation behavior of the diuretic drug hydrochlorothiazide (BCS class IV) was improved through cocrystal formation with picolinamide (PCM), piperazine (PPZ), malonamide (MAM), isoniazid (INZ), tetramethylpyrazine (TMPZ) as shown in Figure 1.11 [120]. The authors related the better permeability of the cocrystal to their high solubility. The high solubility of the cocrystal produces a high concentration gradient in

the membrane layer and results in higher permeation. A similar permeation behavior trend is observed for molecular salts of FAM and TRM with isomeric DHBA and discussed in Chapters 4 and 5 respectively. In another example, Nangia et al. studied the solubility and permeability of the multicomponent solids of the antibiotic and a BCS class IV drug norfloxacin in a phosphate buffer solution of pH 7 [121]. It forms both hydrated and anhydrous cocrystals/salts with these selected coformers. They found that the solubility and permeability of anhydrous forms were higher than their respective hydrated forms.

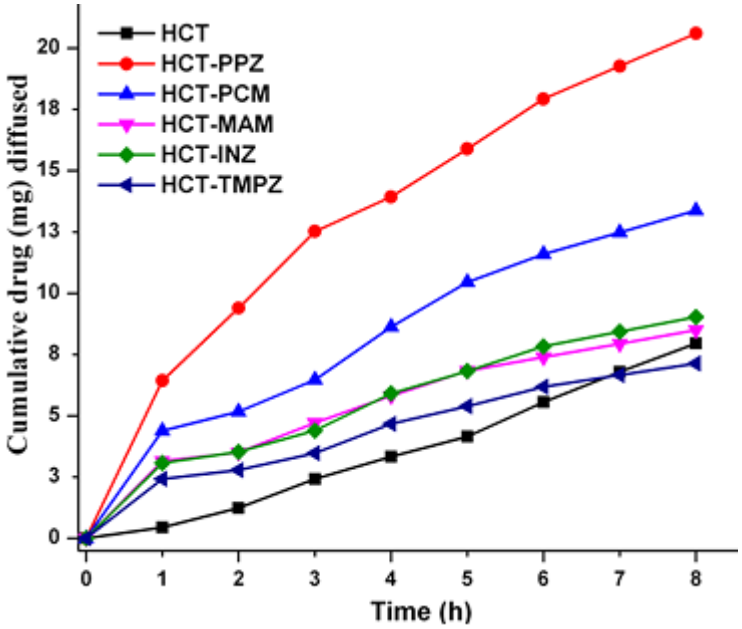


Figure 1.11 A plot of the cumulative amount of HCT and its cocrystals diffused vs time at pH 7.4 [120].

The *in vitro* solubility and permeability improvement of the diuretic drug furosemide (FSM, BCS class IV) was demonstrated via salt and cocrystal formation with 5-fluorocytosine (5FC) and imidazole (IMI) respectively [122]. FSM is an essential drug for the treatment of hypertension, edema, and heart failure, but its oral bioavailability is extremely limited since it has low solubility and membrane permeation. The aqueous solubility of the FSM-IMI salt is 120 times higher than that of the pure FSM. FSM-5FC cocrystal displayed a slight enhancement in solubility in comparison to the parent drug. The permeability of the drug was improved by 2.1 and 2.8-fold from the parent FSM via cocrystal and salt formation respectively.

Dalpiaz et al. reported physical mixtures and cocrystals that show different permeability and effect on the intestinal monolayer integrity [110]. The experiments were performed with the drug nitrofurantoin (NITRO, BCS class IV) and bipyridyl (BIP), isoniazid (ISO),

and phenanthroline (PHE) as coformers. Among cocrystals, Only NITRO-ISO improved the permeability of the drug without inducing effects on the monolayer integrity. From the physical mixtures, only NITRO-PHE improved the permeability by 3-fold from the reference drug, but with altering the monolayer integrity. The disparity in the properties among the cocrystals is generated from the difference in the hydrogen bonding. N−H···O hydrogen bond is noticed in the structure of NITRO−ISO cocrystal, whereas N−H···N hydrogen bond is formed in the remaining two cocrystals.

1.5.3 Bioavailability

The overall bioavailability of drug compounds mainly depends on solubility and membrane permeability. The right balance between the hydrophilic and hydrophobic natures of the API is very crucial for getting desirable bioavailability. The low oral bioavailability of drug candidates because of low solubility, poor membrane permeation, and instability in the gastrointestinal tract is one of the challenges in the process of drug development. Multiple reports in the literature have shown that the enhancement of oral bioavailability of pharmaceuticals can be achieved by improving their solubility and membrane permeability [108–112]. For example, the marketed citrate salt of sildenafil (SLDCIT) has limited bioavailability due to its low solubility. These inadequacies of the drug were resolved through salt formation with glutaric acid [109]. The glutarate salt (SLDGLU) exhibited high solubility and improved oral bioavailability in comparison to the marketed citrate salt. The citrate and glutarate salts were administered orally to 4 male rats and found that the plasm AUC value of glutarate salt was 2-fold of the marketed citrate salt. The reason for such an increase in the plasma concentration is originating from the improvement of the solubility of the drug via cocrystal formation. The oral bioavailability of apixaban (Apx) is low because of its poor solubility. The bioavailability of the drug was improved by cocrystal formation with oxalic acid (Apx-oxa) [112]. The pharmacokinetic study in beagle dogs indicated that the cocrystal's plasma AUC value was ~2.7-fold of the pure Apx (Figure 1.12). The enhancement of the bioavailability is 2attributed to an increase in the solubility/dissolution rate of the cocrystal.

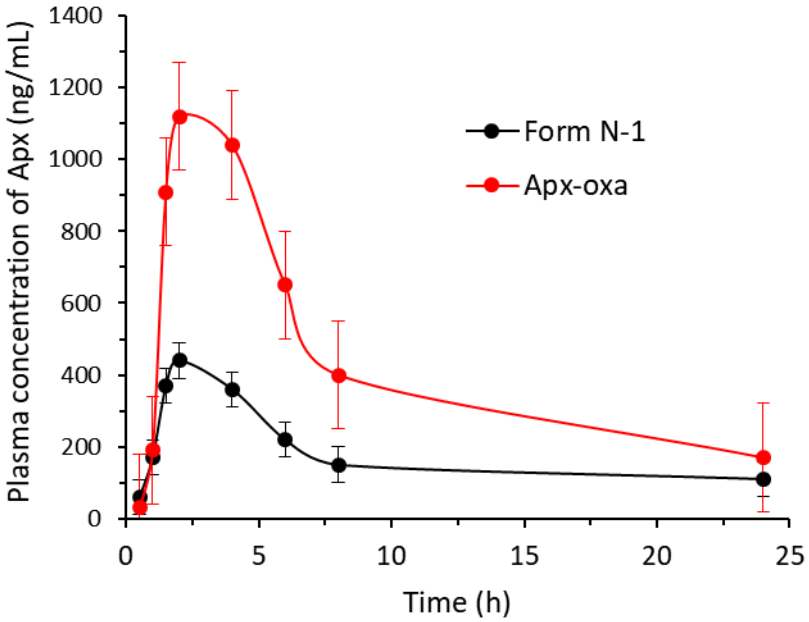


Figure 1.12 The mean plasma concentration vs time profiles of Apixaban (Apx) after oral delivery of pure Apx (black circle) and its cocrystal (red circle) in male beagle dogs [112].

The antifungal drug ketoconazole (KET) has limited bioavailability due to its extremely low solubility (BCS II drug). The 1:1 cocrystal of KET with 4-aminobenzoic acid (KET-PABA) was studied to improve the dissolution and pharmacokinetic profiles [111]. The cocrystal displayed improvement in vitro solubility and in vivo oral bioavailability in comparison to the parent API molecule (Figure 1.13). The bioavailability of the KET-PABA was 6.7 times higher than the reference pure API after 1 h oral administration to rats. The enhanced bioavailability observed for the cocrystal of KET is due to the improvement of aqueous solubility.

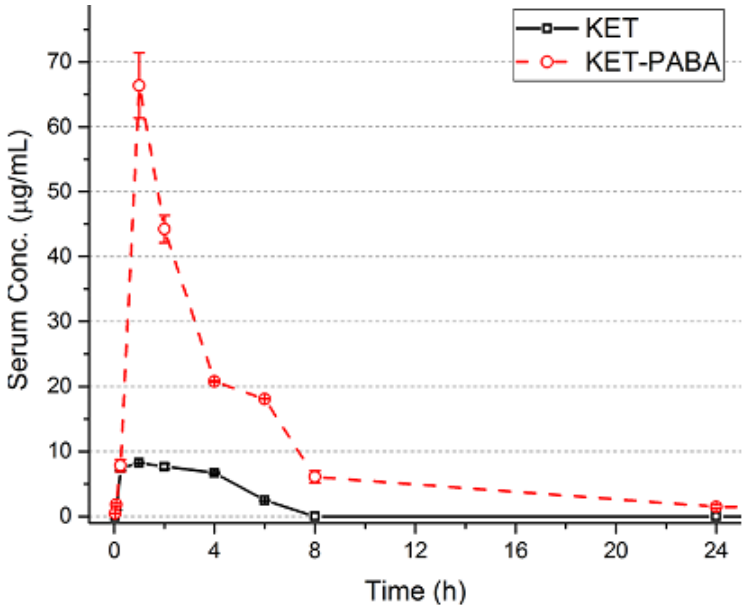


Figure 1.13 Plasma concentration-time profile for pure KET and KET-PABA [111].

Apart from improving the bioavailability of pharmaceutical compounds by increasing their solubility, multicomponent solids were also employed to formulate sustained-release drugs. Pirfenidone is used to treat idiopathic pulmonary fibrosis. The marketed formulation of the drug (PIRFENEX) has rapid absorbance and elimination issues. The drug dose is very high because of frequent delivery to attain the daily dose, as a result, it causes several side effects. *In vitro* dissolution study revealed that cocrystal of pirfenidone with fumaric acid delayed the release rate of the drug (up to 12 h) as compared to the marketed form (within 45 min) [123]. The pharmacokinetic study in healthy humans showed lower C_{max} and delayed T_{max} for cocrystal formulation in comparison to that of the marketed formulation (Figure 1.14), indicating the cocrystal is acting as a sustained-release formulation. The delay in the release rate for the cocrystal tablet formulations was attributed to their reduced solubility.

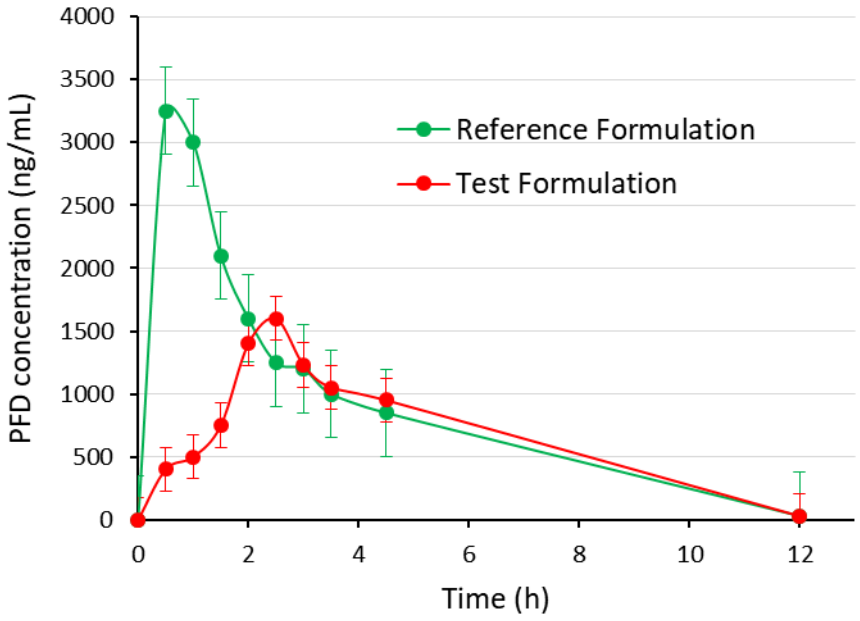
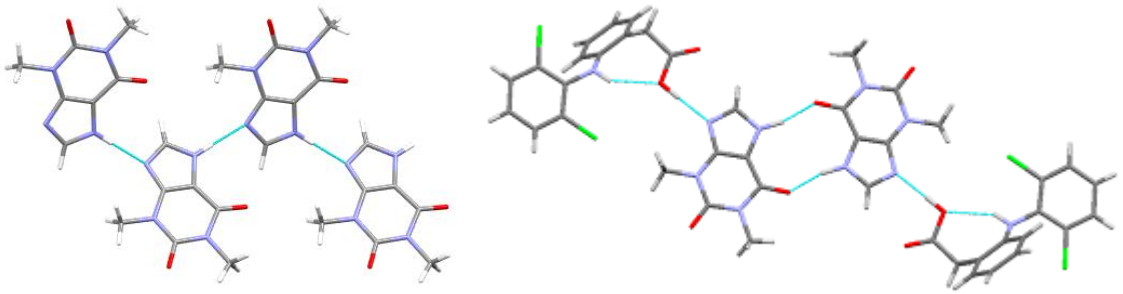


Figure 1.14 Mean plasma concentration vs time profiles of cocrystal (test formulation) and marketed form of pirfenidone (reference formulation) [123].

1.5.4 Stability

Drug stability is vital to maintain its quality and efficacy. Hydration and degradation of drugs lead to a change in their structure and affect the shelf-life and therapeutic properties of the drugs. Many drugs tend to form hydrates or undergo hydrolysis at high humidity [124]. Vitamins and some chromophore drugs are susceptible to light when they are exposed and undergo photochemical transformations. Temperature, air, and the availability of functional groups that are susceptible to acid or base are some of the factors

for drug degradation [5]. Multicomponent crystal formulation is instrumental in controlling stability-related issues of drug molecules [125–130]. Cocrystal of caffeine with oxalic acid is the earliest application of cocrystallization to control the hydrate formation of API compounds [125]. Caffeine is a muscle relaxant and a stimulant but known to form nonstoichiometric hydrate under humidity which makes its manufacturing and storage more difficult. Its oxalic acid cocrystal displayed noticeable stability to humidity for several weeks. Theophylline is used for the therapy of asthma, but it forms hydrate through its N-imidazole in atmospheric moisture. Cocrystals of theophylline with NSAID diclofenac and diflunisal demonstrated remarkable stability to the 100% relative humid conditions for two months [126]. The improved stability of cocrystals might be due to the replacement of the amine-imidazole heterosynthon of the theophylline with acid-imidazole heterosynthon (Figure 1.15). Cocrystals of theophylline with isomeric dihydroxybenzoic acids and phenols also exhibited better hydrate stability [127].

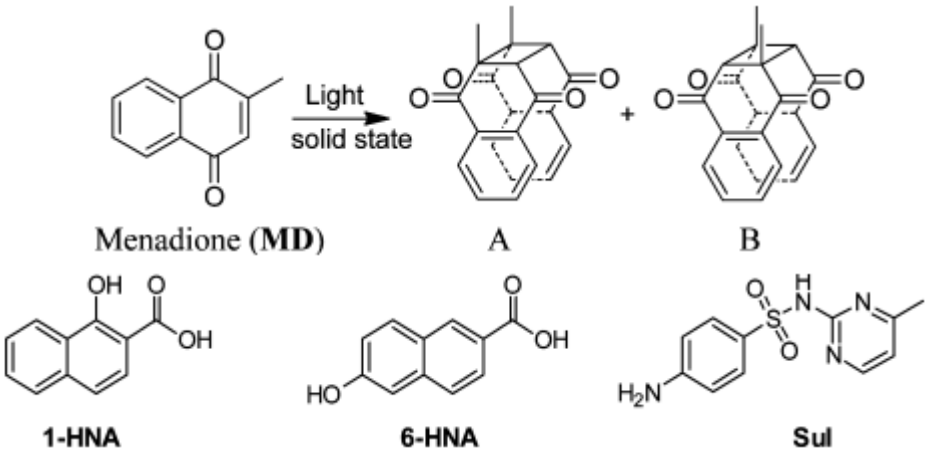


(a) (b)

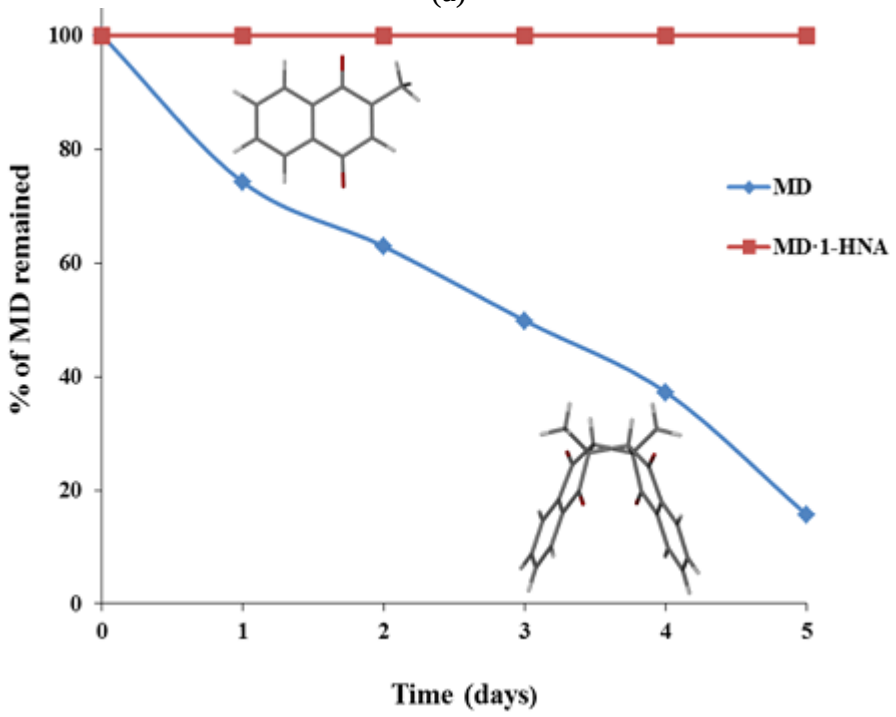
Figure 1.15 (a) In pure theophylline structure, its molecules are connected by N–H···N hydrogen bonds. (b) Theophylline dimers are formed by N–H···O hydrogen bonding in the cocrystal structures. The diclofenac molecules are linked to the theophylline dimers through O–H···N hydrogen bonds [126].

Berberine is utilized clinically for the treatment of diarrhea in the form of chloride salt. The instability of berberine chloride at high humidity was successfully controlled via cocrystallization with fumaric acid. The cocrystal was stable up to 95± 5% humidity [128]. The photostability improvement of vitamin K_3 through cocrystallization with sulfamerazine (Sul) and naphthoic acids (HNA) was demonstrated by Mei and coworkers [129]. Vitamin K_3 has antihemorrhagic and anticancer activities and is marketed as a food additive in the form of menadione sodium bisulfite (MD). When pure crystalline MD is exposed to light, it undergoes topochemical photoreactions that result in the formation of two cyclobutane dimers (A and B) and makes its storage difficult. The poor photostability and low solubility of pure MD limit its use as a food additive and medicine. Cocrystals of

MD with sulfamerazine and naphthoic acids showed better photostability than pure MD (Figure 1.16). The color of the cocrystals remains unchanged for 5 days under UV radiation.



(a)



(b)

Figure 1.16 (a) Molecular structures of vitamin K_3 (MD), its photoproducts, and coformers. (b) Changes in the MD assay quantity in pure MD and its cocrystal with 1-HNA during the illumination of 4500 lx for 5 days [129].

Andrographolide is an herbal drug that shows many pharmacological activities. But the efficacy of the drug is very low because of its poor bioavailability. The *in vivo* biodegradation of the drug into four different metabolites is one of the reasons for the poor bioavailability. Cocrystallization was employed to control the drug biotransformation [130]. Cocrystals (1:1) were prepared with resorcinol, guaiacol, vanillic acid, salicylic

acid, and vanillin. Among these products, the cocrystal of salicylic acid successfully prevented the degradation of the drug into its inactive sulfate metabolite. In Chapters 3 and 4 we demonstrated the stability of the antiulcer drug famotidine through molecular salt formation.

1.5.5 Mechanical Properties

Cocrystals/salts have been also employed to modify the mechanical properties of API molecules such as tensile strength, plasticity, compressibility, etc which determine the quality of tablets. Various studies show that the mechanical properties of crystalline materials are related to the packing patterns in the crystal lattice. For instance, the absence of slip planes in the herringbone structure of the stable polymorph of analgesic paracetamol (form I) causes tableting difficult, whereas the layered structure of metastable polymorph (form II) has slip planes and exhibits better tabletability. The improvement of tabletability for form I was achieved by constructing a layered structure through cocrystal formation with phenazine, oxalic acid, theophylline, caffeine, and naphthalene [131]. In another study, Desiraju et al. demonstrated how the formation of strong ionic interactions and the absence of active slip planes in the crystal structure is responsible for the hardness of the antifungal drug voriconazole salts, whereas the presence of slip planes sustained by weaker interactions makes the cocrystals softer [132]. The drug forms cocrystals with 4-aminobenzoic acid, fumaric acid, and 4-hydroxybenzoic acid and salts with oxalic acid and hydrochloric acid which show the hardness trend as salts ≫ drug > cocrystals. Reddy et al. performed a qualitative mechanical test, nanoindentation, and powder compaction experiments to study the mechanical properties (plasticity, tensile strength, and powder compaction) of cocrystals of food flavoring but very brittle vanillin derivatives [ortho-vanillin's Schiff base with ethylene diamine (sb-oVAN), ethylvanillin (eVAN), isovanillin (iVAN), and vanillin (VAN)] with 6-chloro-2,4-dinitroaniline (CDA) [133]. The cocrystal of sb-oVAN with CDA displayed better plasticity, tensile strengths, and compaction properties in comparison to the other multicomponent systems and pure vanillin derivatives. The highest tabletability of the sb-oVAN cocrystal is due to the formation of slip planes which are connected by van der Waals interactions in the crystal structure (Figure 1.17).

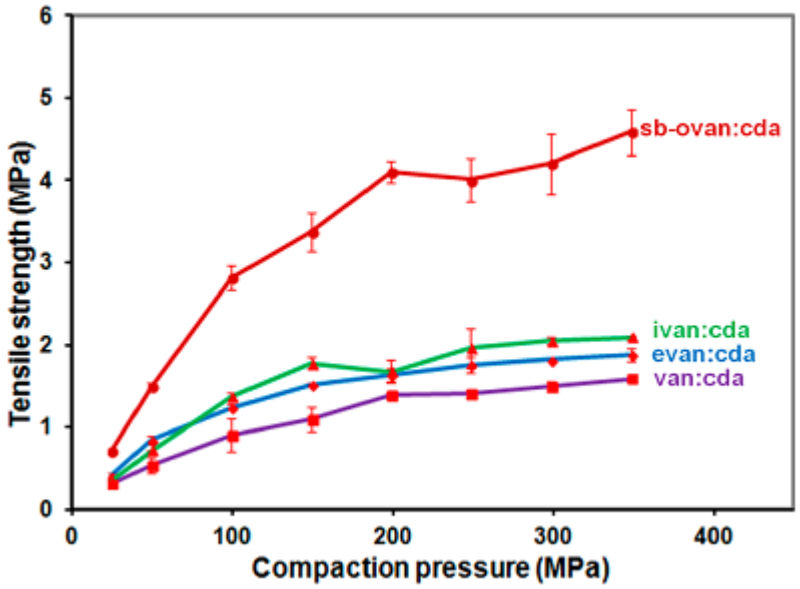


Figure 1.17 Tabletability of vanillin derivatives cocrystals with CDA [133].

Chen et al. demonstrated the enhancement of tabletability of the prodrug temozolomide (TMZ) by inserting a 2D layered structure with slip planes in a cocrystal with hesperetin (HSP) [134]. TMZ shows poor tabletability due to the absence of potential slip planes that enable it easily to deform. HSP exhibits better tabletability as it has 2D layered structures with slip planes. The 2D layered structure of HSP has been partially maintained during the formation of TMZ-HSP and tabletability of the cocrystal is average of the parent starting components. The fragmenting nature of nicorandil (NCR) while tableting was improved through cocrystal/salt formation with fumaric acid (FA), succinic acid (SA), suberic acid (SBA), and oxalic acid (OA) [113]. Except for the cocrystal of SA, all the binary solids of NCR displayed better tabletability than the pure drug (Figure 1.18).

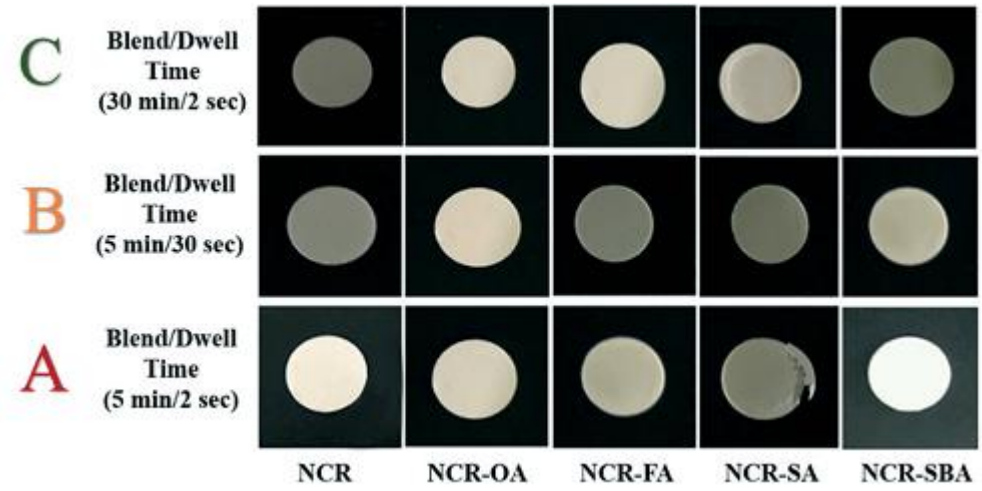


Figure 1.18 The compression properties study of nicorandil and its binary solids, where A–C are the process parameters with different dwell and blending times [113].

1.6 Marketed Pharmaceutical Cocrystals and Salts

According to the current US-FDA definition, a few marketed drugs can be categorized as cocrystals. The pharmaceutical cocrystal drug Entresto was approved by US-FDA in 2015. Entresto was launched by Novartis for chronic heart failure therapy. It is composed of monosodium sacubitril, disodium valsartan, and water molecules. The antidepressant drug Lexapro is a hydrated salt-cocrystal of escitalopram cation, oxalate-oxalic acid, and water molecules. Steglatro is a cocrystal of antidiabetic drug ertugliflozin with L-pyroglutamic acid. Seglentis is an ionic cocrystal that is composed of tramadol hydrochloride and celecoxib, approved for the treatment of acute pain. Depakote is a solid cocrystal drug of the anticonvulsant valproic acid (liquid at ambient temperature) with sodium valproate. Cafcit and Beta-Chlor are also other examples of pharmaceutical cocrystal drugs that are available in the market [3,135,136].

Table 1.4 Summary of commercially available pharmaceutical cocrystals and salts.

Drug	Date of approval	Components	Indication
Depakote	1983	Valproic acid···[valproate sodium]	Epilepsy
Cafcit	1999	Caffeine···[citric acid]	Infantile apnoea
Lexapro	2002	[Escitalopram oxalate]···Oxalic acid	Depression
Suglat	2014	Ipragliflozin···L-proline	Diabetes
Entresto	2015	Valsartan sodium]···[sacubitril sodium]	Heart failure
Steglatro	2017	Ertugliflozin···L-pyroglutamic acid	Diabetes
Seglentis	2021	Tramadol Hydrochloride···Celecoxib	Acute pain

1.7 Summary

Crystal engineering gives vast opportunities for researchers to design and synthesize different novel solid forms of drugs. The fundamental applications of crystal engineering in the process of pharmaceutical development are tailoring stability and biopharmaceutical properties like solubility, membrane permeability, bioavailability, etc. The application of various solid forms such as cocrystals, salts, polymorphs, solvates, and hydrates in the pharmaceutical industry is the focus of this research and is presented in the following chapters. Various physiochemical properties such as stability, aqueous solubility, and membrane permeability of famotidine and trimethoprim are improved via multicomponent crystal technology and presented in this thesis.

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